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# Update on the Clinical Evaluation and Care of Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Benjamin Natelson, MD



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**Target Audience:** This activity is intended for primary care physicians, nurses, nurse practitioners, pharmacists, and other healthcare providers (HCPs) involved in the diagnosis and management of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS).

**Goal Statement:** The goal of this activity is that learners will be better able to recognize the symptoms, diagnosis, and management of ME/CFS.

**Learning Objectives:** After participating in the activity, the learner should be able to:

Have increased knowledge regarding

- Impact of ME/CFS on multiple body systems
- Recognition of ME/CFS symptoms

Have greater competence related to

- Including patients in developing an individualized treatment plan to improve their health

**Disclosures: Faculty, Editors, CME/CE Reviewer/ Nurse Planner**

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**M**yalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, debilitating multisystem illness characterized by impaired ability to function associated with significant fatigue, post-exertional malaise, sleep dysfunction, cognitive challenges, pain, dizziness, and a wide variety of other debilitating symptoms, all of which significantly affect quality of life (QoL).<sup>1,2</sup> Similar syndromes to MS/CFS have been reported under different names in the medical literature for almost 90 years (eg, DaCosta syndrome, Iceland disease, neurasthenia, Akureyri disease, Royal Free disease).<sup>1</sup> Despite this history, ME/CFS remains poorly recognized and is often stigmatized as a made-up disease. Patients are frequently accused of “making up” symptoms, mislabeled as malingerers, or incorrectly diagnosed as having a psychological illness. In the United States, the prevalence of ME/CFS is estimated to range from 836,000 to 2.5 million.<sup>3</sup> These numbers are expected to increase in the COVID-19 era, given that as many as 15% of COVID-19 survivors experience “long COVID,” a condition that shares many symptoms with ME/CFS. Conservative estimates suggest that the number of ME/CFS cases will at least double.<sup>4</sup> Therefore, it is important for clinicians to be equipped to recognize ME/CFS to ensure their patients with ME/CFS are taken seriously and are properly diagnosed and managed.

Medscape discussed ME/CFS with Benjamin Natelson, MD, Professor of Neurology and Director, Pain & Fatigue Study Center, Icahn School of Medicine at Mount Sinai in New York, New York.

### **Medscape: What is the etiology/pathophysiology of ME/CFS?**

**Benjamin Natelson, MD:** The etiology of ME/CFS remains unknown. Evidence suggests it is likely multifactorial. Infection, particularly with viral illnesses, appears to be a triggering factor in some cases. Approximately 10% of patients with Epstein-Barr virus or Ross River virus have been reported to develop ME/CFS, but a broad spectrum of other viral (eg, cytomegalovirus,

various strains of human herpesvirus), bacterial (eg, mycoplasma, *Coxiella burnetii*), and fungal (eg, *Candida albicans*) pathogens have been implicated.<sup>5,6</sup> One theory is that chronic infections cause changes in the immune system that contribute to the development of ME/CFS.<sup>6</sup> For example, a 2020 study found patients with ME/CFS to have impaired T-cell metabolism.<sup>7</sup> Many immune system and cellular metabolism abnormalities, neuroendocrine disturbances, and blood pressure or heart rate regulation abnormalities have been observed in patients with ME/CFS but it remains unclear whether these changes contribute to the onset of this syndrome or represent a consequence of it.<sup>6</sup>

Other triggering factors associated with ME/CFS include physical or emotional trauma, stress, environmental factors (eg, exposure to mold or toxins), and genetic factors.<sup>6</sup> ME/CFS has been observed among multiple members of the same family; however, current evidence does not suggest there is any single genetic aberration that increases the risk of ME/CFS.<sup>8</sup>

### **Medscape: Are any demographic factors associated with ME/CFS?**

**Dr Natelson:** Although ME/CFS can affect people of all ages, ethnicities, sexes, and socioeconomic statuses, some groups are disproportionately affected.<sup>3,9</sup> Women are affected significantly more frequently than men, with an approximate ratio of 3 or 4 to 1.<sup>2,9</sup> For this reason, ME/CFS was once mistakenly considered a women’s disease.<sup>1</sup> ME/CFS usually affects adults, but adolescents and young children can also be affected. The average age of onset is 33 years (range, 2 to 77 years).<sup>3,9</sup> Some evidence also suggests Black and Hispanic individuals are affected at higher rates and have more severe disease than other racial groups.<sup>9</sup>

Patients with chronic illnesses sometimes develop psychiatric illness as a comorbid condition with their chronic illnesses, and some might have psychiatric illness preceding, but not caused by, their chronic illnesses.<sup>2</sup> Following the development of ME/CFS, the prevalence of subsequent depression is

similar to that seen in the setting of other disabling, chronic illnesses.<sup>9</sup>

### **Medscape: What body systems are impacted by ME/CFS?**

**Dr Natelson:** Three key body systems are affected by ME/CFS. They are the nervous system (central and autonomic), cardiovascular/pulmonary system, and musculoskeletal system.<sup>10</sup> Symptoms stemming from these body systems are diverse and range from mild to severe, leading to a heterogeneous presentation. However, a frequently reported finding in patients with ME/CFS is autonomic nervous system (ANS) dysfunction.<sup>11</sup> Because the ANS spans the whole body and involves all organs and tissues, its involvement alone can cause a broad range of symptoms that may affect heart rate, breathing, digestion, perspiration, urination, and other bodily functions. Common ME/CFS symptoms related to altered ANS functioning include dizziness, orthostatic intolerance, heart palpitations, gastric upset, irritable bladder symptoms, and cold hands and feet.

The way in which the ANS is impacted can also affect the severity of symptoms. During a study including 131 patients with ME/CFS, cluster analyses led to patients being classified into 1 of 4 autonomic profiles: sympathetic symptoms with dysautonomia (34%), sympathetic alone (5%), parasympathetic (21%), and sympathovagal balance (40%).<sup>11</sup> Among these profiles, those with sympathetic symptoms and dysautonomia were found to have the most severe disease and the lowest QoL.

### **Medscape: Can you explain the QoL impact of ME/CFS?**

**Dr Natelson:** Studies have indicated that an ME/CFS diagnosis is associated with perceived stigma, financial instability, and difficulty in social interactions and relationships. ME/CFS can significantly reduce QoL, with some clinicians declaring it to be more devastating than HIV/AIDS.<sup>1</sup> This is not surprising since studies have consistently shown individuals with ME/CFS to have a significantly lower health-related QoL (HRQoL) than both the general population and individuals with myriad other

life-altering conditions.<sup>12,13</sup> In a Danish study, patients with ME/CFS reported the lowest HRQoL among all 20 health conditions assessed, which included such devastating conditions as multiple sclerosis, stroke, and cancer.<sup>13</sup> In an Australian study, ME/CFS was found to lead to significant reductions in HRQoL across all domains assessed, including physical functioning, physical role, pain, general health, social functioning, energy/fatigue, emotional role, and emotional well-being.<sup>12</sup> Such findings are not restricted to adults with ME/CFS. In a North American study, HRQoL was found to be substantially lower in children and young adults (aged 10-23 years) than in their counterparts who had no underlying health conditions.<sup>14</sup> It was also lower than has been reported for children with asthma, diabetes mellitus, epilepsy, eosinophilic gastroenteritis, and cystic fibrosis.<sup>14</sup> As in the adult population, post-exertional fatigue or malaise, cognitive impairment, and orthostatic hypertension were found to be core symptoms impacting QoL among children and young adults.

In addition to ME/CFS significantly reducing the QoL of patients, it also has a significant negative impact on the QoL of the patients' family members.<sup>15</sup> One small study reported a significant correlation between adult patients' reported QoL scores and their family members' QoL scores, which were assessed using patient- and family-oriented questionnaires, respectively.<sup>15</sup> No floor effect was observed in any of the family questionnaire responses, suggesting every family member who participated in the study may have been impacted by their loved one's ME/CFS in some way.

**Medscape:** What findings are suggestive of an ME/CFS diagnosis?

**Dr Natelson:** Diagnosis of ME/CFS poses some challenges because there is no simple, widely available, rapid diagnostic test that can be used. To facilitate diagnosis, numerous case definitions have been proposed, including those by Fukuda et al in 1994, also known as the 1994 Research Case Definition, and those by the Institute of Medicine (IOM) in 2015 (TABLE 1).<sup>9,16,17</sup>

The 1994 Research Case Definition has been widely used, but it was intended for research purposes and not to make a diagnosis in clinical practice.<sup>1</sup> These criteria are challenging to apply in clinical settings because they require patients to have medically unexplained chronic fatigue for a positive diagnosis, which necessitates ruling out many other conditions that can result in fatigue, potentially contributing to diagnostic delays or avoidance.<sup>9</sup> Additionally, these criteria do not require important symptoms of ME/CFS, such as post-exertional malaise (now considered a hallmark symptom), to make the diagnosis.<sup>9</sup> The 2015 IOM Case Definition has streamlined the 1994 Research Case Definition by removing the exclusion requirements

and incorporating post-exertional malaise as a requirement. The Centers for Disease Control and Prevention (CDC) has adopted the IOM criteria for diagnosing ME/CFS.<sup>9</sup>

As understanding of ME/CFS continues to evolve, additional helpful diagnostic findings are being discovered, such as hypocapnia.<sup>18,19</sup> Current evaluation of orthostatic intolerance focuses on cardiac findings, such as tachycardia, hypotension, and hypertension, but hypocapnia can serve as another important biological marker of orthostatic intolerance. Unfortunately, the only way to identify hypocapnia is via using a capnograph because respiratory rate is usually not elevated. Capnographs are expensive but very useful in identifying unappreciated hypocapnia.

**TABLE 1. 1994 Research and 2015 IOM Clinical Case Definitions of ME/CFS<sup>3,16</sup>**

1994 Research Case Definition	2015 IOM Case Definition
<p>Diagnosis is made when a patient meets fatigue criteria, has <math>\geq 4</math> of 8 other symptoms, and symptoms are not explained by untreated illness:</p> <p>A <math>\geq 6</math>-month history of new- or definite-onset chronic fatigue that is persistent or relapsing</p> <ul style="list-style-type: none"> <li>✓ Has not been lifelong</li> <li>✓ Not a result of ongoing exertion</li> <li>✓ Unexplained after clinical evaluation</li> <li>✓ Not substantially relieved by rest</li> <li>✓ Results in substantial reduction in occupational, educational, social, or personal activities</li> </ul> <p>At least 4 of the following symptoms must have persisted or recurred during <math>\geq 6</math> consecutive months of illness and must not have predated the fatigue</p> <ol style="list-style-type: none"> <li>1. Self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities</li> <li>2. Sore throat</li> <li>3. Tender cervical or axillary lymph nodes</li> <li>4. Muscle pain</li> <li>5. Multi-joint pain without joint swelling or redness</li> <li>6. Headaches of a new type, pattern, or severity</li> <li>7. Unrefreshing sleep</li> <li>8. Post-exertional malaise lasting <math>&gt; 24</math> hours</li> </ol>	<p>Diagnosis is made when the patient meets all 3 required criteria and has <math>\geq 1</math> of the additional criteria:</p> <p>Required Criteria</p> <ol style="list-style-type: none"> <li>1. Fatigue results in a significant reduction or impairment in patient's ability to function at the same level of activity prior to illness <ul style="list-style-type: none"> <li>✓ Fatigue is new (not life-long)</li> <li>✓ Lasts for <math>&gt; 6</math> months</li> <li>✓ Not just the result of excessive exertion (eg, working out)</li> <li>✓ Not substantially alleviated by rest</li> <li>✓ A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities</li> </ul> </li> <li>2. Post-exertional malaise* <ul style="list-style-type: none"> <li>✓ Increased symptoms after physical, mental, or emotional exertion when engaging in activities that would have been tolerated previously</li> <li>✓ May occur hours to days after exertion</li> <li>✓ May last days, weeks, or months</li> </ul> </li> <li>3. Unrefreshing sleep* <ul style="list-style-type: none"> <li>✓ Can occur despite full night of sleep</li> </ul> </li> </ol> <p>Additional Criteria</p> <ol style="list-style-type: none"> <li>1. Cognitive impairment* or <ul style="list-style-type: none"> <li>✓ Can include memory and executive function challenges and "brain fog"</li> </ul> </li> <li>2. Orthostatic intolerance <ul style="list-style-type: none"> <li>✓ Worsening symptoms when upright</li> <li>✓ Lightheaded, increasing fatigue, worsening "brain fog," fainting</li> <li>✓ Elevated heart rate, decreased blood pressure when upright</li> </ul> </li> </ol> <p>*Symptoms must be moderate to severe and present <math>&gt; 50\%</math> of the time</p>

Legend: CFS, chronic fatigue syndrome; IOM, Institute of Medicine; ME, myalgic encephalomyelitis.

**Medscape: What is the clinical course of ME/CFS?**

**Dr Natelson:** ME/CFS onset may be sudden or gradual, and it often has a fluctuating pattern with patients having good and bad periods, with severity influenced by factors such as physical and emotional stress, infections, and comorbidities.<sup>3,9</sup> The disease course is variable, and no 2 patients are alike.<sup>3</sup> A small number of patients may eventually return to a level of function at or near their previous baseline, but the majority are likely to remain relatively disabled, with some becoming mostly bedridden. In an FDA report, 61% of patients with ME/CFS reported being bedridden on their worst days, with only 6% reporting having the ability to do light housework or work part-time on such days.<sup>20</sup> It is estimated that 25% of patients with ME/CFS will become housebound or bedbound at some point during their illness, and as many as 75% will be unable to work due to physical, cognitive, and/or functional difficulties.<sup>3</sup>

It remains unclear how many patients with ME/CFS make a full recovery, especially since this has not been well studied and many cases remain undiagnosed or may be lost to follow-up.<sup>21</sup> In a systematic review that included 14 studies of participants meeting operational criteria for ME/CFS, the median full recovery rate was only 5% (range, 0% to

31%).<sup>22</sup> Additionally, some patients with ME/CFS may be ill for several years or even decades, during which their symptoms will wax and wane but be ever-present.<sup>9</sup>

**Medscape: What type of work-up is required?**

**Dr Natelson:** Work-up of patients with ME/CFS requires taking a careful medical and family history, paying particular attention to any triggering factors, such as previous infections, exposure to toxins, and trauma or stress, as well as a family history of ME/CFS. It also requires a careful physical examination, during which a NASA lean test and Beighton score can be helpful in establishing the diagnosis.

The NASA lean test (NLT) or a tilt-table test can be used to assess for orthostatic intolerance, which is responsible for many symptoms associated with ME/CFS, including dizziness, heart palpitations, cognitive dysfunction, and muscle pain. A study was conducted comparing NLT findings in patients with ME/CFS for < 4 years or > 10 years with those of healthy controls.<sup>23</sup> The < 4-year cohort had significantly higher heart rates and abnormally narrowed pulse pressures vs the > 10-year ME/CFS cohort and healthy controls. These findings were not related to age or medication use. The < 4-year cohort also had more symptoms of orthostatic

intolerance than their 10-year counterparts, suggesting some adaptation and compensation occurs over time. The NLT is a simple 10- to 20-minute test that can be particularly beneficial in the early diagnosis of ME/CFS and to help guide the treatment of orthostatic intolerance.

The Beighton score is used to screen for joint hypermobility, which has been associated with ME/CFS. In a study including patients with ME/CFS and/or fibromyalgia, conditions with overlapping symptoms that sometimes coexist, 81% met the Brighton criteria for hypermobility syndrome (odds ratio vs healthy controls, 7.08), with hypermobility scores significantly predicting symptom levels, including fatigue, pain, and cognition.<sup>24</sup>

Lab testing is an important part of the workup and may be helpful in identifying issues such as immune impairment, metabolic abnormalities, and other treatable conditions that could contribute to patients' symptom profile (TABLE 2).<sup>25,26</sup>

Additional useful tests may include sleep studies, skin biopsy, and a cardiopulmonary exercise test (CPET). The skin biopsy may provide objective evidence of small fiber neuropathy, whereas the CPET can help investigate exertional intolerance.<sup>27</sup> Small fiber neuropathy has been reported in ~50% of patients with postural orthostatic tachycardia and fibromyalgia, 2 conditions that overlap with ME/CFS. In patients with small fiber neuropathy, the neuropathic dysregulation causes microvascular dilation, which may limit exertion by shunting oxygenated blood from capillary beds and reducing cardiac return.<sup>27</sup>

**Medscape: Once a diagnosis is made, how is ME/CFS treated?**

**Dr Natelson:** There is no cure for ME/CFS; however, many treatments are available that can significantly reduce patients' symptoms, improve their function, and help them regain good QoL. Treatment options will depend on each patient's presentation and preferences. An essential first step is to address the key symptoms associated with ME/CFS (TABLE 3).<sup>9,26</sup>

**TABLE 2. Lab Tests Excluding Other Conditions**<sup>25,26</sup>

Who to Test	Test and Purpose
All patients	ANA, anti-dsDNA - Autoimmune disease CBC - Blood counts CK - Muscle enzyme CMP - Kidney and liver function Cortisol - Adrenal gland function CRP and ESR - Inflammatory markers SPEP - Nutrition deficits, inflammation, kidney/liver disease, and other conditions TSH - Thyroid function Antibody to EBV Early Antigen
As determined by medical history and exposures	<b>Nonviral Infections</b> Lyme disease test <i>Brucella</i> <i>Bartonella</i>  <b>Other Conditions</b> Celiac disease AChR - Myasthenia gravis

Legend: AChR, acetylcholine receptor antibody; ANA, antinuclear antibody; CBC, complete blood count; CK, creatine kinase; CMP, comprehensive metabolic panel; CRP, C-reactive protein; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; SPEP, serum protein electrophoresis; TSH, thyroid-stimulating hormone.

**TABLE 3. Nonpharmacologic and Pharmacologic Interventions for Managing Key Symptoms Associated With ME/CFS<sup>9,26</sup>**

<p><b>Post-exertional malaise</b></p>	<p><b>Nonpharmacologic</b></p> <ul style="list-style-type: none"> <li>• Avoiding overexertion, as this exacerbates ME/CFS and can hinder improvement; strategies patients can use to avoid this include:             <ul style="list-style-type: none"> <li>◦ <i>Interval or time-based activity</i>: The patient remains active only for the amount of time that doesn't trigger symptoms, then rests, and then re-engages in being active for a similar interval, continuing in this way with a goal to increase the interval over time</li> <li>◦ <i>Wear a pedometer to monitor steps</i>: Patients determine how many average daily steps they take over the course of a good week without flares or relapse and then keep their daily step counts in that range, with a goal to take at least 1000 steps daily to prevent deconditioning</li> <li>◦ <i>Monitoring their heart rate</i>: Patients determine the maximum heart rate they can tolerate without triggering or exacerbating symptoms and then avoid exceeding that heart rate, except for short periods</li> </ul> </li> <li>• Low sensory environment for more severely ill patients (eg, use of earplugs and masks)</li> <li>• Assistive devices, such as motorized scooters, shower chairs, and handicap parking stickers</li> <li>• Home health aides for homebound or bedbound patients</li> </ul> <p><b>Pharmacologic</b></p> <ul style="list-style-type: none"> <li>• None recommended</li> </ul>
<p><b>Orthostatic intolerance</b></p>	<p><b>Nonpharmacologic</b></p> <ul style="list-style-type: none"> <li>• Avoiding prolonged sitting or standing</li> <li>• Electrolyte drinks</li> <li>• Compression stockings</li> <li>• Consistent, tailored exercise that does not trigger or exacerbate post-exertional malaise</li> </ul> <p><b>Pharmacologic</b></p> <ul style="list-style-type: none"> <li>• Fludrocortisone, low-dose beta-blockers, alpha-adrenergic agonists, pyridostigmine, desmopressin, and ivabradine</li> <li>• Intravenous saline</li> </ul>
<p><b>Sleep</b></p>	<p><b>Nonpharmacologic</b></p> <ul style="list-style-type: none"> <li>• Good sleep hygiene</li> <li>• Meditation/relaxation exercises</li> <li>• Earplugs and eye masks</li> <li>• Blue light filters and/or light therapy</li> <li>• Referral to a sleep specialist</li> </ul> <p><b>Pharmacologic</b></p> <ul style="list-style-type: none"> <li>• Over-the-counter sleep aids, such as melatonin, theanine, valerian, tryptophan, and antihistamines</li> <li>• Trazadone, low-dose tricyclic antidepressants, mirtazapine, antiepileptics, clonazepam, cyclobenzaprine, zolpidem, eszopiclone, tizanidine, suvorexant, topiramate, hydroxyzine, alpha-blockers, and diphenhydramine</li> </ul>
<p><b>Pain</b></p>	<p><b>Nonpharmacologic</b></p> <ul style="list-style-type: none"> <li>• Same strategies as for post-exertional malaise can help prevent pain flare-ups</li> <li>• Hot/cold packs</li> <li>• Physical therapy</li> <li>• Complementary therapy, such as massage, myofascial release, and acupuncture</li> <li>• Meditation and relaxation</li> <li>• Neurofeedback techniques</li> </ul> <p><b>Pharmacologic</b></p> <ul style="list-style-type: none"> <li>• Low-dose naltrexone, serotonin-norepinephrine reuptake inhibitors, antiepileptics, muscle relaxants, nonsteroidal anti-inflammatory drugs, acetaminophen, amitriptyline, and tramadol</li> </ul>
<p><b>Cognitive dysfunction and fatigue</b></p>	<p><b>Nonpharmacologic</b></p> <ul style="list-style-type: none"> <li>• Same strategies as for post-exertional malaise</li> <li>• Cognitive pacing: Patient focuses on only 1 task at a time and limits the time they engage in the task</li> <li>• Memory aids (eg, notes, calendars, to-do lists)</li> <li>• Performing cognitive functions lying down and staying hydrated can be considered for patients with orthostatic intolerance</li> </ul> <p><b>Pharmacologic</b></p> <ul style="list-style-type: none"> <li>• Methylphenidate, modafinil, armodafinil, and caffeine, if well tolerated</li> </ul>

Legend: CFS, chronic fatigue syndrome; ME, myalgic encephalomyelitis.

Additionally, it is important to identify and address any comorbidities. This includes conditions that overlap with ME/CFS, such as mast cell activation syndrome, postural orthostatic tachycardia syndrome, dysautonomia, and hypocapnia (patient may yawn/sigh a lot and be unable to hold their breath for > 30 seconds), as these conditions may necessitate the use of additional interventions to relieve patients' symptoms.

### **Medscape: What other tips do you have to improve the care of patients suspected to have or diagnosed with ME/CFS?**

**Dr Natelson:** Patients with ME/CFS require physical and emotional support, especially because they are dealing with a stigmatizing, invisible

illness. It is also crucial to validate the illness for the patient and their family.<sup>25</sup> They should be reassured that ME/CFS is a real condition and not laziness, depression, or a psychosomatic or other disorder. They should be educated about their illness so that they have realistic expectations about its management and a good understanding of the range of interventions that are available to them. During these discussions, patients should be involved in decision making, with their priorities, preferences, and past experiences taken into consideration.

In addition to providing medical expertise, clinicians are crucial advocates for their patients. Clinicians can play instrumental roles in helping their patients obtain any special accommodations they may require to

be able to function at work or school and in applying for the assistance they may need to better handle activities of daily living (eg, parking permits, disability, home health aides, securing assistive devices). Additionally, because ME/CFS is a complex, multifaceted disease that affects numerous body systems and has symptoms that overlap with a broad range of other conditions, it is important for clinicians to use an interdisciplinary approach to care, making referrals to specialists as appropriate and cultivating relationships with clinicians who have expertise in ME/CFS or are willing to learn. This will help ensure patients receive care from a team of clinicians who understand their illness and take their symptoms and well-being seriously.

## **REFERENCES**

1. Friedman KJ. Advances in ME/CFS: past, present, and future. *Front Pediatr*. 2019;7:131.
2. Centers for Disease Control and Prevention. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Epidemiology. Reviewed April 21, 2021. Accessed January 3, 2022. <https://www.cdc.gov/me-cfs/healthcare-providers/presentation-clinical-course/epidemiology.html>
3. IOM (Institute of Medicine). Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: The National Academies Press; 2015.
4. Komaroff AL, Bateman L. Will COVID-19 lead to myalgic encephalomyelitis/chronic fatigue syndrome? *Front Med (Lausanne)*. 2021;7:606824.
5. Rasa S, Nora-Kruklic Z, Henning N, et al. Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *J Transl Med*. 2018;16:268.
6. Centers for Disease Control and Prevention. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Etiology and Pathophysiology. Reviewed July 12, 2018. Accessed January 3, 2022. <https://www.cdc.gov/me-cfs/health-care-providers/presentation-clinical-course/etiology-pathophysiology.html>
7. Mandarano AH, Maya J, Giloteaux L, et al. Myalgic encephalomyelitis/chronic fatigue syndrome patients exhibit altered T cell metabolism and cytokine associations. *J Clin Invest*. 2020;130:1491-1505.
8. Dibble JJ, McGrath SJ, Ponting CP. Genetic risk factors of ME/CFS: a critical review. *Hum Mol Genet*. 2020;29(R1):R117-R124.
9. Bateman L, Bested AC, Bonilla HF, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: essentials of diagnosis and management. *Mayo Clin Proc*. 2021;96:2861-2878.
10. Missailidis D, Annesley SJ, Fisher PR. Pathological mechanisms underlying myalgic encephalomyelitis/chronic fatigue syndrome. *Diagnostics (Basel)*. 2019;9:80.
11. Slomko J, Estévez-López F, Kujawski S, et al. Autonomic phenotypes in chronic fatigue syndrome (CFS) are associated with illness severity: a cluster analysis. *J Clin Med*. 2020;9:2531.
12. Eaton-Fitch N, Johnston SC, Zalewski P, et al. Health-related quality of life in patients with myalgic encephalomyelitis/chronic fatigue syndrome: an Australian cross-sectional study. *Qual Life Res*. 2020;29:1521-1531.
13. Falk Hvidberg M, Brinth LS, Olesen AV, et al. The health-related quality of life for patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *PLoS One*. 2015;10:e0132421.
14. Roma M, Marden CL, Flaherty MAK, et al. Impaired health-related quality of life in adolescent myalgic encephalomyelitis/chronic fatigue syndrome: the impact of core symptoms. *Front Pediatr*. 2019;7:26.
15. Brittain E, Muirhead N, Finlay AY, et al. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): major impact on lives of both patients and family members. *Medicina (Kaunas)*. 2021;57:43.
16. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med*. 1994;121:953-959.
17. Lim EJ, Son CG. Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *J Transl Med*. 2020;18:289.
18. Natelson BH, Intriligator R, Cherniack NS, et al. Hypocapnia is a biological marker for orthostatic intolerance in some patients with chronic fatigue syndrome. *Dyn Med*. 2007;6:2.
19. Natelson BH, Brunjes DL, Mancini D. Chronic fatigue syndrome and cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol*. 2021;78:1056-1067.
20. US Food & Drug Administration. The voice of the patient. A series of reports from the U.S. Food and Drug Administration's (FDA's) patient-focused drug development initiative. Published September 2013. Accessed January 3, 2022. <https://www.fda.gov/media/86879/download>
21. Centers for Disease Control and Prevention. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Prognosis. Reviewed July 12, 2018. Accessed January 5, 2022. <https://www.cdc.gov/me-cfs/healthcare-providers/presentation-clinical-course/prognosis.html>
22. Cairns R, Hotopf M. A systematic review describing the prognosis of chronic fatigue syndrome. *Occup Med (Lond)*. 2005;55:20-31.
23. Lee J, Vernon SD, Jeys P, et al. Hemodynamics during the 10-minute NASA Lean Test: evidence of circulatory decompensation in a subset of ME/CFS patients. *J Transl Med*. 2020;18:314.
24. Eccles JA, Thompson B, Themelis K, et al. Beyond bones: the relevance of variants of connective tissue (hypermobility) to fibromyalgia, ME/CFS and controversies surrounding diagnostic classification: an observational study. *Clin Med (Lond)*. 2021;21:53-58.
25. US ME/CFS Clinician Coalition website. Diagnosing/Treating ME/CFS. Published July 2020. Accessed January 3, 2022. <https://drive.google.com/file/d/1SG7hJTCSDrDHqvioPMq-cX-rgRKXjfk/view>
26. Lapp CW. Initiating care of a patient with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Front Pediatr*. 2019;6:415.
27. Joseph P, Arevalo C, Oliveira RKF, et al. Insights from invasive cardiopulmonary exercise testing of patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Chest*. 2021;160:642-651.