



A clinical primer for the expected and potential post-COVID-19 syndromes

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Abstract

In late 2019, a novel coronavirus SARS-CoV-2 (COVID-19) spread unchecked across the world's population. With tens of millions infected, the long-term consequences of COVID-19 infection will be a major health care focus for years after the contagion subsides. Most complications stem from direct viral invasion provoking an over-exuberant inflammatory response driven by innate immune cells and activation of the clotting cascade causing thrombosis. Injury to individual organs and their protective linings are frequent presentations in respiratory, cardiovascular, and neurological systems. Reviewing the historical context of postviral fatiguing symptoms seems relevant to understanding reports of uneven recoveries and persistent symptoms that are emerging as "long-haul COVID-19." The pandemic is also an unprecedented sociocultural event, transforming how people consider their health, gather in groups, and navigate their daily lives. The unprecedented sociocultural stresses of the pandemic will have an invisible, ubiquitous, and predictable impact on neurologic, endocrine, and immune functioning, even in people untouched by the virus. COVID-19 may also have a surprise or two in store, with unique clinical presentations and novel mechanisms of injury which are yet to clearly emerge. Although challenging and unfortunate, these times also represent a unique opportunity to start to unravel the physiology that underlie how viruses may trigger cancers, neurological disease, and postviral fatiguing syndromes.

Keywords: COVID-19, Complications, Post-COVID syndrome, Long haulers, Fatigue, SARS-CoV-2

1. Introduction

In late 2019, a novel coronavirus SARS-CoV-2 (COVID-19) appeared in Wuhan, China, and spread unchecked across the world's population. With 30 million infections already documented worldwide and the potential to infect over a 100 million people, the long-term consequences of COVID-19 infections will be a major health care focus for years after the contagion subsides. The common complications are expected to be accompanied by familiar patterns of pain and aversive sensations. Even the rarest of post-COVID-19 complications (occurring in less than 1/10,000 infected) will be present in tens of thousands

of people. There may even be unique post-COVID-19 syndromes that have yet to be described.

It seems inevitable that medical practitioners will have to manage a pandemic-sized burden of somatic and emotional aversity in the wake of COVID-19. To better navigate the looming health issues, it seems prudent to review the known presentations of COVID-19 and their expected complications, especially postviral fatiguing syndromes, whereas also considering how unique post-COVID-19 syndromes may emerge.

2. Known complications of Coronavirus-19 infections

Acute COVID-19 infections resemble other viral respiratory tract infections, presenting with fever, fatigue, dry cough, myalgias, and dyspnea.²⁰ Headaches, sore throat, rhinorrhea, gastrointestinal symptoms, conjunctivitis, and alterations in olfaction and gustation are also commonly reported presenting features.^{26,71} For many, COVID-19 infection will self-resolve with little impact on their long-term health. Others will have prolonged recoveries that relate to the tissues injured during their initial infection.

COVID-19 penetrates human cells through its exquisite specificity to the angiotensin-converting enzyme-2 receptor. The angiotensin-converting enzyme-2 receptor is widely expressed in human tissue, most notably in lung alveolar cells, small intestine enterocytes, and the vascular endothelium.⁴¹ The complications of COVID-19 are most often related to overexuberant immunological responses to the viral infection in the tissues or protective membranes of affected organs. The most severe damage seems to be a consequence of

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substantial monocyte and macrophage recruitment into affected tissues and their unchecked activation.⁷³ The consequences of this inflammatory response are different for each tissue impacted, ranging from acute respiratory distress syndrome and pleuritis in the lung, to myocarditis and pericarditis in the heart, to encephalitis and meningitis in the brain, and creating a hodge-podge of other problems such as conjunctivitis, pancreatitis, oral ulcers, and epididymitis.³⁷ Inflammatory manifestations may also be age-specific, as evidenced by Kawasaki disease reports in COVID-19-infected children.⁷⁷

Visceral thrombosis represents a second mechanism in which COVID-19 can create complications. Microthrombi during COVID-19 infections have been documented to occur in nearly every organ. Dramatically elevated levels of D-dimer and fibrin degradation products are a hallmark of the coagulopathy. The innate immune activation noted above may have a central role in driving the expression of tissue factor, the initiating enzyme of the extrinsic coagulation pathway.⁷³ Other thrombophilic factors may include complement activation and direct infection of endothelial tissue.⁷⁴ The consequences of this coagulopathic response are different for each target organ, ranging from pulmonary embolism in the lung, myocardial infarction in the heart, stroke in the brain, and other injuries such as renal failure, avascular necrosis, acute limb and mesenteric ischemia, aortic thrombosis, testicular pain, and ovarian vein thrombosis.^{53,56,60,78,81,95}

Of course, inflammation and thrombosis are not mutually exclusive and often both contribute, perhaps synergistically, to severe COVID-19 presentations. We anticipate that, for the most part, these organ-specific presentations will resolve as would be expected when they occur in other clinical settings. However, the novelty of COVID-19 suggests that there may be some surprises along the way. Below we review the known presentations of COVID-19 that may linger on to create persistent pain and discomfort. Estimates of symptom prevalence are provided in **Table 1:**

2.1. Lungs

Pneumonia, pleurisy, chronic cough, and pulmonary emboli can lead to chronic pleuritic pain, shortness of breath, decreased exercise tolerance, and fatigue issues.²² Acute respiratory distress syndrome itself leads to long-standing fatigue, with one study observing 436 of 659 patients reporting clinically substantial fatigue 1 year after recovery.⁷⁶

2.2. Heart

Myocardial injury and myocarditis can lead to chronic cardiac chest pain, exercise intolerance, and fatigue. As seen during prior coronavirus epidemics, COVID-19 infections can induce cardiac arrhythmias. Recurrent pericarditis is currently believed to be a consequence of viral infection leading to a cyclic or persistent autoinflammatory state and may be a sequelae of COVID-19 pericarditis.¹⁷

2.3. Musculoskeletal

Muscle pain, myalgia, and joint pain have been reported as a presenting feature in 35% to 50% of all cases. It is also a symptom that frequently persists after initial recovery.⁵⁹ Avascular necrosis has been reported to occur from COVID-19 infection and the corticosteroids used in treatment.²⁸ Currently, there does not seem to be evidence suggesting that COVID-19 causes an acute or subsequent inflammatory arthritis.

2.4. Gastrointestinal tract

Symptoms such as nausea, vomiting, diarrhea, loss of appetite, and abdominal pain are common presenting features, reported to occur in 1 of 5 of COVID-19 infections, with abdominal pain occurring 6.2% of the time, in a meta-analysis of 78 studies encompassing 12, 797 patients.⁹¹ Whether these symptoms from acute infections will lead to persistent pain disorders and irritable bowel syndrome has not yet been reported. Acute abdominal presentations can cause or mimic inflammatory and thrombotic disorders, such as appendicitis, pancreatitis, cholecystitis, acute intestinal ischemia secondary to mesenteric artery thrombosis, and will create a chronic pain burden for survivors.^{6,16,23}

2.5. Mouth and throat

Sore throat is common, occurring in 5% to 20% of infections and often persisting after other signs of infection have resolved.^{21,59,89} Painful necrotic and aphthous-like ulcers have been reported and may contribute to alterations in taste and smell.¹⁵ Whether these lesions may become a chronic, recurring issue has yet to be determined.

2.6. Eyes

Ocular symptoms range from eye pain, dryness, irritation, or a sensation of a foreign body in the eye. One report assessing ocular symptoms before and after infection noted 15 of 56 participants developed ocular symptoms during the course of COVID-19 infection with 11% indicating that these symptoms had an onset before fever and other respiratory symptoms.⁴⁶ Reports of COVID-19 infections leading to chronic sicca symptoms has not yet been reported.

2.7. Blood

COVID-19 infection has been shown to trigger painful flares in sickle cell disease.¹⁰ One study of 83 patients with sickle cell disease and acute COVID-19 noted vaso-occlusive crisis in 54% and acute chest syndrome with COVID-19 in 28%.⁸

2.8. Autoimmune

The rare relationship between acute COVID-19 infection and the development of pediatric inflammatory multisystemic syndrome, which is a variant of Kawasaki Disease, has been demonstrated, with 497% increase in number of cases reported in France during the first 4 months of the pandemic.⁷⁷ Other acute autoimmune manifestations have been reported even less frequently, including idiopathic thrombocytopenic purpura, Guillain-Barré syndrome (GBS), and autoimmune hemolytic anemia.³⁸ However, the development of other autoimmune diseases have not yet been reported.

2.9. Cancer

Coronaviruses are not currently recognized as viruses with oncogenic potential.⁷² However, coronavirus infections in the society are ubiquitous and not characterized in the standard of practice health care. It is possible that COVID-19 may confer an increased risk of developing malignancy that can only be recognized over time with epidemiological surveillance. Even if COVID-19 is not directly oncogenic, it is possible that the

Table 1
Prevalence of COVID-19 symptoms.

System	Symptom	Estimated frequency
General	Myalgia and fatigue	35%–50% [31,35]
	Fever	43%–90% [31,23,35]
Pulmonary	Cough	50%–82% [31,23,35]
	Dyspnea	29%–31% [31,23]
	Pneumonia	Up to 75% [23]
	Pulmonary emboli	† ^[6]
Cardiovascular	Chest pain	22% [31]
	Cardiac arrhythmia	17% [31]
	Myocarditis	12% [35]
Gastrointestinal	Nausea and/or vomiting	9.0%–12% [31,19]
	Diarrhea	5%–19% [31,19,35]
	Loss of appetite	22.3% [19]
	Abdominal pain	6.2%–10% [31,19]
	Rhabdomyolysis	† ^[35]
	Mesentery artery thrombosis, appendicitis, and pancreatitis	† ^[20,21,22]
Oropharynx	Sore throat	5%–20% [31,17,23,24]
	Aphthous-like ulcers	† ^[25]
Ocular symptoms	Sore eyes, itching, foreign body sensation, tearing, redness, and/or dry eyes	27% [26]
Hematologic	Vaso-occlusive crisis and acute chest syndrome in sickle cell disease*	† ^[27,28]
Autoimmune	Pediatric inflammatory multisystem syndrome	† ^[6]
Neurological	Altered mental status*	7.5%–31% [35,45]*
	Headache	11%–40% [31,34,35]
	Neuropathic pain	† ^[35]
	Anosmia and ageusia	30%–66% [35]
	Stroke*	2.8%–8% [35]*
	Guillain–Barre syndrome	† ^[38,39,40]
	Dysautonomia	† ^[40,41]
	Meningitis/encephalitis*	† and up to 18% [35,45]*

* Small or focused studies in hospitalized populations that may not generalizable to identify the risk to the population at large.

† Case reports of individual cases; generalized prevalence information is not available.

inflammation it invokes may be. The long-term impact of pulmonary inflammation on cancer development remains an open question.⁴

2.10. Nervous system

Abnormal neurological findings on examination themselves are a frequent presenting feature of COVID-19 infection. A case series of 58 patients admitted to the ICU indicated that 14% had neurological symptoms on admission, and 67% presented symptoms when sedation and neuromuscular blockade were withheld. Symptoms ranged from agitation, encephalopathy, as well as two-thirds displaying corticospinal tract findings such as enhanced deep tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes.⁴³

Headache is a common presenting symptom, with a reported prevalence of 11% to 40%.^{13,14} These reports describe moderate to severe bilateral pressing or pulsing pain in the tempoparietal, periorbital, or bifrontal areas. Both sudden and gradual onset has been reported and are often resistant to traditional analgesics. Headaches affiliated with meningitis and encephalitis will likely be more severe and potentially affiliated with other focal neurologic symptoms based on inflamed areas. It can be expected that some individuals will develop chronic headaches or have previous headache disorders substantially aggravated from their infections. Likewise, neuropathic pain in the back and neck corresponding to the spinal nerves has been reported, which was not responsive to typical analgesics, but some relief was found with gabapentin.³

More severe functional disability is expected for neurologic etiologies that bear thrombotic, demyelinating, inflammatory, and direct viral insult to the central nervous system. As with all things neurologic, the long-term morbidity will vary widely based on the etiology and precise location of the primary insult. Large vessel strokes related to COVID-19 infections are affecting a much younger population than typically have strokes.⁶⁷ These strokes will cause devastating long term effects, including deficits with motor and sensory function, cognition, pain, and bowel and bladder function. Likewise, demyelination of GBS has also been reported in COVID-19 patients, which can cause paraplegia, paresthesia, and further compromise the respiratory system by weakening respiratory muscles.^{85,92} Dysautonomia has been linked to GBS⁸⁸ and in critically ill COVID patients independent of GBS.³²

One of the most striking presentations of COVID-19 has been its ability to diminish and alter taste and smell. Although the anosmia typically resolves itself, there are already reports of people not recovering these senses.³⁰ The long-term consequences of the loss or distortion of smell and taste will have nutritional, safety, and psychological consequences.

It is also possible that unexpected neurological issues may emerge from this targeted encephalitis. During the 1918 “Spanish” flu, a coepidemic of a suspected viral infection known as *encephalitis lethargica* created profound lethargy in the afflicted that resolved over weeks to months. Patients seemed to recover to normal health but developed an aggressive form of Parkinson’s disease after a few years.⁶³ As anosmia frequently

precedes the motor symptoms of Parkinson's disease by years, it raises concerns that MRI changes in the deep and subcortical hemispheric white matter, corpus callosum, and basal ganglia¹³ by COVID-19 may have a still unknown neurological toll on COVID-19 survivors.

With pervasive neurological involvement, alterations in the nervous system structure and function related to injury and healing will have neuropsychological consequences. COVID-19-related psychosis has been reported, including structured delusions and pseudodementia.⁵² The potential for subtle alterations in somatic, emotion, and behavioral neural circuitry may lead to persistent alterations in the psychological state. Survivors of the severe presentations of COVID-19 will also suffer the neuropsychological sequelae related to critical illness stressors, lengthy hospitalization, and intensive care interventions. Many of these individuals will suffer ongoing medical and psychological morbidity associated with their critical illness and its care, including posttraumatic stress disorder, obsessive compulsive disorder, and major depressive disorder.⁸⁶

3. Postviral fatigue syndromes

The tissue-specific complications noted above ultimately may not be the most prevalent source of aversive morbidity from the COVID-19 pandemic. Postviral fatigue syndromes have been increasingly recognized within the medical community, with the term coming into use in the late 1980s.⁷ Initial descriptions describe an aversive constellation of symptoms where the "principle symptom is severe muscle fatigability, but there may be a range of secondary symptoms, such as the aching of muscles, disequilibrium, and psychiatric manifestations."¹² Cognitive alterations, unrefreshing sleep, and postexertional malaise are also common symptoms that have been additionally recognized. Prospective studies estimating the incidence of postviral fatigue syndromes range between 10% and 12% for a variety of infections, including viral meningitis, Epstein-Barr virus, and Ross River Virus.^{44,50} Even if COVID-19 has an incident rate that is one-tenth of these other viruses, it suggests that a million cases of post-COVID-19 fatigue syndrome may emerge from the pandemic.

It is difficult to pin-point when medical science became aware that viral infections are temporally related to chronically fatiguing syndromes. The existence of pathogens smaller than bacteria was first described by Löffler and Frosh in 1898 using a Chamberland filter, but viruses would not be visualized until the invention of electron microscopy in 1931. It was recognized that filter-passing agents could cause chronic neurological complications as early as 1908 with Landsteiner and Popper's identification of poliovirus. However, there was little recognition at that time of a relationship of infections to a chronically fatiguing syndrome. Syndromes of pain and fatigue of that age, such as fibrositis and neurasthenia, were not generally considered linked to infections. The first to do this was Evans' 1934 description of chronic brucellosis.³³ She described a brucellosis-related syndrome that was typically diagnosed as neurasthenia, characterized by "exhaustion, insomnia, irritability, and complaints of aches and pains for which no objective signs can be found."

Before that time, chronic fatiguing symptoms were not typically described as consequences of infectious epidemics. Today, it might be expected that the "Spanish" influenza pandemic of 1918 to 1919 would have been accompanied by a surge of postinfectious fatiguing symptoms. However, such an event is not reflected in the medical literature. It was not due to a lack of expert medical observational skills. Von Economo's descriptions of how a filter-passing agent caused "the sleepy sickness" and the postinfectious Parkinsonism that followed in encephalitis lethargica patients was exceptional contemporary work.⁶³

H1N1 influenza has been later shown capable of creating postviral fatiguing symptoms in modern reports.^{66,93} Why there is no obvious record of a "post-Spanish flu syndrome" may relate to several factors. In part, it may reflect the period's tendency to attribute somatic symptoms to psychiatric causation, perhaps as part of the "psychoses of influenza".⁴⁷ It may also reflect a generational stoicism and selective amnesia that led societies to put the consequences of the pandemic behind them swiftly, with such success that historians consider the 1918 influenza a "forgotten" event.⁴⁸

At the same time Evans' described chronic brucellosis, the first report of fatiguing symptoms occurring during acute epidemic was described by Gilliam. His 1934 description of "atypical poliomyelitis" at the Los Angeles County Hospital included rapid muscle weakness, vasomotor instability, clonic twitches and cramps, ataxia, severe pain aggravated by exercise, neck and back stiffness, menstrual disturbance, and dominant sensory involvement.⁴⁰ Similar symptoms emerged as part of other epidemic outbreaks, including 1948 Akureyri Disease, 1955 Royal Free Hospital benign myalgic encephalomyelitis, 1984 Incline Village Chronic Fatigue Syndrome, and 1985 Lyndonville Chronic Fatigue Syndrome among others.^{1,5,455} As described by Ramsay, cases started with generalized respiratory, gastrointestinal, or vertiginous symptoms which evolved into chronic fatiguing symptoms. Lymphadenopathy was a notable feature of many, but not all patients during these epidemics.⁸² These epidemics provoked scientific and societal interest in the concept of postviral syndromes. To date, no decisive evidence of an infective agent being the cause of these epidemics was ever demonstrated, creating controversy over the nature of these events.^{31,70,97}

In contradistinction, there is little controversy that Epstein-Barr Virus (EBV) can lead to postviral fatiguing symptoms. In its report on myalgic encephalomyelitis/chronic fatigue syndrome, the Institute of Medicine noted that EBV is the only virus consistently associated with the development of chronic fatiguing symptoms.²⁵ Mononucleosis typically presents with malaise, headache, and low-grade fever that presage oropharyngeal inflammation, lymphadenopathy, and fevers. Prolonged recoveries after the resolution of viremia requiring months to a year are very common. The prevalence of prolonged symptoms after EBV ranges from 1.5% to 56% in the literature.¹⁹ Epstein-Barr Virus infections have been temporally related to chronic fatiguing symptoms.⁸⁷ Several prospective studies have demonstrated that EBV infection can be a trigger postviral fatigue syndrome.^{18,34,44,98} There are some immunological differences noted in those who develop symptoms after infection. High titers of certain antibodies to EBV, including viral capsid antigen (VCA) IgG, persistent titers of VCA immunoglobulin M, or the persistence of early antigen IgG have been associated with the development of chronic fatiguing symptoms, whereas healthy individuals who were previously infected with EBV had only VCA IgG and nuclear antigen IgG antibodies.^{54,62,64,68,84} Some studies, however, including a study of twins discordant for disease,⁵⁵ were unable to find this difference.^{36,42,69,90} Differential kinetics of anti-EBV antibody development and immune protein production has also been described.¹⁸ Premorbid lifestyle factors have also been related to prolonged recoveries.⁷⁹ Unfortunately, the studies above provide little insight into the underlying biological mechanisms responsible for delayed EBV viral recovery.

4. Coronavirus and postviral syndromes

Today, it is generally accepted that a proportion of patients will develop prolonged symptoms after viral infections. Review of outcomes from prior coronavirus epidemics suggest that coronavirus infections are sufficient to cause a postviral

syndrome. Studies of survivors of the 2003 severe acute respiratory syndrome (SARS) epidemic suggest that nonspecific pain, fatigue, and mood alterations in the absence of demonstrable pathology are the most common aversive outcome. A recent meta-analysis of 5 survivor studies describe mostly psychological issues in the wake of SARS, with substantial rates of posttraumatic stress disorder [23.3%-42%], depression [15.6%-40.7%], and anxiety [15.2%-51.5%] after follow-up periods between 12 and 48 months.² However, only 1 of the 5 studies queried fatigue and pain. Of 181 SARS survivors followed over a mean of 41.3 months, 15.5% reported a somatic pain disorder. Of the 146 survivors completing fatigue instruments, 40.3% had persistent fatigue, and 27.1% met the modified CDC 1994 chronic fatigue syndrome criteria. Overall, SARS survivors scores on the SF-36 after 6 months were lower than both population norms and those with chronic conditions. Another small Canadian study of SARS and 2 small studies of Middle East respiratory syndrome survivors reported similar results.^{9,11,58} Taken together, coronavirus epidemics demonstrate a temporal relationship to the development of postviral fatigue syndromes. However, it is important to recognize that these small studies all suffer from substantial ascertainment and attrition biases that make their epidemiological estimates unreliable.

These observations of persistent aversity from other coronavirus epidemics suggests that similar issues will be observed in COVID-19 survivors, except in an exponentially larger scale. Six months into the pandemic, this may already be coming to pass. Numerous reports about COVID-19 “long-haulers” have been described in both medical journals and the lay press.^{27,75} Reports of nonlinear improvements with symptoms such as fatigue, headache, chest pain, musculoskeletal pain, shortness of breath, chronic cough, cognitive alterations, sleep disturbances, anxiety, exercise intolerance, and autonomic symptoms have been well described.^{49,65} A patient-led effort to describe long-haul symptoms identified 62 unique symptoms.⁵⁹ At least one case report of a presentation with lymphatic involvement resembling that seen in prior epidemic fatiguing syndromes has been published.⁶⁰ It seems obvious that the COVID-19 virus is sufficient to trigger a postviral syndrome. The descriptions to date resemble the range of historic postinfectious syndromes that currently do not have an organically demonstrable basis, providing a unique research opportunity to better understand the pathophysiology of postviral syndromes.

5. Sociocultural impact

The COVID-19 pandemic is also an unprecedented sociocultural event. COVID-19 has transformed how people consider their health, gather in groups, and navigate their daily lives and will impact the health of even those that were never infected. These times have created severe health, social, and financial uncertainties for many citizens of the United States. The 2003 SARS epidemic and the COVID-19 experience in China has been associated with moderate to severe anxiety, depression, and insomnia. Distress related to SARS in hospital workers was observed to persist for years for some, and COVID-related stress has led to recent prominent suicides.^{57,63,96} Financial downturns, job loss, and increased parental stresses from school closures with teleworking have also been observed to increase stress, depression, anxiety, domestic violence, divorce, and problematic drug and alcohol use that can persist over years.^{24,35,61} Social isolation and quarantine are factors that increase the risk of developing mental health disorders.^{29,39} These omnipresent stresses will have biological ramifications, leading to alterations of neuronal structure and function in all of us.

6. Conclusions

The COVID-19 pandemic is certain to leave a substantial burden of health issues in its wake. The problems caused by direct tissue injury and the body’s responses should be observable and are anticipated to follow typical clinical courses. For each of these clinical COVID-19 “faces,” there are pathways to the development of long-term pain and disability. The unprecedented sociocultural stresses of the pandemic will have an invisible, ubiquitous, and predictable impact on neurologic, endocrine, and immune functioning, even in people untouched by the virus.⁵¹ We suspect the most complex problems will arise at the neuropsychiatric level, created from the interactions between the neuronal specificities of COVID-19, the functional architecture of the brain, the mechanisms of neuronal injury, healing, and plasticity, and how these neuronal mechanisms are influenced by the concomitant activation of biological stress mechanisms invoked by critical illness and sociocultural stressors. We anticipate that the most common sequelae to COVID-19 will be a postviral fatiguing syndrome and its persistent mix of somatic and psychiatric complaints in the absence of a clearly observable cause. We also suspect that COVID-19 may have a surprise or two in store, with unique clinical presentations and novel mechanisms of injury which are yet to clearly emerge.

These predictable difficulties also represent a unique opportunity to start to unravel the physiology that underlie postviral syndromes, including how viruses may trigger cancers and neurological disease. This may be the first time in the human history where it is feasible to prospectively study the mechanistic changes that accompany the shift from a state of normal health to that of a postviral fatiguing syndrome. Insights gleaned from such studies of COVID 19 infection could provide new understandings to similar disorders, such as fibromyalgia, ME/CFS, and Gulf War Illness. A better mechanistic understanding of pain and fatiguing disorders as they occur in real time seems the most likely way to develop targeted interventions and providing hope to COVID-19 survivors for meaningful treatments and cures.

Disclosures

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