

# Drawing on findings from critical illness to explain Myalgic Encephalomyelitis / Chronic Fatigue Syndrome

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DS wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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### ***Abstract***

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We propose an initial explanation for how myalgic encephalomyelitis / chronic fatigue syndrome (ME/ CFS) could originate and perpetuate by drawing on findings from critical illness research. Specifically, we combine emerging findings about (a) hypoperfusion and endotheliopathy, and (b) intestinal injury in these illnesses with our previously published hypothesis about the role of (c) pituitary suppression, and (d) low thyroid hormone function associated with redox imbalance in ME/ CFS. Moreover, we describe interlinkages between these pathophysiological mechanisms as well as “vicious cycles” involving cytokines and inflammation that may contribute to explain the chronic nature of these illnesses. This paper summarizes and expands on our previous publications about the relevance of findings from critical illness for ME/ CFS. New knowledge on diagnostics, prognostics and treatment strategies could be gained through active collaboration between critical illness and ME/ CFS researchers, which could lead to improved outcomes for both conditions

### ***Contribution to the field***

Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/ CFS) is a debilitating illness that affects millions of people worldwide (an estimated 800,000 to 2.5 million in the USA). Symptoms include severe exhaustion, chronic pain, brain fog and sleep dysfunction. At least one-quarter of ME/ CFS patients are house- or bedbound at some point in their lives. The etiology of the illness is unclear, yet the most common peri-onset events include infection-related episodes (64%). In this submission we propose to explain the emergence and persistence of ME/ CFS by drawing on the research from critical care medicine. Specifically, we provide an overview of the pathophysiological mechanisms found during critical illness as well as initial arguments for suggesting that similar mechanisms may underlie ME/ CFS. These mechanisms include alterations to the vascular system, intestines, endocrine axes and thyroid hormone function. This submission synthesizes prior work and describes areas for additional inquiry. It contributes to form a basis for future research collaboration across these two fields of medical research.

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In review

# Perspective: Drawing on findings from critical illness to explain Myalgic Encephalomyelitis / Chronic Fatigue Syndrome

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12 **fatigue, splanchnic hypoperfusion, endotheliopathy, gut permeability, endotoxemia, pituitary,**  
13 **non-thyroidal illness syndrome. (Min.5-Max. 8)**

14 **Abstract**

15 We propose an initial explanation for how myalgic encephalomyelitis / chronic fatigue syndrome  
16 (ME/CFS) could originate and perpetuate by drawing on findings from critical illness research.  
17 Specifically, we combine emerging findings about (a) hypoperfusion and endotheliopathy, and (b)  
18 intestinal injury in these illnesses with our previously published hypothesis about the role of (c)  
19 pituitary suppression, and (d) low thyroid hormone *function* associated with redox imbalance in  
20 ME/CFS. Moreover, we describe interlinkages between these pathophysiological mechanisms as well  
21 as “vicious cycles” involving cytokines and inflammation that may contribute to explain the chronic  
22 nature of these illnesses. This paper summarizes and expands on our previous publications about the  
23 relevance of findings from critical illness for ME/CFS. New knowledge on diagnostics, prognostics  
24 and treatment strategies could be gained through active collaboration between critical illness and  
25 ME/CFS researchers, which could lead to improved outcomes for both conditions.

26 **1 Introduction**

27 Myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is a debilitating illness that affects  
28 millions of people worldwide (an estimated 800,000 to 2.5 million in the USA) (1, 2). Impaired  
29 function, post-exertional malaise, and unrefreshing sleep are core symptoms (1, 3, 4). At least one-  
30 quarter of ME/CFS patients are house- or bedbound at some point in their lives (1); the illness can be  
31 completely incapacitating (5). The etiology of the illness is unclear (6, 7) and peri-onset events  
32 include infection-related episodes, stressful incidents, and exposure to environmental toxins (8).

33 Critical illness refers to the physiological response to virtually any severe injury or infection, such as  
34 head injury, burns, cardiac surgery, SARS-CoV-2 infection and heat stroke (9). Researchers make a  
35 distinction between the *acute* phase of critical illness – in the first hours or days following severe  
36 trauma or infection; and the *chronic* or *prolonged* phase – in the case of patients who survive the  
37 acute phase but for unknown reasons do not start recovering and continue to require intensive care  
38 (10-13). Regardless of the initial injury or infection, these “chronic Intensive Care Unit (ICU)  
39 patients” experience profound muscular weakness, cognitive impairment, pain, vulnerability to  
40 infection, etc. (9, 11, 14). The treatment of *prolonged* critical illness is incomplete and remains an  
41 active area of research. Moreover, cognitive and/or physical disability can last for months or even  
42 years after treatment in ICUs (i.e., post intensive care syndrome, PICS) for as of yet unexplained  
43 reasons (15-17).

44 Drawing on findings from critical illness, we here propose an initial explanation for how ME/CFS  
45 could originate and perpetuate. Specifically, we combine emerging findings about (a) hypoperfusion  
46 and endotheliopathy, and (b) intestinal injury in these illnesses with our previously published  
47 hypothesis about the role of (c) pituitary suppression, and (d) low thyroid hormone *function*  
48 associated with redox imbalance in ME/CFS. Moreover, we describe interlinkages between these  
49 pathophysiological mechanisms as well as “vicious cycles” involving cytokines and inflammation  
50 that may contribute to explain the chronic nature of these illnesses. This explanation summarizes and  
51 expands on our previous publications about the relevance of findings from critical illness for  
52 ME/CFS (18-20) and builds on the work by Nacul et al. (21). The general lack of large high-quality  
53 ME/CFS studies (a reflection of the lack of funding in this field) poses a challenge for the assessment  
54 of overlaps between the two conditions.

## 55 **2 Pathophysiological mechanisms**

56 In the following sections we describe four central pathophysiological mechanisms in critical illness,  
57 including their relationship to inflammation. We also provide initial arguments for suggesting that  
58 similar mechanisms may underlie ME/CFS. Readers are referred to our prior publications for  
59 additional details about these mechanisms in critical illness (including heat stroke) and possible  
60 lessons for understanding ME/CFS (18-20).

### 61 **2.1 Hypoperfusion and endotheliopathy**

62 It has long been suggested that inadequate oxygen circulation is central to critical illness (22).  
63 Specifically, the redistribution of blood away from the splanchnic area to critical tissues is considered  
64 an adaptive androgenic response to physiological stress (23, 24). However, the resulting ischemia /  
65 reperfusion (I/R) can contribute to tissue injury driving sepsis and multi-organ dysfunction (25, 26).  
66 The relative importance of reduced blood flow, vasoconstriction (27), capillary flow disturbances  
67 (28) and impaired cellular oxygen utilization (29, 30) in driving critical illness continues to be  
68 debated.

69 Endothelial dysfunction appears to occur in parallel with circulation disturbances during critical  
70 illness. Probable drivers of distortions in the structure and function of endothelial lining (i.e.,  
71 glycocalyx) are cytokines (31), inflammation, exposure to oxidative stress (28, 32) and/or sympatho-  
72 adrenal hyperactivation (33). Crucially, endothelial dysfunction during critical illness has been  
73 associated with altered cerebral blood flow (34, 35) and increased blood–brain barrier (BBB)  
74 permeability resulting in long-term cognitive impairment (36, 37). A leaky BBB could also  
75 contribute to increased intracranial pressure (38, 39). Finally, researchers have found that

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76 endotheliopathy and coagulation disorder bolster each other via inflammatory pathways (40).  
77 Coagulation abnormalities vary in critical illness, but coagulopathy is associated with unfavorable  
78 outcomes in prolonged critical illness (i.e., length of ICU stay and mortality) (41).

79 We propose that similar alterations of the vascular system in response to a physical, infectious and /  
80 or emotional stressor (i.e., physiological insult) may also contribute to explain the emergence of  
81 ME/CFS. This is consistent with recent hypotheses describing vasoconstriction in muscle and brain  
82 as a principal element of ME/CFS (42-46), and findings of cerebral hypoperfusion (47-49) and  
83 intracranial hypertension (50) in ME/CFS patients. It is also consistent with studies that have shown  
84 that endothelial function is impaired in ME/CFS (51, 52), both in large vessels and in the  
85 microcirculation (53, 54) – associated with redox imbalance (51). Finally, it is consistent with a new  
86 hypothesis for ME/CFS which suggests that endothelial senescence underpins ME/CFS by disrupting  
87 the intestinal barriers and BBBs (55), as well as with suggestions that leakage from dysfunctional  
88 blood vessels could explain many of the symptoms in ME/CFS (56).

### **89 2.2 Intestinal injury**

90 Critical illness researchers have found profound intestinal alterations within hours following a  
91 physiological insult: a dramatic shift in the composition and virulence of intestinal microbes (57-59),  
92 an erosion of the mucus barrier, an increase in the permeability of the gut (i.e., “leaky gut”) (60-62),  
93 and a disruption in gut motility (63). This intestinal injury is thought to be largely a consequence of  
94 local I/R and redox imbalance resulting from splanchnic hypoperfusion (58, 61, 64-67). Indeed,  
95 studies in the field of exercise immunology have shown that even relatively low levels of splanchnic  
96 hypoperfusion during exercise result in intestinal injury (68).

97 Critically, this intestinal injury may lead to bacterial translocation from the gut into circulation (i.e.,  
98 endotoxemia) and/or the formation of toxic gut-derived lymph (57, 60). This in turn can induce pro-  
99 inflammatory cytokines and systemic inflammation (69, 70). Moreover, changes in the intestinal  
100 microbiome or the mucus barrier may also impact the immune system directly (57). Thus, researchers  
101 have long considered the gut “the motor of critical illness” driving sepsis and distant organ  
102 dysfunction (71). Some have suggested that a self-perpetuating vicious inflammatory cycle centered  
103 around intestinal injury can hinder recovery from critical illness (61, 72).

104 We propose that the sequence during critical illness – from splanchnic hypoperfusion to hypoxia,  
105 redox imbalance, altered gut microbiome, intestinal injury, gut-related endotoxemia, pro-  
106 inflammatory cytokines and systemic inflammatory – may also contribute to explain the emergence  
107 of ME/CFS following a physiological insult. Our proposal is in alignment with others’ findings that  
108 intestinal injury and resulting inflammation are central to ME/CFS (73-81) and consistent with  
109 findings linking the gut microbiome to inflammation (82-85) and to fatigue symptoms in ME/CFS  
110 (86). If verified, the existence of a vicious inflammatory cycle centered around intestinal injury could  
111 contribute to explain the perpetuation of ME/CFS. Post-exertional malaise – a key symptom of  
112 ME/CFS – could be the manifestation of an accentuation in intestinal injury following exertion.  
113 Moreover, the translocation of gut microbes or toxin from the intestines to the brain (55) might  
114 contribute to explain central nervous system inflammation in ME/CFS (87-89). Finally, leaky gut is  
115 also associated with auto-immunity (90, 91) – an important factor in ME/CFS pathology (92-94).

### **116 2.3 Pituitary suppression**

117 Almost immediately after a physiological insult, endocrine axes experience profound alterations  
118 considered a vital response to severe stress or injury to allow for a shift in energy and resources to

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119 essential organs and repair (95-97). Whereas in critically ill patients who begin to recover, endocrine  
120 axes essentially normalize within 28 days of illness, in cases of *prolonged* critical illness the  
121 pituitary's *pulsatile* secretion of tropic hormones (unexpectedly) remains suppressed.

122 Why and how this central suppression is maintained in *prolonged* critical illness continues to be  
123 debated. Inflammatory pathways likely play a role irrespective of the nature of the original injury or  
124 infection. For example, cytokines increase the abundance and affinity of glucocorticoid receptors  
125 (GR) at the level of the hypothalamus / pituitary, thereby enhancing the negative feedback loop of the  
126 hypothalamic-pituitary-adrenal (HPA) axis, and consequently suppressing pituitary release of  
127 adrenocorticotrophic hormone (ACTH) (95, 98). Similarly, cytokines up-regulate deiodinase enzymes  
128 in the hypothalamus resulting in higher local levels of the *active* thyroid hormone (T3), thereby  
129 enhancing the hypothalamic-pituitary-thyroid (HPT) axis' negative feedback loop and consequently  
130 suppressing pituitary secretion of thyroid stimulating hormone (TSH) irrespective of circulating  
131 thyroid hormone concentrations (99-101). Cytokines may also suppress the release of TSH by the  
132 pituitary directly (102, 103) contributing to a virtual complete loss of *pulsatile* TSH secretion (96).

133 The loss of *pulsatile* pituitary secretions has important implications for the autonomic nervous  
134 system, metabolism, and the immune system. Without sufficient *pulsatile* stimulation by ACTH,  
135 adrenal glands begin to atrophy (104, 105), compromising patients' ability to cope with external  
136 stressors and permitting excessive inflammatory responses. Erratic rather than *pulsatile* pituitary  
137 production of growth hormone (GH) leads to an imbalance between catabolic and anabolic  
138 hormones, resulting in loss of muscle and bone mass, muscle weakness, and changes in glucose and  
139 fat metabolism (106-108). Finally, suppression of the HPT axis is associated with tiredness and other  
140 hypothyroid-like symptoms (109, 110).

141 We propose that the sequence during critical illness – from increased release of pituitary hormones  
142 during the acute phase to suppression of the pituitary gland's *pulsatile* secretion in the prolonged  
143 phase – could also contribute to explain the emergence of ME/CFS following a physiological insult.  
144 This proposal is consistent with descriptions of ME/CFS as a progression from a hypermetabolic to  
145 hypometabolic state (21). It also aligns with a recent hypothesis relating many of the symptoms in  
146 severe ME/CFS to impaired pituitary function (111). Further support for this proposal is provided by  
147 the many previous ME/CFS studies that have documented dysfunctions in the hypothalamic–  
148 pituitary–somatotrophic (HPS) axis (112-114), the HPT axis (115-120) and the HPA axis (121-136) –  
149 notably associated with inflammation and oxidative & nitrosative stress (O&NS) (137-140).  
150 Strikingly, models relating the persistence of a suppressed HPA axis in ME/CFS to a change in  
151 central GRs concentrations resemble the explanations provided for pituitary suppression in critical  
152 illness (141-146). Moreover, suppression of ACTH release would explain why in a small study  
153 ME/CFS patients were found to have 50% smaller adrenals than controls (147), resembling adrenal  
154 atrophy in prolonged critical illness. However, the relationship between the pituitary's *pulsatile*  
155 secretions, physiological alterations and severity of illness – which proved revelatory in  
156 understanding *prolonged* critical illness – remains unexplored in ME/CFS.

### 157 **2.4 Low thyroid hormone function**

158 Peripheral mechanisms involving cytokines lead to the rapid depression of thyroid hormone activity  
159 following a severe physiological insult (148-152). This is termed “non-thyroidal illness syndrome”  
160 (NTIS), “euthyroid sick syndrome” or “low T3 syndrome” and is thought to be an adaptive response  
161 to conserve energy resources during critical illness (152-154). The mechanisms involved include  
162 alterations in the half-life of thyroid hormone in circulation (155-157); modifications in the uptake of

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163 thyroid hormone by cells (158, 159); down- and up-regulation of deiodinase enzymes that convert the  
164 thyroid hormone into active and inactive forms respectively (156, 160); and alterations in sensitivity  
165 of cells to thyroid hormones (161-163). These alterations can lead to important tissue-specific  
166 depression in thyroid hormone *function* (164, 165) which is, however, often missed altogether in  
167 clinical settings (166) because most of the alterations do not translate into changes in the blood  
168 concentrations of thyroid hormones (164, 167, 168). Indeed, the decrease in the ratio of the *active*  
169 form of thyroid hormone (T3) relative to the *inactivated* thyroid hormone (rT3) (150, 152, 169) –  
170 considered the most sensitive marker of NTIS – may be just the “tip of the iceberg” of the depressed  
171 thyroid hormone *function* in target tissues (120, 170).

172 While NTIS may be beneficial in the *acute* phase of critical illness, it is increasingly seen as  
173 maladaptive and hampering the recovery of patients in the case of *prolonged* critical illness (96, 101,  
174 152, 169, 171-173). Low thyroid hormone *function* may hamper the function of organs (170) and the  
175 activity of immune cells, including natural killer cells (174-185). Immune dysfunctions might in turn  
176 explain other pathologies, such as viral reactivation observed in ICU patients (186-188). Some  
177 critical illness researchers have proposed a model that describes how NTIS is maintained by  
178 reciprocal relationships between inflammation (notably pro-inflammatory cytokines), O&NS and  
179 reduced thyroid hormone *function*, forming a “vicious cycle” (101, 173). This model can help to  
180 explain the perplexing failure to recover of some critically ill patients in ICUs that survive their  
181 initial severe illness or injury.

182 We propose that low thyroid hormone *function* could also contribute to explain the emergence of  
183 ME/CFS following a physiological insult. An immune-mediated loss of thyroid hormone *function* in  
184 ME/CFS has long been suspected (117). A recent study showed that the thyroid panel of ME/CFS  
185 patients resembles that of critical illness patients, including significantly lower ratio of T3 to rT3  
186 hormones (120). Moreover, the other elements for a “vicious cycle” which researchers have  
187 suggested perpetuate a hypometabolic and inflammatory state in critical illness are also present in  
188 ME/CFS, including inflammation (140, 189), increased O&NS (190-192) and altered cytokine  
189 profiles (193, 194).

### 190 3 Discussion

191 Hypoperfusion and endotheliopathy, intestinal injury, pituitary suppression, and low thyroid hormone  
192 *function* are each central to *prolonged* critical illness regardless of the nature of the initial severe  
193 injury or infection (101, 173, 195, 196). We propose that, similarly, these mechanisms and their  
194 reciprocal relationships with inflammation could underlie ME/CFS regardless of the nature of the  
195 peri-onset event (i.e., infection, stressful incident, exposure to environmental toxins or other) (Table  
196 1). Moreover, the severity of ME/CFS may be a function of the strength of these mechanisms.

197 However, each of these pathological mechanisms has largely been studied in isolation and rarely  
198 have the linkages between them been explored. Yet, the aggregate of these mechanisms is likely  
199 necessary to fully explain the perpetuation of critical illness – and to inform the understanding of  
200 ME/CFS (Figure 1). Additional areas for inquiry thus include the following:

201 **Linkages between intestinal injury and pituitary suppression:** Intestinal injury during critical  
202 illness results in decreased secretion of gastrointestinal hormones including ghrelin (63, 197).  
203 Decreased stimulation of the pituitary and hypothalamus by ghrelin during *prolonged* critical illness  
204 in turn results in lower secretion of GH by the pituitary (198). Researchers have found that the  
205 administration of an artificial ghrelin in chronic ICU patients reactivated the pulsatile secretion of



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206 GH by the pituitary and – when done in combination with thyrotropin-releasing hormones (TRH) –  
207 had beneficial metabolic effects (96, 108, 199). Similarly, the administration of ghrelin to the I/R rats  
208 “inhibited pro-inflammatory cytokine release, reduced neutrophil infiltration, ameliorated intestinal  
209 barrier dysfunction, attenuated organ injury, and improved survival” (200). The sequence between  
210 intestinal injury, ghrelin secretion and GH release by the pituitary could be particularly relevant for  
211 solving ME/CFS given that “several of the main typical symptoms in severe ME/CFS, such as  
212 fatigue, myalgia, contractility, delaying muscle recovery and function, exertional malaise,  
213 neurocognitive dysfunction, and physical disability may be related to severe GH deficiency” (111).

214 **Linkages between pituitary suppression and low thyroid hormone function:** There are several  
215 pathways linking the activity of the pituitary with that of thyroid hormones. Firstly, GH secreted by  
216 the pituitary co-regulates the activity of the deiodinase enzyme (D3) responsible for the conversion of  
217 thyroid hormones into inactive forms (i.e., rT3 and inactivate forms of T2) (106, 201). Researchers  
218 showed that normalization of the GH secretion in *prolonged* critically ill patients is necessary to  
219 inhibit the increase in plasma rT3 concentrations (96, 108, 199). In other words, dampened GH  
220 release by the pituitary during *prolonged* critical illness enables low thyroid hormone *function*.  
221 Secondly, the lack of stimulation of the adrenals by ACTH could (by causing an atrophy of adrenals)  
222 create the condition necessary for persistent inflammation which depresses the activity of thyroid  
223 hormones during critical illness (148-152). In other words, dampened ACTH release by the pituitary  
224 during *prolonged* critical illness might permit the vicious inflammatory cycles described above.  
225 Thirdly, there is evidence that thyroid hormone conversely also stimulates ACTH secretion (202,  
226 203). In summary, the bi-directional relationships between the endocrine axes and thyroid hormone  
227 *function* (in addition to reciprocal relationships with inflammation) could contribute to explain the  
228 persistence of chronic ICU and ME/CFS.

229 **Linkages between low thyroid hormone function and endothelial function:** Upon binding to  
230 specific receptors on endothelial cells, thyroid hormones (T3 and T4) activate the endothelial nitric  
231 oxide synthase (eNOS) responsible for nitric oxide (NO) production (204), which in turn impacts  
232 vasodilation and inflammation (205-207). A further line of inquiry may thus be the role of thyroid  
233 hormone *function* in endotheliopathy in ME/CFS, including as relates to the new finding that plasma  
234 from ME/CFS patients inhibits eNOS and NO production in endothelial cells (208). Relatedly,  
235 critical illness researchers have found that serum from patients with NTIS inhibits the uptake of  
236 thyroid hormone (209, 210); the mechanisms remain unresolved (165).

237 **Linkages to mitochondrial function:** The impaired perfusion, redox imbalance, lower thyroid  
238 hormone *function* and inflammation appear to collectively affect mitochondrial activity in critical  
239 illness (via inhibition, damage, and/or decreased turnover of new mitochondrial protein) (30, 211-  
240 213). Mitochondrial activity may be similarly affected in ME/CFS (190). Some have suggested that  
241 this down regulation of mitochondrial activity (and oxygen utilization) in critical illness may be an  
242 adaptive form of “hibernation” to protect cells from death pathways (30, 213). This suggestion  
243 echoes the hypothesis that ME/CFS is a form of “dauer” or “cell danger response” (214-216). Lower  
244 mitochondrial activity in turn affects the immune system and the gut endothelial “such that the host’s  
245 immune response and physical barriers to infection are simultaneously compromised” (29).

246 **Relevance of critical illness treatment trials for ME/CFS:** Although prolonged critical illness  
247 remains unresolved, early treatment trials – such as the reactivation of the pituitary, or interruption of  
248 the vicious inflammatory cycles centered around either gut injury or low thyroid hormone *function* –  
249 may provide therapeutic avenues for ME/CFS (19). Longitudinal studies of (spontaneous) recovery  
250 from critical illness may also give clues about prerequisites for recovery from ME/CFS. Researchers

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251 have, for example, found that “supranormal TSH precedes onset of recovery” from prolonged critical  
 252 illness (96) and that metabolic rate rises > 50% above normal in the recovery phase (213).

253 **Commonality with other illnesses:** Researchers have suggested commonality in the illnesses  
 254 induced by physical, infectious, and / or emotional stressors (132, 217). These include heat stroke,  
 255 fibromyalgia, ME/CFS, prolonged critical illness, PICS, cancer-related fatigue, post-viral fatigue,  
 256 post-acute COVID-19 syndrome (PACS) and long-COVID. Specifically, it is necessary to explore  
 257 whether the pathological mechanisms described above also underlie long COVID – a disease which  
 258 resembles ME/CFS (218-228) and can arise even after mild COVID-19 cases.

259 **4 Conclusion**

260 Decades of research in the field of critical illness medicine have demonstrated that in response to the  
 261 stress of severe infection or injury, the vascular system, intestines, endocrine axes and thyroid  
 262 hormone function experience profound alterations. Self-reinforcing interlinkages between these  
 263 pathophysiological mechanisms as well as “vicious cycles” involving cytokines and inflammation  
 264 may perpetuate illness irrespective of the initial severe infection or injury. Without excluding  
 265 possible predisposing genetic or environmental factors, we propose that the pathological mechanisms  
 266 – and the interlinkages between them – that prevent recovery of some critically ill patients may also  
 267 underlie ME/CFS. This initial proposal is in line with and complements several existing hypotheses  
 268 of ME/CFS pathogenesis. If this hypothesis is validated, past treatment trials for critical illness may  
 269 provide avenues for a cure for ME/CFS. Certainly, given the similarities described above, active  
 270 collaboration between critical illness and ME/CFS researchers could lead to improved understanding  
 271 of not only both conditions, but also PICS, long-COVID, PACS, and fibromyalgia.

272 **5 Tables and Figures**

273 **Table 1:** Central pathophysiological mechanisms in prolonged critical illness, probable drivers and  
 274 implications, and initial evidence suggesting similar mechanisms in ME/CFS.

Pathophysiological mechanisms	In prolonged critical illness (Probable drivers and implications)	In ME/CFS (Initial evidence)
<b>Hypoperfusion</b>	<p><b>Drivers:</b></p> <ul style="list-style-type: none"> <li>• redistribution of blood away from the splanchnic area to critical tissues (23, 24)</li> <li>• reduced blood flow, vasoconstriction (27)</li> <li>• capillary flow disturbances (28)</li> <li>• additional: impaired cellular oxygen utilization (29, 30)</li> </ul> <p><b>Implications:</b></p> <ul style="list-style-type: none"> <li>• ischemia / reperfusion (I/R)</li> <li>• tissue injury driving sepsis and multi-organ dysfunction (25, 26)</li> </ul>	<p><b>Initial evidence</b></p> <ul style="list-style-type: none"> <li>• vasoconstriction in muscle and brain (42-45)</li> <li>• cerebral hypoperfusion (47-49)</li> <li>• intracranial hypertension (50)</li> </ul>
<b>Endotheliopathy</b>	<p><b>Drivers:</b></p> <ul style="list-style-type: none"> <li>• cytokines (31), inflammation, exposure to oxidative stress (28, 32)</li> <li>• sympatho-adrenal hyperactivation (33)</li> </ul> <p><b>Implications:</b></p> <ul style="list-style-type: none"> <li>• altered cerebral blood flow (34, 35)</li> <li>• increased blood–brain barrier (BBB) permeability (36, 37)</li> <li>• increased intracranial pressure (38, 39).</li> <li>• (variable) coagulation disorder (40)</li> </ul>	<p><b>Initial evidence</b></p> <ul style="list-style-type: none"> <li>• impaired endothelial function (51, 52), in large vessels and microcirculation (53, 54) – associated with redox imbalance (51)</li> <li>• endothelial senescence disrupting</li> </ul>

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		<p>the intestinal barriers and BBBs (55)</p> <ul style="list-style-type: none"> <li>• redox imbalance</li> </ul>
<b>Intestinal injury</b>	<p><b>Drivers:</b></p> <ul style="list-style-type: none"> <li>• local I/R and redox imbalance resulting from splanchnic hypoperfusion (58, 61, 64-67)</li> <li>• disruption in gut motility (63)</li> <li>• shift in the composition and virulence of intestinal microbes (57-59)</li> </ul> <p><b>Implications:</b></p> <ul style="list-style-type: none"> <li>• erosion of the mucus barrier, increase in the permeability of the gut (i.e., “leaky gut”) (60-62)</li> <li>• bacterial translocation from the gut into circulation (i.e., endotoxemia) and/or the formation of toxic gut-derived lymph (57, 60)</li> <li>• pro-inflammatory cytokines and systemic inflammation (69, 70)</li> <li>• direct impacts on the immune system (57)</li> <li>• vicious inflammatory cycle centered around intestinal injury (61, 72)</li> <li>• decreased secretion of gastrointestinal hormones including ghrelin (63, 197) impacting pituitary activity</li> </ul>	<p><b>Initial evidence</b></p> <ul style="list-style-type: none"> <li>• intestinal injury and resulting inflammation (73-81)</li> <li>• altered gut microbiome linked to inflammation (82-85)</li> <li>• lack of beneficial gut bacteria linked to fatigue symptoms (86)</li> <li>• endothelial senescence disrupting the intestinal barriers (55)</li> <li>• auto-immunity (92-94)</li> </ul>
<b>Suppression of pulsatile pituitary function</b>	<p><b>Drivers</b></p> <ul style="list-style-type: none"> <li>• cytokines acting on abundance and affinity of glucocorticoid receptors (GR) at central level (95, 98)</li> <li>• cytokines affecting deiodinase enzymes in the hypothalamus (99-101)</li> <li>• direct action of cytokines on TSH release by the pituitary directly (102, 103)</li> </ul> <p><b>Implications</b></p> <ul style="list-style-type: none"> <li>• loss of ACTH pulsatility: atrophy of adrenal glands (104, 105) compromising patients' ability to cope with external stressors and permitting excessive inflammatory responses</li> <li>• loss of GH pulsatility: imbalance between catabolic and anabolic hormones, resulting in loss of muscle and bone mass, muscle weakness, and changes in glucose and fat metabolism (106-108). Alterations in deiodinase enzyme (D3) activity enabling low thyroid hormone <i>function</i> (96, 108, 199).</li> <li>• loss of TSH pulsatility (109, 110)</li> </ul>	<p><b>Initial evidence</b></p> <ul style="list-style-type: none"> <li>• progression from a hypermetabolic to hypometabolic state (21)</li> <li>• impaired pituitary function (hypothesis) (111).</li> <li>• dysfunctions in HPS axis (112-114), HPT axis (115-120) and HPA axis (121-136) – associated with inflammation O&amp;NS (137-140)</li> <li>• changes in central GRs concentrations (models) (141-146)</li> <li>• smaller adrenals (147)</li> </ul>
<b>Low thyroid hormone function</b>	<p><b>Drivers</b></p> <ul style="list-style-type: none"> <li>• alterations in the half-life of thyroid hormone in circulation (155-157)</li> <li>• modifications in the uptake of thyroid hormone by cells (158, 159)</li> <li>• down- and up-regulation of deiodinase enzymes that convert the thyroid hormone into active and inactive forms respectively (156, 160)</li> <li>• alternations in sensitivity of cells to thyroid hormones (161-163)</li> </ul> <p><b>Implications</b></p> <ul style="list-style-type: none"> <li>• tissue-specific depression in thyroid hormone <i>function</i> (164, 165) (166)</li> <li>• hampered function of organs (170)</li> </ul>	<p><b>Initial evidence</b></p> <ul style="list-style-type: none"> <li>• immune-mediated loss of thyroid hormone <i>function</i> in ME/CFS (suspected) (117).</li> <li>• significantly lower ratio of T3 to rT3 hormones (120)</li> </ul>

	<ul style="list-style-type: none"><li>• altered activity of immune cells, including natural killer cells (174-185)</li><li>• viral reactivation (186-188)</li><li>• vicious inflammatory cycle (101, 173)</li></ul>	
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275

276 **Figure 1 Title:** Central pathophysiological mechanisms in critical illness including selected  
277 consequences and inter-linkages

278 **Figure 1 Caption:** Hypoperfusion and endotheliopathy, intestinal injury, pituitary suppression, and  
279 low thyroid hormone *function* are each central to prolonged critical illness regardless of the nature of  
280 the initial severe injury or infection. These pathophysiological mechanisms are in reciprocal  
281 relationships with inflammation; specifically, researchers have proposed vicious cycles involving  
282 intestinal injury and low thyroid hormone *function*. Moreover, linkages have been described between  
283 these pathophysiological mechanisms, including (i) hypo-perfusion and intestinal injury (i.e., leaky  
284 gut resulting from ischemia/reperfusion, hypoxia and redox imbalance); (ii) intestinal injury and  
285 pituitary suppression (i.e., suppressed growth hormone release resulting from reduced ghrelin  
286 secretion by the intestines); (iii) pituitary suppression and low thyroid hormone *function* (i.e.,  
287 increased inactivated thyroid hormone resulting from the upregulation of D3 deiodinase as a  
288 consequence of lower growth hormone); and (iv) low thyroid hormone *function* and pituitary  
289 suppression (i.e., decreased ACTH secretion resulting from lower levels of activated thyroid  
290 hormone). We propose that these mechanisms and the linkages between them – alongside reciprocal  
291 relationships with inflammation – could also underlie ME/CFS.

## 292 **6 Conflict of Interest**

293 *The authors declare that the research was conducted in the absence of any commercial or financial*  
294 *relationships that could be construed as a potential conflict of interest.*

## 295 **7 Author Contributions**

296 DS wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and  
297 approved the submitted version.

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## 300 **9 Abbreviations**

301 Blood–brain barrier (BBB); Adrenocorticotrophic hormone (ACTH); Growth hormone (GH);  
302 glucocorticoid receptors (GR); hypothalamus-pituitary-adrenal axis: “Adreno-cortical axis” (HPA);  
303 Hypothalamic-pituitary-somatotropic axis: “Somatropic axis” (HPS); Hypothalamic-pituitary-  
304 thyroid: “Thyrotropic axis” (HPT); Intensive Care Unit (ICU); Ischemia / reperfusion (I/R); Myalgic  
305 Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS); Nitrox oxide (NO); Non-thyroidal illness  
306 syndrome (NTIS); oxidative and nitrosative stress (O&NS); Post-acute COVID-19 syndrome  
307 (PACS); Post-intensive care syndrome (PICS); Thyrotropin-releasing hormone (TRH); Thyroid  
308 stimulating hormone (TSH)

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Figure 1.TIFF

