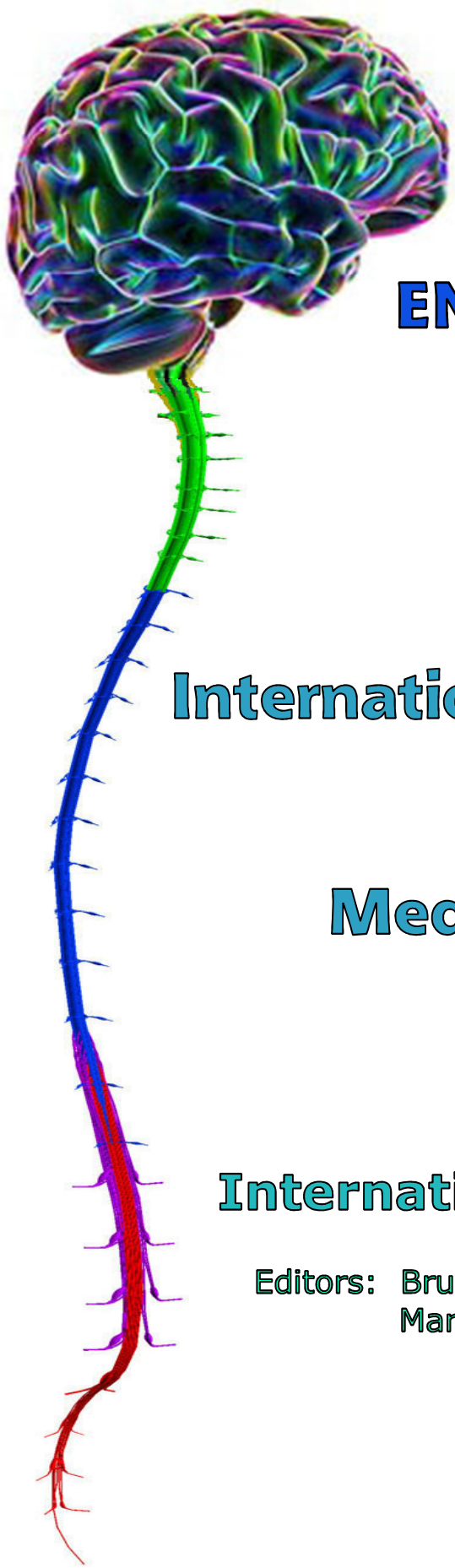

MYALGIC ENCEPHALOMYELITIS

- Adult & Paediatric:

International Consensus Primer for Medical Practitioners

International Consensus Panel

Editors: Bruce M. Carruthers, MD, CM, FRACP(C)
Marjorie I. van de Sande, B Ed

Myalgic Encephalomyelitis International Consensus Panel

Carruthers, Bruce M, MD, CM, FRCPC; ***clinician: internal medicine with focus on ME***
Independent, Vancouver, British Columbia, Canada

van de Sande, Marjorie I, BEd; ***educator***
Independent, Calgary, Alberta, Canada

De Meirleir, Kenny L, MD, PhD; ***clinician and researcher: physiology & medicine***
Professor: Physiology and Medicine, Vrije Universiteit Brussel, Belgium
Director: Himmunitas Foundation, Brussels, Belgium

Klimas, Nancy G, MD; ***clinician and researcher: microbiology, immunology, allergy***
Professor of Medicine and Director: Institute for Neuro-Immune Medicine, Nova Southeastern University, Ft. Lauderdale-Davie, Florida
Director: GWI and CFS/ME Research Center, Miami Veterans Affairs Medical Center, Miami, Florida, USA

Broderick, Gordon, PhD; ***researcher: systems biology, mathematical immunology, computational genomics – ME, CFS, Gulf War Illness (GWI)***
Associate Professor: Pulmonary Medicine, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada

Mitchell, Terry, MA, MD, FRCPath; ***clinician: internal medicine - pathophysiology and haematology***
Retired clinical haematologist with 28 years of experience of ME and chronic fatigue syndrome, Suffolk, UK

Staines, Don, MBBS, MPH, FAFPHM, FAFOEM; ***public health medicine, occupational and environmental medicine, researcher***
Public Health Physician: Gold Coast Public Health Unit, Robina, Queensland
Associate professor: Faculty of Health Sciences and Medicine, Bond University, Robina, Queensland
Faculty of Medicine, Griffith University, Southport, Queensland, Australia

Powles, A C Peter, MBBS, FRACP, FRCPC, ABSM; ***clinician: internal medicine: sleep medicine, respirology***
Professor Emeritus: Division of Respirology, Department of Medicine, McMaster University, Hamilton, Ontario
Sleep Disorders Consultant: St. Joseph's Healthcare Hamilton, Ontario, Canada
Diplomate: American Board of Sleep Medicine

Speight, Nigel, MA, MB, BChir, FRCP, FRCPCH, DCH; ***paediatrics***
Retired clinical paediatrician with many years of experience of ME and chronic fatigue syndrome.
Durham, United Kingdom

Vallings, Rosamund, MNZM, MB, BS, MRCS, LRCP; ***clinician: primary care with focus on ME***
Howick, New Zealand

Bateman, Lucinda, MS, MD; ***clinician: internal medicine with focus on ME & FM***
Fatigue Consultation Clinic, Salt Lake City
Utah hospital affiliation: Salt Lake Regional Medical Center
Adjunct Instructor: Departments of Anesthesiology and Family and Preventive Medicine, University of Utah, Salt Lake City, Utah, USA

Bell, David S, MD, FAAP; ***clinician and researcher: paediatrics***
Retired clinical paediatrician with many years of experience of ME and CFS, Lyndonville, New York
Department of Pediatrics, State University of New York, (SUNY – Buffalo) New York, USA

Authors and their affiliations are continued on the back inside cover.

MYALGIC ENCEPHALOMYELITIS – Adult & Paediatric: International Consensus Primer for Medical Practitioners

Authors - International Consensus Panel: **Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Bell DS, Carlo-Stella N, Chia J, Darragh A, Gerken A, Jo D, Lewis D, Light AR, Light K, Marshall-Gradisnik S, McLaren-Howard J, Mena I, Miwa K, Murovska M, Steven S**

Co-Editors: **Carruthers B. M. & van de Sande M. I.**

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Correspondence to: Dr. Bruce M. Carruthers: bcarruth@telus.net
4607 Blenheim Street, Vancouver, British Columbia V6L 3A3, Canada

Inquiries regarding reprinting the primer to:
Marj van de Sande: mvandes@shaw.ca
151 Arbour Ridge Circle NW, Calgary, Alberta T3G 3V9, Canada

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Development of the International Consensus Primer for Myalgic Encephalomyelitis (ME)

An International Consensus Panel, consisting of clinicians, research investigators, teaching faculty, and an independent educator, represent diverse backgrounds, medical specialities and geographical regions. Collectively, the members of the panel have:

- diagnosed and/or treated more than 50 000 patients who have ME;
- more than 500 years of clinical experience;
- approximately 500 years of teaching experience;
- authored hundreds of peer-reviewed publications, as well as written chapters and medical books; and
- several members have co-authored previous criteria.

Panel members contributed their extensive knowledge and experience to the development of the International Consensus Criteria and this Primer. In addition, an International Symptom Scale will be developed to complement the criteria and promote clearer identification of patients for research studies.

Primer Consensus: The authors, representing twelve countries, reached 100 % consensus through a Delphi-type process.

International Consensus Criteria (ICC)

Problem

The label 'chronic fatigue syndrome' (CFS), coined in the 1980s, has persisted due to lack of knowledge of its etiologic agents and pathophysiology. Misperceptions have arisen because the name 'CFS' and its hybrids ME/CFS, CFS/ME and CFS/CF have been used for widely diverse conditions. Patient sets can include those who are seriously ill with ME, many bedridden and unable to care for themselves, to those who have general fatigue or, under the Reeves criteria, patients are not required to have any physical symptoms. There is a poignant need to untangle the web of confusion caused by mixing diverse and often overly inclusive patient populations in one heterogeneous, multi-rubric pot called 'chronic fatigue syndrome'. We believe this is the foremost cause of diluted and inconsistent research findings, which hinders progress, fosters scepticism, and wastes limited research monies.

Solution

The rationale for the development of the ICC was to utilize current research knowledge to identify objective, measurable and reproducible abnormalities that directly reflect the interactive, regulatory components of the underlying pathophysiology of ME. Specifically, the ICC select patients who exhibit explicit multi-systemic neuropathology, and have a pathological low threshold of physical and mental fatigability in response to exertion. Cardiopulmonary exercise test-retest studies have confirmed many post-exertional abnormalities. Criterial symptoms are compulsory and identify patients who have greater physical, cognitive and functional impairments. The ICC advance the successful strategy of the Canadian Consensus Criteria (CCC) of grouping coordinated patterns of symptom clusters that identify areas of pathology. The criteria are designed for both clinical and research settings.

1. **Name:** **Myalgic encephalomyelitis,** a name that originated in the 1950s, is the most accurate and appropriate name because it reflects the underlying multi-system pathophysiology of the disease. Our panel strongly recommends that **only** the name 'myalgic encephalomyelitis' be used to identify patients meeting the ICC because a distinctive disease entity should have one name. Patients diagnosed using broader or other criteria for CFS or its hybrids (Oxford, Reeves, London, Fukuda, CCC, etc.) should be reassessed with the ICC. Those who fulfill the criteria have ME; those who do not would remain in the more encompassing CFS classification.

2. **Remove patients who satisfy the ICC from the broader category of CFS.** The purpose of diagnosis is to provide clarity. The criterial symptoms, such as the distinctive abnormal responses to exertion can differentiate ME patients from those who are depressed or have other fatiguing conditions. Not only is it common sense to extricate ME patients from the assortment of conditions assembled under the CFS umbrella, it is compliant with the WHO classification rule that a disease cannot be classified under more than one rubric. The panel is not dismissing the broad components of fatiguing illnesses, but rather the ICC are a refinement of patient stratification. As other identifiable patient sets are identified and supported by research, they would then be removed from the broad CFS/CF category.

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3. **Research on ME:** The logical way to advance science is to select a relatively homogeneous patient set that can be studied to identify biopathological mechanisms, biomarkers and disease process specific to that patient set, as well as comparing it to other patient sets. It is counterproductive to use inconsistent and overly inclusive criteria to glean insight into the pathophysiology of ME if up to 90% of the research patient sets may not meet its criteria (Jason 2009). Research on other fatiguing illnesses, such as cancer and multiple sclerosis (MS), is done on patients who have those diseases. There is a current, urgent need for ME research using patients who actually have ME.

4. **Research confirmation:** When research is applied to patients satisfying the ICC, previous findings based on broader criteria will be confirmed or refuted. Validation of ME being a differential diagnosis, as is multiple sclerosis (MS), or a subgroup of chronic fatigue syndrome, will then be verified.

5. **Focus on treatment efficacy:** With enhanced understanding of biopathological mechanisms, biomarkers and other components of pathophysiology specific to ME, more focus and research emphasis can target expanding and augmenting treatment efficacy.

International Consensus Primer (ICP)

Problem

Overly inclusive criteria have created misperceptions, fostered cynicism and have had a major negative impact on how ME is viewed by the medical community, patients, their families, as well as the general public. Some medical schools do not include ME in their curriculum with the result that very significant scientific advances and appropriate diagnostic and treatment protocols have not reached many busy medical practitioners. Some doctors may be unaware of the complexity and serious nature of ME. Patients may go undiagnosed and untreated; they may be shunned or isolated.

Solution

The ICP was written to provide clinicians a one-stop, user-friendly reference for ME. It includes a concise summary of current pathophysiological findings upon which the ICC are based. A comprehensive clinical assessment and diagnostic worksheet enables clear and consistent diagnosis of adult and paediatric patients world-wide. The treatment and management guidelines offer a blueprint for a personalized, holistic approach to patient care, and include non-pharmaceutical and pharmaceutical suggestions. Patient self-help strategies provide recommendations for energy conservation, diet, and more. Educational considerations for children are included.

The ICP specifically targets primary care clinicians, as well as specialists in internal medicine. Other medical care practitioners may find it helpful. Medical school faculties are encouraged to include this primer in their curriculum.

The International Consensus Primer represents the collective wisdom and experience of the members of the panel. They share their insights into this complex disease gleaned through research and hundreds of thousands of hours of clinical investigations.

The International Consensus Panel anticipates that the primer will bring forward movement in enhancing clarity and consistency of diagnoses and treatment of ME internationally.

Acknowledgements

Patients: The panel would like to gratefully acknowledge the participation and support of the patients and their families, both in the clinical setting and in the research described within, upon which these physicians' guidelines are based.

Anne-Marie Kemp, BA, M Ed; David Kemp, BA, M Ed: proof-reading

This Primer will be updated when appropriate.

Authors and their affiliations are listed on the front and back inside covers.

MYALGIC ENCEPHALOMYELITIS - Adult & Paediatric: International Consensus Primer for Medical Practitioners

An International Consensus Panel was formed to develop International Consensus Criteria (ICC)[1] and a physicians' primer that includes the ICC, pathophysiology, and diagnostic and treatment protocols for myalgic encephalomyelitis (ME) based on current knowledge and clinical experience.

Goal: to enhance the understanding of ME and promote clarity and consistency in optimal clinical identification and treatment internationally

Target groups: primary care physicians, internists, pain and other health care practitioners, medical students

Myalgic Encephalomyelitis (ME): complex, acquired multi-systemic disease

Pathophysiology: Profound dysfunction/dysregulation of the neurological control system results in faulty communication and interaction between the CNS and major body systems, notably the immune and endocrine systems, dysfunction of cellular energy metabolism and ion transport, and cardiac impairments.

Cardinal symptom: a pathological low threshold of fatigability that is characterized by an inability to produce sufficient energy on demand. There are measurable, objective, adverse responses to normal exertion, resulting in exhaustion, extreme weakness, exacerbation of symptoms, and a prolonged recovery period.

Note: Myalgic encephalomyelitis (ME) is the name recommended for those meeting the ICC.

Classification: Myalgic encephalomyelitis has been classified as a **neurological** disease by the WHO since 1969. WHO stipulates that the same condition cannot be classified to more than one rubric because, by definition, individual categories and subcategories must remain mutually exclusive. Thus, it is essential that patients meeting the ICC for ME are removed from overly inclusive groups.

Myalgic encephalomyelitis: neurological disease WHO ICD G93.3

Epidemiology

Prevalence: ~ 0.4 – 1%[2, 3]

- affects all age groups, including children, all racial/ethnic groups, and all socioeconomic strata
- onset most commonly occurs between the ages of 30 and 50
- higher prevalence in females

ME:
- **generally sporadic**
- **endemic**
- **widely dispersed epidemics**

Prognosis

- **Currently** there is no known cure.
- **Early intervention** and appropriate treatment strategies may lessen severity of symptoms.
- **Restoration** to full pre-morbid health and function is rare.[4]
- **Prognosis** for an individual cannot be predicted with certainty.

Paediatric: Children can be very severely afflicted.

- Children with less severe symptoms are more likely to go into remission than adults.

Etiology

Predisposing Factors: multifactorial and fairly individual

1. **Genetic predisposition:** increased susceptibility associated with
   - **Gene expression modifications:** neurological, hematological, metabolic, sensory, immunological disease, function/response, infection, inflammation, cardiovascular, cancer, cell death and endocrine[5-12]
   - **Clusters of combined gene data** suggest distinct genomic subtypes and disease associations.[12, 13]
   - **Familial and twin studies** indicate there is a higher degree of ME in relatives, to third generation. [14]

Environmental factors *may outweigh genetic predisposition.*[15] *Several epidemics support an infectious cause.*[16]

2. **Pre-onset environmental events** that may compromise the neurological and immune systems, and increase susceptibility to infection: ● minor infections ● immunization ● exposure to new infectious agents, especially when traveling or following recent infections ● contaminated water ● recycled air in flights

● blood transfusions ● anaesthetics ● toxic chemicals ● heavy metals ● severe physical trauma: whiplash/spinal injury/surgery ● undue psychological stress[17-23]

Precipitating Events and Causal Factors: Most patients enjoyed healthy, active lifestyles prior to the onset of ME. Widely dispersed epidemics support an infectious cause. Symptoms at onset are usually consistent with an infectious process.

Onset Survey
1,000+ patients
75.6%: infection alone or infection + 1 or more factors:
environmental exposure,
physical trauma,
vaccinations,
other stressors
Vernon SD. CFIDS of America

1. **Infectious agents associated with ME**

   Viruses: ● Enterovirus[24-26] ● Epstein Barr virus (EBV)[27] ● Human herpes virus (HHV 6 and 7)[28, 29] ● Cytomegalovirus[30] ● Parvovirus B19[31]

   Bacteria: Chlamydophila pneumonia[32] ● Mycoplasma[33] ● Coxiella burnetii[27]

   It is unclear whether these infectious agents initiated ME or are opportunistic and developed due to an impaired immune system. No one virus has been universally implicated for all patients. A prospective study reported that six months following acute infections of Epstein-Barr virus, Coxiella Burnetii, or Ross River virus, 11% of the patients had CFS.[34] This supports the presence of ME subtypes. Antibody testing for a number of viruses revealed subtype-specific relationships for Epstein Barr virus and enterovirus, two of the most common infectious triggers for ME.[27]

2. **Possible etiological process:** A growing body of evidence suggests that a primary cause of ME is neuropathic viruses that may infect neurological and immune cells and damage the capillaries and micro-arteries in the CNS bed causing diffuse brain injury. The initial infection may cause profound dysregulation of immune system pathways that may become chronic or cause autoimmunity even when the level of the infectious agent is reduced.[35]

ME Phases

1. **Infectious Onset/Acute Phase < 6 months:** Most patients have a distinct acute onset where flu-like or upper respiratory symptoms or other signs of an infectious process are evident. The **incubation period** usually runs a few days to a week. Instead of recovering, the patient's condition worsens, and the symptoms that identify the distinctive character of ME begin to appear as a cluster. Approximately 20% of patients have a gradual onset that may follow events that compromise the immune system, making them vulnerable to new or reactivation of persistent latent infections that can further overwhelm the immune system.[26]
2. **Chronic Phase > 6 months:** Generally, symptoms tend to be more stable in the chronic phase. Some patients have some improvement in the chronic phase while others have a progressive decline in health.

PATHOPHYSIOLOGY

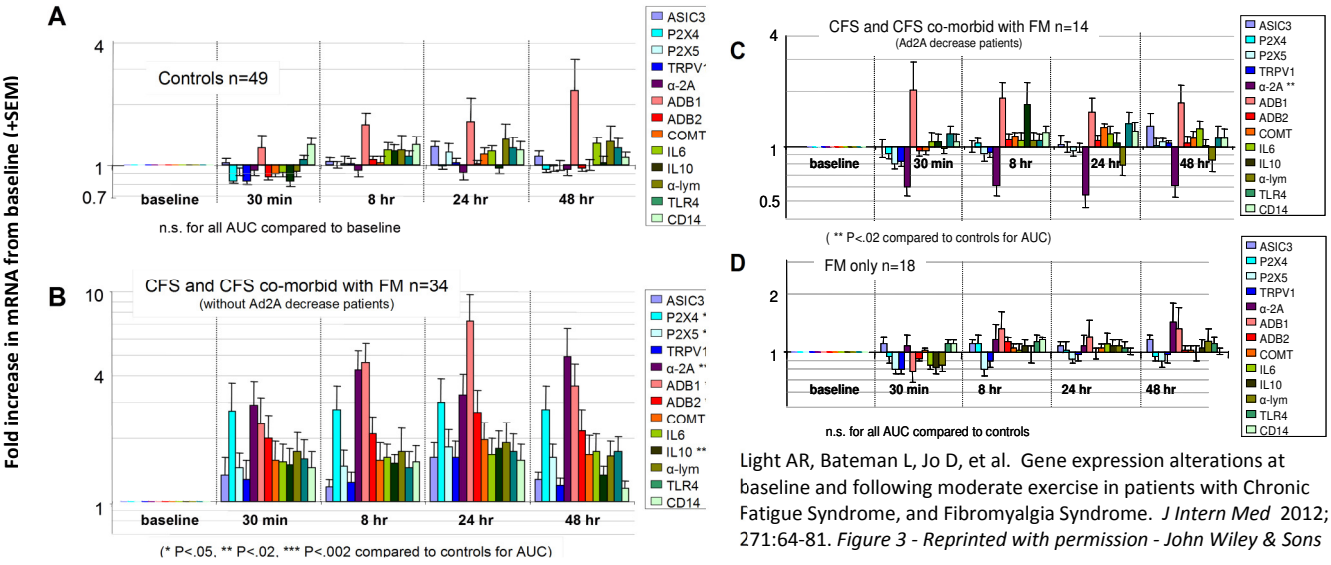
PENE: a pathological, low threshold of fatigability
- post-exertional exhaustion & symptom flare
  - immediate or delayed, & not relieved by rest
- prolonged recovery period

Post- Exertional Neuroimmune Exhaustion (PENE pen'-e)

Normal fatigue is proportional to the intensity and duration of activity, followed by a quick restoration of energy. PENE is characterized by a pathological low threshold of physical and mental fatigability, exhaustion, pain, and an abnormal exacerbation of symptoms in response to exertion. It is followed by a prolonged recovery period. Fatigue and pain are part of the body's global protection response and are indispensable **bioalarms** that alert patients to modify their activities in order to prevent further damage.

The underlying pathophysiology of PENE involves a profound dysfunction of the regulatory control network within and between the nervous systems[36, 37] This interacts with the immune and endocrine systems affecting virtually all body systems, cellular metabolism and ion transport.[38] The dysfunctional activity/rest control system and loss of homeostasis result in impaired aerobic energy production and an inability to produce sufficient energy on demand. A test-retest cardiopulmonary exercise study revealed a drop of 22% in peak VO_2 and 27% in VO_2 at AT on the second day evaluation.[39] Both submaximal and self-paced exercise resulted in PENE.[40] These impairments and the loss of invigorating effects distinguish ME from depression.

Post-exertional mRNA receptor expression: *Patients: ME & comorbid fibromyalgia (B) had significantly elevated sensory, adrenergic & immune system receptor expression than controls (A) and FM only (D). Subgroup (C) had decreased Alpha 2A receptors & reported orthostatic intolerance (OI) symptoms.*[41]



Light AR, Bateman L, Jo D, et al. Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome, and Fibromyalgia Syndrome. *J Intern Med* 2012; 271:64-81. *Figure 3 - Reprinted with permission - John Wiley & Sons*

Response to Exercise	Normal	ME Patients
Resting heart rate (HR)	normal	↑ elevated[42, 43]
HR at maximum workload	↑	↓ reduced maximum heart rate[42, 44, 45]
Maximum oxygen consumption (VO_2)	↑	↓ reduced peak oxygen uptake at maximum work load - approximately ½ of sedentary controls[42, 45 - 50]
Age predicted heart rate	yes	often cannot achieve it[42, 43]
Cardiac output	↑	sub-optimal level[42, 43, 51]
Cerebral blood flow	↑	↓ decreased cerebral blood flow[46, 47, 52 - 54]
Cerebral oxygen	↑	↓ decreased cerebral oxygen[46 - 48, 52]
Blood pressure	↑	insufficient blood pressure increase on exertion[48]
Body temperature	↑	↓ decreased body temperature[47]
Respiration	↑	↓ breathing irregularities: shallow breathing, shortness of breath[47]
Oxygen utilization	↑	↓ decreased capacity to use oxygen[42]
Oxygen delivery to muscles	↑	↓ reduced[42]
Anaerobic threshold & maximum exercise	normal	↓ are reached at a much lower oxygen consumption level[45, 55]
Gait production	normal	↑ increased abnormalities in gait[56]
Sensory signaling to brain	↓	↑ elevated sensory signaling interpreted by the brain as pain and fatigue[11, 57]
Chronic pain & fatigue receptors	↓	↑ unique post-exercise mRNA increases in metabolite-detecting receptors[58] ↑ 70% of ME patients comorbid with FM: significantly elevated sensory, adrenergic & immune system receptor expression[41] ↓ 30% ME patients (with POTS): adrenergic receptors decreased, alpha 2A[41] ↑ ME & MS patients show abnormal increases in adrenergic receptors.[58]
Cytokine activity Pro-inflammatory Anti-inflammatory	 ↑ ↓	↑ distinct inflammatory to anti-inflammatory imbalance Immune activation: initial response to infection tends to be an exaggerated pro-inflammatory cytokine response (e.g. interleuken 6 & 8), followed by a blunted anti-inflammatory response.[35, 59, 60]
Channelopathy, oxidative stress, nitric oxide toxicity	normal	↑ elevated oxidative stress markers[61, 62] ↑ increased with exertion[50, 63]
Exhaustion and ATP	normal	↑ exhaustion reached more rapidly,[64] accompanied by ↓ relatively reduced intracellular concentrations of ATP.[64]
Pain threshold	↑	↓decreased with exercise, suggesting abnormal pain processing[39, 65-67]

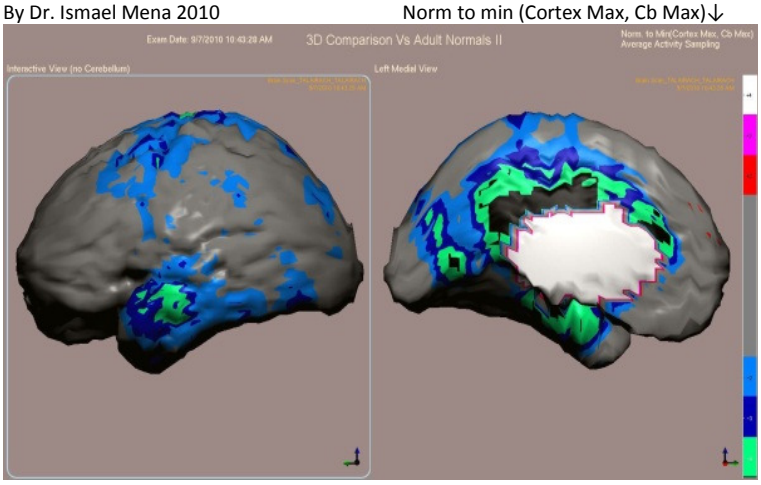
Response to Exercise	Normal	ME Patients
Acidosis in exercising muscles Post-exercise recovery from acidosis	yes	↑ increased intracellular acidosis in exercising muscles [68] ↓ Normal inverse correlation between maximum proton efflux and nadir muscle pH following exercise is lost. Slow recovery time (~4-fold increase) from intramuscular acidosis following exercise and repeat exercise.[45, 69]
Sense of well-being	↑	↓ loss of invigorating & antidepressant effects, physical and mental exhaustion, flu-like symptoms, pain, and worsening of other symptoms[70]
Symptom exacerbation	no	↑ Activation and worsening of symptoms can be immediate or delayed by several days.[1, 46, 70] When exercise is repeated the next day, abnormalities are more severe. [40]
Cognitive function	↑ alert	↓ cognitive functioning: prolonged reaction time,[71] ↑perceived effort[72]
Recovery period	short	prolonged recovery period: usually 24 hours, often 48 but can last days, weeks or cause a relapse.[39, 40, 42]

Neurological Abnormalities

Neurocognitive, sleep, autonomic and sensory disturbances, pain, headaches, and paresthesias are prominent neurological signs and symptoms. Cognitive impairments including slow processing of information, poor attention, word finding, and working memory are some of the most functionally disabling symptoms.[1, 73, 74]

Structural and functional abnormalities within the brain and spinal cord are consistent with pathological dysfunction of the regulatory centers and communication networks of the brain, CNS and ANS, and are essential for effective ongoing self-organization.[1, 75] Reduced brainstem gray matter volume is consistent with insult to the midbrain at fatigue onset. Feedback control loops may suppress cerebral motor and cognitive activity, disrupt CNS homeostasis, and reset elements of the ANS.[76] These abnormalities play crucial roles in neurological and neurocognitive symptoms.[1, 5, 11, 57, 65] Greater source activity and more parts of the brain are utilized in cognitive processing, which supports patients' perception of greater effort.[73, 77, 78] Reduced duration of uninterrupted sleep may explain reported unrefreshed sleep, pain and overwhelming fatigue.[79] These observed pathological changes are consistent with neurological disorders but not psychiatric conditions.

3D Comparison VS Adult Norms II – Avg. activity sampling
By Dr. Ismael Mena 2010 Norm to min (Cortex Max, Cb Max)↓



↑Interactive view – no cerebellum ↑Left medial view

Extensive areas of hypoperfusion are characteristic of ME: HMPAO c99m radiopharmaceutical for brain blood flow assessment. Images of the patient are reconstructed and compared against normal age matched data-base by means of Oasis Segami USA Software. In color gray normal perfusion equal to mean ± 2 St Dev, colors blue, green and black, 2-5 St dev. below the normal mean denoting hypoperfusion. Left lateral view shows marked hypoperfusion in the lateral aspects of the temporal lobe, extending to the frontal and parietal lobes. Left medial view shows extensive hypoperfusion in the limbic system involving anterior, medial and posterior cingulates. There is left temporal medial hypoperfusion that denotes hypofunction in the projection of the hippocampus. Both posterior cingulate and hippocampal hypofunction denote cognitive impairment. (Ventricular system is in color white.) Finally, there is hypoperfusion in the occipital lobe. *Ismael Mena, MD, nuclear medicine*

Neurological Structural & Functional Abnormalities

Hypoperfusion [80 - 84] **(Neuro-SPECT, arterial spinning labeling)**
↓ **regional blood flow** (rCBF), ↓ **absolute cortical blood flow** [46, 85]
↓ **hypoperfusion in brainstem** distinguishes ME from depression[83]
↓ **further reduction in cerebral blood flow after exercise**
Greater involvement of the brain correlates with greater severity[46]

Neurological Structural & Functional Abnormalities
Punctate lesions – white matter hyperintensities (MRI)
↑ **Plaque or hyperintensities** in the white matter & tracts is consistent with demyelination or inflammation & increase risk of cerebrovascular events[86, 87]
• **brain stem injury** and loss of homeostasis [76]
Reduced brain matter – (MRI)
↓ **Reduced regional gray and white matter volumes** are consistent with impaired memory and visual processing. [88]
↓ **global reduction** of gray matter volume [54, 89]
↓ gray matter volume in midbrain & pulse pressure suggest impaired cerebrovascular auto-regulation [76]
↓ white midbrain matter volume decreased with fatigue duration [76]
↓ **Hypometabolism – (PET)**
↓ metabolism of glucose in the brain, [36] ↓ metabolism in brain stem differentiates ME from depression [46, 83]
Neurocognitive – (fMRI, qEEG & SPECT)
↑ **Greater effort is required** - elevated source current & more regions of the brain are utilized in cognitive activity & fatiguing tasks: poor processing of auditory & spatial information, poor working memory. [73, 77, 78]
↓ **slower performance in visual imagery & motor tasks -** ventral anterior cingulate cortex was active when controls made an error but not in patients. [54]
↓ **reduced blood flow in temporal lobes** may contribute to memory and cognitive impairment & fatigue [80, 81]
Pain and Fatigue – mRNA assays
↑ **Elevated sensory signaling** perceived by the brain as pain and fatigue [11, 57, 90]
Musculoskeletal – (surface EEG scalp)
CNS signals are altered when controlling voluntary muscle activities, especially when they are fatiguing.[90]
↓ **poor and slower motor performance** [90] & abnormal spatial and temporal symmetry of gait [91]
Sleep – (EEG)
↑ **prolonged sleep onset latency** [79]
↓ **disruption of REM sleep** & **reduced duration of uninterrupted sleep** [92, 93]
↑ **increased alpha intrusion into delta sleep** [79]
Cerebral spinal fluid - (spinal tap) *increased opening pressure on lumbar puncture*
Proteomes distinguish ME from post-treatment Lyme disease and controls. [94]
↑ **increased lymphocytes** [95] and protein[94, 95]
• **IL-10 increased** with granulocyte-macrophage (GM), colony-stimulating factor (CSF) suppression [95]
↑ **elevated lactate** is consistent with reduced cortical blood flow, mitochondrial dysfunction & oxidative stress [96] Lateral ventricular: 297% vs. anxiety disorder & 348% vs. controls [96]
Spinal cord and ganglia - (autopsy)
↑**neuroinflammation in the dorsal root ganglia,** (modulators of peripheral sensory information traveling to the brain)[97]

Immune Impairments

Neuropathic viruses can infect and damage the brain, ganglia and immune cells. The initial infection may cause profound dysregulation of the immune system, which in turn may result in persistent infection or abnormal immune response.[35] Activated immune complexes, including elevated levels of various cytokines, cause chronic inflammation against a background of immunosuppression, which makes the body more vulnerable to opportunistic infectious agents and may play a role in post-exertional flares and flu-like symptoms.[35, 39, 98, 99]

Immune Impairments
Chronic Immune Activation: [7, 9, 35, 100-104]
↑ **increased inflammatory cytokines**[35] • pro-inflammatory alleles • chemokines • T lymphocytes • CD26 expression
↑ indirect evidence of **B cell activation** (rituximab drug study - depleting B-cells with CD20 markers – 2/3 improved) [105]
↑ **bioactive transforming growth factor-beta** (TGF-beta) [106]
↑ **rate of active HHV-6, HHV-7 and B19 infection**/coinfection with the simultaneous increase in plasma proinflammatory cytokine level and distinctive types of clinical symptoms may suggest subtypes of ME [107]
Immune Functional Defects: [98, 102, 108 – 115]
→ **Th1 shift towards Th2** dominant immune response[110] • patient self-test for Th2 shift [108]
↑ **decreased natural killer (NK) cell** signalling , function, & cell cytotoxicity [102, 108] • ↓ neutrophil respiratory bursts[98]

↓ decreased perforins and granzymes[104] • abnormal growth factor profiles[111] • macrophage abnormalities [95]
antiviral riboneuclease L **(RNase L) pathway dysregulation:** ↑ 37kDa (cleaved) to 80 KDa (normal) ratio of RNase-L [112,113]
• IL 8, 23, 6, with IL-1a, IL-2 and IFN-gamma associated with Th17 function may discriminate post-mononucleosis ME [116]

Gastro-intestinal Tract [26, 117-119]

- **chronic enterovirus infection** of the stomach[26]
- **intestinal dysbiosis:** breakdown in balance between 'protective' and harmful' bacteria with increased levels of D Lactic acid producing bacteria [117]

↑ **hyperpermeable gut** &/or bowel can induce low-grade systemic inflammation & alcohol intolerance[117]

Sensitivities: ↑ new sensitivities to sensory input, food, medication, alcohol, or chemicals[118]

Energy Production and Ion Transport Impairments

Profound energy impairment suggests dysregulation of the mitochondria and cellular energy production, channelopathy, and ion transport. There is an inverse relationship between diurnal variation in blood pressure (BP) and fatigue. Impairments increase risk of cardiovascular events. Orthostatic intolerance (OI) suggests impaired cerebral circulatory autoregulation.[53] Low oxygen consumption, stroke volume, and reduced circulation are associated with symptom severity and functional impairment.[48, 53, 120, 121, 141]

Energy Production & Ion Transport Impairments

Energy Production and Ion Transport Impairments

- **mitochondria and cellular energy metabolism and ion transport dysregulation** [38, 122 – 125]

↓ mitochondrial dysfunction involves partial blocking of the translocator protein TL, and/or lack of substrate or essential co-factors [126]

↓ **exhaustion is reached rapidly**, at which point there is relatively reduced intracellular concentrations of ATP [64]

↑ **oxidative stress** [50, 118, 119, 127, 128, 134]

- **channelopathy impairments**[129, 130]
- **NO/ONOO- cycle**: biochemical positive feedback cycle may contribute to chronicity[118, 119, 131]

Cardiovascular and Autonomic Impairments

↓ **insufficient increase in blood pressure (BP) on exertion** [48]

↓ **low blood pressure and exaggerated diurnal variation** may be due to abnormal blood pressure regulation, inverse relationship with fatigue [132]

↓ **reduced blood flow and vasculopathy**[118]

↑ **arterial elasticity dysfunction -** hyper-elasticity/contractibility of arterial walls[133]

↑ **elevated response to acetylcholine** [133] • ↑ **increased arterial wave reflection**[134]

↓ **'small heart' with small left ventricular chamber** [135, 136]

↓ **cardiac and left ventricular dysfunction** [137-139]

↓ **reduced heart rate variability during sleep** suggests a pervasive state of nocturnal sympathetic hyper-vigilance and may contribute to poor sleep quality[140]

↓ **low circulating erythrocyte volume** (~ 70% of normal). Vascular abnormalities suggest there is insufficient circulating blood volume in the brain when in an upright position, and blood may pool in the extremities.[53, 141]

Abnormal Thermoregulatory Responses

- loss of thermostatic control [142]

PERSONALIZED ASSESSMENT AND DIAGNOSIS

International Consensus Criteria

The ICC encompass symptoms that had the greatest ability to select ME patients in a study of more than 2,500 patients[143] and are supported by other studies.[141, 144] The ICC capture the unique characteristics of ME. Operational notes following criterial categories clarify how symptoms may be expressed and interpreted. Grouping symptoms by regions of pathogenesis provides focus. Making criterial symptoms compulsory improves consistency and accuracy in patient selection.[145 – 150]

Myalgic Encephalomyelitis: International Consensus Criteria (ICC)

Adult and Paediatric ● Clinical and Research

Myalgic encephalomyelitis is an acquired neurological disease with complex global dysfunctions. Pathological dysregulation of the nervous, immune and endocrine systems, with impaired cellular energy metabolism and ion transport are prominent features. Although signs and symptoms are dynamically interactive and causally connected, the criteria are grouped by regions of pathophysiology to provide general focus.

Compulsory	Post-Exertional Neuroimmune Exhaustion – PEN'-E (A)
3	Neurological Impairments : at least 1 symptom from 3 symptom categories (B)
3	Immune/gastro-intestinal/genitourinary Impairments: at least 1 symptom from 3 symptom categories (C)
1	Energy metabolism/ion Transport Impairments: 1 symptom (D)

A. Post-Exertional Neuroimmune Exhaustion (PENE pen'-e) Compulsory

This cardinal feature is a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuroimmune regions. Characteristics are:

1. **Marked, rapid physical and/or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse.**
2. **Post-exertional symptom exacerbation: *e.g. acute flu-like symptoms, pain and worsening of other symptoms***
3. **Post-exertional exhaustion may occur immediately after activity or be delayed by hours or days.**
4. **Recovery period is prolonged, usually taking 24 hours or longer. A relapse can last days, weeks or longer.**
5. **Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level.**

Operational Notes: *For a diagnosis of ME, symptom severity must result in a significant reduction of a patient's premorbid activity level.* ***Mild*** *(meet criteria, significantly reduced activity level),* ***Moderate*** *(an approximate 50% reduction in pre-illness activity level),* ***severe*** *(mostly housebound),* ***or very severe*** *(mostly bedridden and needs help with basic functions).* ***There may be marked fluctuation of symptom severity and hierarchy*** *from day to day or hour to hour.* ***Consider activity, context and interactive effects. Recovery time: e.g.*** *Regardless of a patient's recovery time from reading for ½ hour, it will take much longer to recover from grocery shopping for ½ hour and even longer if repeated the next day – if able. Those who rest before an activity or have adjusted their activity level to their limited energy may have shorter recovery periods than those who do not pace their activities adequately.* ***Impact: e.g.*** *An outstanding athlete could have a 50% reduction in his/her pre-illness activity level and still be more active than a sedentary person.*

B. Neurological Impairments At least One Symptom from three of the following four symptom categories

1. **Neurocognitive Impairments**
   - **Difficulty processing information: slowed thought, impaired concentration *e.g.*** *confusion, disorientation, cognitive overload, difficulty with making decisions, slowed speech, acquired or exertional dyslexia*
   - **Short-term memory loss: *e.g.*** *difficulty remembering what one wanted to say, what one was saying, retrieving words, recalling information, poor working memory*
2. **Pain**
   - **Headaches: *e.g.*** *chronic, generalized headaches often involve aching of the eyes, behind the eyes or back of the head that may be associated with cervical muscle tension; migraine; tension headaches*
   - **Significant pain** can be experienced in muscles, muscle-tendon junctions, joints, abdomen or chest. It is non-inflammatory in nature and often migrates. ***e.g.*** generalized hyperalgesia, widespread pain (may meet fibromyalgia criteria), myofascial or radiating pain
3. **Sleep Disturbance**
   - **Disturbed sleep patterns*: e.g.*** *insomnia, prolonged sleep including naps, sleeping most of the day and being awake most of the night, frequent awakenings, awaking much earlier than before illness onset, vivid dreams/nightmares*
   - **Unrefreshed sleep: *e.g.*** *awaken feeling exhausted regardless of duration of sleep, day-time sleepiness*
4. **Neurosensory, Perceptual and Motor Disturbances**
   - **Neurosensory and perceptual: *e.g.*** *inability to focus vision, sensitivity to light, noise, vibration, odour, taste and touch; impaired depth perception*
   - **Motor: *e.g.*** *muscle weakness, twitching, poor coordination, feeling unsteady on feet, ataxia*

Notes: ***Neurocognitive impairments,*** *reported or observed, become more pronounced with fatigue.* ***Overload phenomena*** *may be evident when two tasks are performed simultaneously.* ***Abnormal accommodation*** *responses of the pupils are common.* ***Sleep disturbances*** *are typically expressed by prolonged sleep, sometimes extreme, in the acute phase and often evolve into marked sleep reversal in the chronic stage.* ***Motor disturbances*** *may not be evident in moderate cases but abnormal tandem gait and positive Romberg test may be observed in severe cases.*

C. Immune, Gastro-intestinal & Genitourinary Impairments

At least One Symptom from three of the following five symptom categories

1. **Flu-like symptoms may be recurrent or chronic and typically activate or worsen with exertion.** ***e.g.*** *sore throat, sinusitis, cervical and/or axillary lymph nodes may enlarge or be tender on palpitation*
2. **Susceptibility to viral infections with prolonged recovery periods**
3. **Gastro-intestinal tract:** ***e.g.*** *nausea, abdominal pain, bloating, irritable bowel syndrome (IBS)*
4. **Genitourinary: e.g.** *urinary urgency or frequency, nocturia*
5. **Sensitivities** ***to food, medications, odors or chemicals***

Notes: *Sore throat, tender lymph nodes, and flu-like symptoms obviously are not specific to ME but their activation in reaction to exertion is abnormal. The throat may feel sore, dry and scratchy. Faucial injection and crimson crescents may be seen in the tonsillar fossae, which are an indication of immune activation.*

D. Energy Metabolism/Ion Transportation Impairments: At least One Symptom

1. **Cardiovascular:** ***e.g.*** *inability to tolerate an upright position - orthostatic intolerance (OI), neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (POTS), palpitations with or without cardiac arrhythmias, light-headedness/dizziness*
2. **Respiratory:** ***e.g.*** *air hunger, laboured breathing, fatigue of chest wall muscles*
3. **Loss of thermostatic stability:** ***e.g.*** *subnormal body temperature, marked diurnal fluctuations; sweating episodes, recurrent feelings of feverishness with or without low grade fever, cold extremities*
4. **Intolerance of extremes of temperature**

Notes: ***Orthostatic intolerance (OI)*** *may be delayed by several minutes. Patients who have OI may exhibit mottling of extremities, extreme pallor or Raynaud's Phenomenon. Moons of fingernails may recede in chronic phase.*

Paediatric Considerations

Symptoms may progress more slowly in children than in teenagers or adults. In addition to post-exertional neuroimmune exhaustion, the most prominent symptoms tend to be neurological: headaches, cognitive impairments, and sleep disturbances.

- **Headaches:** Severe or chronic headaches are often debilitating. Migraine may be accompanied by a rapid drop in temperature, shaking, vomiting, diarrhoea and severe weakness.
- **Neurocognitive Impairments:** Difficulty focusing eyes and reading are common. Children may become dyslexic, which may only be evident when fatigued. Slow processing of information makes it difficult to follow auditory instructions or take notes. All cognitive impairments worsen with physical or mental exertion. Young people will not be able to maintain a full school program.
- **Pain** may seem erratic and migrate quickly. **Joint hypermobility** is common.

Note: ***Fluctuation and severity hierarchy*** *of numerous prominent symptoms tend to vary rapidly and dramatically.*

Classification

____ **Myalgic Encephalomyelitis**

____ **Atypical Myalgic Encephalomyelitis:** meets criteria for PENE but has a limit of two less than required of the remaining criterial symptoms. Pain or sleep disturbance may be absent in rare cases.

Notes*: Patients who have met the full criteria for ME but treatment is effective in reducing their severity still have ME.*

Exclusions: *As in all diagnoses, exclusion of alternate explanatory diagnoses is achieved by the patient's history, physical examination, and laboratory/biomarker testing as indicated. It is possible to have more than one disease but it is important that each one is identified and treated.* **Primary psychiatric disorders, somatoform disorder and substance abuse are excluded. Pediatric:** *'primary' school phobia.*

Co-morbid Entities: Fibromyalgia, Myofascial Pain Syndrome, Temporomandibular Joint Syndrome, Irritable Bowel Syndrome, Interstitial Cystitis, Raynaud's Phenomenon, Prolapsed Mitral Valve, Migraines, Allergies, Multiple Chemical Sensitivities, Hashimoto's Thyroiditis, Sicca Syndrome, Reactive Depression. *Migraine and irritable bowel syndrome may precede ME but then become associated with it. Fibromyalgia overlaps.*

Carruthers BM, van de Sande MI, De Meirleir KL, Klimas DG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, et al. **Myalgic encephalomyelitis: International Consensus Criteria.** *J Intern Med* 2011; 270: 327-338. Reprinted with permission of John Wiley & Sons. *Some notes are slightly modified.* http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/pdf

Clinical Application Principles

General Considerations: *The Clinical Interview develops through observations and dialogue that follows the flow of the illness and its impact as felt by the individual patient. Remain open-minded and be alert to:*

1. **Symptom cluster variability:** Patients exhibit unique combinations of symptoms.
2. **Symptom interaction and coherence:** Symptoms that interact dynamically within a cluster and 'travel together' likely share the same underlying causal system, e.g. be alert to symptoms that activate or worsen with PENE. Flu-like symptoms and delayed exhaustion suggest activation of the immune system.
3. **Separate primary symptoms from secondary symptoms and aggravators:** Primary symptom clusters formed by a disease process, e.g. undue cognitive fatigue following normal cognitive effort, must be separated from the secondary effects of coping with a chronic disease, e.g. anxiety about finances. Many objective indices can differentiate ME from primary depression, e.g. reactions to exercise, joint and muscle pain, severe headaches, recurrent sore throats. Patients' contextual observations will help determine which symptoms are part of the primary illness structure and which are caused by the impact of environmental aggravators and stress enhancers, e.g. fast paced environments, exposure to toxins.
4. **Symptom severity & impact:**
   Mild: meet criteria and have a significant reduction in activity level;
   Moderate: approximately 50% reduction in pre-illness activity level; ***Severe:*** mostly housebound;
   Very severe: mostly bedbound and require assistance with daily functions.
   Those who are very severely affected are too ill to attend regular medical appointments.
5. **Symptom severity hierarchy:** Periodically rank the severity of symptoms to ensure the treatment regimen is focused on the more severe symptoms. Symptom severity and hierarchy frequently fluctuate.
6. **Determine total illness burden:** All aspects of the patient's life – physical, occupational/educational, social, emotional and personal activities of daily living (ADL) must be considered when assessing overall impact. Talk with the patient to determine accumulative effects of symptom severity, interaction and total illness burden. Some patients who prioritize activities may be able to do one important activity by severely reducing activities in other areas of their life. Others are totally bedridden and need assistance.
7. **Diagnosis:** A tentative diagnosis is based on symptoms and evolves throughout the clinical assessment. Laboratory and other investigations confirm or refute the tentative diagnosis.
8. **Differential diagnosis:** The collective pathophysiology of ME is quite distinctive. However, based on the patient's history, risks, and symptoms, it is important to rule out other infectious diseases that could simulate the collective, complex pathophysiology of ME. New symptoms need to be investigated.

Paediatric considerations: *See paediatric personalized treatment - page 19.*

Each child (all young people) will have his/her own unique combination of the ME criterial symptoms. The onset of ME in children often occurs around twelve years of age but it has been diagnosed in a child who was two years old. More than one member of the family may have ME or other neurological diseases.

1. **Interview:** Have both parents present if possible because each may remember different symptoms or interactive events that may help determine onset of illness and interactive symptom clusters. Children may not report symptoms because they are unaware that they are not normal.
2. **Assess impact:** Children cannot be expected to judge their pre-illness function with current function. Compare educational, social and sport activities, and hobbies before and after onset.
3. **Neurological impairments:** Pain, headaches, slowed processing of information, difficulty understanding and remembering information, difficulty focusing eyes and following verbal instructions are prominent features that make learning very challenging. There is often a marked deterioration in school performance.
4. **Exhaustion, irritability and accommodation:** Children may have brief periods of hyperactivity followed by extreme weakness. They often have mood swings and may become irritable when exhausted. Children may accommodate exhaustion by resting, which may be erroneously interpreted as laziness.
5. **Secondary school phobia:** Young patients spend most of their out-of-school hours resting; children with primary school phobia are participating in activities and socializing. Patients may develop 'secondary school phobia' due to academic difficulties caused by ME or bullying.

PERSONALIZED CLINICAL ASSESSMENT & DIAGNOSTIC WORKSHEET FOR ME

Name: **Date:**

Clinical Interview

Patient History *(specify items when possible)*

1. **Pre-onset environmental events:** ***Infectious exposure or events*** ☐ minor infections, ☐ immunization, ☐ upper respiratory infections, ☐ sinusitis, ☐ pneumonia, ☐ gastrointestinal illness after sinusitis or pneumonia, ☐ dental infections, ☐ vaginal infection, cystitis, ☐ prostatitis, ☐ blood transfusion; ***exposure to:*** ☐ sick people, ☐ unfamiliar infectious agents when travelling, particularly following vaccinations, ☐ contaminated water, ☐ poor quality recycled air ***Non-infectious exposure or events:*** ☐ post-chemical toxins, ☐ heavy metals, ☐ moulds; ☐ severe physical trauma e.g. whiplash/spinal injury/surgery, ☐ anaesthetics, ☐ undue stress, ☐ steroids (before or during acute respiratory illness can turn immune response to Th2 and suppress T cell numbers) _____
   Onset: date _____, ☐ sudden, ☐ gradual; ☐ infectious_____, ☐ other_____
   Symptoms at onset (indicate interrelated clusters if possible) _____
   Severity of symptoms at onset _____
   Duration of symptoms _____
2. **Medication history** _____
   Immunizations & sensitivities _____
   Other therapies _____
3. **Past history:** pre-illness functioning _____ premorbid activity level _____%
4. **Family history** _____

Systems Review: Many symptoms involve more than one system. Be alert to the following & specify when possible:

Neurological: ☐ **cognition:** ☐ difficulty processing information, ☐ difficulty organizing tasks, ☐ difficulty remembering sequences, ☐ information overload, ☐ short term memory loss _____
☐ **pain:** ☐ headaches, ☐ musculoskeletal pain, ☐ worsens with physical or cognitive exertion_____
☐ **sleep disturbance:** ☐ disturbed sleep pattern, ☐ unrefreshed sleep: quantity ____ hr., quality (1-10) _____
☐ **neurosensory & perceptual disturbance:** ☐ sensory overload, ☐ motor disturbance _____

Immune: ☐ recurrent flu-like symptoms that activate/worsen with exertion, ☐ susceptible to repeated infections

GI: ☐ nausea, ☐ abdominal pain, ☐ bloating, ☐ IBS, ☐ food &/or alcohol sensitivities, ☐ chemical sensitivities (specify) _____

GU: ☐ urinary urgency, ☐ frequency, ☐ nocturia _____

Energy production/ion transport

Cardiovascular: ☐ orthostatic intolerance (OI) - inability to tolerate upright position, ☐ neutrally mediated hypotension (NMH), ☐ postural orthostatic tachycardia syndrome POTS), ☐ palpitations with or without cardiac arrhythmias, ☐ light headedness _____

Respiratory: ☐ air hunger, ☐ laboured breathing, ☐ fatigue of chest wall muscles _____

Endocrine & ANS: ☐ loss of thermostatic stability, ☐ intolerance of extremes of temperature_____

Post-exertional neuroimmune exhaustion (PENE)

☐ Marked, rapid physical or cognitive fatigability in response to exertion _____
☐ Symptoms that worsen with exertion _____
☐ Post-exertional exhaustion: ☐ immediate, ☐ delayed; ☐ prolonged recovery period _____
☐ Exhaustion is not relieved by rest _____
☐ Substantial reduction in pre-illness activity level due to low threshold of physical and mental fatigability (lack of stamina) _____ Activity level: ☐100%, ☐90%, ☐80%, ☐70%, ☐60%, ☐50%, ☐40%, ☐30%, ☐20%, ☐10%

Symptom hierarchy, quality & severity _____
Secondary symptoms & aggravators _____
Sleep quality: scale of 1-10 (excellent sleep 10): ____, onset____, duration ____, problems _____
Pain: scale of 1-10 (worst pain ever 10): _____, problems _____
Energy/fatigue: scale of 1-10 (great energy 10): good day _____, bad day _____, today _____

Physical Examination: Standard examination with attention to:

temp. _____; **pH:** _____; **BP/pulse:** 1. lying down: **BP** _____/_____, **Pulse** _____;
2. immediately after standing: **BP** _____/_____, **Pulse** _____; 3. after standing 3 min.: **BP** _____/_____, **Pulse** _____ ;
4. after standing 5 min.: _____/_____, **Pulse** _____ *(Caution: Someone should stand beside the patient.)*

Neurological

CNS: reflex examination: (neck flexion & extension may accentuate abnormalities from cervical myelopathic changes)

Neurocognitive: ☐ slowed thought, ☐ impaired concentration, ☐ difficulty remembering questions;
☐ cognitive fatigue: during assessment, serial 7 subtraction (subtracting by 7 from 100)_____
☐ cognitive interference: (e.g. serial 7 subtraction done simultaneously with tandem walk) _____

Pain/musculoskeletal: ☐ hyperalgesia, ☐ widespread, ☐ myofascial or radiating, ☐ muscle-tendon junctions,
☐ taut muscles; joints: ☐ inflammation, ☐ hypermobility, ☐ restricted movement; positive tender points ____/18;
☐ meets fibromyalgia criteria; muscle tone: ☐ paretic, ☐ spastic; muscle strength _____

Neurosensory, perceptual and motor disturbance: ☐ abnormal accommodation responses of the pupils, ☐ suborbital hyperpigmentation; tandem walk: ☐ forward, ☐ backwards; ☐ Romberg test; ☐ reflex examination _____

Immune: Tender lymphadenopathy: ☐ cervical, ☐ axillary, ☐ inguinal regions (more prominent in acute phase),
☐ flares with exertion; ☐ crimson crescents in the tonsillar fossa: ☐ demarcated along margins of both anterior and pharyngeal pillars, ☐ if patient has no tonsils, they assume a posterior position in the oropharynx; ☐ splenomegaly

GI: ☐ increased bowel sounds, ☐ abdominal bloating, ☐ abdominal tenderness: epigastrium (stomach), right lower quadrant (terminal ileum) and left lower quadrant (sigmoid colon) – *most patients have tenderness in 2-3/3 areas*

Cardiovascular & respiratory: ☐ arrhythmias: ☐ BP as above; ☐ mottling of extremities, ☐ extreme pallor,
☐ Raynaud's phenomenon, ☐ receded moons of finger nails (chronic phase) _____

Laboratory/Investigative Protocol: Diagnose by criteria. Confirm by laboratory and other investigations. A broad panel of tests provides a more robust basis to identify symptom patterns, abnormalities and orient treatment.

Routine laboratory investigation: ☐ CBC, ☐ ESR, ☐ CA, ☐ P, ☐ RBC Mg, ☐ vitamin D3, ☐ B12 & folate, ☐ ferritin, ☐ zinc, ☐ FBS, ☐ PC, ☐ Hb A1C, ☐ serum electrolytes, ☐ TSH, ☐ protein electrophoresis screen, ☐ CRP, ☐ creatinine, ☐ ECG (U+ T wave notching), ☐ CPK and liver function, ☐ rheumatoid factor, ☐ antinuclear antibodies, ☐ urinalysis, ☐ essential fatty acids, ☐ CoEnzyme Q10, ☐ immunoglobulins, ☐ diurnal cortisol levels, ☐ TTG, ☐ serotonin

Additional laboratory investigation: *(as indicated by symptoms, history, clinical evaluation, lab findings, risk factors)*
☐ 24 hour urine free cortisol, ☐ DHEA sulphate, ☐ ACTH, ☐ chest x-ray, ☐ hormones including free testosterone ☐ panoramic x-ray of dental roots, ☐ amino acid profile, ☐ abdominal ultra sound, ☐ lactose/fructose breath test

Further testing with specificity to ME*, if and as indicated*. *Some tests are in the research stage but can identify abnormalities and focus treatment. Viral tests should be interpreted by a physician experienced in these infections.*

Pathogen	*Tests*	*Pathogen*	*Tests*
☐ Enterovirus	RT-PCR, serology, stomach biopsy	☐ mycoplasma	DNA-PCR, serology
☐ EBV, ☐ CMV, ☐ HHV-6	DNA-PCR, serology, antigenemia	☐ Borrelia burgdorferi	DNA-PCR, serology, Western Blot
☐ Clamydia pneumonia	DNA PCR, serology	☐ Parvovirus B19	DNA-PCR, IgG, IgM,

Immune system profiles: ☐ ***↓NK cell function & ↑ cytotoxicity**; ☐ B & T-cell function: ☐ IgG, ☐ IgG subclasses 1-4; ☐ IgA, ☐ IgM (shift from T1 to T2), ☐ cytokine/chemokine profile panel (94% accuracy): IL-8, IL-13, MIP-1β, MCP-1, IL4, ☐ flow cytometry for ↑ lymphocyte activity, ☐ ↑ 37 kDa 2-5A RNase L immunoassay – defect/ratio & bioactivity, ☐ food sensitivity panel, ☐ chemical sensitivities, ☐ stool for WCB - D-lactic acid bacteria balance, ova & parasites, ☐ autoimmune profile, **Intestinal dysbiosis:** ☐ IgA & IgM for intestinal aerobic bacteria in serum, ☐↑ leukocyte elastase activity in PBMCs, ☐ IgG food intolerance test, ☐ toxoplasmosis

Neurological & static testing: ☐ ***SPECT scan with contrast - ↓** cortical/cerebellar region cerebral blood flow (rCBF) in the frontal, parietal, temporal and occipital & brain stem regions - *more brain involvement indicates increased illness severity*, ☐ **MRI of brain –** *(increased T2-weighted images in high white matter tracts & loss of GM volume) & rule out MS,* ☐ **MRI of spine** *(dynamic disc bulges/herniation , stenosis),* ☐ **sleep study** *(↓ stage 4 sleep, sleep pattern & rule out treatable sleep dysfunctions – upper airway resistance syndrome, sleep apnea, etc.)*

PENE: *A 2 consecutive day comprehensive 8-12 minute cardiopulmonary exercise stress test (measuring heart, lung, and metabolic function) - only ME patients have significantly worse scores the second day & abnormal recovery from exertion.*
***** **Exercise tolerance test with expired gas exchange -** (2 consecutive days) – *measure cardiovascular, pulmonary &*

metabolic responses at rest & during exercise: □ peak oxygen consumption VO_2 or VO_2 at anaerobic threshold (AT) - *decline of 8% or greater on test 2 indicates metabolic dysfunction*, □ post-exercise blood analysis - increase in sensory, adrenergic and immune genes - increase in metabolite receptors unique to ME

Energy metabolism/ion transport: □ ATP profile **–** identifies insufficient energy due to cellular respiration dysfunction □ further ATP related parameters, superoxide dismutase and cell-free DNA ***Respiratory:*** □ pulmonary function test ***Cardiovascular:*** □ **Tilt table test** to confirm OI (70 -80% tilt, measure HR continuously, BP periodically – 30 min or presyncope); □ **Cardiac output decreases -** left ventricular dysfunction in the heart; □ **24-Hour Monitor** for suspected arrhythmia, NMH/POTS, myocarditis *(Note: Repetitively oscillating T-wave inversions &/or T-wave flats, typical of ME, may be subsumed under non-specific T-wave changes.)*

Differential Diagnosis: When indicated on an individual basis, rule out other diseases that could plausibly simulate the widespread, complex, symptom pathophysiology defining ME. E.g.: **Infectious disorders**: TB, AIDS, Lyme, chronic hepatitis, endocrine gland infections; **Neurological:** MS, myasthenia gravis, B12; **Autoimmune disorders**: polymyositis & polymyalgia rheumatica, rheumatoid arthritis; **Endocrine:** Addison's, hypo & hyper thyroidism, Cushing's Syndrome; **cancers**; **anemias**: iron deficiency, B12 [megaloblastic]; **diabetes mellitus; poisons**

Exclusions: Primary psychiatric disorders, somatoform disorder, substance abuse & paediatric 'primary' school phobia.

Comorbid Entities: Myofascial Pain Syndrome, TMJ, interstitial cystitis, Raynaud's phenomenon, prolapsed mitral valve, Irritable Bladder Syndrome, prolapsed mitral valve, Hashimoto's thyroiditis, Sicca Syndrome, secondary depression, allergies, MCS, etc. FMS is an overlap condition. IBS & migraine may precede ME and then become associated with it.

ME International Consensus Criteria	
_____ Compulsory	**Post-exertional neuroimmune exhaustion (PENE)** 1. Marked, rapid physical or cognitive fatigability in response to exertion 2. Post-exertional symptom exacerbation 3. Post-exertional exhaustion: immediate or delayed 4. Recovery period is prolonged 5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level.
_____ 3	**Neurological impairments:** 1 or more symptom from 3 symptom categories ___ 1. Neurocognitive impairments ___ 2. Pain ___ 3. Sleep Disturbance ___ 4. Neurosensory, perceptual and motor disturbances
_____ 3	**Immune, gastro-intestinal & genitourinary impairments:** 1 or more symptoms from 3 categories ___ 1. Flu-like symptoms: recurrent, chronic, worsen with exertion ___ 2. Susceptibility to viral infections – prolonged recovery periods ___ 3. Gastro-intestinal tract disturbances ___ 4. Genitourinary disturbances ___ 5. Sensitivities
_____ 1	**Energy production/transportation impairments:** At least one symptom ___ 1. Cardiovascular ___ 2. Respiratory ___ 3. Loss of thermostatic stability ___ 4. Intolerance of extremes of temperature

Diagnosis	_____ **ME**; ____ **Atypical ME**: meets criteria for PENE but has a limit of two less than required of the remaining criterial symptoms. ____**other** _____
Onset	□ sudden, □ gradual; □ infectious _____, □ other_____
Severity	□ **mild**: meets criteria, significantly reduced activity level; □ **moderate:** ~ 50% reduction in activity level; □ **severe:** mostly housebound; □ **very severe:** mostly bedbound, needs assistance with personal care
Subgroups	**Prominent cluster**: □ neurological; □ immune; □ metabolism/cardiorespiratory; □ eclectic (balanced)

PERSONALIZED MANAGEMENT & TREATMENT

Goals

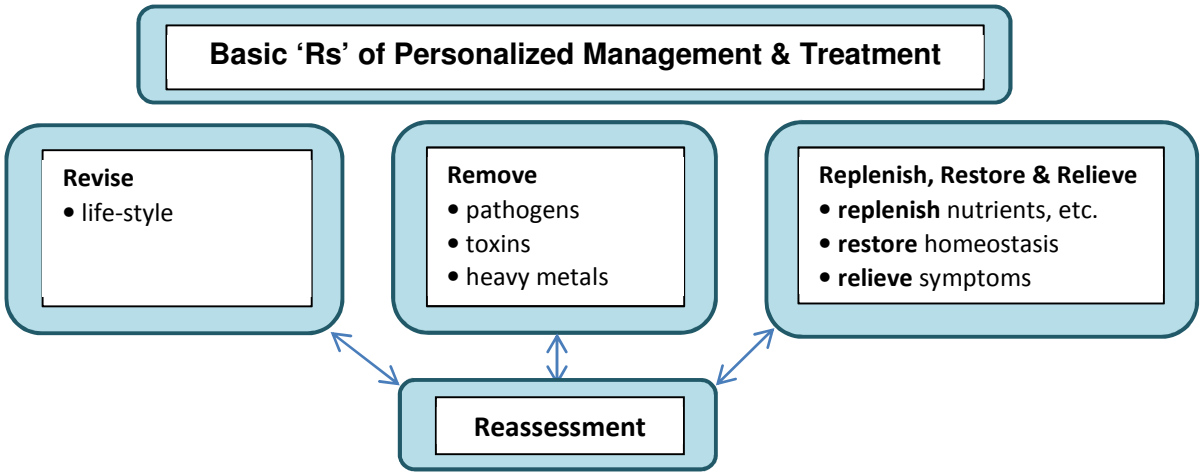
1. ***To support the well-being of the patient*** *by providing a definite diagnosis, respecting his/her illness experiences, assuring that the disease is real, and providing realistic hope and continuing care*
2. ***To empower the patient*** *by collaborating with the patient on the management of ME and assuring s/he will maintain autonomy regarding the complexity and pacing of activities and management*
3. ***To optimize functionality*** *without aggravating symptoms*

Guidelines

1. ***The pathophysiology of ME and laboratory findings*** *must be reflected in all treatment/management programs. Adverse reaction to exertion accompanied by a prolonged recovery period must be respected and accommodated. All health-care personnel must be knowledgeable about ME.*
2. ***Prioritize greatest symptom concerns and dysfunctions*** *in order to determine the best treatment strategies.*
3. ***Begin treatment promptly*** *based on present clinical parameters and laboratory test findings.*
4. ***Identify and treat comorbid conditions & aggravators.***
5. ***The treating physician is responsible for overseeing the patient's care.*** *Coordinate referrals and treatment efforts. Bedridden patients may require appointments via phone, home care services and assistance devices.*
6. ***A comprehensive, holistic approach is vital.*** *Laboratory findings are enormously helpful but it is important to understand the difference between treating the patient and treating laboratory test results.*
7. ***Personalized treatment plan: Involve the patient in setting realistic goals and developing a personalized program based on his/her top priority health issues.*** *The plan should be flexible, reflect the pathophysiology and be conducive to healing. Consider all aspects of the patient's life. Begin at a level that will ensure patient success, assist in recognizing early warning signs, conserving energy, and planning alternate strategies for low-energy days. Therapeutic alliance is an integral part of the patient's self-management support.*

Medication Principles and Caveats

1. ***Identify pathological components of symptoms*** *and* ***target treatment at cause.***
2. ***Most patients are extremely sensitive to medication.*** *Start low – Go slow! Dosage levels are not given because it is recommended that dosage be reduced, at least initially. Start at ¼ - ½ of the recommended dose. Medications may need to be adjusted or changed periodically to avoid building up tolerance to a medication. Avoid the use of TCAs, Pregabalin, and Quetiapine for overweight patients.*
3. ***Patients need to understand*** *the reason they are taking a particular medication. Warn of side-effects!*
4. ***No pharmaceutical is universally effective.*** *In order to determine effectiveness and side effects, add or change one medication at a time. Balance benefits against adverse effects.*
5. ***Keep regime as simple, safe, effective and inexpensive as possible.***



Revise Life-Style: Patient Self-Help Strategies (SHS)

SHS assist patients in being proactive in conserving their energy, minimizing symptom flare-ups, and maximizing functionality. SHS are what patients can do to support and optimize their body's ability to heal. The health care provider and patient should work as a collaborative team. It is important that patients learn how to problem-solve and manage their day to day self-care, if able. SHS empower patients.

Education and Personal Development: Knowledge is power.

1. **Meet with the patient's partner/family** as soon as possible after the diagnosis to discuss ME, what to expect, assist in developing SHS, and provide realistic hope. Provide written educational information.
2. **Notes:** It is helpful if the patient brings someone to appointments to take notes that can be reviewed later.
3. **Encourage patients** to trust their feelings and experiences.
4. **Recognize and avoid stressors and aggravators.** Develop energy and environmental modifications.

Maximizing Sleep

Sleep disturbance is typically expressed by prolonged sleep, sometimes extreme in the acute phase, and often evolves into marked sleep reversal in the chronic phase. Patients should:

1. **Reduce stimulants** such as coffee, alcohol, and decongestants. Create a quiet environment.
2. **Pace day-time activities** and incorporate rest periods. Over-exertion can increase insomnia.
3. **Listen to the body** and rest or sleep when needed. Sleep dysfunction and an inability to produce sufficient energy on demand makes it essential that low energy reserves are not depleted.
4. **Establish a regular bedtime** as much as possible. However sleeping when needed takes priority. In the chronic phase, incorporating short naps into the day may assist in being able to establish a regular bedtime.
5. **Quiet activities** or listening to a relaxation DVD before bedtime are helpful. Those who are severely ill or in the acute phase may sleep much of the time but sleep is non-restorative.
6. **Have a warm bath** prior to bed and keep the body warm at night.
7. **Keep the bedroom dark and quiet**: use black-out curtains, turn the face of clocks away from the bed, use eye masks and/or ear plugs if necessary.
8. **Postural support**: make sure the mattress and pillow give proper postural support.
9. **Keep the bedroom as a 'worry free sanctuary'** reserved for sleep and sex.
10. **If sleep is impossible**, get up and go to another room and do calming meditations or relaxing activities.

Nutrition, Diet and Hydration

The biochemistry and nutritional needs of each patient are unique. Standards for vitamin intake are based on estimated amount required to prevent overt deficiency symptoms. Vitamin, mineral, digestive enzyme, and food sensitivity profiles are helpful in assuring that patients receive the nutrient intake required to facilitate healing.

1. **Keep well hydrated:** approximately 30 ml. of water/kg. of body weight daily (½ oz./lb./day)
2. **Eat a balanced, highly nutritious diet at regular times**. Eating 3 small meals and 2-3 snacks daily, rather than three bigger meals is less stressful on the digestive system, and helps stabilize blood sugar levels and avoid hypoglycemia. Most fresh vegetables, fruits and herbs are high in antioxidants and nutrients.
3. **No diet fits all**. Generally, patients do better on a diet that is higher in low fat protein, vegetables and fruit. Eat a small portion of protein at each meal. Eat a variety of nutritional foods.
4. **Sensitivities/intolerance** to gluten, milk & dairy, and eggs are common. Do elimination trials as indicated.
5. **Reduce refined foods**: e.g. white sugar & flour. Reduce polished rice intake to avoid vitamin B1 deficiency.
6. **Avoid processed foods**: glutamate additives, artificial sweeteners. Limit sugar and alcohol.
7. **Eat organic food** as much as possible. Prioritize: greens, berries, apples, soft skin fruit. Soaking non-organic produce in water with 1 tablespoon of both lemon juice and sea salt for 20 minutes helps remove toxins.
8. **Take multi-enzyme tablet** with meals as indicated or if IBS is present.
9. **Take nutritional supplements** as indicated. A multi-vitamin and a multi-mineral supplement will ensure minimal RDA intake. Consider vitamin B complex, D3, fish Omega 3 essential fatty acids and Co-enzyme Q10.
10. **Replenishing electrolytes** may be helpful.

Energy Budget/Bank (EBB)

Pacing is not a cure but it is essential as it enables patients to make the best use of their limited energy. Similar to a household budget, the more limited the patient's energy, the more important it is to **prioritize** energy needs and **budget** its use. Ideally patients should work towards having four energy accounts.

EBB Accounts	Description
ADL	First priority is to conserve energy for the essential activities of daily living.
Emergency	Conserve some energy for unexpected events that require additional energy.
Sharing	Budget some time to share with others, whether by phone, email or in person. Talking and listening can be exhausting so these periods should be kept very short, with rest periods before and after. Prioritizing is essential.
Energy Savings Investment	Ideally, work towards saving a little energy every day in order to get stronger and invest in their future health.

Problem: *Typically patients consistently overestimate what they can do and are not aware that they have overexerted themselves until after they are in a 'crash mode'.*

Objective: Optimize daily functionality and activity endurance **without** aggravating symptoms.

Pathological components: PENE: post-exertional physical and mental exhaustion, pain, immune activation and symptoms flare • decreased cerebral oxygen • impaired aerobic energy metabolism • reduced anaerobic threshold heart rate, VO_2 peak and peak work • drop in ability to produce energy after repeated exercise • OI • abnormalities in heart function • prolonged recovery period • inability to recover from acidosis

Both submaximal & self-paced physiological limited exercise can result in PENE.

EBB Self-Help Strategies: education, functionality, and activities

Patients must always be in control of the pacing and duration of any activity. *Encourage patients to:*

1. **Pay attention to body signals & become alert to subtle clues of overexertion:** It is essential that patients learn is to recognize early warning signs that they have exceeded energy boundaries.
   SHS: Wear a **heart rate monitor** set approximately 5% below the anaerobic threshold. Stop when the beeper rings. Lie down and rest. Try to determine what activity, duration of activity or aggravator set off the beeper and detect subtle differences in how they feel - e.g. feet are cold, feel more confused, etc.
   Other tools: • activity logs • charts • devices, such as wearing a step counter, or an Actigraph monitor can assist the patient in becoming attuned to subtle cues of over-exertion • Take temperature before and after activity: a drop in temperature indicates the patient has done too much.
   A daily activity log should include duration and quality of sleep, functional level (scale of 0 – 10), activity, time and duration of activity, change in symptoms or severity, change in temperature, aggravators, etc.
2. **Prioritize, prioritize, prioritize!** The more limited the energy, the more important it is to prioritize which items are essential. Patients need to know their energy limits and the specific pacing required to do an activity in order to make knowledgeable decisions when choosing which activities are best for them.
3. **Stay active within their limitations and rest frequently:** **Alternating short activity and rest periods enables patients to do more in the long run.** Always rest before and after an activity. Find an enjoyable activity.
4. **Set personal boundaries and activity limits.** Learn to say "No" without guilt. Save energy for ADLs, etc.
5. **Adjust body position:** (standing vs. sitting vs. lying down) Use joint protection devices as indicated.
6. **Optimize functionality:** Depending on severity, some but **not all** patients in the chronic phase are able to incorporate some brief activities into their day to assist in maintaining and improving function. Monitor functional level (1-10) initially and on an ongoing basis. **Start low – go slow**. Use a heart rate monitor set a little below the anaerobic threshold to give activity biofeedback. Breathing exercises promote relaxation and strengthen respiratory muscles. Active stretching with breathing improves range of motion/flexibility. These can be done either seated or supine. If and when able, add slight resistance (elastic bands), then take brief walks or swim. Use good body mechanics and ergonomics. Do not exceed energy boundaries – obey the heart rate monitor. ***Notes:*** *Aerobic metabolism may be impaired. Do not exercise in pollution*.

7. **Develop alternate strategies** for days when energy is low.
8. **Simplify routines & conserve energy** e.g. cook enough for 2^{+} meals. Have a special place for items e.g. keys.
9. **Make environmental modifications,** avoid multisensory overload, and use functional assistant devices.
10. **Avoid owing any energy account** at the end of the day, if possible.

REMOVE PATHOGENS & TOXINS

Remove Pathogens, Toxins and Heavy Metals

1. **Microorganisms:** Persistent infections worsen symptoms and increase disability. Antivirals and antibiotics should be used with caution. Identify infectious agent (pg. 11) and refer patients to an infectious disease specialist. The following brief description is provided for your information.
   Non-pharmaceutical: *• prebiotics • probiotics • vitamins C • B12 • L-glutathion • antioxidants*
   Pharmaceutical: Antivirals - lymphotropic viruses and other viruses: *• Valacyclovir (for confirmed herpes viruses) • Ganciclovir • Valganciclovir (Ganciclovir prodrug) • Cidofovir • CMX001 • Foscarnet • Acyclovir* ***Immune boosters*** *• oxymatrine (for enteroviral infections)• Omega 3 essential fatty acids (EFA)*
   Antibiotics: 21 consecutive days **or** alternate 8-10 days of antibiotics followed by 3 weeks of prebiotics and probiotics until under control. Older antibiotics are recommended in order to avoid developing resistance to newer antibiotics that may be needed in acute medical situations. ***Bacteria, mycoplasma & Chlamydophila pneumoniae:*** *• Doxycycline • Clarithromycin • Ciprofloxacin • Azithromycin.*
   Intestinal dysbiosis*: • Erythromycin or • Clarithromycin or • Xifaxan with* ***probiotics*** *• VSL-3 • Mutaflor* - to recover from each treatment & restore gut bacteria. Treatment suppresses overgrowth.
   Anaerobic dental bacteria produce very toxic wastes. *Photo disinfection utilizes a cold, low-power diode laser to inactivate many bacteria and toxins and reduces gum pockets.*
   Antifungals: such as candida change sugars to aldehydes. *Treat with anti-fungals.*
2. **Toxins:** Remove toxins from chemicals (e.g. PCP, DU, organophosphates), and from microorganisms that can build up within and around cells. The toxins can cause a Th1/Th2 shift and inhibit cellular respiration.
   • drink non-chlorinated water • omega 3 essential fatty acids • bentonite
3. **Heavy metals:** disrupt the immune system. The structure of one of the RNase L fragments is almost identical to a protein involved in the removal of heavy metals and toxic chemicals. When this protein is blocked, the cells become highly sensitive to mercury. Remove heavy metals • consider *chelation (not confirmed)*

REPLENISH NUTRIENTS

Replenish Nutrients, Restore Homeostasis, and Relieve Symptoms

Replenish ***probiotics, hydration, nutrients, vitamins, minerals/electrolytes, enzymes, antioxidants.***
Restore ***cellular oxygenation, acid/alkaline balance (pH), sleep, intestinal flora balance, hormonal balance***

1. **Cellular oxygenation:** When cellular oxygenation drops, respiratory enzymes decrease and the cells cannot produce adequate energy aerobically, mitochondria become damaged and restrict transport of cellular oxygen. Insufficient Omega 3 essential fatty acids levels may restrict oxygen exchange through the cell walls.
   Non-pharmaceutical: *• Omega 3 essential fatty acids – fish oils, flax seed oil • methyl sulfonyl methane (MSM)*
2. **Hydration:** *Approximately 30 ml of water per kilogram of patient's weight daily (½ ounce/pound/day).*
3. **Acid/alkaline balance:** In order to maintain blood pH of 7.4, the body uses stored alkalizing minerals as buffers to neutralize elevated acidic load. Excess acidic substances and toxins are deposited in the cells, which decreases their oxygen levels and increases susceptibility to disease.[151] Check pH regularly.
   Non-pharmaceutical: *• eat fresh fruit and vegetables • replenish minerals and vitamins • remove toxins • alkaline water • betaine hydrochloride with meals • pH balancers • sodium bicarbonate – 1 teaspoon of baking soda dissolved in a glass of water - at least one hour after meals, 2 times a day.*
4. **Vitamins & Minerals:** Vitamins are generally cofactors that aid enzymes in utilizing nutrients. Standard recommended intake is based on amount needed to prevent overt deficiency. A vitamin/mineral profile is helpful to ensure patients are getting optimal nutrients for healing. Deficiencies in vitamins C, D3, B12, other B complex vitamins, magnesium, potassium, sodium, zinc, L-tryptophan, L-carnitine, coenzyme Q10, and essential fatty acids have been reported.[152]
   Vitamins: **Vitamin D3**: calcium metabolism, healthy bones & helps regulate heartbeat; • **B complex**: metabolism, RNA & DNA synthesis, cell oxidation, antibody production & nerve health; • **C**: antioxidant,

healthy adrenals, collagen, capillary tissue, fights infection; • **A & E**: antioxidants, red cell health, protein synthesis. Vitamins A, D & E are fat soluble and can cause toxicity if taken in excess.

Minerals: **Calcium**: healthy bones & teeth, heart rhythm regulation; • **magnesium**: calcium & vit. C metabolism, nervous & muscular systems; **potassium**: nerves, muscle tone, heart action, enzymes reaction; **zinc:** normal tissue function, protein & carbohydrate metabolism; **manganese:** activates enzymes; **sodium:** helps regulate acid-base balance, muscle contraction. **Trace minerals:** involved in many body processes.

Neurological

1. **Sleep Disturbance:** consider sleep quantity and restorative quality

Possible pathological symptoms/components: • reduced stages 3 and 4 sleep, which is when the body is restored • feeling tired but wired • prolonged sleep onset • restless sleep • coma-like sleep • awakening early • can't go back to sleep • unrefreshed sleep • morning stiffness & mental 'fog'.

Identify and treat associated sleep dysfunctions: • upper airway resistance syndrome • sleep apnea • restless leg syndrome • periodic limb movement • leg cramps

Non-pharmaceutical: *• sleep hygiene • relaxation • cervical pillow • calcium & magnesium salts • melatonin*

Pharmaceutical: ***sleep onset:*** *sedative/hypnotics • Zopiclone • Zolpidem • Zaleplon • Eszopiclone;*

sleep sustainers: *• Trazodone • tricyclic antidepressants (TCA) – Doxepin, Amitriptyline, (short term low dose – side effects can be severe) • L-tryptophan;* ***muscle relaxant****: • Baclofen*

2. **Pain**

Possible pathological types/components: • altered sensory information and pain processing in the brain that is perceived as pain • peripheral neuropathies • decreased pain threshold • dysregulation of sodium channels & ion transport • magnesium deficiency • inflammatory conditions • **muscle pain generated by movement:** paretic (decrease in muscle bulk/tone), spastic – (increase in muscle bulk/tone) • **structural pain**: failure of supportive structures; • differential pain diagram and descriptive words help determine type of pain: • aching • stabbing • shooting • pins & needles; (visual analogue scale: estimate severity)

Treat localized pain because it can intensify general pain.

Non-pharmaceutical: *avoid pain exacerbators • pacing • local heat or cold • gentle stretching;* ***manipulative body therapy:*** *• massage • physiotherapy • chiropractic • myofascial release techniques;* ***relaxation techniques:*** *• biofeedback • ultrasound • meditation; • TENS (Transcutaneous Electrical Nerve Stimulation) • acupuncture • magnesium sulfate (for muscle spasm) • hydrotherapy • Synaptic® Electronic Activation*

Pharmaceutical: *topical ointments;* ***anti-inflammatory/degenerate/neuropathies:*** *• NSAIDs • ibuprofen • naproxen;* ***COX-2 inhibitors:*** *• Celecoxib;* ***anticonvulsants:*** *Gabapentin • Pregabalin; TCA – low dose for short time • Amitriptyline • Nortriptyline • Doxepin;* ***muscle relaxants:*** *• Baclofen • Cyclobenzaprine;* ***migraines*** *• Sumatriptan Succinate;* ***narcotic/opiates****: only if severe – requires rationale & documentation*

3. **Cognition and Fatigue:** not relieved by rest

Possible pathological types/components • **neuropathy**: sensory information is interpreted by the brain as fatigue • **cognitive fatigue**: more parts of the brain are utilized during auditory processing • brain hypotension • **arousal fatigue**: poor sleep quality & quantity • **metabolic fatigue**: cells are unable to transform substrates of energy into useful function • **oxygenation fatigue**: insufficient oxygen is delivered to the brain & tissue • **OI:** inability to maintain upright position • **muscle fatigue**: generated by movement • **structural fatigue**: failure of weight bearing supportive structures; • hypoadrenalism • hypothyroidism • food intolerance • nutrient malabsorption • insulin imbalance • stress • medication • MCS

Non-pharmaceutical: *• energy budget/bank (EBB) pg. 15 • pacing • sleep management • simple, quiet environment • simplifying tasks • adaptive devices • relaxation techniques • restorative postures • some patients think better in a semi-reclined position • speech therapy may help problems with word finding, processing information, & memory • read within one's ability & then learn new information/skills – as able*

B12/Cyanocobalamin or Methylcobalamin: *anecdotal studies suggest some patients with normal blood counts improve in energy level, cognition, weakness and mood with mega B12 injections.*

Pharmaceutical: ***CNS stimulants*** *for fatigue • Methylphenidate (for concentration) • Modafanil • Armodafinil • Moclobemide. Most drugs have short-term effects and may not improve endurance.*

a. **PENE** is the pronounced summation effects and after–effects of numerous interactive dysfunctions.
Effects: physical and mental exhaustion, weakness, symptom flare and a prolonged recovery.
Possible pathological components: • neuroimmune exhaustion • decreased cerebral oxygen & blood volume flow, cardiac output & pain threshold • impaired aerobic metabolism & oxygen delivery to muscles • elevated sensory signalling to the brain perceived as fatigue and pain • immune activation
Treatment*: Pacing is the best prevention. (pg. 15) A heart rate monitor can assist in keeping cardiovascular responses below the anaerobic threshold. Treat sleep, pain, fatigue & cognitive problems.*

b. **Overload Phenomena:** hypersensitive to many kinds of sensory input
It can cause a "crash" – a temporary period of immobilizing physical and/or cognitive exhaustion.
Possible pathological components: • hypersensitivity to and overload of sensory stimuli • more than one source of information • mixed modalities of input – auditory & visual, physical & cognitive • physical or mental exertion • fast paced or confusing environments • extremes of temperature
Non- pharmaceutical*: Treat sleep, pain, fatigue and cognitive problems.*
Pharmaceutical: *Sensory overload crash sometimes responds to gentle, low dose benzodiazepines: • Lorazepam • Alprazolam*

Immune and Gastro-Intestinal

Intestinal dysbiosis: leaky gut syndrome, nausea, indigestion, reflux, bloating, vomiting, abdominal pain
Possible pathological components: • bacterial imbalance – elevated levels of D Lactic acid-producing bacteria in the gastrointestinal tract • chronic enteroviral infection of the stomach • slow gastric emptying
Non-pharmaceutical: *test for food sensitivities • food elimination trials to determine food intolerance • adjust diet (See nutrition/diet pg.14) Common food sensitivities: gluten, lactose, fructose, milk, eggs*
Pharmaceutical: *Confirm infection. Refer to specialist. See pg. 16, Remove pathogens - #1*

Energy Metabolism and Ion Transportation

1. **Orthostatic intolerance (OI):** *sympathetic response to decreased venous return. Confirm with tilt table test.*
Possible pathological components: • cerebral hypoperfusion • dehydration • decreased cardiac output • reduced circulating red cell count • reduced plasma volume • reduced ability of the blood to carry oxygen to the brain • decreased venous return • neck problems • medication • low ADH • CNS disorder
Non-pharmaceutical: *• supine or semi-supine posture • proprioceptive neck disturbances– avoid extension or quick rotation • support stockings • get up slowly while holding on to something • eat small meals • keep well hydrated • elevate legs • lying down at the first sign of dizziness usually relieves symptoms caused by POTS and NMH • electrolytes •* ***volume expansion:*** *• quality sea salt with adequate water intake*
Pharmaceutical: ***volume expansion:*** *sodium chloride – IV normal saline, if salt helps initially then wanes consider Fludrocortisone (monitor potassium) • can add a beta blocker to increase ventricular filling and reduce postural tachycardia or palpitations e.g. • Atenolol • Pindolol; peripheral alpha agonist • midodrine*
2. **Urinary difficulties:** urinary urgency, frequency, nocturia Rule out infection and refer patient to urologist.
3. **Neuroendocrine: Hypothalamic-Pituitary-Adrenal (HPA) Axis:** *• Galangtamine • Melatonin*

Other Symptoms

1. **Altered mood:** Patients may become anxious or develop secondary depression due to coping with a poorly understood, chronic disease, and greatly reduced functionality. Let patients know that research is advancing. Evaluate suicide risk. Refer those with severe depression for **supportive** counseling.
Non-pharmaceutical: *Support patients through the grieving process from loss of health, lifestyle, occupation, income, etc. • bright light therapy • massage • uplifting music or activities • support groups*
Pharmaceutical: *SNRIs: • Venlafaxine • Duloxetine; MAOIs: • moclobemide (improves fatigue); • buprolon*
2. **Gynecological:** Female patients have a higher than normal incidence of peri-menstrual symptoms, which can last two weeks, and more severe peri-menopausal and post-menopausal symptoms. [153]

Pharmaceutical: ***peri-menstrual****: low-dose progesterone may be helpful (only use on a 3-6 monthly cycle - risk of thromboembolism);* ***peri-menopausal/post-menopausal****: hormone replacement therapy (HRT) may help some and reduce risk of osteoporosis (only use short-term - risk of breast, uterus & ovarian cancer)*

Reassessment – Regular Ongoing Follow-Up

1. **Monitor and reassess symptom severity,** evaluate improvements and concerns, and problem solve.
2. **Revise prioritized items and adjust treatment strategies** and action plan as indicated.
3. **Follow-up tests** can be limited to a small number of key parameters but the importance of the co-relations between test findings and clinical progress cannot be overemphasized.
4. **Determine total illness burden** by talking with the patient to determine the severity of symptoms, the dynamics of interaction within their cluster of symptoms, their accumulative effects, and the overall impact to patients' lives over longer periods of time. All aspects of patients' lives must be considered – physical, occupational/educational, social, personal and emotional.
5. **Investigate new symptoms** appropriately because ME patients can develop other medical problems. Do not assume that all new symptoms are part of the ME complex.
6. **Charts, etc.** Activity logs and scales are helpful. ***International Symptom Scale*** (being developed) will help position a patient within the group, orient the treatment program and monitor its effectiveness.
7. **Coordinate care and extended care referrals:** specialists, peer support groups, group appointments, etc.

Paediatric Treatment Considerations

Prompt treatment can lessen the impact of ME in some cases. Monitor the child's health on an ongoing basis.
Management is similar to adults. Great caution is required in prescribing any medications - use low dosage.
Involvement of family members is essential. They monitor the child's health and are the primary care givers.
Additional support: Provide information about relevant agencies, support groups, and other resources.

Considerations for the Child's Education: *The clinician may be required to make serious decisions regarding the child's education. Consider options in conjunction with the parents, child, and liaise with the school when appropriate. (Child refers to all young people of school age.)* ***See letter to educators, pgs. 27-28***

The GP and specialist should work in partnership but it is usually the GP, in consultation with the family, who stewards the child's educational management to assure that ongoing medical care is not undermined. The GP is more accessible to the family and can have a positive influence on the child's education and well-being.

Marked cognitive impairments in concentration and slowed processing of information make learning very challenging and exhausting. The speed of the teacher's speech may be a barrier to learning. Difficulty in processing information compounded by impaired ability to retain the information after making so much effort often results in feelings of failure. This causes anxiety and can lead to depression or school phobia.

Minimal physical and mental effort often results in relapse that may be delayed. The child has lost approximately 50 % or more of their pre-illness activity level due to pathophysiological exhaustion, etc. The Advice Line Records (UK) indicate that education is frequently the main source of relapse.[154]

Determine whether the patient is well enough and has the ability to benefit from education at this time. Unfortunately, the education to which all children are entitled may worsen their medical condition. Generally it is better to stop education until the child is stronger and his/her health has stabilized and then tutor at home. Children diagnosed with ME cannot maintain a full educational program.

Educational accommodations must be selected on an individual basis, according to the patient's health status, capabilities, and special educational needs, in order to provide the best opportunity for recovery.

Other Considerations

Pregnancy and raising a child requires very careful consideration for ME patients. Important issues include the patient's health, creating a healthy environment for the fetus, whether or not the patient has sufficient energy to nurture the child into adulthood, and opportunities for long-term assistance in the child's care.

Risks: ME is not inherited but research suggests a person can inherit a genetic susceptibility to ME.

Medications: Are they a risk to the fetus? • Can they be gradually stopped prior to pregnancy? • Avoid DHEA.

Pregnancy: frequent, small meals of optimum nutrition are essential • keep well hydrated • draining on iron and calcium • folic acid is advised • iodine supplement may be indicated • avoid stress • need extra rest • some patients feel better during pregnancy with the increased production of hormones

Lactation: Breast milk is best but babies can thrive on formula. When nursing, some medications must be avoided. If breast feeding, milk can be expressed so the partner can bottle feed if the patient needs to rest.

Nurturing baby & child: The responsibility and joy must be shared by both partners. Accept all help offered. *Pregnancy and raising a child are physically and emotionally draining, but also joyful and rewarding. The decision to have a child should be made jointly by the patient and partner. That decision must be respected.*

Surgery: Prior to surgery, alert the surgeon to important factors of ME: hypersensitivity to pharmaceuticals including anesthetics, low circulating blood volume, OI, NMH, low intracellular magnesium and potassium levels, rapid fatigability and elevated pain and fatigue levels. Ensure patients are well hydrated prior to surgery. Patients take longer to recover and may need extra time in the hospital.

Immunization: Live vaccine immunization is generally not recommended because of the weakened immune system plus risk of worsening symptoms and triggering relapses. Decisions regarding vaccinations must remain with the treating physician and patient. If immunization is chosen, it is recommended that injections are administered by the treating physician. Some clinicians have found it helpful to divide the dose into two to four mini doses, with each dose given a full month apart to ensure there are no delayed reactions.

Blood and Tissue Donations: The Red Cross and most countries stipulate that donors should be healthy. Therefore, ME patients should not donate blood or tissue. In addition, genetic blood testing and other tests suggest that some patients carry infectious agents in their blood. This is a potentially serious health issue.

Medical Documentation: Clinicians often are required to provide medical documentation regarding the severity of symptoms and level of functionality. Requirements vary from country to country and between policies. Check the wording of the policy. Generally, the following items need to be documented:

Medical history should include assessment by a clinician conversant on the ICC criteria, abnormal laboratory findings, objective physiology findings, severity of symptoms, duration of illness, responses to treatments, functionality and total illness burden.

Biomarkers & tests: Cardiopulmonary exercise test-retest, recorded by use of an electrocardiogram (ECG) can confirm many symptoms: PENE, decreased cerebral oxygen, prolonged recovery period, loss of capacity to recover from acidosis. There is significant peak oxygen consumption VO_2 or VO_2 at AT - *decline of 8% or greater on test 2 indicates metabolic dysfunction*. Brain scans support cognitive impairments. Refer to pathophysiology and laboratory assessment for further objective impairment markers.

Scales, patient diaries and questionnaires completed on first visit and then periodically are helpful.

Functional limitations: Consider physical, cognitive and emotional functional limitations, effects of unpredictability and fluctuation of symptom dynamics, lack of endurance, neurocognitive impairments, chronicity, and the cumulative effects of cognitive and physical fatigue. Describe how functional limitations affect ability to do ADL, instrumental ADL (e.g. housework), rehabilitative programs and work activities.

Prognosis is a clinical estimate. It is not possible to predict prognosis for an individual with certainty. Generally, the greater the severity of symptoms at onset, the poorer is the prognosis.

Provide medical opinion as to whether or not the patient is ready to return to work.

Exciting Research: More comprehensive approaches and new developments in research technology are advancing the understanding of clinical correlates. It is anticipated that research using patient sets selected by the ICC will elicit or confirm biopathological mechanisms and biomarkers that are specific to ME. The members of the International Consensus Panel wish to acknowledge the more than 50,000 patients they have diagnosed and/or treated and from whom they have gleaned much of the insight offered in this primer. The authors hope that clinicians will find this primer to be a helpful, user-friendly resource and that it will enhance clarity and consistency of diagnosis and efficacy of treatment world-wide.

REFERENCES

1. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas DG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumbarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, et al. **Myalgic encephalomyelitis: International Consensus Criteria.** *J Intern Med* 2011; **270:** 327-338. [PMID: 21777306] http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/pdf
2. Jason LA, Richman JA, Rademaker AW, et al**. A community-based study of Chronic Fatigue Syndrome.** *Arch Int Med* 1999; **159:** 2129-2137.
3. Lorusso L, Mikhaylova SV, et al. **Immunological aspects of chronic fatigue syndrome**. *Autoimmun Rev* 2009; **8**: 287-91. [PMID: 18801465]
4. Joyce J, Hotopf M, Wessely S. **The prognosis of chronic fatigue and chronic fatigue syndrome; a systematic review.** *QJ Med* 1997; **90:** 223-233.
5. Meeus M, Nijs J, McGregor N, Meeusen R, et al. **Unravelling intracellular immune dysfunctions in chronic fatigue syndrome: interactions between protein kinase R activity, RNase L cleavage and elastase activity, and their clinical relevance.** *In Vivo.* 2008; **22:** 115-21. [18396793]
6. Kaushik N, Fear D, Richards SC, McDermott CR, Nuwaysir EF, Kellam P, Harrison TJ, Wilkinson RJ, Tyrrell DA, Holgate ST, Kerr JR. **Gene expression in peripheral blood mononuclear cells from patients with chronic fatigue syndrome.** *J Clin Pathol* 2005; **58:** 826-832. [PMID: 16049284]
7. Aspler AL, Bolshin C, Vernon SD, Broderick G. **Evidence of inflammatory immune signalling in chronic fatigue syndrome: A pilot study of gene expression in peripheral blood.** *Behav Brain Funct* 2008; **4:** 44. [PMID: 18822143]
8. Falkenberg VR, Gurbaxani BM, Unger ER, Rajeevan MS. **Functional genomics of serotonin receptor 2A (HTR2A): interaction of polymorphism, methylation, expression and disease association.** *Neuromolecular Med* 2011; **13**: 66-76. [PMID: 20941551]
9. Carlo-Stella N, Bozzini S, De Silvestri A, et al. **Molecular study of receptor for advanced glycation end product gene promoter and identification of specific HLA haplotypes possibly involved in chronic fatigue syndrome.** *Int J Immunopathol Pharmacol* 2009; **22**: 745-54. [PMID: 19822091]
10. Goertzel BN, Pennachin C, de Souza Coelho L, Gurbaxani B, Maloney EM, Jones JF. **Combinations of single nucleotide polymorphisms in neuroendocrine effector and receptor genes predict chronic fatigue syndrome.** *Pharmacogenomics* 2006; **7**: 475-83. [PMID: 16610957]
11. Light AR, White AT, Hughen RW, Light KC. **Moderate exercise increases expression for sensory, adrenergic and immune genes in chronic fatigue syndrome patients but not in normal subjects.** *J Pain* 2009; **10**: 1099-112. [PMID: 19647494]
12. Kerr JR, Petty R, Burke B, Gough J, Fear D, et al. **Gene expression subtypes in patients with chronic fatigue syndrome/ myalgic encephalomyelitis.** *J Infect Dis* 2008; **197:** 1171-84. [PMID: 18462164]
13. Kerr JR, Burke B, Petty R, Gough J, Fear D, et al. **Seven genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis: a detailed analysis of gene networks and clinical phenotypes.** *J Clin Pathol* 2008; **61:** 730-9. [PMID: 18057078]
14. Albright F, Light K, Light A, et al. **Evidence for a heritable predisposition of Chronic Fatigue Syndrome.** *BMC Neurol* 2011;11:62. [PMID: 21619629]
15. Sullivan PF, Evengård B, et al. **Twin analyses of chronic fatigue in a Swedish national sample**. *Psychol Med* 2005; 35: 1327-36. [PMID: 16168155]
16. Hyde B. **The Clinical and Scientific Basis for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome**. Nightingale Research Foundation. 1992 p. 172-86.
17. Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, et al. **Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols**. *J Chronic Fatigue Syndr* 2003; **11:** 7-115.
18. Carruthers BM, van de Sande MI. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: **A Clinical Case Definition and Guidelines form Medical Practitioners. An Overview of the Canadian Consensus Document.** Carruthers & van de Sande 2005/6.
19. Stewart CC, Cookfair DL, Hovey KM, Wende KE, Bell DS, Warner CL. **Predictive immunophenotypes: Disease-related profile in chronic fatigue syndrome.** *Cytometry B Clin Cytom* 2003; **53:** 26-33. [PMID: 12717688]
20. De Meirleir K, De Becker P, Campine I. **Blood transfusion and chronic fatigue syndrome.** Abstract. *CFS Conference, Sydney, Australia*, 1999.
21. Bell IR, Baldwin CM, Schwartz GE. **Illness from low levels of environmental chemical: relevance to chronic fatigue syndrome and fibromyalgia.** *Am J Med* 1998; **105**(3A): 74S-82S. [PMID: 9790486]
22. Fernándes-Solà J, Lluis Padierna M, Norgué Xarau S, Munné Maes P. **Chronic fatigue syndrome and multiple chemical hypersensitivity after insecticide exposition.** *Med Clin (Barc).* 2005; **124:** 451-3. [PMID: 15826581]
23. Goldberg B. **Chronic Fatigue, Fibromyalgia & Environmental Illness.** *Future Medicine Publishing, Inc., Tiburon, CA.* 1998; pp 190-211.
24. Chia J, Chia A, Voeller M, Lee T, Chang R. **Acute enterovirus infection followed by myalgia encephalomyelitis/chronic fatigue syndrome and viral persistence.** *J Clin Pathol* 2010; **63**: 165-8. [PMID: 19828908]
25. Chia JK. **The role of enterovirus in chronic fatigue syndrome.** *J Clin Pathol* 2005; **58:** 1126-32. [PMID: 16254097]
26. Chia JK, Chia AY. **Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach.** *J Clin Pathol* 2008;**61**:43-48. [17872383]
27. Zang L, Gough J, Christmas D, Mattey DL, Richards SC, Main J, Enlander D, Honeybourne D, Ayres JG, Nutt DJ, Kerr JR. **Microbial infections in eight genomic subtypes of chronic fatigue syndrome myalgic encephalomyelitis.** *J Clin Pathol* 2010; **63:** 156-64. [PMID: 19955554]
28. Ablashi DV, Eastman HB, Owen CB, Roman MM, Friedman J, Zabriskie JB, Peterson DL, et al. **Frequent HHV-6 antibody and HHV-6 reactivation in multiple sclerosis (MS) and chronic fatigue syndrome (CFS) patients.** *J Clin Virol* 2000; **16:** 179-91. [PMID: 10738137]
29. Chapenko S, Krumina A, Kozireva S, Nora Z, Sultanova A, Viksna L, Murovska M**. Activation of human herpesviruses 6 and 7 in patients with chronic fatigue syndrome.** *J Clin Virol* 2006; **37** Suppl 1: S47-S51. [PMID: 17276369]
30. Beqaj SH, Lerner AM, Fitzgerald JD. **Immunoassay with cytomegalovirus early antigens from gene products P52 and CM 2 (UL44 and UL 57) detects active infection in patients with chronic fatigue syndrome.** *J Clin Pathol* 2008; **61:** 623-6. [PMID: 18037660]
31. Kerr JR, Cunniffe VS, Kelleher P, Bernstein RM, Bruce IN. **Successful intravenous immunoglobulin therapy in 3 cases of parvovirus B19-associated chronic fatigue syndrome.** *Clin Infect Dis* 2003; **36:** e100-6. [PMID: 12715326]
32. Chia JK, Chia LY. **Chronic Chlamydia pneumonia infection: a treatable cause of chronic fatigue syndrome**. *Clin Infect Dis* 1999; **29**:452-3. [10476765]
33. Nicolson GL, Gan R, Haier J. **Multiple co-infections (Mycoplasma, Chlamydia, human herpes virus-6) in blood of chronic fatigue syndrome patients: association with signs and symptoms.** *APMIS* 2003; **111**: 557-66. [PMID: 12887507]
34. Hickie I, & the Dubbo Infection Outcomes Study Group**. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study.** *BMJ* 2006; **333** (7568): 575. [PMID: 16950834]
35. Broderick G, Fuite J, et al. **A formal analysis of cytokine networks in chronic fatigue syndrome.** *Brain Behav Immun* 2010; **24:** 1209-17. [20447453]
36. Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P, Ferlin G**. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data.** *Amer J Med* 1998; **105**(3A): 54S-58S. [PMID: 9790483]
37. De Lange F, Kalkman J, et al. **Gray matter volume reduction in the chronic fatigue syndrome.** *Neuroimage* 2005; **26:** 777-81. [PMID: 15955487]
38. Myhill S, Booth NE, McLaren-Howard J. **Chronic fatigue syndrome and mitochondrial dysfunction.** *Int J Clin Exp Med* 2009;**2:**1-16. [PMID: 19436827]
39. VanNess JM, Snell CR, Stevens SR. **Diminished cardiopulmonary capacity during post-exertional malaise.** *J Chronic Fatigue Syndr* 2007; **14:** 77-85.

40. Van Oosterwijck J, Nijs J, Meeus M, Lefever I, Huybrechts L, et al**. Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome; an experimental study.** *J Intern Med* 2010; **268:** 265-78. [PMID: 20412374]
41. Light AR, Bateman L, Jo D, Hughen RW, Vanhaitsma TA, White AT, Light KC. **Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome, and Fibromyalgia Syndrome.** *J Intern Med* 2012; **271:** 64-81. [PMID: 21615807]
42. De Becker P, Roeykens J, Reynders M, et al**. Exercise capacity in chronic fatigue syndrome.** *Arch Intern Med* 2000;**160**:3270-77. [PMID: 11088089]
43. Inbar O, Dlin R, Rotstein A, Whipp BJ**. Physiological responses to incremental exercise in patients with chronic fatigue syndrome.** *Med Sci Sports Exerc* 2001; **33:** 1463-70. [PMID: 11528333]
44. VanNess JM, Snell CF, et al. **Subclassifying chronic fatigue syndrome using exercise testing.** *Med Sci Sports Exerc* 2003;**35**:908-13.[12783037]
45. Jones DE, Hollingsworth KG, Jakovljevic DG, Fattakhova G, Pairman J, Blamire AM, Trenell MI, Newton JL**. Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study.** *Eur J Clin Invest* 2012; **42:** 186-94.. [PMID: 21749371]
46. Yoshiuchi K, Farkas I, Natelson BH. **Patients with chronic fatigue syndrome have reduced absolute cortical blood flow**. *Clin Physiol Funct Imaging* 2006; **26:** 83-6. [PMID: 16494597]
47. Goldstein JA. **Chronic Fatigue Syndrome: The Limbic Hypothesis**. Binghamptom, New York: Haworth Medical Press 1993; **19:** 116.
48. Streeten DH**. Role of impaired lower-limb venous innervation in the pathogenesis of the chronic fatigue syndrome.** *Am J Med Sci* 2001;**321:**163-7.
49. Farquhar WB, Hunt BE, Taylor JA, Darling SE, Freeman R. **Blood volume and its relation to peak O2 consumption and physical activity in patients with chronic fatigue.** *Am J Physiol Heart Circ Physiol* 2002; **282:** H66-71. [PMID: 11748048]
50. Jammes Y, Steinberg JG, Mambrini O, Brégeon F, Delliaux S. **Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise.** *J Intern Med* 2005; **257**: 299-310. [PMID: 15715687]
51. Peckerman A, La Manca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH. **Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome.** *Am J Med Sci* 2003; **326**: 55-60. [PMID: 12920435]
52. Neary PJ, Roberts AD, Leavins N, Harrison MF, Croll JC, Sexsmith JR. **Prefrontal cortex oxygenation during incremental exercise in chronic fatigue syndrome.** *Clin Physiol Funct Imaging* 2008; **28:** 364-72. [PMID: 18671793]
53. Streeten DH, Thomas D, Bell DS. **The roles of orthostatic hypotension, orthostatic tachycardia and subnormal erythrocyte volume in the pathogenesis of the chronic fatigue syndrome.** *Am J Med* 2000; **320**: 1-8. [PMID: 10910366]
54. de Lange FP, Kalkman JS, et al. **Gray matter volume reduction in chronic fatigue syndrome.** *NeuroImage* 2005; **26**: 777-781. [PMID: 15955487]
55. Vermeulen RCW, Kurk RM, Visser FC, Sluiter W, Scholte HR. **Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity.** *J Transl Med* 2010; **8:** 93. [PMID: 20937116]
56. Boda WL, Natelson BH, Sisto SA, Tapp WN. **Gait abnormalities in chronic fatigue syndrome.** *J Neurol Sci* 1995; **131**: 156-161. [PMID: 7595641]
57. Demitract MA, Crofford LJ. **Evidence for and pathophysiologic implications of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome.** *Ann NY Acad Sci* 1998; **840:** 684-97. [PMID: 9629295]
58. White AT, Light AR, Hughen RW, et al. **Differences in metabolite-detecting, adrenergic, and immune gene expression after moderate exercise in patients with chronic fatigue syndrome, patients with multiple sclerosis, and healthy controls.** *Psychosom Med*. 2012;**74:**46-54. [22210239]
59. White AT, Light AR, Hughen RW, Bateman L, Martins TB, Hill HR, Light KC. **Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome.** *Psychophysiol* 2010; **47:** 615-24. [PMID: 20230500]
60. Fletcher MA, Zeng XR, Barnes Z, Levis S, Klimas NG. **Plasma cytokines in women with chronic fatigue syndrome.** *J Transl Med* 2009;**7**:96. [PMID: 19909538]
61. Broderick G, Craddock RC, Whistler T, Taylor R, Klimas N, Unger ER. **Identifying illness parameters in fatiguing syndromes using classical projection methods.** *Pharmacogenomics.* 2006; **7**: 407-19. [PMID: 16610951]
62. Maes M, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. **Increased plasma peroxides as a marker of oxidative stress in myalgic encephalomyelitis/chronic fatigue syndrome** (ME/CFS). Med Sci Monit 2011; **17:** SC11-5. [PMID: 21455120]
63. Suárez A, Guillamó E, Roig T, Blázquez A, Alegre J, Bermúdez J, Ventura JL, García-Quintana AM, Comella A, et al. **Nitric oxide metabolite production during exercise in chronic fatigue syndrome: a case-control study.** *J Womens Health (Larchmt)* 2010; 19: 1073-7. [PMID: 20469961]
64. Wong R, Lopaschuk G, Zhu G, Walker D, Catellier D, Burton D, Teo K, Collins-Nakai R, Montague T. **Skeletal muscle metabolism in the chronic fatigue syndrome. In vivo assessment by 31P nuclear magnetic resonance spectroscopy**. *Chest.* 1992; **102:** 1716-22. [PMID: 1446478]
65. Meeus M, Roussel NA, Truijen S, Nijs J**. Reduced Pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study.** *J Rehabil Med* 2010; **42:** 884-90. [PMID: 2087801]
66. Whiteside A, Hansen S, Chaudhuri A. **Exercise lowers pain threshold in chronic fatigue syndrome.** *Pain* 2004; **109:** 497-99. [PMID: 15157711]
67. Nijs J, Meeus M, McGregor NR, Meeusen R, de Schutter G, van Hoof E, De Meirleir K. **Chronic fatigue syndrome: exercise performance related to immune dysfunction.** *Med Sci Sports Exerc* 2005; **37:** 1647-54. [PMID: 16260962]
68. Chaudhuri A, Behan PO. **In vivo magnetic resonance spectroscopy in chronic fatigue syndrome.** Prostaglandins Leukot Essent Fatty Acids. 2004; **71**: 181-3. [PMID: 15253888]
69. Jones DE, Hollingsworth KG, Taylor R, Blamire AM, Newton JL**. Abnormalities in pH handling by peripheral muscle and potential regulation by the autonomic nervous system in chronic fatigue syndrome.** *J Intern Med* 2010; **267:** 394-401. [PMID: 20433583]
70. VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. **Postexertional malaise in women with chronic fatigue syndrome.** *J Womens Health (Larchmt)* 2010; **19:** 239-244. [PMID: 20095909]
71. La Manca JJ, Sisto SA, DeLuca J, Johnson SK, Lange G, Pareja J, Cook S, Natelson BH. **Influence of exhaustive treadmill exercise on cognitive functioning in chronic fatigue syndrome.** *Am J Med* 1998; **105:** 59S-65S. [PMID: 9790484]
72. Wallman KE, Morton AR, Goodman C, Grove R. **Physiological responses during a submaximal cycle test in chronic fatigue syndrome.** *Med Sci Sports Exerc* 2004; **36:** 1682-8. [PMID: 15595287]
73. Lange G, Steffener J, Cook DB, Bly BM, Christodoulou C, Liu WC, Deluca J, Natelson BH. **Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: a BOLD fMRI study of verbal working memory.** *Neuroimage* 2005; **26:** 513-24. [PMID: 15907308]
74. Michiels V, Cluydts R, Fischler B. **Attention and verbal learning in patients with chronic fatigue syndrome.** *J Int Neuropsychol Soc* 1998; 4: 456-66.
75. Chen R, Liang FX, Moriay J, et al. **Chronic fatigue syndrome and the central nervous system.** *J Int Med Res* 2008; 36: 867-74. [PMID: 18831878]
76. Barnden LR, Crouch B, Kwiatek R, Burnet R, Mernone A, Chryssidis S, Scroop G, Del Fante P**. A brain MRI study of chronic fatigue syndrome: evidence of brainstem dysfunction and altered homeostasis.** *NMr Biomed* 2011; **24:** 1302-12. [PMID: 21560176]
77. Cook DB, O'Connor PJ, Lange G, Steffener J. **Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls.** *Neuroimage* 2007; **36:** 108–22. [PMID: 17408973]
78. Flor-Henry P, Lind JC, Koles ZJ. **EEG source analysis of chronic fatigue syndrome.** *Psychiatry Res* 2010; **181:** 155-64. [PMID: 20006474]

79. Van Hoof E, De Becker P, Lapp C, et al. **Defining the occurrence and influence of alph-delta sleep in chronic fatigue syndrome.** *Am J Med Sci* 2007; **333:** 78-84. [PMID: 17301585]
80. Mena I, Villanueva-Meyer J. **Study of Cerebral Perfusion by NeuroSPECT in Patients with Chronic Fatigue Syndrome.** In: Hyde BM, Goldstein J, Levine P, eds. *The Clinical and Scientific Basis of Myalgic Encephalomyelitis, Chronic Fatigue Syndrome.* Ottawa, Ontario & Ogdensburg, New York State: The Nightingale Research Foundation; 1992: 432-8.
81. Goldstein JA, Mena I, Jouanne E, Lesser I. **The assessment of vascular abnormalities in late life chronic fatigue syndrome by brain SPECT: Comparison with late life major depressive disorder**. *J CFS* 1995; **1:** 55-79.
82. Goldberg MJ, Mena I, Darcourt J. **NeuroSPECT finding in children with chronic fatigue syndrome.** *J CFS* 1996; **3:** 61-67.
83. Costa DC, Tannock C, Brostoff J**. Brainstem perfusion is impaired in chronic fatigue syndrome**. *QJM* 1995; **88:** 767-773. [PMID: 8542261]
84. Ichise M, Salit I, Abbey S, Chung DG, Gray B, Kirsh JC, Freedman M. **Assessment of regional cerebral perfusion by Tcm-HMPAO SPECT in chronic fatigue syndrome.** *Nucl Med Commun* 1992; **13:** 767-772. [PMID: 1491843]
85. Biswal B, Kunwar P, Natelson BH. **Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling.** *J Neurol Sci*. 2011; **301:** 9-11. [PMID: 21167506]
86. Lange G, Wang S, Deluca J, Natelson BH. **Neuroimaging in chronic fatigue syndrome.** *Am J Med* 1998; **105:** 50S-53S. [PMID: 9790482]
87. Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpes virus type 6 infection. *Ann Intern Med* 1992; **116:** 103-113. [PMID: 1309285]
88. Puri BK, Jakeman PM, Aqour M, Gunatilake KD, Fernando KA, et al. **Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3 T MRI study.** *Br J Radiol* 2012; **85:** e270-3. [PMID: 22128128]
89. Okada T, Tanaka M, Kuratsune H, Watanabe Y, Sadato N. **Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome.** *BMC Neurol* 2004; **4:** 14. [PMID: 15461817]
90. Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue GH**. Altered central nervous system signal during motor performance in chronic fatigue syndrome.** *Clin Neurophysiol*. 2004; **115:** 2372-81. [PMID: 15351380]
91. Saggini R, Pizzigallo E, Vecchiet J, Macellari V, Giacomozzi C. **Alterations of spatial-temporal parameters of gait in Chronic Fatigue Syndrome patients**. *J Neurol Sci* 1998; **154:** 18-25. [PMID: 9543318]
92. Togo F, Natelson BH, Cherniack NS, FitzGibbons J, Garcon C, Rapoport DM. **Sleep structure and sleepiness in chronic fatigue syndrome with or without coexisting fibromyalgia.** *Arthritis Res Ther* 2008; **10:** R56. [PMID: 18474105]
93. Kishi A, Struzik ZR, Natelson BH, Togo F, Yamamoto Y. **Dynamics of sleep stage transitions in healthy humans and patients with chronic fatigue syndrome.** *Am J Physiol Regul Integr Comp Physiol* 2008; **294:** R1980-7. [PMID: 18417644]
94. Schutzer SE, Angel TE, Liu T, Schepmoes AA, Clauss TR, Adkins JN, Camp DG, Holland BK, et al. **Distinct cerebrospinal fluid proteomes differentiate post-treatment lyme disease from chronic fatigue syndrome.** *PLoS ONE* 2011; **6:** e17287**.** [PMID: 21383843]
95. Natelson BH, Weaver SA, Tseng CL, Ottenweller JE. **Spinal fluid abnormalities in patients with chronic fatigue syndrome.** *Clin Diagn Lab Immunol* 2005; **12:** 52-5. [PMID: 15642984]
96. Mathew SJ, Mao X, Keegan KA, Levine SM, Smith EL, et al. **Ventricular cerebrospinal fluid lactate is increased in chronic fatigue syndrome compared with generalized anxiety disorder: an in vivo 3.0 T (1)H MRS imaging study.** *NMR Biomed* 2009; **22:** 251-8. [PMID: 18942064]
97. Chaudhuri A. Abstract presentation at the Royal Society of Medicine Meeting 2009.
98. Brenu EW, Staines DR, Baskurt OK, Ashton KJ, Ramos SB, Christy RM, Marshall-Gradisnik SM. **Immune and hemorheological changes in chronic fatigue syndrome.** *J Transl Med* 2010; **8;** 1. [PMID: 20064266]
99. Brenu EW, van Driel ML, Staines DR, Ashton KJ, Hardcastle SL, Keane J, et al. **Longitudinal investigation of natural killer cells and cytokines in chronic fatigue syndrome/myalgic encephalomyelitis.** *J Transl Med* 2012; **10:** 88. [Epub ahead of print] [PMID: 22571715]
100. Landay AL, Jessop C, et al**. Chronic fatigue syndrome: clinical condition associated with immune activation**. *Lancet* 1991; **338:** 707-12.
101. Cameron B, Hirschberg DL, et al. **Serum cytokine levels in post-infective fatigue syndrome.** *Clin Infect Dis* 2010; **50:** 278-9. [PMID: 20034348]
102. Klimas NG, Salvato FR, Morgan R, et al. **Immunologic abnormalities in chronic fatigue syndrome**. *J Clin Microbiol* 1990; **28:** 1403-10. [2166084]
103. Fletcher MA, Maher K, Patarca-Montero R, Klimas N. **Comparative analysis of lymphocytes in lymph nodes and peripheral blood of patients with chronic fatigue syndrome.** *J CFS* 2000; **7:** 65-76.
104. Klimas NG, Koneru AO. **Chronic fatigue syndrome: inflammation, immune function, and neuroendocrine interactions.** *Curr Rheumatol Rep* 2007; **9:** 482-7. [PMID: 18177602]
105. Fluge Ø, Bruland O, Risa K, Storstein A, et al. **Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study.** *PLoS One.* 2011; **6:** e26358. Epub 2011 Oct 19. [PMID: 22039471]
106. Bennett AL, Choa CC, Hu S, Buchwald D, Fagioli LR, Schur PH, Peterson PK, Komaroff AL**. Elevation of bioactive transforming growth factor-beta in serum from patients with chronic fatigue syndrome.** *J Clin Immunol* 1997; **17:** 160-6. [PMID: 9083892]
107. Chapenko S, Krumina A, Logina I, Rasa S, Chistjakovs M, et al. **Association of active human herpesvirus-6, -7 and parvovirus b19 infection with clinical outcomes in patients with myalgic encephalomyelitis/chronic fatigue syndrome**. *Adv Virol.* 2012;2012:205085. [PubMed: 22927850]
108. Roelant C, De Meirleir K**. Self-test monitoring of the Th1/Th2 balance in health and disease with special emphasis on chronic fatigue syndrome/myalgic encephalomyelitis.** *J Med Lab Diagnosis* 2012; **3:** 1-6.
109. Fletcher MA, Zeng XR, Maher K, Lewis S, Hurwitz B, Antoni M, Broderick G, Klimas NG. Biomarkers in chronic fatigue syndrome: Evaluation of natural killer cell function and dipeptyl peptidase IV/CD26. *PLoS ONE* 2010; 5: e10817. [PMID: 20520837]
110. Torres-Harding S, Sorenson M, Jason LA, Maher K, Fletcher MA. **Evidence for T-helper 2 shift and association with illness parameters in chronic fatigue syndrome (CFS).** *Bull IACFS* 2008; **16:** 19-33. [PMID: 21234277]
111. Maes M, Mihaylova I, De Ruyter M. **Decreased dehydroepiandrosterone sulphate but normal insulin-like growth factor in chronic fatigue syndrome (CFS): relevance for the inflammatory response in CFS.** *Neuro Endocrinol Lett* 2005; **26:** 487-92. [PMID: 16264414]
112. De Meirleir K, Bisbal C, Campine I, De Becker P, Salehzada T, Demettre E, Lebleu B. **A 37 kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome.** *Am J Med* 2000; **108:** 99-105. [PMID: 11126321]
113. Suhadolnik RJ, Peterson DL, O'Brien K, Cheney PR, Herst CVT, et al**. Biochemical evidence for a novel low molecular weight 2-5A-dependent RNase L in chronic fatigue syndrome.** *J Interferon Cytokine Res* 1997; **17:** 377-85. [PMID : 9243369]
114. Maes M, Twisk FN. **Why myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) may kill you: disorders in the inflammatory and oxidative and nitrosative stress (IO&NS) pathways may explain cardiovascular disorders in ME/CFS.** *Neuro Endocrinol Lett* 2009; **30:** 667-93. [20038921]
115. Brenu EW, van Driel ML, Staines DR, Ashton KJ, Ramos SB, Keane J, Klimas NG, Marshall-Gradisnik SM. **Immunological abnormalities as potential biomarkers in Chronic Fatigue/Myalgic Encephalomyelitis**. *J Transl Med* 2011; **9:** 81. [PMID: 21619669]

116. Broderick G, Katz BZ, Fernandes H, Fletcher MA, Klimas NG, Smith FA, O'Gorman MR, Vernon SD, Taylor R. **Cytokine expression profiles of immune imbalance in post-mononucleosis chronic fatigue.** *J Transl Med* 2012; **10:** 191. [PMID: 22973830]
117. Sheedy JR, Wettenhall RE, Scanion D, Gooley PR, Lewis DP, McGregor N, Stapleton DI, Butt HL, De Meirleir KL. **Increased D-lactic acid intestinal bacteria in patients with chronic fatigue syndrome.** *In Vivo* 2009; **23:** 621-8. [PMID: 19567398]
118. Pall ML**. Explaining "unexplained Illnesses": Disease Paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitives, Fibromalgia, Post-Traumatic Stess Disorder, Gulf War Syndrome and Others.** Bighamton, NY: Harrington Park (Haworth) Press, 2007.
119. Pall ML, Satterlee JD. **Elevated nitric oxide/peroxynitrite mechanism for the common etiology of Multiple Chemical Sensitivity, Fibromyalgia, Post-Traumatic Stress Disorder, Gulf War Syndrome and Others.** Binghamton, NY: Harrington Park (Haworth) Press, 2007.
120. Hollingsworth KG, Jones DE, Taylor R, Blamire AM, Newton JL, et al. **Impaired cardiovascular response to standing in chronic fatigue syndrome.** *Eur J Clin Invest* 2010; **40:** 608-15. [PMID: 20497461]
121. Costigan A, Elliott C, McDonald C, Newton JL. **Orthostatic symptoms predict functional capacity in chronic fatigue syndrome: implications for management.** *QJM* 1010; **103:** 589-95. [PMID: 20534655]
122. Pieczenik SR, Neustadt J**. Mitochondrial dysfunction and molecular pathways of disease.** *Exp Mol Pathol* 2007; **83:** 84-92. [PMID: 17239370]
123. Behan WM, More IA, Behan PO. **Mitochondrial abnormalities in the postviral fatigue syndrome.** *Acta Neuropathol* 1991; **83:** 61-5. [1792865]
124. Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. *Int J clin Exp Med* 2009; **2:** 1-16. [19436827]
125. Kurup RK, Kurup PA. Hypothalamic digoxin, cerebral chemical dominance and myalgic encephalomyelitis. *Int J Neurosci* 2003;**133:**683-701.
126. Booth NE, Myhill S, McLaren-Howard J. **Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).** *Int J Clin Exp Med* 2012; **5:** 208-20. [PMID: 22837795]
127. Miwa K, Fujita M. **Fluctuation of serum vitamin E (α-tocopherol) concentrations during exacerbation and remission phases in patients with chronic fatigue syndrome**. *Heart Vessels*. 2010; **25:** 319-23. [PMID: 20676841]
128. Richards RS, Wang L, Jelinck H. **Erythrocyte oxidative damage in chronic fatigue syndrome**. *Arch Med Res* 2007; **38:** 94-8. [PMID: 17174731]
129. Nijs J, De Meirleir K, Meeus M, McGregor NR, Englebienne P. **Chronic fatigue syndrome: intracellular immune deregulations as a possible etiology for abnormal exercise response.** *Med Hypotheses* 2004; **62:** 759-65. [PMID: 15082102]
130. Chaudhuri A, Watson WS, Pearn J, Behan PO. **The symptoms of chronic fatigue syndrome are related to abnormal ion channel function**. *Med Hypotheses* 2000; **54:** 59-63. [PMID: 10790725]
131. Pall ML. **Elevated sustained peroxynitrite levels as the cause of chronic fatigue syndrome.** *Med Hypotheses* 2000; **54:** 115-25. [PMID: 10790736]
132. Newton JL, Sheth A, Shin J, Pairman J, Wilton K, Burt JA, Jones DE. **Lower ambulatory blood pressure in chronic fatigue syndrome.** *Psychosom Med* 2009; **71:** 361-5. [PMID: 19297309]
133. Spence VA, Khan F, Kennedy G, Abbot NC, Belch JJ. **Acetylcholine medicated vasodilation in the microcirculation or patients with chronic fatigue syndrome.** *Prostaglandins Leukot Essent Fatty Acids* 2004; **70:** 403-7. [PMID: 15041034]
134. Spence VA, Kennedy G, Belch JJ, Hill A, Khan F. **Low-grade inflammation and arterial wave reflection in patients with chronic fatigue syndrome.** *Clin Sci (Lond).* 2008; **114:** 561-6. [PMID: 18031285]
135. Miwa K, Fujita M. **Cardiac function fluctuates during exacerbation and remission in young adults with chronic fatigue syndrome and "small heart".** *J Cardiol* 2009; **54:** 29-35. [PMID: 19632517]
136. Miwa K, Fujita M**. Small heart syndrome in patients with chronic fatigue syndrome.** *Clin Cardiol* 2008; **31:** 328-33. [PMID: 18636530]
137. Peckerman A, LaManca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH. **Abnormal impedance cardiography predicts symptom severity in Chronic Fatigue Syndrome.** *Am J Med Sci* 2003; **326**: 55-60. [PMID: 12920435]
138. Lerner AM, Lawrie C, Dworkin HS. **Repetitively negative changing T waves at 24-h electrocardiographic monitors in patients with the chronic fatigue syndrome.** Left ventricular dysfunction in a cohort. *Chest* 1993; **104:** 1417-21. [PMID: 8222798]
139. Miwa K, Fujita M. **Small heart with low cardiac output for orthostatic intolerance in patients with chronic fatigue syndrome**. *Clin Cardio* 2011; **34:** 782-6. [PMID: 22120591]
140. Burton AR, Rahman K, Kadota Y, Lloyd A, Vollmer-Conna U**. Reduced heart rate variability predicts poor sleep quality in case-control study of chronic fatigue syndrome.** *Exp Brain Res* 2010; **204:** 71-8. [PMID: 20502886]
141. Rowe KS, Rowe KJ. **Symptom patterns of children and adolescents with chronic fatigue syndrome.** In N.N. Singh, T.H. Ollendick & A.N Singh (Eds.) *Intern Perspect Child Adolesc Men Health*. Elsevier Science Ltd: Oxford. 2002; **2:** 395-421.
142. Wyller VB, Godang K, Mørkrid L, Saul JP, Thaulow E, Walløe L**. Abnormal thermoregulatory responses in adolescents with chronic fatigue syndrome: relation to clinical symptoms.** *Pediatrics* 2007; **120:** e129-37. [PMID: 17606539]
143. De Becker P, McGregor N, De Meirleir K. **A definition–based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome.** *J Intern Med* 2001; **250:** 234-240. [PMID: 11555128]
144. Vernon S. **Symptom Survey Responses Indicate Cardinal Symptoms of CFS.** http://www.cfids.org/cfidslink/2009/090202.asp
145. Jason LA, Helgerson J, Torres-Harding SR, Carrico AW Taylor RR. **Variability in diagnostic criteria for chronic fatigue syndrome may result in substantial differences in patterns of symptoms and disability**. *Eval Health Prof* 2003; **26:** 3-22. [PMID: 12629919]
146. Jason LA, Taylor RR, Kennedy CL, et al. **A factor analysis of chronic fatigue symptoms in a community-based sample**. *Soc Psychiatry Psychiatr Epidemiol.* 2002; **37**: 183-189. [PMID: 12027245]
147. Dowsett EG, Goudsmit EM, Macintyre A, Shepherd C. **London criteria for Myalgic Encephalomyelitis.** In: Report from the National Task Force on Chronic Fatigue Syndrome (CFS), Post Viral Fatigue Syndrome (PVFS), Myalgic Encephalomyelitis (ME). *Westcare* 1994; pp96-98.
148. Lloyd AR, Hickie I, Boughton CF, Spencer O, Wakefield D**. Prevalence of chronic fatigue syndrome in an Australian population.** *Med J Australia* 1990; **153:** 522-528. [PMID: 2233474]
149. Goudsmit E, Shepherd C, Dancey CP, Howes S**. ME, Chronic Fatigue Syndrome or a distinct clinical entity?** *Health Psychol Update* 2009;**18:**26-31.
150. Jason LA, Torres-Harding SR, Jurgens A, Helgerson J. **Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome.** *J Chronic Fatigue Syndr* 2004*;* ***12*****:** 37-52.
151. Vasey C. ***The Acid-Alkaline Diet for Optimum Health.*** Rochester, Vermont: Healing Arts Press, 1999.
152. Werbach MR. Nutritional strategies for treating chronic fatigue syndrome. Altern Med Rev 2000; **5:** 93-108. [PMID: 10767667]
153. Wilbur J, Shaver J, Kogan J, Buntin M, Wang E. **Menopausal transition symptoms in midlife women living with fibromyalgia and chronic fatigue.** *Health Care Women Int* 2006; **27**: 600-14. [PMID: 16844673]
154. Colby J. **The GPs Good Practice Guide to Education for Children with ME.** http://www.tymestrust.org

Appendix 1: Myalgic Encephalomyelitis: INTERNATIONAL CONSENSUS CRITERIA (ICC) Short Form

Adult and Pediatric ● Clinical and Research

Compulsory	***Post-Exertional Neuroimmune Exhaustion** (A)*
3	***Neurological :** 1 symptom from 3 symptom categories (B)*
3	***Immune/gastro-intestinal/genitourinary :** 1 symptom from 3 symptom categories (C)*
1	***Energy metabolism/ion transportion :** 1 symptom (D)*

___ **A. Post-Exertional Neuroimmune Exhaustion (PENE pen'-e) Compulsory Characteristics are:**

1. **Marked, rapid physical and/or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse.**
2. **Post-exertional symptom exacerbation: Post-exertional exhaustion may occur immediately after activity or be delayed by hours or days.**
3. **Prolonged recovery period, usually 24 hours or longer. A relapse can last days, weeks or longer.**
4. **Low threshold of physical and mental fatigability (lack of stamina) results in a substantial (approximately 50%) reduction in pre-illness activity level.**

___ **B. Neurological Impairments: At least One Symptom from three of the following four symptom categories**

___ **1. Neurocognitive Impairments**

- **Difficulty processing information: slowed thought, impaired concentration:** *slowed speech*
- **Short-term memory loss:** *poor working memory, difficulty remembering what one wants to say, etc.*

___ **2. Pain**

- **Headaches:** *chronic, generalized headaches associated with cervical muscle tension, migraines*
- **Significant pain in muscles, muscle-tendon junctions, joints, abdomen or chest:** *hyperalgesia*

___ **3. Sleep Disturbance**

- **Disturbed sleep patterns:** *hypersomnia, sleep reversal, frequent awakenings, vivid dreams*
- **Unrefreshed sleep:** *awaken feeling unrefreshed regardless of duration of sleep, day-time sleepiness*

___ **4. Neurosensory, Perceptual and Motor Disturbances**

- **Neurosensory hypersensitivity**, *inability to focus vision; impaired depth perception*
- **Motor:** *muscle weakness, poor coordination, feeling unsteady on feet, ataxia*

___ **C. Immune, Gastro-intestinal & Genitourinary Impairments**

At least One Symptom from three of the following five symptom categories

___ **1. Flu-like symptoms may be recurrent or chronic and typically activate or worsen with exertion.**
___ **2. Susceptibility to viral infections with prolonged recovery periods**
___ **3. Gastro-intestinal tract symptoms:** *nausea, bloating, irritable bowel syndrome*
___ **4. Genitourinary:** *urinary urgency or frequency, nocturia*
___ **5. Sensitivities to food medications odors or chemicals:** *food, chemicals, odours, medications, alcohol*

___ **D. Energy Production/Ion Transportation Impairments: At least One Symptom**

___ **1. Cardiovascular:** *orthostatic intolerance, palpitations with or without cardiac arrhythmias, dizziness*
___ **2. Respiratory:** *air hunger, laboured breathing, or fatigue of chest wall muscles*
___ **3. Loss of thermostatic stability:** *marked diurnal fluctuations, sweating episodes, cold extremities*
___ **4. Intolerance of extremes of temperature**

Classification: ____ Myalgic Encephalomyelitis

____ Atypical Myalgic Encephalomyelitis: meets criteria for PENE but has two or less than required of the remaining criterial symptoms. Pain or sleep disturbance may be absent in rare cases.

Differential Diagnosis: When indicated on an individual basis, rule out other diseases that could plausibly simulate the widespread, complex, symptom pathophysiology defining ME. E.g.: **Infectious disorders**: TB, AIDS, Lyme, chronic hepatitis, endocrine gland infections; **Neurological:** MS, myasthenia gravis, B12; **Autoimmune disorders**: polymyositis & polymyalgia rheumatica, rheumatoid arthritis; **Endocrine:** Addison's, hypo & hyper thyroidism, Cushing's Syndrome; **cancers**; **anemias**: iron deficiency, B12/megaloblastic; **diabetes mellitus; poisons**

Exclusions: Primary psychiatric disorders, somatoform disorder, substance abuse and paediatric 'primary' school phobia.

Comorbid Entities: Myofascial Pain Syndrome, TMJ, interstitial cystitis, Raynaud's phenomenon, prolapsed mitral valve, Irritable Bladder Syndrome, prolapsed mitral valve, Hashimoto's thyroiditis, Sicca Syndrome, secondary depression, allergies, MCS, etc. FMS is considered an overlap syndrome. IBS and migraine may precede ME and then become associated with it.

Appendix 2: Sleep and Pain Profile

Name: Date: to

Date	Energy % a.m.	Pain 0-10	HR	BP	Activities/Factors	Energy Day ↑↓	Pain Day↑↓	Body temp.	Min. to fall asleep	Time Slept	Awake # of min.	Depth 1-5	Refresh-ed 0-10
Sun													
Mon													
Tues													
Wed													
Thur													
Fri													
Sat													
Sun													
Mon													
Tues													
Wed													
Thur													
Fri													
Sat													

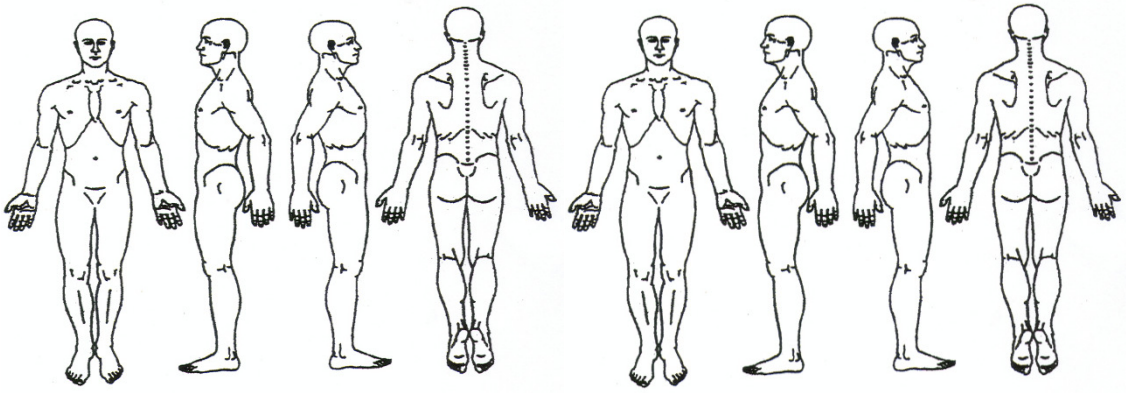
Pain Visual Analog Scale (PAIN VAS): Indicate the amount of pain you have had in the last 48 hours by marking a '/' through the line.

0 1 2 3 4 5 6 7 8 9 10

No Pain **Excruciating Pain**

Body Pain Diagrams:

Aching: =====, Burning Pain: xxxxx, Stabbing Pain: //////, Pins & Needles: ooooo, Joint Pain: •••••
Other Pain: ppppp Describe:



Pain on Day 1 Pain on Day 14

Visual Energy & Pain Chart Blue line: Energy Red line: Pain

	Sun.	Mon.	Tues.	Wed.	Thur.	Fri.	Sat.	Sun.	Mon.	Tues.	Wed.	Thur.	Fri.	Sat.
100%														
90%														
80%														
70%														
60%														
50%														
40%														
30%														
20%														
10%														

Letter to educators & agencies regarding young people with myalgic encephalomyelitis (ME)

My = muscle
algic = pain
Encephalo = brain
mye= spinal cord
itis = inflammation

Educators may be perplexed by the many symptoms and degree of disability in students who have ME. A long-term study of absence of students in 1,098 schools indicated that 51% of students absent had ME [Dowsett E, Colby J. JCFS 1997]. In a long-term follow-up study, the average loss of school was 1.8 years per child [Speight N]. It is hoped that this letter will enhance your understanding of ME and its educational implications. Educators have an opportunity to support these young people, accommodate their educational needs, and make a positive difference in their delicate lives.

ME affects all age groups, including young children, all ethnic/racial groups, and all socioeconomic strata. Currently there is no curative treatment. Prognosis for an individual cannot be predicted with certainty.

ME: WHO ICD G93.3 neurological disease

Myalgic encephalomyelitis (ME) is a severe, complex neurological disease that affects all body systems. The initial infection may damage the brain and cause profound dysregulation of the nervous and immune systems, impair cellular energy production, and cardiovascular function. ME is more debilitating than most diseases. Symptom severity and hierarchy of symptoms in children can fluctuate rapidly and may appear to be erratic.

They can't produce the energy they need. Simple activities are exhausting.

Hallmark feature: The **body is unable to produce sufficient energy on demand**, like a furnace that has its pilot light on but it cannot be turned up to address the need for additional heat.

- **Neuroimmune exhaustion:** Physical or mental exertion, which can be minimal such as activities of daily living, causes rapid exhaustion and worsening of symptoms.
- **Post-exertional exhaustion and flare of other symptoms** can be immediate or delayed by hours or days.
- **Recovery period is long,** taking 24 hours to several days. A relapse can last days, weeks or much longer.
- **The lack of physical and mental stamina** results in a substantial reduction in pre-illness energy and activity levels.

Cognitive and central nervous system impairments: Children may have

- **Difficulty processing information:** slowed thought and speech, poor concentration, confusion, disorientation, difficulty making decisions, difficulty absorbing information, dyslexia that may only be evident when fatigued, difficulty sequencing words and numbers, cannot multi-task
- **Short-term memory loss:** difficulty remembering what one wanted to say, what one was saying, retrieving words, recalling information, poor working memory
- **Headaches:** severe and chronic headaches are often debilitating; migraine can be accompanied by rapid drop in temperature, shaking, severe weakness, vomiting
- **Pain**: muscles, joints, chest, abdomen, etc. Pain can be widespread, and quickly fluctuate and migrate.

Messages between the brain and the other body systems are miscommunicated and are misinterpreted.

- **Sleep disturbances:** In the acute stage, patients typically have prolonged sleep, sometimes extreme, and cannot stay awake. This often evolves into sleep reversal – insomnia and sleeping much of the day. When patients "crash" (immobilizing exhaustion), they revert to being unable to stay awake. No matter how long they sleep, they awaken feeling very tired physically and mentally.
- **Motor impairments:** muscle weakness, twitching, "pins and needles", poor balance, poor coordination and fine motor skills, may appear clumsy, joint hypermobility
- **Sensory/perception disturbances:** inability to focus vision, hypersensitivity to light, sound, vibration, odour (including perfume & paint), taste, some foods, chemicals, medications; poor depth perception

Other prominent symptoms

ME is like having the flu every day. Symptoms worsen with mental or physical exertion.

- **Immune:** flu-like symptoms frequently reoccur or activate with exertion
- **Digestive**/gastro-intestinal disturbances, urinary urgency or frequency
- **Cardiovascular:** inability to tolerate an upright position, light-headedness/dizziness, periods of heart racing
- **Body temperature:** fluctuates, cold hands and feet, periods of feeling feverish without fever, shivery
- **Temperature:** cannot tolerate extremes in temperature

Secondary symptoms

- **Mood:** When young people are trying to cope with this complex, poorly understood disease that can be very debilitating, they often have mood swings and become anxious or depressed. Temporary hyperactivity is followed by overwhelming exhaustion. They may become irritable or appear lazy when exhausted.
- **Secondary school phobia** may develop due to bullying and academic difficulties. Children with ME spend most of their out-of-school time resting, whereas those with primary school phobia are socializing and participating in activities.

The physician may stop the child's education until the child is stronger and his/her health has stabilized.

Educational considerations and recommendations: Ensure the child receives the education to which s/he is entitled. The pathophysiology of ME must be respected and reflected in all educational programs.

It is helpful for teachers to meet with the parents and student as soon as the student has been diagnosed with ME and at the beginning of each year if attending school. Liaise with the child's physician when appropriate.

Educational accommodations should be selected on an individual basis according to the patient's health status, capabilities, special educational needs, and in order to provide the best opportunity for recovery.

1. **Modes of education** to be considered include home education, tutoring, on-line and virtual learning, correspondence courses, part-time school attendance, or combinations of various modes.
2. **Location of learning environment for education:** **"What environment provides the best opportunity for this child to learn and become educated?"** In the past there has been too much emphasis on returning the child to school as quickly as possible. This strategy has failed because the fast paced school environment is too demanding, even on a part-time basis, and in many cases it has caused the child's fragile health to spiral downward.
   - ***Energy Efficient Education:*** Home educating is becoming the method of choice as it makes the most efficient use of the child's limited energy in a quiet environment without distractions, and is more conducive to recovery. It is easier to prioritize and streamline course work in the home setting. Not only does it accommodate pacing and rest periods as needed, but the mode in which information is given can be adjusted to the individual child. This ensures the child understands the information at each step and eliminates much of the stress. Ideally a teacher or tutor should be part of the program. On-line virtual tutoring, with the use of Skype or similar program, can be beneficial.
   - ***School environment:*** • usually very busy • fast-paced • multi-sources of input • several things may be going on simultaneously • requires social interaction • sensory overload - bright lights, noise, odours, etc. The physical, mental, sensory and emotional overload can cause exhaustion, symptom flare, anxiety, depression and relapse.
   - ***Attending school part-time:*** Is the child strong enough? Does school exacerbate symptoms?
   - ***Combination of part-time school and home tutoring*** may be considered in mild cases.
   - ***Social contact*** is secondary to the child's health and education. Visiting school for social contact may be beneficial when the child becomes strong enough.
3. **Curriculum must be modified, course-work streamlined, and submissions minimalized**.
   - **Prioritize** the essentials and focus on concepts.
   - **Begin a program at a level that will ensure success.** Short intervals on a daily basis are better than longer intervals that can cause exhaustion. After resting during the summer, children typically overestimate what they can do.
   - **Exams:** Focus on exams that are necessary for qualifications. Patients may need to write exams at home under the supervision of an invigilator. Marked cognitive impairments should entitle a minimum of a 25% increase in the allotted test time to reflect the work quality of which the patient is capable.

With patience, understanding and support, educators can help these children acquire the education they desire.

Sincerely,
International Consensus Panel for Myalgic Encephalomyelitis (physicians, researchers & an educator representing 12 countries)

References & helpful resources

- TEACH-ME: *online in both English & French:* http://www.mefmaction.com/index.php?option=com_content&view=article&id=288&Itemid=356
- Tymes Trust: most comprehensive information regarding education of young people with ME http://www.tymestrust.org
- Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. *J Intern Med* 2011;270(4):327-38.

Access to Education School Pass: Simple accommodations that have been prearranged and agreed upon by the teacher and student, such as taking a rest, eating a snack to regain strength, wearing sunglasses due to light hypersensitivity, not standing in a cue, or being excused to the bathroom can be made without discussion or disruption of the class by showing the school pass.

Myalgic Encephalomyelitis International Access to Education School Pass

photo

_____ student's name **has permission to use disabled facilities and obtain other assistance.**

_____ teacher's signature

_____ principal/head teacher's signature

Endorsed by: ME International Consensus Panel

(Physician's confirmation of diagnosis is required.)

Authors and their affiliations continued from front inside cover.

Carlo-Stella, Nicoletta, MD, PhD; ***clinician and researcher: immunology, immunogenetics of ME***
Azienda Ospedaliera della Provinca di Pavia, Pavia
Primary care private practice with focus on ME, Pavia, Italy

Chia John, MD; ***clinician and researcher: internal medicine - infectious diseases, immunopathogenesis***
Clinical assistant professor: Harbor-UCLA Medical Center, University of California, Los Angeles, CA
Director: EV Med Research, Lomita, California, USA

Darragh, Austin, MA, MD, FFSEM (RCPI, RCSI), FRSH, FI Biol I (Hon); ***clinician and researcher: endocrinology***
University of Limerick, Limerick, Ireland

Gerken, Anne, MB, BS, D ObstRCOG, FRCPath: ***clinical microbiologist***
Retired consultant microbiologist with many years of experience working with ME, Suffolk, United Kingdom

Jo, Daehyun, MD, PhD; ***clinician and researcher: pain and anesthesiology***
Director: Pain Clinic, Konyang University Hospital, Daejeon
Professor: Department of Anesthesiology and Pain Medicine, Konyang University, Daejeon, Korea

Lewis, Don, MD; ***clinician: primary care with focus on ME***
Donvale Specialist Medical Centre, Donvale, Victoria, Australia

Light, Alan R, PhD; ***researcher: physiology, neuroscience, medical neurobiology and neuroanatomy, mechanisms of pain & fatigue***
Professor: Anesthesiology and Neurobiology and Anatomy; Molecular and Cellular Neuroscience, University of Utah School of Medicine, Salt Lake City, Utah, USA.

Light, Kathleen C, PhD; ***researcher: behavioral medicine – physiological dysregulation in chronic pain and fatigue disorders, behavioral factors in cardiovascular disease, health benefits of family support, minority and women's health issues***
Professor: Anesthesiology and Psychology, University of Utah School of Medicine, Salt Lake City, Utah, USA.

Marshall-Gradisnik, Sonya, PhD; ***researcher: immunology - natural killer cells, vasoactive neuropeptide dysfunction and receptor expression, T cell regulatory dysfunction***
Professor: School of Medical Sciences, Griffith Health Institute, Griffith University, Southport, Australia

McLaren-Howard, John, DSc, FACN; ***clinical biochemistry, biochemistry of nutrition, biochemical features of ME, mitochondrial dysfunction, vascular disease & intestinal dysbiosis***
Fellow: American College of Nutrition
Director: Acumen Medical Limited, Tiverton, Devon, United Kingdom

Mena, Ismael, MD; ***nuclear medicine***
Director: Imagenologia Funcional Cerebral, Department of Medicina Nuclear, Clinica las Condes, Santiago, Chile
Professor Emeritus: Radiological Sciences, UCLA School of Medicine, California, USA
Doctor Honoris Causa: University, d'Auvergne, France

Miwa, Kunihisa, MD, PhD; ***clinician and researcher: internal medicine: cardiology, cardiovascular physiology***
Director: Miwa Naika Clinic, Toyama, Japan

Murovska, Modra, MD, PhD; ***researcher: virology, medical microbiology, molecular biology***
Director: A. Kirchenstein Institute of Microbiology and Virology, Riga Stradins University, Riga, Latvia
Associate Professor: Riga Stradins University, Riga, Latvia

Stevens, Staci, MA; ***exercise physiology***
Director: Workwell Foundation, Ripon, California, USA

Conflict of interest statement

Dr. McLaren-Howard has declared a vested interest in Acumen Medical Ltd., UK.
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Consensus Coordinator: Marj van de Sande