ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome): Information for Medical Professionals

by Jonathan CW Edwards, Professor in Connective Tissue Medicine, University College London and members of the Science for ME Forum

Definition and Context

An ME/CFS diagnosis is used to identify people with a syndrome of long-term disabling symptoms, restricting both physical and mental activity, not explained by another disease, together with a feature known as post-exertional malaise. Almost nothing is known about mechanisms involved in ME/CFS but recent genetic studies confirm that the syndrome picks out a specific pattern of disturbed biology, with a combined profile of genetic risk factors not found in other conditions.

Although often described as 'fatigue', symptoms of ME/CFS are unlike both normal fatigue and the fatigue of, for instance, cardiac failure. They include exhaustion, orthostatic intolerance, 'flu'-like malaise, unrefreshing sleep, pain and sensitivity to environmental stimuli like light and sound. Specifically, an increase in severity and range of symptoms (and feeling *unwell* rather than tired) occurs following either physical or mental exertion: post-exertional malaise. Post-exertional malaise is typically delayed and often prolonged, for days, weeks or longer, and unlike normal post-exertion fatigue or soreness. Symptoms loosely described as fatigue, with no identifiable cause, are a common reason to seek medical advice; ME/CFS covers only a small proportion of these cases.

There are a few clinical clues to the underlying biology. Frequent onset following an infection and a chronic fluctuating course suggest an immune basis. Sensitivity to stimuli, sleep disturbance and unexplained pain suggest central nervous system involvement. Genetic studies confirm these. Risk of developing ME/CFS, defined around post-exertional malaise, is carried by at least 8 segments of the genome, including loci within the MHC region, bearing several genes involved in immune and synaptic processes (one being shared with chronic pain) (Boutin et al., 2025). Further genetic studies should clarify which genes and what pathways are involved.

ME/CFS is broadly comparable to multiple sclerosis and rheumatoid arthritis in prevalence. Epidemiology suggests it is based on a similar mix of life-long genetic predisposition, environmental triggers and stochastic (random) factors. In ME/CFS no inflammation or structural tissue changes have been found, but it is comparable in terms of degree of disability.

ME/CFS is not the myalgic encephalomyelitis of 'Royal Free Disease'. The use of 'ME' in ME/CFS is a historical confusion. ME/CFS is a persistent condition, without localising neurological signs, that can follow both epidemic and endemic infections.

Descriptions like ‘complex’ or ‘multisystemic’ have no useful basis. Terms like ‘functional’, suggesting knowledge or explanation, while merely hiding our ignorance, are seriously unhelpful. ME/CFS is not simply chronic fatigue. It is a validated syndrome that causes major disability and needs to be much better understood.

Core Features

A firm diagnosis of ME/CFS requires significant impairment of ability to carry out normal daily activities over a period of many months. This requirement is arbitrary - no doubt there are milder ‘possible’ or ‘probable’ cases - but it helps to ensure the diagnosis covers a reasonably homogeneous clinical problem. ME/CFS should be considered a possibility earlier on but may be difficult to separate from spontaneously resolving post-viral fatigue (both can follow Covid-19 infection).

Since 2003 (Carruthers et al., 2003; see also CDC, 2015), post-exertional malaise has been taken as the unifying characteristic of ME/CFS. Following physical or mental exertion, which can be trivial in normal terms, patients experience a worsening of, and increase in range of, symptoms, together with loss of function. Post-exertional malaise is unlike normal fatigue following activity. The worsening may start during exertion but is often delayed by hours or days. Moreover, it may last for days, weeks or longer – commonly called a ‘crash’. ME/CFS involves unpredictable shifts in severity, suggesting regulatory abnormalities that at present we do not understand. Worsening is often sudden, and improvement gradual, but occasionally sudden improvements occur. Inconstancies in the clinical picture from hour to hour or month to month are typical of the condition (as they are for rheumatoid arthritis, lupus, multiple sclerosis), meaning that assessment at one point in time must be interpreted in the context of the full history.

ME/CFS is associated with a range of sleep problems including shifts in sleep cycle and feeling unrefreshed following sleep – waking up as if there had been no rest.

Orthostatic intolerance (OI) is a common and characteristic feature of ME/CFS. It goes wider than inability to tolerate standing; sitting up is also a problem. Most people with ME/CFS need to lie flat at least some of the time. Some have (‘postural orthostatic’) tachycardia on standing but it is not clear how relevant this is to the general phenomenon of OI in ME/CFS.

Many patients experience difficulty in thinking clearly and quickly – known as brain fog. There is no documented intellectual impairment but completing tasks that involve thought can be very difficult. Brain fog, OI, physical fatiguability and sensitivity to sensory stimuli can combine to make social situations difficult or impossible.

Additional Symptoms

Diffuse or generalised pain is quite common but not universal.

Sensitivity to light, sound, vibration, taste, temperature, odour or touch is common, particularly in severe cases. Patients may also have intolerances for foods or drugs but without clear evidence for an increase in allergy.

Nausea, abdominal discomfort and change in bowel habit may all be experienced. Recurrent sore throat and tender lymph nodes are often reported.

Fatiguability (in contrast to ‘fatigue’) during basic activities such as walking, showering or eating is often reported, although it has not been formally recognised as demonstrable on physical examination, as it is for myasthenia.

Onset and Course

Onset of ME/CFS is often reported as following an infection, most often with a virus but also with certain other organisms, such as Rickettsia and Borrelia. Time lapse from infection to ME/CFS onset is very variable, which makes the link hard to interpret. Certain infections such as Epstein-Barr virus are documented not only to be followed by a self-limiting post-viral fatigue over a few months but also by long term ME/CFS.

Onset of ME/CFS may be sudden, but in some cases the illness develops gradually, or stepwise, over a period of years. Some moderately or severely affected patients have extended periods of being relatively well before relapsing. The reasons for this are unknown, but similar unpredictable fluctuations occur in conditions such as rheumatoid arthritis and lupus. When onset is in teenage years or early twenties the chances of complete recovery or ability to lead a reasonably normal life are said to be quite good (figures are hard to establish). For later onset disease lasting more than two years, complete remission probably occurs in less than 10% of cases.

Most people with ME/CFS find it difficult to continue in work or school and in severe cases they may be confined to bed and unable to leave a darkened room. Some are unable to move, do any tasks independently, communicate in any way, or tolerate any stimuli or input like text, sound, smell, light, colours or the presence of others. Overall, disability is as severe as in conditions such as multiple sclerosis. The rate of suicide is increased, and a small number of people continue to die from nutritional failure.

Diagnosis and Assessment

There are no diagnostic tests for ME/CFS, but tests to exclude other illnesses are important. The UK NICE Guideline NG206 (NICE, 2021) gives a good summary.

Several suggestions for ‘diagnostic criteria’ exist but, as for other chronic diseases, are of little direct relevance to clinical care. Patients should not be told they do not have a condition if they do not fit a set of criteria at a particular point in time (whether ME/CFS or lupus). Care and advice must be based on probabilities for the future and clinical diagnosis must reflect that. As indicated above, a diagnosis of ME/CFS centres around *long-term*, otherwise unexplained, disabling symptoms associated with the atypical response to exertion of post-exertional malaise, but advice on not pushing activity levels may be important before a diagnosis is certain. Diagnosis is often straightforward, but a proportion of patients prove to have other diagnoses with time; re-assessment is an important part of long-term care.

Level of symptoms and disability fluctuates in ME/CFS, particularly in relation to post-exertional malaise. Assessment needs to reflect this, rather than being based on a single point in time when the patient may have been able to attend because they are at their best.

Management

Unfortunately, we have almost no reliable evidence regarding the best way to manage ME/CFS. There are no reliable texts on management to refer to. The best evidence we have is the account people give of the course of their illness and what seems to help or make it worse. The main factor is that exertion is followed by worsening. People with long term ME/CFS find that it is useful to monitor their level of activity and keep within certain limits. Goudsmit (2012) called this “pacing”. Pacing, in this sense, is not a treatment. It is not intended to produce improvement or set a baseline for incremental increase in activity (despite some professionals using the term this way, devised for locomotor pain management). It is simply a way to avoid symptom aggravation: a strategy to cope as well as possible within the limits of the illness.

Advice to pace is often discussed in terms of conserving ‘energy’. However, it is important to note that concepts connecting the effect of pacing to energy metabolism have no evidence base. There is no documented defect in energy metabolism known to be responsible for symptoms and several clinical features suggest that this is not the central problem. Measures like heart rate may or may not reflect the signals that trigger post-exertional malaise. The most appropriate guide to coping remains the person’s own experience.

Health care professionals have often recommended various forms of rehabilitation in terms of increasing levels of activity and/or psychotherapy. Trials have shown reasonably conclusively that these provide no useful benefit. As might be expected from post-exertional malaise, exercise programmes are often followed by reports of deterioration. There is no evidence of benefit from ‘stimulus challenge’ approaches for people with environmental sensitivity. Equally, there is no evidence for benefit

from strict bed rest regimens for those who are not already bedridden. People with ME/CFS will naturally tend do as much as their illness will allow without provoking post-exertional malaise. (It may take some time to learn how to gauge activity limits, which may change over time.) As far as we know this is the best policy. The biggest problem may be resisting pressures to be more active, from health professionals, family, peers and the need to maintain self-esteem.

Medication/Supplements

People with ME/CFS may benefit from drugs to control pain and nausea or improve sleep, on general principles, but beyond that there is no reliable evidence for medication being useful. There is no reason to recommend supplements unless there are specific risk factors for deficiency. Many people with ME/CFS will be at risk from osteopenia from inactivity and lack of sunlight, justifying preventive management.

People with ME/CFS may find medications hard to tolerate. This may mean careful choice of alternatives when a co-existent condition needs treating.

Orthostatic Intolerance

Although OI is common in ME/CFS we do not understand the mechanism. Changes in blood pressure and heart rate may occur but it is not clear what role these play. OI may be aggravated by long periods lying flat but how best to manage it is not known. There is no reliable trial evidence for benefit from drug treatment aimed at cardiac function, although tachycardia may be controlled. Increasing salt intake or use of intravenous saline do not have a well-founded theory or evidence base and may have adverse effects.

Care of Severe and Very Severe Cases

People with more severe ME/CFS are often confined to bed and may require low light and sound levels. Many are dependent on family or professional carers, and medical care needs to be as far as possible provided on a domiciliary basis. If hospital visits are necessary, people with ME/CFS need to have facilities for lying flat. If admitted for inpatient care they are likely to require rooms with low light and sound levels.

Plantar flexion contractures and other complications of immobility can occur and may need preventive measures.

A small number of people with ME/CFS are unable to eat and drink enough to maintain nutrition. The reasons are usually not understood. Suggested ‘functional’

causes such as gastroparesis probably do not assist care. It is important to identify failure of nutrition early and, if necessary, use artificial feeding support, either enteral, with a nasogastric tube or gastrostomy, or parenteral. There is no evidence for psychological ‘support’ being useful in this context and deaths from nutritional failure continue to occur due to inadequate feeding support. There has been a recent policy trend in several countries to deny nutritional support on the basis that the problem is neither structural nor psychiatric, but ‘functional’. This policy has probably contributed to a number of avoidable deaths and has no justification.

General Support

In the absence of an evidence base for specific management policies, some aspects of supportive care are justified on grounds of safety and avoiding unnecessary harm or distress.

1. At least an annual review by a physician to ensure that an alternative diagnosis has not been missed, and that symptoms of new, unrelated, medical problems are not misattributed to ME/CFS.
2. Advice and support for managing schooling, work and activities of daily living; input from an occupational therapist or nurse specialist familiar with ME/CFS patients' needs is likely to help in optimising life circumstances with mobility aids and home adaptations.
3. Minimisation of adverse effects of travelling to appointments by maximum use of domiciliary visits (including phlebotomy) or telephone/video consultations. When referring to other healthcare teams ensure that needs are met.
4. Management of pain, sleep and nausea.
5. If inpatient care is necessary, provision for minimising environmental stimuli.

Referrals

The current arrangements for management of people with ME/CFS in most countries are hopelessly inadequate and inappropriate. There has been a push to focus management in primary care but primary care professionals do not have the experience or resources needed to deal with severe cases. ‘Community’- based care programmes, being based on exercise and psychology, are likely to be counterproductive. There is a desperate need for expert specialist care based on physician and nurse specialist teams within hospitals, with domiciliary outreach, to cover the range of needs, including those of very severe cases who cannot feed themselves. Private care is frequently based on expensive unproven treatments. This context makes referral decisions very difficult.

Summary

Understanding of the nature and care of ME/CFS has in the past been impeded by confusion and false starts. Knowledge of the biology remains restricted to a few clues. There is no reliable evidence for effective management beyond basic principles of harm avoidance and safety. Nevertheless, recognition of ME/CFS as a valid clinical/biological entity and committed interest from research scientists provide hope that progress in both biology and treatment will be made in the near future. In the meantime, ensuring general supportive care to make life more tolerable and minimise unnecessary harm is an essential need that is still seldom met.

Bibliography

Boutin T, Bretherick AD, Dibble JJ et al. (2025) Initial findings from the DecodeME genome-wide association study of myalgic encephalomyelitis/chronic fatigue syndrome. MedRciv doi: https://doi.org/10.1101/2025.08.06.25333109

Carruthers BM, Jain AK, De Meirleir KL et al. (2003). Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnotic and treatment protocols. Journal of Chronic Fatigue Syndrome, 11(2): 7-115. doi:10.1300/J092v11n01_02

Centres for Disease Control (USA) Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, Institute of Medicine (2015). *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*. National Academies Press. ISBN 978-0-309-31689-7.

Goudsmit EM, Nijs J, Jason LA and Wallman KE (2012). Pacing as a strategy to improve energy management in myalgic encephalomyelitis/chronic fatigue syndrome: a consensus document Disabil. Rehabil. 34(13):1140-7. doi: 10.3109/09638288.2011.635746.

National Institute for Health and Care Excellence (2021). Guideline NG206; Myalgic encephalomyelitis/chronic fatigue syndrome: diagnosis and management. https://www.nice.org.uk/guidance/ng206