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Review Article

ME/CFS: Current Insights and Future Directions

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Abstract

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic multisystem illness marked by persistent, disabling fatigue lasting over six months and involving various organ systems. Although recognized as a neurological disorder by the WHO since 1969, its exact cause remains unknown, and no definitive biomarkers are available. ME/CFS mainly affects adults aged 30–50, especially women, often triggered by infections like Epstein–Barr virus or SARS-CoV-2, with incidence rising after the COVID-19 pandemic. Diagnosis relies on clinical criteria and exclusion of other diseases, with post-exertional malaise (PEM), a delayed and severe symptom worsening after exertion, as a key feature. The Canadian Consensus Criteria, widely used in Europe, require specific symptoms to diagnose the disease. No curative treatment exists; management focuses on symptom relief and careful pacing to prevent PEM, alongside supportive care such as sleep optimization, pain control, and psychosocial support. Pharmacological treatments target individual symptoms, but have limited proven efficacy. Severe cases present significant challenges. ME/CFS imposes a heavy burden on patients and families, exacerbated by diagnostic delays and limited awareness. Current research seeks to elucidate disease mechanisms and identify biomarkers for targeted therapies. Meanwhile, multidisciplinary care and increased recognition remain crucial to reduce condition's impact.

Abbreviations: Myalgic Encephalomyelitis; Chronic Fatigue Syndrome; ME/CFS; Post-exertional Malaise; Diagnosis by exclusion; Canadian Consensus Criteria; Symptom management

Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic multisystem disorder. Despite classification by the WHO as a neurological disease (ICD-10 code G93.3) since 1969, its pathogenesis remains unresolved and no routine clinical biomarkers exist. Women represent about two-thirds of patients, typically aged 30-50, often experiencing disease onset following infections in approximately 80% of cases; other triggers include surgery, resuscitation, or trauma, although many cases have no identifiable cause [1-3]. Potential infectious agents linked to ME/CFS include Epstein–Barr virus, COVID-19 (with 20% Long COVID cases presenting as ME/CFS), herpesviruses, enteroviruses, influenza viruses, various bacterial pathogens (e.g. Borrelia, Mycoplasma), and rarer fungal or protozoal infections [3] Prevalence estimates are uncertain due to diagnostic challenges, lack of biomarkers, and frequent misdiagnosis, with incidence rising notably since the COVID-19 pandemic.

Emerging evidence suggests dysfunction of central and autonomic nervous systems, neuroinflammation, immune

dysregulation with viral reactivation, cardiovascular abnormalities (including endothelial dysfunction and impaired perfusion), muscle damage, cerebral hypoperfusion, mitochondrial impairment, and gut microbiome alterations [1,3]. However these hypotheses lack definitive molecular or cellular confirmation, underscoring the urgent need for basic and clinical research to refine disease definition, improve diagnosis, and accurately assess epidemiology. Enhanced understanding would also support public awareness, patient care, and funding allocation. As for the current status, it appears that a diagnostic proof for ME/CFS will likely be integrated into diagnostics, as well as the differentiation of disease stages and potential therapies, in the near future. From daily clinical experience it can be confirmed, that the perception and acceptance of the illness as an independent somatic disease entity, possibly as a consequence of a previous infectious disease, is of great importance of those affected. Clinically, ME/CFS manifests with varying severity, causing physical and cognitive impairment from mild restrictions to complete bedridden status [1]. Disease severity is commonly classified as mild (work possible with limitations), moderate (majority, mostly homebound), severe (largely bedridden, requiring support), and very severe (fully dependent with need for sensory shielding). Substantial improvement or recovery in adults is rare [2]. Approximately 60% of patients cannot work, 25% stay at home, and many family caregivers face significant burdens. Quality of life and life expectancy may be reduced in severe cases due to complications such as heart failure, malignancies, and suicide [1].

Diagnostic Approach

The diagnostic process begins with a thorough medical history and review of symptom diaries, followed by physical examination. Clinical signs may include cold, clammy extremities, Raynaud's phenomenon, mottled skin, elevated resting heart rate, reddened eyes, facial swelling, lymphadenopathy, and throat pain [1,3]. A broad screening panel helps exclude other, more easily identifiable conditions. This includes complete blood count, CRP, ferritin, HbA1c, lipid profile, kidney and liver function tests, CK, LDH, electrolytes (including phosphate), TPO-Ab, thyroid function, immunoglobulin subclasses, ANA (and ENA if positive), ANCA, anticardiolipin antibodies, prothrombin, ACE-2, celiac antibodies, and NT-pro-BNP. These tests may identify treatable abnormalities or comorbidities, though often no clinically actionable findings are revealed beyond, for example, non-specific autoantibodies [1.3]. As a diagnosis of exclusion, ME/CFS requires that potential neurological, psychiatric, endocrine, or metabolic causes be ruled out. In the absence of validated biomarkers, diagnosis relies on internationally accepted criteria and scoring systems. Post-exertional malaise (PEM) is a mandatory symptom in most scorings. PEM refers to a marked and prolonged worsening of baseline symptoms following minimal exertion, whether physical, cognitive, emotional, orthostatic, or sensory. By definition it is delayed by 12-72 hours after exertion and lasts for days or longer, often resulting in symptom "crashes"

(appearance of new symptoms) and posing a risk of lasting deterioration. Unlike fatigue seen in depression and burn-out, PEM uniquely distinguishes ME/CFS: patients are typically motivated and physically active when able, but suffer exacerbation after exertion [1-3]. PEM must also be differentiated from fatigue due to other chronic conditions, especially internal medical (and among these, especially) oncological diseases. Common comorbidities include fibromyalgia, irritable bowel syndrome, endometriosis, and Hashimoto's thyroiditis. [1-3] While the pathophysiology of PEM remains unclear, it is not considered life-threatening and is based on patient self-report, but remains integral to the CCC and IOM diagnostic frameworks [4]. In Europe, the Canadian Consensus Criteria (CCC) are preferred for adults due to their specificity, whereas the Institute of Medicine (IOM) criteria are more commonly applied in the United States. CCC require five major criteria, pathological fatigue, PEM, unrefreshing sleep, pain, and cognitive/neurological impairments, plus at least two of three minor criteria: autonomic, neuroendocrine, and immune dysfunction. A minimum symptom duration of six months is necessary to distinguish ME/CFS from transient post-infectious fatigue [1-3,5]. Diagnostic aids, such as structured questionnaires, are available for clinical use. Post-diagnostic tools include severity scoring (e.g., Bell scale), symptom monitoring (e.g. MBSQ), and functional capacity assessments (e.g., FUNCAP55) [1]. Timely and accurate diagnosis is critical, as delayed identification may worsen prognosis. Currently, the average time to diagnosis is approximately five years [1], often due to nonspecific symptoms, limited awareness, and insufficient medical training on ME/CFS.

Austria lacks specialized ME/CFS care facilities as of October 2025. In contrast, Germany, offers some specialized centers, including the Immunodeficiency Outpatient Clinic at Charité Berlin (all ages) and the Chronic Fatigue Centre at TU Munich (for patients under 20). However, care remains fragmented, and long travel distances, combined with patient's functional limitations, often hinder access to adequate care. [2]

Treatment

Currently, no curative treatment for ME/CFS exists, which is why management focuses on patient education, self-care, symptom relief, and psychosocial support [1].

a) Non-pharmacological Interventions

The cornerstone of therapy is "pacing", a strategy of individualized energy management to prevent PEM by respecting physical and psychological limits and taking timely rest [1-2]. In advanced stages, pacing however becomes difficult as even basic activities can trigger PEM [6]. Tools like diaries and wearables may aid pacing, with AI holding future potential. Additional interventions include sleep hygiene, relaxation methods, physiotherapy tailored to pain and circulation, manual therapy, occupational therapy, and dietary adjustments

addressing intolerances and nutritional deficiencies. Sensory shielding (e.g. noise-canceling headphones, darkened rooms), hydration, compression garments, and electrolyte supplementation may relieve orthostatic symptoms. Nutritional support emphasizes protein intake and correcting micronutrient deficits, with cautious use of supplements [1-3]. Ribose, vitamins, and coenzymes may potentially be benefiting mitochondrial dysfunction, though clinical evidence is limited [7].

Psychological comorbidities such as depression and anxiety should be treated appropriately, with psychotherapy focused on coping rather than cure [1]. Support groups and workplace

accommodations can improve patient quality of life and work retention. [3,8] Social and financial assistance is critical due to high rates of work incapacity, especially because access is often hindered by bureaucratic and social barriers [1]. Seriously ill patients require specialized care with attention to nutrition, hygiene, and sensory needs [6].

b) Pharmacological Interventions

Pharmacotherapy is largely off-label and symptom-oriented, with careful dose titration and risk-benefit evaluation due to heightened sensitivity to side effects. Treatment includes beta-blockers, ivabradine, or fludrocortisone for orthostatic symptoms; melatonin, low-dose antidepressants, or pregabalin/gabapentin for sleep and pain (for the latter also other pain medication from the WHO step scheme or low-dose naltrexone); and antihistamines or mast cell stabilizers for allergic symptoms. Antivirals (e.g. aciclovir) can be used against herpesvirus reactivation, and antibiotics like azithromycin may provide immunomodulatory effects early in the disease. Vaccinations are recommended, and infections should be treated according to the current guidelines. Immunoglobin therapy is reserved and strictly limited for specific immune deficiencies [1-3]. Low-dose aripiprazole shows promise in alleviating fatigue and cognitive symptoms, possibly modulating neuroinflammation [9]. Evidence for hyperbaric oxygen, anticoagulants, and rheological agents is limited [1]. Experimental immunotherapies (e.g. rituximab, cyclophosphamide) are under investigation for severe cases [3].

During acute exacerbations, supportive care with hydration and sensory shielding is vital; benzodiazepines may be used short-term with caution [6]. Detailed treatment guidelines are available from major institutions such as Charité Berlin, NICE, CDC and relevant ME/CFS societies. The German Society of Neurology advocates a multidisciplinary, evidence-based approach addressing immunological, psychosomatic, and functional aspects. Transparent patient education and appropriate psychiatric support are essential due to the disease's psychological impact [10]. ME/CFS is unequivocally classified as an organic neurological disorder by WHO and ICD-11 standards [11].

Conclusion

ME/CFS is a complex multisystem disorder that poses significant challenges for patients and clinicians due to its profound impact, lack of biomarkers, limited specialized care, and absence of consistently effective treatments. The burden on patients, families, and their social environments is substantial, worsened by inadequate recognition of the disease. There is clear need for ongoing education, certified evidence-based case management, and allocation of sufficient resources within public health and social systems in developed countries. Research must prioritize uncovering disease triggers and elucidating pathophysiological mechanisms to enable targeted therapies.

According to WHO criteria, ME/CFS is unequivocally a chronic somatic illness. While psychological comorbidities are common, they are considered consequences of the disease. Recognition challenges stem from its heterogeneous presentation, limited public visibility of affected individuals, and the absence of definitive biomarkers or pathognomonic imaging. In summary, ME/CFS is a debilitating, poorly understood condition gaining growing political and medical attention. Despite extensive research, reliable biomarkers and effective treatments remain elusive. The neurological community questions the term "encephalomyelitis," as CNS inflammation is generally undetectable. Symptom overlap with other medical and psychiatric disorders complicates diagnosis, and methodological issues in many studies hinder progress toward evidence-based therapies.

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References

1. Hoffmann, K, Astrid Hainzl, Michael Stingl, Katharina Kurz, Beate Biesenbach, Christoph Bamm, et al. (2024) Interdisziplinäres, kollaboratives D-A-CH-Konsensus-Statement zur Diagnostik und Behandlung von MyalgischerEncephalomyelitis/Chronischem Fatigue-Syndrom. In: Wiener klinische Wochenschrift. 136: 103-123.
2. Hainzl A, Rohrhofer J, Schweighardt J, et al. (2024) Care for ME/CFS-Praxisleitfaden für die Versorgung von ME/CFS-Betroffenen (MyalgischeEnzephalomyelitis/Chronisches Fatigue-Syndrom). Medizinische Universität Wien/Österreichische Gesellschaft für ME/CFS, Wien.
3. Renz-Polster H, Scheibenbogen C (2022) Post-COVID-Syndrom mit Fatigue und Belastungsintoleranz: Myalgische Enzephalomyelitis bzw. Chronisches Fatigue-Syndrom. In: Die Innere Medizin 63: 830-839.
4. Vøllestad NK, Mengshoel AM (2023) Post-exertional malaise in daily life and experimental exercise models in patients with myalgic encephalomyelitis/chronic fatigue syndrome. Frontiers in Physiology 14: 1257557.
5. Carruthers BM, Kumar Jain A, De Meirleir KL, et al. (2003) Myalgic Encephalomyelitis/Chronic Fatigue Syndrom: Clinical Working Case Definition, Diagnostic and Treatment Protocols. In: Journal of Chronic Fatigue Syndrom 11: 7-97.
6. Scheibenbogen C (2023) Empfehlungen für die Behandlung von Patienten mit schwerem postinfektiösem/Post-COVID-19 chronic fatigue syndrome (ME/CFS) (G93.3G). Charité Berlin.
7. Scheibenbogen C, Grabowski P. (2020) Information zu ME/CFS, Energiestoffwechsel und Nahrungssupplemente. Charité Berlin.
8. Scheibenbogen, C, et al. (2023) Chronisches Fatigue Syndrom ME/CFS und Komorbiditäten-Begutachtung. In: J. Breuer et al. (Hrsg.): Die Ärztliche Begutachtung, Springer Reference Medizin.
9. Crosby LB, S Kalanidhi, A Bonilla, A Subramanian, J S Ballon, H Bonilla, et al. (2021) Off label use of Aripiprazole shows promise as a treatment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a retrospective study of 101 patients treated with a low dose of Aripiprazole. In: Journal of Translational Medicine. 19: Springer Nature.
10. Deutsche Gesellschaft für Neurologie (2025) Stellungnahme zum aktuellen Forschungsstand bei ME/CFS. Zuletzt abgerufen am: 01.09.2025; Online abrufbar unter.
11. WHO (2025) chronic fatigue syndrome.