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Therapeutic plasma exchange and immunomodulatory strategies in post-infectious syndromes: A review of immune dysregulation in PTLDS, long COVID, ME/CFS, and PANS/PANDAS

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ABSTRACT

Post-infectious syndromes including post-treatment Lyme disease syndrome (PTLDS), long COVID, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and pediatric acute-onset neuropsychiatric syndrome (PANS)/pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) share overlapping clinical phenotypes characterized by fatigue, cognitive dysfunction, sleep disturbance, and neuropsychiatric symptoms. Increasing evidence suggests that immune dysregulation—including persistent inflammation, autoantibody production, and cellular immune dysfunction—may underlie these conditions. This narrative review synthesizes peer-reviewed literature describing immune abnormalities across these syndromes and evaluates the rationale for immunomodulatory therapies, including intravenous immunoglobulin (IVIG), rituximab, and therapeutic plasma exchange (TPE). Evidence supporting immune-targeted treatment strategies is strongest in subsets of patients with identifiable immunologic abnormalities. Notably, the phase III RituxME trial in ME/CFS and a phase II trial of TPE in post-COVID condition both failed to demonstrate efficacy in unselected populations, reinforcing the importance of biomarker-guided patient stratification. TPE functions by removing circulating immune complexes, autoantibodies, and inflammatory mediators, and observational data suggest benefit in patients with demonstrable autoantibody burden. Further controlled studies incorporating immunologic phenotyping and early intervention are needed to define the therapeutic role of immune-directed interventions across these conditions.

1. Introduction

Post-infectious syndromes represent a growing clinical challenge characterized by persistent symptoms following resolution of acute infection. Conditions such as PTLDS, long COVID, ME/CFS, and PANS/PANDAS share overlapping symptom clusters including fatigue, cognitive impairment ("brain fog"), mood disturbances, and autonomic dysfunction [1–3]. Although the etiologies are heterogeneous, converging evidence suggests that immune dysregulation plays a central role in a subset of patients [4,5].

The biological similarities between these post-infectious syndromes have been increasingly recognized. Shared abnormalities include autoantibody production, endothelial dysfunction, mitochondrial impairment, and pro-inflammatory changes in the gut microbiome [5]. Recent advances in deep phenotyping and multi-omics technologies have begun to delineate the immunologic architecture of these conditions with greater resolution, identifying candidate biomarkers and potential therapeutic targets [6,7].

This narrative review evaluates immunologic findings across these syndromes and examines the therapeutic rationale for immunomodulatory interventions, including IVIG, rituximab, and therapeutic plasma exchange (TPE). We emphasize the importance of biomarker-guided patient selection and highlight the implications of recent negative randomized controlled trials for future study design.

2. Methods

This narrative review was conducted by searching PubMed, Scopus, and Google Scholar for English-language peer-reviewed articles published through March 2026 using the search terms "post-treatment Lyme

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disease," "long COVID," "post-acute sequelae of SARS-CoV−2," "ME/CFS," "PANS," "PANDAS," each combined with "immune," "autoantibody," "cytokine," "IVIG," "rituximab," "plasma exchange," and "apheresis." Reference lists of included articles were hand-searched for additional relevant publications. Preference was given to randomized controlled trials, systematic reviews, and studies published in high-impact peer-reviewed journals. This is not a systematic review, and the selection of studies reflects the author's assessment of relevance and quality.

3. Immune dysregulation across post-infectious syndromes

3.1. Post-treatment lyme disease syndrome (PTLDS)

PTLDS is characterized by persistent symptoms—including fatigue, musculoskeletal pain, and cognitive complaints—following appropriate antimicrobial therapy for Lyme disease. The pathogenesis is increasingly understood to involve maladaptive host immune responses rather than ongoing active infection [8]. Proposed mechanisms include persistent immune activation driven by retained spirochetal antigenic material, immune complex deposition, and dysregulated cytokine responses [9].

Recent work has demonstrated that structural components of Borrelia burgdorferi, particularly its chemically unique peptidoglycan, can persist in host tissues weeks to months after antibiotic treatment and drive chronic inflammatory responses [10]. Autoimmune mechanisms have also been implicated: studies of post-infectious Lyme arthritis have shown that a majority of patients develop CD4 + T-cell responses to extracellular matrix proteins including fibronectin, laminin, and collagen, consistent with molecular mimicry or bystander activation [11]. Additionally, genetic factors such as TLR1 polymorphisms have been associated with dysregulated inflammatory responses and heightened risk of persistent post-treatment symptoms [12].

Coinfections with Babesia, Ehrlichia, and Anaplasma, which share the Ixodes tick vector, may contribute to symptom persistence and cumulative immune burden [13–15].

3.2. Long COVID

Long COVID is associated with persistent immune abnormalities that may last months to years following acute SARS-CoV−2 infection. Phetsouphanh et al. demonstrated sustained immune dysregulation at eight months, including altered T-cell phenotypes and elevated cytokines [4]. More recent studies have confirmed activation of pro-inflammatory and immune exhaustion pathways persisting beyond 180 days, with upregulation of JAK-STAT, IL−6, complement, and T-cell exhaustion signatures [16].

Autoantibodies targeting G-protein–coupled receptors and other self-antigens have been identified in affected individuals [17]. A systematic review encompassing 44 studies and 7571 participants found that 71% of studies reported significant associations between autoantibodies and long COVID, with antinuclear antibodies and anti-GPCR antibodies emerging as potential biomarkers [18]. Microvascular and coagulation abnormalities, including persistent fibrin amyloid microclots, have also been described [19].

3.3. ME/CFS

ME/CFS is a chronic multisystem illness characterized by post-exertional malaise, cognitive dysfunction, and unrefreshing sleep. Immune abnormalities include altered cytokine profiles, impaired natural killer (NK) cell function, and evidence of immune activation [20,21]. A landmark NIH intramural deep phenotyping study in 2024 used comprehensive clinical and laboratory evaluation—including neuroimaging, autonomic testing, and cerebrospinal fluid analysis—to characterize post-infectious ME/CFS, identifying sex-specific immune abnormalities and a physiological mismatch between perceived and actual physical capacity [6].

Although an initial phase II trial of rituximab in ME/CFS suggested possible benefit, the subsequent phase III RituxME trial—a multicenter, randomized, double-blind, placebo-controlled study—failed to demonstrate clinical improvement with rituximab compared with placebo (overall response rates: 26.0% rituximab vs. 35.1% placebo) [22]. A six-year follow-up of participants in the RituxME and CycloME trials confirmed the absence of sustained benefit from B-cell depletion [23]. These results did not support a primary role for B-cell depletion in unselected ME/CFS populations, although they do not exclude B-cell–mediated mechanisms in specific immunologically defined patient subsets.

3.4. PANS/PANDAS

PANS/PANDAS are neuropsychiatric syndromes hypothesized to involve autoimmune or post-infectious mechanisms. Molecular mimicry between streptococcal antigens and neuronal tissue may trigger antibody-mediated neuroinflammation [24]. A landmark controlled trial by Perlmutter et al. demonstrated benefit from both IVIG and TPE in children with infection-triggered OCD and tic disorders [25]. More recently, a 2024 study demonstrated that IVIG response in PANS correlates with reduction in pro-inflammatory monocytes, providing a mechanistic biomarker for treatment response [26]. The American Academy of Pediatrics published a clinical report in 2025 acknowledging PANS as a clinical entity while noting that evidence for specific immunomodulatory treatments remains limited by the absence of large randomized trials [27].

4. Rationale for immunomodulatory therapy

4.1. Intravenous immunoglobulin (IVIG)

IVIG has immunomodulatory effects including Fc receptor blockade, neutralization of autoantibodies, and modulation of cytokine production. Its established role in autoimmune conditions provides a biological rationale for use in immune-mediated post-infectious syndromes [28]. Evidence supports its use in PANS/PANDAS, where clinical improvement has been demonstrated in controlled and open-label studies [25,26,29]. In ME/CFS and long COVID, IVIG has been used in small studies and case series with variable outcomes, suggesting potential benefit in immune-mediated subgroups, although large controlled trials are lacking.

4.2. Rituximab

Rituximab, a monoclonal anti-CD20 antibody, depletes B cells and has demonstrated efficacy in several autoimmune disorders. In ME/CFS, early-phase studies suggested clinical improvement in a subset of patients; however, the definitive phase III RituxME trial failed to show benefit over placebo [22]. These negative results highlight the challenge of treating heterogeneous post-infectious syndromes with a single immunomodulatory approach and underscore the need for biomarker-guided patient selection. The lesson from the rituximab experience in ME/CFS—that unselected patient populations may dilute treatment effects in immunologically heterogeneous conditions—is directly relevant to the design of future TPE trials.

4.3. Therapeutic plasma exchange (TPE)

TPE removes circulating autoantibodies, immune complexes, cytokines, and other inflammatory mediators [30]. It is widely used in autoimmune neurological disorders and has a well-established safety profile when performed in appropriate settings [31].

In PANS/PANDAS, TPE has demonstrated clinical benefit in a controlled trial [25]. In long COVID, an observational apheresis study

reported clinical improvement associated with reduction in autoantibodies, lipids, and inflammatory markers [32]. However, a subsequent phase II, double-blind, placebo-controlled, randomized trial (n = 50) did not demonstrate significant improvement in functional status, symptomology, or quality of life with TPE compared with sham exchange [33]. The investigators noted that the average interval from infection to treatment was approximately two years, raising the possibility that earlier intervention during the period of active immune dysregulation may yield different results.

In severe acute COVID−19, meta-analyses have suggested that TPE may reduce mortality through removal of cytokines and correction of coagulopathy [34,35], and mechanistic studies have demonstrated that TPE may accelerate immune cell recovery and modulate T-cell responses [36]. These findings from the acute setting provide pathophysiologic rationale for investigating TPE in chronic post-infectious immune dysregulation, although direct extrapolation must be made cautiously.

4.4. Immunoadsorption as an emerging alternative

Immunoadsorption (IA) is a more selective apheresis technique that removes immunoglobulins while preserving other plasma components. A double-blinded, randomized, sham-controlled trial (IA-PACS-CFS) is currently evaluating immunoadsorption in patients with chronic fatigue syndrome including those with post-acute COVID−19 [37]. This approach may offer theoretical advantages over TPE by selectively depleting pathogenic autoantibodies while minimizing loss of beneficial plasma proteins, and the sham-controlled design addresses a key methodological limitation of prior observational apheresis studies (Table 1).

5. Biomarker-based phenotyping and TPE response

Evidence across these syndromes suggests that subsets of patients may exhibit shared immunologic features amenable to targeted intervention, including elevated inflammatory cytokines (e.g., IL−6, TNF-α, IFN-γ), presence of autoantibodies (e.g., anti–G-protein–coupled receptor antibodies, antinuclear antibodies), complement activation, impaired cellular immunity (e.g., NK cell dysfunction, T-cell exhaustion), and persistent antigenic stimulation or circulating immune complexes.

Patients with these profiles may represent a biomarker-defined responder phenotype more likely to benefit from TPE, which directly removes circulating pathogenic immune factors. The discordance between the observational apheresis data showing autoantibody reduction and clinical improvement [32] and the negative randomized trial [33] is instructive. The negative phase II trial enrolled patients without immunologic stratification and at a mean of two years post-infection, a time point at which immunologic abnormalities may have partially resolved [4]. Future studies should incorporate baseline immunologic profiling—including autoantibody panels, cytokine assays, and complement markers—to identify patients most likely to respond, and should target an earlier intervention window.

6. Outpatient therapeutic plasma exchange safety

Therapeutic apheresis, including TPE, has been shown to be safe in outpatient settings when appropriate protocols are followed. Complications are generally mild and include transient hypotension, citrate-related hypocalcemia, and vascular access issues [30,31]. The American Society for Apheresis (ASFA) guidelines, most recently updated in their ninth special issue in 2023, support the use of TPE in a variety of autoimmune conditions with established monitoring protocols [30].

7. Discussion

Post-infectious syndromes likely represent heterogeneous conditions with overlapping immunologic features rather than a single unified disease entity. Immune dysregulation—including autoantibody production, persistent inflammation, and altered cellular immunity—appears to play a central role in a subset of patients across PTLDS, long COVID, ME/CFS, and PANS/PANDAS. The pathophysiologic mechanisms driving persistent symptoms vary: in PTLDS, retained spirochetal peptidoglycan may perpetuate inflammation [10]; in long COVID, autoantibody production and immune exhaustion appear central [16,18]; in ME/CFS, multi-system immune and metabolic dysfunction has been demonstrated [6]; and in PANS/PANDAS, molecular mimicry triggers antibody-mediated neuroinflammation [24].

Immunomodulatory therapies such as IVIG, rituximab, and TPE may offer benefit in carefully selected patients, particularly those with objective evidence of immune dysfunction. However, recent evidence has provided important lessons. The phase III RituxME trial demonstrated that B-cell depletion with rituximab was not effective in an unselected ME/CFS population [22], and a phase II trial of TPE in post-COVID condition did not show benefit over sham exchange [33]. These findings do not necessarily indicate that immunomodulatory therapy is ineffective in post-infectious syndromes; rather, they underscore that patient selection based on immunologic phenotype and timing of intervention may be critical determinants of treatment response.

The emerging immunoadsorption trial (IA-PACS-CFS) represents a methodological advance by employing sham-controlled design and more selective antibody depletion [37]. Similarly, the identification of pro-inflammatory monocyte reduction as a biomarker of IVIG response in PANS [26] illustrates the potential for mechanistic biomarkers to guide treatment decisions across post-infectious conditions.

Table 1
Summary of immunomodulatory therapy evidence across post-infectious and immune dysregulation syndromes.

Therapy	Condition / Population	Study Type	Key Findings	References
IVIG	PANS/PANDAS	RCT	IVIG significantly improved neuropsychiatric symptoms compared with placebo; response correlated with reduction in pro-inflammatory monocytes.	[25,26]
IVIG	Autoimmune conditions (general)	Review	IVIG is established in autoimmune conditions with immunomodulatory effects including Fc receptor blockade and autoantibody neutralization.	[28]
Rituximab	ME/CFS (B-cell depletion)	Phase III RCT	Phase III RituxME trial: no significant benefit (26.0% vs. 35.1% placebo). Six-year follow-up confirmed absence of sustained benefit.	[22,23]
TPE	Long COVID (autoantibody-mediated)	Observational	Clinical improvement associated with reduction in autoantibodies, lipids, and inflammatory markers following therapeutic apheresis.	[32]
TPE	Long COVID / post-COVID condition	Phase II RCT	No significant improvement in functional status or quality of life with TPE vs. sham exchange (n = 50); mean 2-year delay from infection to treatment.	[33]
TPE	Severe COVID−19	Meta-analyses	TPE associated with reduced mortality in severe COVID−19; cytokine removal and immune modulation proposed as mechanisms.	[34,35]
TPE	Severe infection (immune recovery)	Mechanistic	TPE may accelerate immune cell recovery and modulate T-cell responses in severe inflammatory states.	[36]
IA	Long COVID / ME/CFS	Phase II RCT (ongoing)	Sham-controlled trial of immunoadsorption in CFS including post-COVID patients; selective IgG removal may target autoantibodies more precisely than TPE.	[37]

Future research should prioritize standardized biomarker panels—including autoantibody profiles, cytokine assays, and complement markers—to identify immunologic responder phenotypes prior to treatment; controlled trials of TPE and immunoadsorption with earlier intervention windows and immunologic stratification in long COVID and ME/CFS; comparative effectiveness studies of IVIG, rituximab, TPE, and immunoadsorption in biomarker-defined patient subgroups; and longitudinal immune profiling to define disease subtypes, predict treatment response, and determine optimal timing of intervention.

8. Limitations

This review has several limitations. As a narrative review, the literature search and study selection were not conducted according to systematic review methodology, and the findings may be subject to selection bias. The evidence base for immunomodulatory therapies in post-infectious syndromes remains limited by small sample sizes, heterogeneous study designs, and the absence of validated diagnostic biomarkers for most of these conditions. The syndromes reviewed are clinically defined and may encompass distinct pathophysiologic entities, complicating direct comparisons across conditions. Additionally, publication bias may favor positive findings in observational studies, potentially overestimating the effect of interventions such as TPE. The negative results from randomized trials of rituximab in ME/CFS and TPE in long COVID serve as important counterweights and highlight the gap between observational data and controlled trial evidence.

9. Conclusion

Post-infectious syndromes are increasingly recognized as disorders involving immune dysregulation in a subset of patients. Recent advances in deep phenotyping, autoantibody profiling, and multi-omics approaches have strengthened the immunologic basis for these conditions. Evidence supports the continued investigation of immunomodulatory therapies—including IVIG, rituximab, TPE, and immunoadsorption—particularly when guided by biomarker-based phenotyping. The negative results from recent randomized controlled trials in ME/CFS and long COVID highlight that unselected patient populations are unlikely to demonstrate benefit and that immunologic stratification is essential. Therapeutic plasma exchange represents a mechanistically rational intervention for patients with demonstrable circulating immune mediators; further controlled studies incorporating early intervention, rigorous sham controls, and biomarker-guided patient selection are needed to define its therapeutic role across these conditions.

Declaration of Generative AI and AI-assisted technologies in the writing process

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Declaration of Competing Interest

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