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ABSTRACT & COMMENTARY

COVID-19 Long-Haulers May Show Signs of Chronic Fatigue, Myalgic Encephalitis

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SYNOPSIS: Many patients with COVID-19 will go on to develop persisting symptoms that resemble those of myalgic encephalitis/chronic fatigue syndrome, regardless of symptoms experienced at viral onset.

SOURCE: Logue JK, Franko NM, McCulloch DJ, et al. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Netw Open* 2021;4:e210830.

Persistent disease after an acute illness is a fact of life. Some diseases, such as myalgic encephalitis/chronic fatigue syndrome (ME/CFS), feature a well-known profile but an unknown specific trigger. ME/CFS may persist for years, carrying with it social stigma, financial ruin, and personal loss.

COVID-19 presents within a spectrum of symptoms from asymptomatic to mild to severe disease. Early in 2020, a certain percentage of COVID-19-infected patients began complaining of persistent symptoms, particularly fatigue, brain fog, low-grade fever, chest pain, muscle discomfort, sweats, persisting anosmia and dysgeusia, and more.[1] These post-viral sequelae of COVID-19 resembled the disease ME/CFS, so researchers were eager to record and understand the duration and progression of sequelae in post-COVID-19 illness in those who have become known as "long-haulers."

The authors of earlier studies had followed COVID-19 patients for one to three months, observing the persistence of symptoms occurred in 4% to 10% of patients with symptomatic illness. In the Logue et al study, patients reported experiencing symptoms many months later. Logue et al examined 234 patients with COVID-19 between August and November 2020 who

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completed subsequent questionnaires between three and nine months after their COVID-19 illness. Data analysis used R Project for Statistical Computing, version 4.0.2. A total of 177 patients completed the survey: 6% were asymptomatic, 85% were outpatients, and 9% were hospitalized. Surveys were completed between 31 and 300 days. There were 82 patients who reported persistent symptoms. The most common persistent symptoms were fatigue (13.6%) and loss of taste and smell (13.6%). Twenty-three patients reported other symptoms, including brain fog. Interestingly, of 51 outpatient and hospitalized patients, 30.7% reported a worse quality of life.

■ COMMENTARY

The Logue et al study is the first to extend a study period to nine months following COVID-19 illness to determine persistent symptoms. The researchers found about 30% fell into this category, many of whom had mild outpatient disease. Persistent symptoms tended to be worse with age. Fatigue persisted in 24 of 177 patients. The authors also observed persistent cranial nerve I dysfunction, meaning abnormalities in smell and taste. In a recent research letter, Lee et al observed activated microglia, a type of viral footprint, in the olfactory bulb, substantia nigra, dorsal motor nucleus of the vagal nerve, and the pre-Bötzinger complex in the medulla, related to spontaneous rhythmic breathing.[2] Thus, like ME/CFS, which produces some central nervous system dysfunction, COVID-19 can cause changes in the brain.

For years, researchers in ME/CFS have searched for a "stealth organism." Despite many false starts, no culprit has been identified. Nevertheless, the search still pertains since many ME/CFS patients will experience some inciting event (e.g., mild upper respiratory infection, trauma, or surgery). Moreover, even though there are various eponyms for ME/CFS, it remains a disease with many symptoms involving several organs. For some younger patients with ME/CFS, the disease will recede (as one ages, the likelihood of remission decreases).

If we assume that at least 100 million Americans have been infected with COVID-19, an estimation from the Logue et al study predicts that at least 14 million Americans may emerge with fatigue plus other chronic symptoms. As a clinician who follows many patients with ME/CFS, my immediate advice is to offer these post-COVID-19 patients hope, listen to all their symptom descriptions, help them adapt to their new malady, and assure them that several medications can alleviate their symptoms. Patients with ME/CFS have been stigmatized for years as having somatization syndromes and silly ills such as "yuppie flu." Ironically, the historic plight of the ME/CFS patient likely will be targeted with new COVID-19 clinics (several of which already are established across the United States) and intense laboratory studies.

ME/CFS is a terrible disease, and medical science, now confronted with a known viral culprit as a trigger for chronic post-COVID-19 disease, must respond with a cadre of specialized medical scientists who can solve the enigma of the long-hauler. ■

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ABSTRACT & COMMENTARY

How to Safely Open Schools in the Time of COVID-19

By Stan Deresinski, MD, FACP, FIDSA

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SYNOPSIS: Multiple COVID-19 transmission clusters were identified in a Georgia school district, with educators often the index cases. The CDC has provided recommendations for safely opening schools.

SOURCE: Gold JAW, Gettings JR, Kimball A, et al; Georgia K-12 School COVID-19 Investigation Team. Clusters of SARS-CoV-2 infection among elementary school educators and students in one school district — Georgia, December 2020-January 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:289-292.

Cases of COVID-19, either self-reported or identified by local public health personnel, occurring between Dec. 1, 2020, and Jan. 22, 2021, in eight public elementary schools in a single district in Georgia were evaluated to determine the patterns of transmission. Nine clusters involving at least three epidemiologically linked cases were identified at six schools. These cases involved 13 educators and 32 students. In two clusters, transmission from one educator to another preceded educator-to-student transmission, and these accounted for 15 of the 31 student cases. In addition, 18 of 69 household contacts who were tested were positive for COVID-19. If household members are included, the median cluster size was six (range, 3-16). The index case was an educator in four clusters, a student in one cluster, and the index case was indeterminate in the remainder. An investigation revealed inadequate social distancing as a consequence of space limitations had occurred in each transmission cluster and that student mask use was inadequate in five of nine clusters.

■ COMMENTARY

The issue of reopening of K-12 schools during the COVID-19 pandemic is the subject of much heat and less light. The CDC has published recommendations to safely open schools. *(http://bit.ly/38XfGhE)* These recommendations include the consistent implementation of mitigation tactics, including mask use, physical distancing, handwashing and respiratory etiquette, cleaning and maintenance of facilities, and collaboration with the health department for contact tracing, together with isolation and quarantine. Additional activities for consideration include testing symptomatic students and personnel and, in selected instances, screening asymptomatic people. The CDC also recommends vaccinating staff and educators (who were found to constitute critical elements in networks of transmission in the Georgia cases) as soon as supplies allow. Most students are not currently eligible for vaccination. In this regard, it is of interest to note that the governor of California now has set aside 10% of vaccine doses for educators. ■

ABSTRACT & COMMENTARY

Low BNP Levels in Up to 16% of Heart Failure Patients

By Jamie L. W. Kennedy, MD, FACC

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SYNOPSIS: In patients with clinical heart failure and low B-type natriuretic peptide levels, the authors found these patients usually are young and obese, with higher ejection fraction and better renal function.

SOURCE: Bachmann KN, Gupta DK, Xu M, et al. Unexpectedly low natriuretic peptide levels in patients with heart failure. *JACC Heart Fail* 2021;9:192-200.

The myocardium releases natriuretic peptides in response to elevated wall stress. There are two forms: atrial natriuretic peptide (ANP) and brain, or B-type, natriuretic peptide (BNP). They exert their effects in several ways, including increasing renal sodium and water excretion, promoting vasodilation, and reducing myocardial fibrosis. Clinical use of BNP levels started with the evaluation of patients in the

ED for dyspnea in the Breathing Not Properly trial.[1] They have become powerful tools for risk assessment, not only in heart failure but also in patients with atrial fibrillation, pulmonary arterial hypertension, acute pulmonary embolism, and systemic hypertension. Serial BNP measurements can help track disease course over time. BNP levels are increasingly incorporated into clinical trial criteria as well to enrich the study population in patients at high risk for clinical events. For example, some heart failure therapy trials have required BNP levels above a certain threshold before enrollment. BNP has become a therapeutic target, too; sacubitril inhibits neprilysin, resulting in higher levels of natriuretic peptides.

Interestingly, there is a subset of patients with clear heart failure with normal or even low BNP values. To further evaluate this phenomenon, Bachmann et al queried a de-identified version of their institution's electronic medical record to find patients with measured BNP values and heart failure based on echo or hemodynamic criteria or hospitalized with heart failure. Echo criteria included left ventricular ejection fraction 35% or lower or left ventricular hypertrophy based on estimated left ventricular mass (> 162 g for women, > 224 g for men). BNP measurement was required within 90 days of the study.

Hemodynamic criteria included left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, or right atrial pressure of 20 mmHg or greater or cardiac index less than 2 L/min/m^2, with BNP measurements required within one day of the procedure. Heart failure hospitalizations required at least one dose of IV diuretic and an ICD diagnosis code for heart failure, and that the BNP measurement was recorded in the 24 hours preceding admission or during the hospitalization.

The authors identified 47,970 adult patients with a measured BNP value: 9,153 were associated with a heart failure hospitalization, 7,041 met echo criteria, and 363 met hemodynamic criteria (some patients fell into multiple groups). BNP levels below 50 pg/mL were present in 4.9% of patients hospitalized for heart failure, 14% of patients with abnormal echoes, and 16.3% of patients with abnormal hemodynamics.

Bachmann et al studied the characteristics of patients hospitalized with heart failure, looking for differences between patients with low (< 50 pg/mL) vs. normal or elevated BNP levels. In a multivariate analysis, higher BMI, younger age, higher ejection fraction, and lower creatinine predicted low BNP levels. Finally, the authors sequenced whole exomes for nine patients with low BNP levels (less than 10 pg/mL to 37 pg/mL). They did not find any loss of function variants in the synthetic pathway for BNP production or mutations that would prevent accurate measurement of BNP levels in lab assays. They found two loss-of-function variants in the NP clearance receptor; one would expect this to result in higher BNP levels. These findings suggest up to 16% of patients with significant hemodynamic derangements produce normal BNP values, and the data confirm the previously observed trend: lower BNPs are seen in younger patients with higher BMIs, higher ejection fraction, and lower creatinine levels.

■ COMMENTARY

The heart failure hospitalization criteria are the most subjective. Patients with dyspnea and low BNP levels may be erroneously diagnosed with something other than heart failure and inappropriately treated. Thus, they were not captured in this study. The timing of BNP measurement during hospitalization also is relevant. A normal BNP at admission would be surprising, while a normal BNP at discharge may be a marker of aggressive heart failure management. The authors' analysis did not include this consideration.

Bachmann et al accepted a surprisingly wide period between BNP measurement and echo study. Unfortunately, this was a significant limitation of their study. It is not uncommon for cardiac function to change dramatically over a 90-day period. For example, an acute myocardial infarction and stress cardiomyopathy often exhibit marked improvement in left ventricular function within days of hospitalization, making interpretation of widely spaced echo and BNP results difficult, at best. The hemodynamically defined patients are the most compelling. Significantly elevated filling pressures or low cardiac index closely correlated with BNP measurements.

Management of obese patients with heart failure can be challenging. Assessment of volume status by physical exam is limited: neck veins can be hard to visualize, hepatomegaly hard to appreciate, and peripheral edema from venous stasis is common. As demonstrated in this study, BNP levels can be low, too, taking away another diagnostic tool. Implantable pulmonary artery pressure sensors can be helpful, although patients with large chest circumferences are not candidates for this device. Further compounding the problem: Obese patients are more likely to be excluded from clinical trials based on low BNP levels, limiting our understanding of heart failure therapies in this significant patient population. ■

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BRIEF REPORT

Compression Garments Effective in Reducing Cellulitis

By Carol A. Kemper, MD, FACP

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SOURCE: Webb E, Neeman T, Bowden FJ, et al. Compression therapy to prevent recurrent cellulitis of the leg. *N Engl J Med* 2020;363:630-639.

Webb et al examined the benefit of compression garments in patients with lower extremity edema at risk for cellulitis. Eligible patients reported significant edema for more than three months in one or both legs, and a history of two or more episodes of cellulitis in the same leg within the previous two years. They could not be using compression garments already for more than four days per week. Patients who were at end of life or immunosuppressed were excluded.

Participants were assigned to wear compression garments throughout the day, every day. The garments generally consisted of knee-high stockings including the foot (with or without the toes) or leg and foot wraps. Participants were followed every six months for up to three years. Control patients who developed cellulitis were crossed over to the compression therapy group. Clinical characteristics were similar between the two groups at entry to the study. A total of 84 participants were enrolled in study, including 41 in the compression group. During the study, 78% of participants in the compression group reported wearing their stockings or wraps five or more days per week, and 88% reported using them at least four days per week.

The trial ended prematurely when the authors recognized a large difference in outcomes between the two groups. At the time the study ended, 23 episodes of cellulitis had occurred, including six in the compression therapy group and 17 in the control group ($P = 0.002$). Three patients in the compression group and six in the control group required hospitalization. Three patients died (one in the compression group and two in the control group), and one in each group developed wound infection. Two patients in each group were receiving prophylactic antibacterials at the time of study entry, which were continued. The median duration of follow-up was 209 days in the compression group and 77 days in the control group — simply because patients were removed from the control group when they developed cellulitis. ■

PHARMACOLOGY UPDATE

Bamlanivimab and Etesevimab Injection

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

The FDA issued an emergency use authorization (EUA) for a second monoclonal antibody combination to treat mild-to-moderate COVID-19. Bamlanivimab and etesevimab (BAM/ETE) are recombinant neutralizing human IgG1k monoclonal antibodies directed at the spike protein of SARS-CoV-2.[1] They bind to different but overlapping targets in the receptor binding domain of the spike protein. This combination is expected to lower the risk of emergent resistance to SARS-CoV-2 vs. administering bamlanivimab alone.

INDICATIONS

BAM/ETE should be prescribed to treat mild-to-moderate COVID-19 in adults and pediatric patients (age 12 years and older, weight at least 40 kg) who test positive for COVID-19 and are at high risk for progressing to severe disease and/or hospitalization.[1] High risk includes comorbidities (e.g., cardiovascular disease, diabetes, immunosuppressive disease, chronic kidney disease, and respiratory disease), age ≥ 65 years, obesity (body mass index ≥ 30 kg/m^2), or on immunosuppressive treatment.

BAM/ETE is not authorized for use in patients who are hospitalized because of COVID-19, who require oxygen therapy or increase from baseline oxygen because of COVID-19, or those who are on chronic oxygen therapy.

DOSAGE

The recommended dose is BAM (700 mg) and ETE (1,400 mg), administered by intravenous infusion together as soon as possible after a positive viral test and within 10 days of symptom onset.[1] BAM and ETE each are available as 700 mg/20 mL single-use vials.

POTENTIAL ADVANTAGES

BAM/ETE cuts the risk of emergent resistant variants of SARS-CoV-2 and treatment failure compared to BAM alone.[1] It also provides another therapeutic option to casirivimab and imdevimab (the first monoclonal antibody therapy to receive an FDA EUA to treat COVID-19) for mild-to-moderate COVID-19.

POTENTIAL DISADVANTAGES

BAM/ETE is not authorized for use in hospitalized patients or those who require oxygen therapy, which limits when the combination can be used. Serious hypersensitivity reactions, including anaphylaxis, have been observed with BAM.

COMMENTS

The EUA was based on an interim analysis of a Phase III clinical trial. There, investigators sought to assess the effect of BAM as monotherapy or in combination with ETE in high-risk patients with mild-to-moderate COVID-19. Initially, this work was carried out in an ongoing Phase II/III trial.[2] In the interim analysis, of 1,035 nonhospitalized adults, 518 received a single infusion of BAM (2,800 mg) and ETE (2,800 mg) and 517 received placebo.[1] The primary endpoint was COVID-19-related hospitalization or death by any cause during 29 days of follow-up. Thirty-six hospitalization/deaths occurred in the placebo arm vs. 11 in the BAM/ETE arm. This represented a 70% risk reduction ($P = < 0.001$). There were 10 deaths in the placebo group vs. no deaths in the BAM/ETE group. BAM/ETE patients also recorded faster time to symptom resolution (median six days vs. eight days for placebo). The authorized dose of 700 mg/1,400 mg was based on comparable virological response to the 2,800 mg/2,800 mg dose as well as pharmacokinetic/pharmacodynamic modeling.[2]

CLINICAL IMPLICATIONS

Contrasted against BAM/ETE, the casirivimab/imdevimab combination binds to different (but not overlapping) regions of the SARS-CoV-2 receptor binding domain.[1,3] This combination reduced the risk of hospitalization and ED visits in high-risk patients, but did not show a significant difference in median time to symptom improvement (five days vs. six days).[3] Because of this, the current Infectious Diseases Society of America (IDSA) guidelines suggest the use of BAM/ETE in patients with mild to moderate COVID-19 at high risk for progression to severe disease.[4] IDSA considers the data strongest for BAM/ETE. ■

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CME QUESTIONS

1. **In recent studies of chronic COVID-19 illness, fatigue may be present in up to what percentage of patients?**
   a. 2%
   b. 5%
   c. 10%
   d. 14%

2. **Low brain natriuretic peptide levels often are seen in heart failure patients with:**
   a. obesity.
   b. low left ventricular ejection fraction.
   c. acute kidney injury.
   d. advanced age.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Patient Preference for Statin Therapy

Modified Ketogenic Diet and Alzheimer's Disease

The Effect of Metformin on Musculoskeletal Pain

Internal Medicine [ALERT]

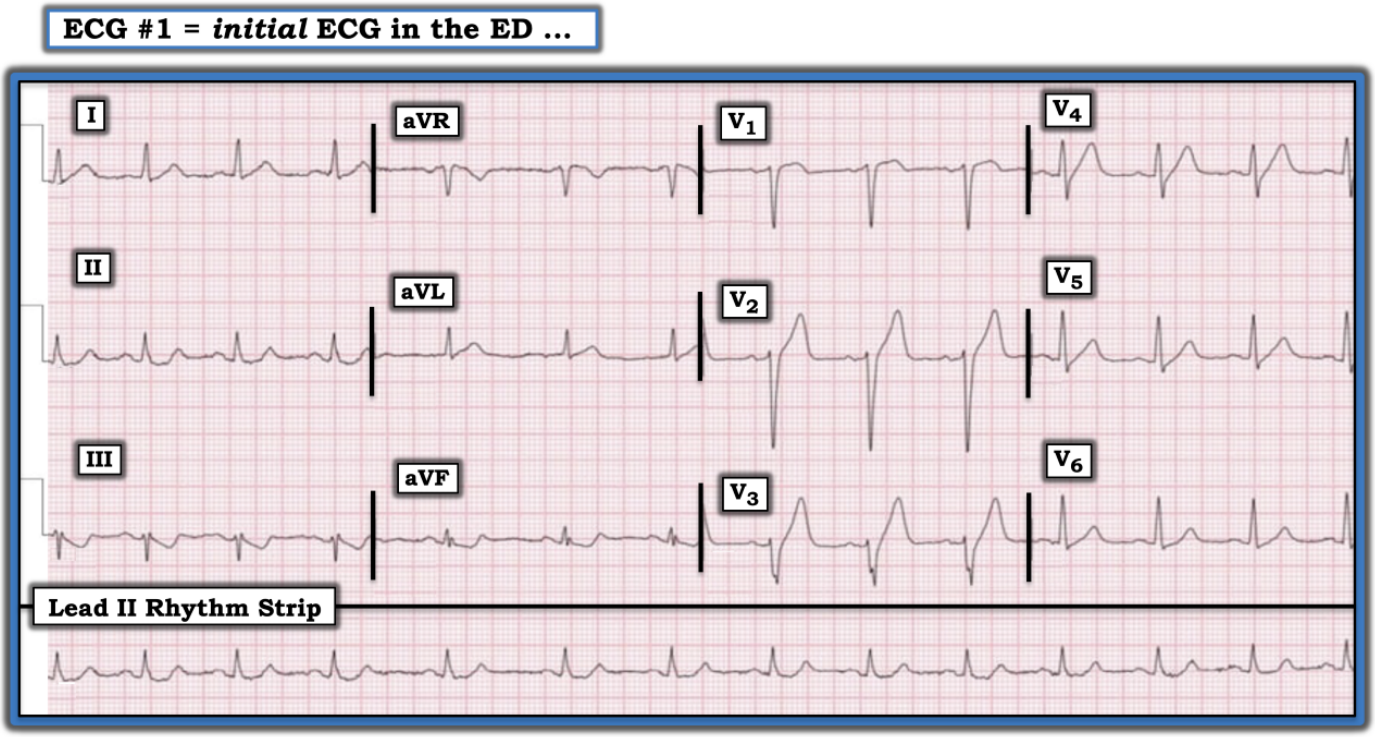
ECG Review

By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

What About These T Waves?

The ECG in the figure below was obtained from a middle-aged man with new-onset chest pain. How would one interpret this tracing?



Sinus rhythm is present, with some initial irregularity (i.e., sinus arrhythmia). The intervals and frontal plane axis both are normal. There is no chamber enlargement.

No Q waves are present. R waves remain small for the initial three chest leads. Tall, peaked T waves in anterior chest leads is the most remarkable finding in this tracing. This is most easy to appreciate in lead V3, in which the height of the T wave equals the depth of the S wave. More than simply increased T wave amplitude, the base of the T wave in lead V3 is obviously widened. This differs from the usual appearance of hyperkalemia, in which the base of the tall T waves tends to be much narrower than seen here.

A look at T wave appearance in neighboring leads V2 and V4 suggests that regarding the size of the S wave in lead V2 and the R wave in lead V4, T waves are disproportionately taller at their peak and wider at their base than expected. The presence of reciprocal ST-T wave depression to varying degrees in each inferior lead supports the described anterior T wave lead findings.

In the setting of new-onset chest pain, the ECG in the figure should suggest acute occlusion of the left anterior descending (LAD) coronary artery until proven otherwise. The ECG findings described so far are similar to the pattern known as de Winter T waves, in which extremely large T waves are found in at least several chest leads in a patient with new chest pain. One or more millimeters of J-point ST depression often is seen just before the abrupt rise to a disproportionately large T wave (as is seen in lead V4 in the figure).

Clinically, prompt recognition of de Winter-like T waves is important because it often signals acute or recent LAD occlusion. This was confirmed on cardiac catheterization in this patient. For more information about and further discussion on this case, please visit: http://bit.ly/3rJDUTx.