Chronic fatigue syndrome following infections in adolescents

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**Purpose of review**
To review the recent epidemiology, pathophysiology, and treatment of postinfectious chronic fatigue syndrome (CFS) in adolescents.

**Recent findings**
Thirteen percent of adolescents (mainly women) met the criteria for CFS 6 months following infectious mononucleosis; the figure was 7% at 12 months and 4% at 24 months. Peak work capacity, activity level, orthostatic intolerance, salivary cortisol, and natural killer cell number and function were similar between adolescents with CFS following infectious mononucleosis and recovered controls. Autonomic system, oxygen consumption, peak oxygen pulse, psychological and cytokine network differences were documented between those who recovered and those who did not.

**Summary**
The prognosis of CFS is better in adolescents than in adults. Activity level, exercise tolerance, and orthostatic testing could not distinguish patients with CFS from adolescents who have recovered from infectious mononucleosis (controls), while certain cytokine network analyses, life stress factors, and autonomic symptoms could.

**Keywords**
chronic fatigue syndrome, infectious mononucleosis, postinfectious fatigue

**INTRODUCTION**
Fatigue is a common complaint. A total of 10–20% of patients seeking care from internists complain of fatigue [1,2].

Fatigue can follow many systemic infections, but usually not minor ones, as demonstrated by White et al. [3], who assessed patients 16–65 years of age for the development of fatigue with either glandular fever (the British term for infectious mononucleosis) or an upper respiratory tract infection (URI). Nine percent of patients with glandular fever, whether because of Epstein–Barr virus (EBV, the most common cause of infectious mononucleosis/glandular fever) or a different causative agent, were fatigued and complained of excessive sleeping at 6 months, compared with none in the URI group. Other systemic diseases (mainly infectious) have also been associated with post-illness fatigue, including Q fever and Ross River virus (both common infections in Australia [4]), sarcoidosis [5,6], enteroviruses [7], St Louis encephalitis [8], toxic shock syndrome [9], brucellosis [10], parvovirus B19 [11], giardiasis [12,13], Lyme disease [14], and severe acute respiratory syndrome (SARS, a coronaviral infection [15]).

Chronic fatigue syndrome (CFS) is defined as at least 6 months of severe fatigue and disabling musculoskeletal and cognitive symptoms (impairment in short-term memory or concentration, headache, tender lymphadenopathy, muscle or joint pain, unrefreshed sleep, and postexertional malaise lasting >24 h) without another explanation [16]. About 10% of adults 6 months following infectious mononucleosis or other similar systemic infections fulfill
Infectious diseases and immunization

KEY POINTS

- About 13% of adolescents, mainly women, met the criteria for CFS 6 months following infectious mononucleosis, and at 12 and 24 months' follow-ups 7 and 4% of adolescents met the criteria, respectively.
- Adolescents who met the criteria for CFS 6 months following infectious mononucleosis were able to exercise to the same extent as recovered controls, although less efficiently, and appear to be just as active.
- There were no significant differences in the standing orthostatic tolerance testing or NK cell function between those with Pi-CFS and those without it.
- Significant differences between those adolescents who did and did not go on to develop CFS following infectious mononucleosis emerged for autonomic symptomatology, network analyses involving cytokine profiles, life stressors, and psychological risk factors.

the criteria for CFS [4,17]. Conversely, anywhere from about 15 to 90% of adolescents with CFS can identify a trigger, often an infection [18–23]; the number of adults who can identify an infectious trigger for their CFS tends to be lower [24].

However, these disorders are not necessarily a cause of CFS [25]; it is rather that following these inflammatory conditions one is more than occasionally left with a fatigued patient who meets the criteria for CFS. Why this happens has been the subject of much investigation. Some studies purport to show a direct, lingering infection with the inciting pathogen, such as the presence of parvoviral DNA in plasma [26], or enteroviral sequences in muscle [27], although these findings have been challenged [28,29]. Others have insisted on a purely psychological explanation for the development of CFS following an infectious trigger [30].

Those who favor psychological explanations of postinflammatory CFS argue that stressful life-events can contribute to CFS following viral infection. Theorell et al. [31] measured the relationship between CFS onset, stressful life-events, and infections in 46 patients with CFS and matched controls. Patients with CFS demonstrated a greater prevalence of negative life-events 3 months prior to CFS onset. Ray et al. [32] demonstrated an association between negative life-events and anxiety among patients with CFS. Buchwald et al. [17] found that a greater number of stressful life-events predicted a functional and fatigue symptom profile consistent with CFS at 6 months. Salit [33] found that stressful life-events were common in the year preceding fatigue onset. Jason et al. [34] indicated that half of the patients with CFS were able to identify a stressful event occurring at the time of onset. Hatcher and House [35] found that patients with CFS had more severe events and difficulties than controls 3 months and 1 year prior to the onset of CFS. These findings suggest that stressful life-events play a role in postinfectious CFS; yet, they are not consistently observed [3,36].

Those who favor biological causes for postinfectious CFS usually point to data related to the severity of the initial infectious trigger, autonomic system dysfunction, and abnormalities of the immune system. For example, Hickie et al. [4] found that the severity of the acute illness correlated with the development of CFS in adults, although specific measures of infectious mononucleosis severity were not detailed. Chretien et al. [37] showed that the gastrointestinal symptoms, such as anorexia, nausea or vomiting, and palatal petechiae correlated with prolonged recovery from infectious mononucleosis. Taylor et al. [38] found that higher baseline fatigue scores predicted greater fatigue severity at follow-up. Finally, Macsween et al. [39] have recently shown a statistically significantly longer duration of fatigue following infectious mononucleosis in women who could not walk 100 m at the time their acute illness was most severe.

Symptoms of autonomic system dysfunction have also been examined. In adults with CFS, about 75% have symptoms indicative of autonomic dysfunction [40]. There is also a high rate of orthostatic intolerance in adolescents with CFS referred to tertiary care centers, and there is much overlap between the symptoms of orthostatic intolerance, such as fatigue, nausea, headache, exercise intolerance, sleep disturbance, and cognitive problems, and those of CFS [41–49].

Whether hypothalamic–pituitary–adrenal (HPA) axis abnormalities accompany CFS is controversial. The HPA axis is activated by stress, Addison’s disease can cause a clinical picture similar to CFS, and HPA dysregulation may be seen with depression. Salivary cortisol has been shown to be the best way to assess cortisol levels because it avoids the stress of venipuncture. Previous studies in adults have reported mixed results regarding CFS and salivary cortisol [50–57].

Finally, the most consistently reported immunological abnormality, at least in adults with CFS, is abnormal natural killer (NK) cell number and function [58]. Cytokines have also been examined. Early measurements of cytokine concentrations in blood samples from patients with CFS produced discordant results due in part to the differences in the case definition used and the methods of sampling and analysis (reviewed in [59]). Limiting factors also included the focus on a varied but narrow selection...
of cytokines [60], as well as conventional univariate analysis that did not account for the coordinated and context-specific expression of cytokines [61].

**CHARACTERIZATION OF POSTINFECTIOUS CHRONIC FATIGUE SYNDROME IN ADOLESCENTS**

To better understand postinfectious chronic fatigue syndrome (PI-CFS), we undertook a prospective study of 301 adolescents with heterophile-positive infectious mononucleosis in the greater Chicago area [62]. The vast majority of cases of heterophile-positive infectious mononucleosis are caused by EBV [63].

**Methodology**

A telephone screening interview identified those not fully recovered (70 patients), 53 of whom, along with 50 recovered controls, agreed to a clinical evaluation 6 months following infectious mononucleosis and clinical evaluations at home 12 and 24 months postinfectious mononucleosis. All evaluations included NK cell quantitation and functional analysis, and morning and evening salivary cortisol measurements that were performed blinded to patient diagnosis (B.Z. Katz, D. Zimmererman, M.R.G. O’Gorman, et al., submitted). Fatigue was assessed using the Chalder Fatigue Scale [64], the CFS Screening Questionnaire, the Fatigue Severity Scale, and the Modifiable Activity Questionnaire [65–68]. Autonomic symptoms were assessed using the Autonomic Symptom Checklist – Patient Version (ASC), adapted from The Autonomic Symptom Profile [69], which has been validated for CFS [40] and has been used down to age 12 [70]. The 6-month clinical evaluation was performed in a clinical research center and consisted of a complete history, physical examination and laboratory screening to rule out medical or psychological causes of fatigue (e.g., anemia, hypothyroidism, depression). Twelve and 24 months following the diagnosis of infectious mononucleosis, patients were evaluated in their homes, with the same blood, urine, and saliva testing, history, interviews, and measures used at the 6-month clinical visit. We used the Jason et al. [71] revision of the Fukuda [16] criteria to diagnose CFS. When a well-recognized underlying condition, such as primary depression, could explain the patient’s symptoms, that patient was classified as having ‘CFS-explained’. Using the clinical data from the 6-month evaluation, the physicians examining the patients made a diagnosis of CFS, CFS-explained, or recovered on each patient; these diagnoses were then reviewed by an expert panel before being permanently assigned to the patient.

Standing orthostatic tolerance testing (SOTT) was performed by nurses blinded to patient category (recovered vs. nonrecovered) at the 6-month visit. Interpretation of SOTT data was performed by an expert blinded to subject diagnosis [72].

A subset of CFS case patients and controls participated in a graded, maximal exercise tolerance test following the 6-month visit. Participants’ saliva was collected 10 min before, immediately after, and 60 min after the exercise tolerance test to measure cortisol, a known stress response to exercise. Spirometry was performed before the exercise test to measure forced expiratory volume in 1 s (FEV1). Peak work capacity (exercise tolerance), oxygen consumption, and oxyhemoglobin saturation were monitored. Technicians administering the exercise test and the pulmonologist interpreting the test were blinded to the subject diagnosis [73].

**Results**

Similarly to what had been seen in adults [3,4,17,52,74], 6, 12, and 24 months following infectious mononucleosis, 13, 7, and 4% of adolescents, respectively, met criteria for CFS [62], and, at all time points examined, significantly more persistently fatigued patients were women. When the course of fatigue over time was examined for the 13 adolescents who retained the diagnosis of CFS at 24 months, there was a general trend for the fatigue to peak at 12 months. Although 20–30% of adolescents in our cohort were treated with steroids during the course of their acute illness, there was no significant association between the treatment with steroids and the development of CFS [62].

Twenty-one of the 39 adolescents diagnosed with CFS at 6 months (18 women) and 21 of 50 recovered controls (18 women) participated in the exercise tolerance test. There was no difference between cases and controls who did and did not undergo exercise testing, nor were there significant differences in age, sex, stature, weight, body mass, baseline spirometry, or baseline oxyhemoglobin saturation between CFS patients and recovered controls. Surprisingly, the peak work capacity (a global indicator of exercise tolerance) was similar for both CFS and recovered controls. However, oxygen consumption was significantly higher in the control group, indicating that patients with CFS had a lower degree of fitness than the recovered controls. Measures of ventilator response (respiratory rate and minute ventilation at peak exercise), gas exchange (respiratory quotient and peak end-tidal CO2), and peak heart rate (HR) were also similar.
between patients with CFS and recovered controls. Peak oxygen pulse was significantly higher in the recovered controls, again implying that recovered controls exercised more efficiently than patients with CFS. Though there seemed to be a greater rise in salivary cortisol levels in response to exercise in recovered controls (51% increase) compared with patients with CFS (7% increase), this was not statistically significant. A sluggish cortisol response in patients with CFS would also be consistent with patients with CFS exercising less efficiently than recovered controls [73].

Similarly, there was no correlation between the abnormalities on orthostatic tolerance testing and the diagnosis of CFS at 6 months. Twenty-seven of 36 patients with CFS had normal SOTT (75%) compared with 34 of 43 recovered controls (79%). Two patients with CFS vs. four recovered controls had either syncope or presyncope during the SOTT. Peak HR differences were also similar between cases and recovered controls, as were the number of cases and recovered controls with HR greater than 115 beats/min. There was no correlation between those with abnormal exercise testing and those with either syncope or presyncope [72]. Perhaps we did not see a relationship between orthostatic intolerance and CFS, as has been found by others [40–49], because our cohort consisted of all comers with infectious mononucleosis rather than a population of patients with CFS referred to a tertiary care center.

Despite reporting higher fatigue severity than controls, adolescents who later developed CFS did not differ significantly from recovered controls in their activity levels during their bout of infectious mononucleosis, and at the 24-month time point there were no significant differences in sleep or activity level between adolescents with CFS and recovered controls (although power was restricted in these analyses because of smaller sample sizes). Indeed, the only differences seen were at the 6-month and 12-month time points, at which adolescents with CFS napped more during the day [75].

Nine of the 13 adolescents who continued to meet criteria for CFS 24 months following infectious mononucleosis and nine recovered controls matched for age, sex, and Tanner stage had blinded NK cell quantitation and functional analysis at 6, 12, and 24 months following infectious mononucleosis. There was no difference in NK cell numbers (percentages) between cases and recovered controls at any of the three time points examined. NK function was also not significantly lower in case patients with CFS 6 months following infectious mononucleosis than in recovered controls at 6, 12, or 24 months (B.Z. Katz, D. Zimemerman, M.R.G. O’Gorman, et al., submitted). Perhaps our results differ from many of those previously reported because of our having restricted our study to adolescents.

These same nine adolescents with CFS 24 months following infectious mononucleosis and nine matched, recovered controls had morning and nighttime salivary cortisols measured (and interpreted) blindly using standard methodology 6, 12, and 24 months following infectious mononucleosis. There were only three depressed morning salivary cortisols among the patients with CFS, while among the recovered controls there was a single depressed nighttime cortisol (B.Z. Katz, D. Zimemerman, M.R.G. O’Gorman, et al., submitted).

**RISK FACTORS FOR THE DEVELOPMENT OF POSTINFECTIOUS CHRONIC FATIGUE SYNDROME**

A total of 38 of 39 adolescents diagnosed with PI-CFS at baseline, 34 of 39 diagnosed with PI-CFS 6 months following infectious mononucleosis, 20 of 22 diagnosed with CFS at 12 months, and all 13 diagnosed with PI-CFS at 24 months, along with the recovered controls, completed the ASC. Baseline was a median of 2 months following infectious mononucleosis. Four cases were men, as were 12 recovered controls.

**Medical**

There was no difference between cases and controls who did and did not complete the ASC in age, socioeconomic status, body mass index, or modifiable activity questionnaire responses. Adolescents diagnosed with PI-CFS and recovered controls did not differ significantly in age, weight or body mass index. The ASC at baseline, 6, 12, and 24 months following infectious mononucleosis in patients diagnosed with PI-CFS was always statistically significantly higher than the ASC of the recovered controls. Thus, the ASC at baseline was able to distinguish those adolescents who were able to meet the criteria for CFS 6, 12, and 24 months following infectious mononucleosis, arguing that adolescents destined to develop CFS following infectious mononucleosis may have a preillness disposition to autonomic dysfunction [76**].

Two studies have prospectively evaluated the cytokine production in patient populations, in which the infectious trigger of CFS has been uniform and supported by serology. In the Dubbo Australian cohort study, in which CFS followed either infectious mononucleosis/glandular fever, Q fever, or Ross River virus, no differences were seen in the ex-vivo production of eight cytokines (IL-1 beta, IL-2, IL-4, IL-6, ...
IL-10, IL-12, TNF-alpha, and IF-gamma) in 22 case patients vs. 42 recovered controls over a 12-month period following acute infection [77]. In contrast, in our sample, Broderick et al. [78] found that the levels of the proinflammatory cytokines IL-2 and IL-6 trended higher in patients with PI-CFS than those without PI-CFS, while lower levels of IL-23 and higher levels of IL-8 (another proinflammatory cytokine) were seen in CFS patients following infectious mononucleosis compared with recovered controls. Using network analysis, Broderick et al. [78] were able to classify patients based on the levels of IL-2, IL-6, IL-8, and IL-23 into the case patient or recovered control group with an accuracy exceeding 80% when applied relative to interferon gamma (IF-gamma, another proinflammatory cytokine) concentration. Probable explanations for the differing results between our study and the negative results from the seminal Dubbo trial are that IL-8 and IL-23 were not measured in the Dubbo study and that network analysis was not performed [77]. If confirmed, using network analysis, these cytokines (IL-2, IL-6, IL-8, and IL-23 relative to IF-gamma) may be able to differentiate those adolescents who do and do not develop CFS following infectious mononucleosis.

**Psychological**

Two recent, prospective trials have examined the possible psychological risk factors leading to the development of CFS following infectious mononucleosis. In the first, 737 patients with infectious mononucleosis/glandular fever were identified; 440 of these patients were successfully contacted and sent baseline questionnaires. A total of 260 useable questionnaires were returned, of which 14 were excluded because of a previous diagnosis of CFS, another medical condition which could produce fatigue or an excessive time lag between the receipt of the questionnaire and the diagnosis of glandular fever. The mean age of the remaining 246 patients was 23 years, 62% of whom were women; 217 of these patients returned follow-up assessment questionnaires 6 months later. Almost 8% of patients in this study met criteria for CFS at 6 months, 94% of whom were women. The average age of patients who developed PI-CFS was a bit younger (19 years) than those who did not. Symptoms during the acute illness were no different between cases and recovered controls. Logistic regression analysis revealed that psychological risk factors for the development of PI-CFS included anxiety, depression, somatization, perfectionism, negative illness beliefs (e.g., believing infectious mononucleosis/glandular fever to be a serious illness), and responding to symptoms with an all-or-nothing behavior pattern (i.e., overdoing things and then needing to rest); the latter was the single most psychologically predictive factor for developing PI-CFS at 6 months [79**]. Perceived stress and consistently limiting activity at the time of the acute illness were not associated with PI-CFS at 6 months.

In our adolescent cohort, perceived stress and stressful life-events at baseline, and difficulty functioning and attending school following infectious mononucleosis (e.g., days spent in bed, school days missed, and difficulties with learning/concentrating/remembering) were associated with PI-CFS at 6 months, while family stress around, prior to and following infectious mononucleosis and psychiatric disorders were not (L.A. Jason, B.Z. Katz, Y. Shiraishi, et al., submitted). Why these two well-done, prospective studies yielded different psychological risk factors is unclear, although the same measures were not used in both studies, our cohort was slightly younger (all patients 12–18 years of age) and our study design allowed more complete follow-up.

**PROGNOSIS AND TREATMENT**

The prognosis for CFS is generally better in adolescents and young adults than in older individuals, probably because CFS in young adults is more likely to be postinfectious. However, Brown et al. [80**] examined long-term health, symptom, and disability outcomes between 25 adolescents diagnosed with CFS 25 years previously and healthy controls. Five reported that they maintained a diagnosis of CFS, while 20 reported no longer having that diagnosis. Those who reportedly remitted from CFS still showed significant impairments on 21 of 23 outcomes, compared with healthy controls. This study suggests that, over time, many individuals will not maintain a CFS diagnosis but will not return to their premorbid level of functioning.

Nonpharmacologic treatments that have shown benefits in CFS have included recumbent or semirecumbent graded exercise [81] and cognitive behavioral therapy (CBT) [82]. However, Price et al. [83] recently reviewed 15 studies of CBT. At the end of treatment, 40% of those in the CBT group showed clinical improvement, in contrast to only 26% in usual care, but changes were not maintained at a 1–7-month follow-up. However, a large, prospective, unblinded treatment trial recently demonstrated the efficacy of an internet-based CBT platform (FITNET) for Danish adolescents with CFS and their parents [84*]. Adolescents 12–18 years of age were randomized to either FITNET or standard therapy, which often included standard face-to-face CBT and a graded exercise program; cross-over could
occur after 6 months. Nearly 70 patients were in each group, 80–85% of whom were women. About 25% of the patients stated that their symptoms began after infection. At 6 months, school attendance, fatigue severity, and physical functioning were significantly more likely to have improved in the FITNET group, and those patients rated themselves as either completely recovered or much better nearly 80% of the time vs. only about 30% in the control group. These improvements were sustainable to 12 months, and the same percentage of adolescents who crossed over to the FITNET group at 6 months improved by 12 months. It is likely that involving both parents as well as the convenience and ease of use of the internet played a role in this program’s success for adolescents. However, the response rate in the control group was lower than is often reported in adolescents, perhaps because patients knew they could cross-over to the FITNET group at 6 months [85].

Finally, Envelope Theory provides an alternative approach to the rehabilitation management of CFS. This theory posits that healthcare professionals who treat patients with CFS incorporate strategies that help patients self-monitor and self-regulate energy expenditures. Proof of concept of envelope theory comes from Jason et al. [86], who performed a randomized trial of several nonpharmacologic interventions for CFS. About 100 patients with CFS were randomly assigned to four interventions. Baseline, posttreatment, and 6-month and 12-month follow-up data were collected. Although there were some differences among the four types of interventions, overall, patients demonstrated general improvement across interventions. Jason et al. [87] then divided this sample into two groups of patients: those who were able to keep expended energy close to available energy and those who were not able to do so. Those who were able to stay within their ‘energy envelope’ had significant improvements in physical functioning and fatigue severity. A review article on envelope theory provides more examples of this promising approach that certainly needs more clinical trials to determine its long-term efficacy [88].

CONCLUSION

Autonomic symptoms at baseline may be predictive of those adolescents who go on to develop CFS following infectious mononucleosis, arguing that adolescents destined to develop CFS following infectious mononucleosis have a preillness disposition to autonomic dysfunction. In addition, network analysis may allow a cytokine profile to differentiate those adolescents who do and do not develop PI-CFS. Some factors such as life stressors may pose a risk for the development of PI-CFS, but psychiatric disorders do not. More research has been directed at recumbent graded exercise and cognitive behavioral therapy than alternative approaches such as the envelope theory, and interventions implemented via the internet hold promise; however, most treatment trials for adolescents have not had long-term follow-ups, thus making definitive conclusions difficult. There is a need for more pharmacologic and nonpharmacologic treatment trials to identify the best way to help adolescents with this condition.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the period of review, have been highlighted as:

■ of special interest

** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 156).


This study shows that, at a median of 2 months following the diagnosis of infectious mononucleosis, adolescents fated to develop CFS had many more autonomic complaints than those fated to recover.
This study describes a cytokine profile that was able to distinguish those adolescents with CFS 24 months following infectious mononucleosis from recovered controls.
This study was the first prospective cohort study to describe psychological risk factors which favor the development of CFS following infectious mononucleosis / glandular fever.
This is the first long-term follow-up study of adolescents with CFS.
[Accessed August 2012]
A promising trial of internet-based CBT for adolescents with CFS.