

Fatigue and exhaustion

Mechanism: Fatigue is a nonspecific symptom generated by dysregulation across multiple interacting biological systems. It affects up to ~38% of adults at any point and accounts for 10–20% of primary care visits. Clinically useful is distinguishing performance fatigability (objective, measurable decline in motor or cognitive output) from self-perceived fatigue (the subjective sensation), and primary fatigue (intrinsic to a disease) from secondary fatigue (driven by treatable contributors such as anemia, medications, sleep disorders, depression, or deconditioning).

Most common causes:

- A) Immune / inflammatory** - typical in infections, autoimmune diseases (MS, RA, Sjögren's synd.), tumors, post-viral states
- B) Neuroendocrine** hypocortisolemia, blunted diurnal cortisol variation, blunted stress response
- C) Central neurological:** Altered functional connectivity, brain lesion (brainstem, hypothalamus)
- D) Peripheral:** decreased muscle force, ATP metabolism impairment - Myopathy, neuropathy
- E) Neurotransmitter** - serotonergic dysregulation, circadian disruption, autonomic dysfunction (POTS - fatigue in up to ~94% of patients)
- F) Behavioral / psychological:** - Sleep disorders, stress, depression crucial in chronification.

Red flags: Unintentional weight loss, fever / night sweats, lymphadenopathy, new focal neurologic deficit, exertional dyspnea / chest pain, pallor/bleeding. Neuromuscular fatigue is characterized by worsening muscle strength with repeated exertion; this type of fatigue is a possible symptom of a myasthenic or myopathic syndrome.

Syndromes:

- Acute fatigue** - normal response to exertion, stress, infection
- Prolonged fatigue (1–6 mos.)** - ~18% of population
- Myalgic encephalomyelitis / chronic fatigue syndrome** - prevalence ~0.2–2.6%
- Cancer-related fatigue** - ~49% of patients
- Fatigue in multiple sclerosis** - ~60% of patients
- Post-viral / long-COVID fatigue** - very frequent
- Fatigue in POTS** - ~94%.

Examination: Primarily laboratory tests (inflammatory, metabolic parameters, TSH, CBC+diff), sleep and medication history, depression screening, eventually oncologic screening.

Treatment: According to the cause + sleep hygiene + exercise program (aerobic + stretching), psychoeducation.

Onset	Children	Adults
Acute	viral infection, poor sleep, acute anemia, dehydration	infection, acute anemia, adverse medication effect
Subacute	post-viral fatigue, iron deficiency, mononucleosis, ADHD - in 62% of patients	thyroid disorders, anemia (4%), depression (18.5%), post-viral/long COVID, sleep disorders (frequent)
Chronic	Myalgic encephalomyelitis (chronic fatigue syndrome), postural orthostatic tachycardia syndrome, depression (in 65%)	Myalgic encephalomyelitis (chronic fatigue syndrome), hypothyroidism, OSA (frequent), depression, malignancy

Explanatory notes: MS - multiple sclerosis, RA - rheumatoid arthritis, POTS - postural orthostatic tachycardia syndrome, OSA - obstructive sleep apnea, ADHD - Attention Deficit Hyperactivity Disorder.