



Expert perspectives on Myalgic encephalomyelitis/chronic fatigue syndrome – Insights from the 3rd International Conference of the Charité Fatigue Center

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ABSTRACT

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, multisystemic disorder mostly triggered by viral infections, with core symptoms including post-exertional malaise (PEM), fatigue, pain, and cognitive dysfunction. Its prevalence has increased significantly in the context of the coronavirus disease 2019 (COVID-19) pandemic. Despite its severity and impact on patients' quality of life, ME/CFS remains poorly understood. On May 12 and 13, 2025, the 3rd International Conference hosted by the Charité Fatigue Center brought together nearly 200 researchers from various disciplines on-site, and around 3,700 participants online to discuss recent advances in ME/CFS research, diagnostics, clinical care, and therapeutic trials. The program featured 33 lectures by international experts on key topics such as post-COVID syndrome (PCS), care structures, and pathophysiological mechanisms including cardiovascular dysregulation, immune dysregulation, autoimmune mechanisms, and metabolic dysfunction. In addition, results from clinical trials addressing disease mechanisms, including those specifically targeting autoantibodies, were presented. While public awareness and funding opportunities have increased in the wake of the pandemic and the emergence of PCS, ME/CFS remains severely underresearched. Sustained and adequately funded research efforts are urgently required to advance understanding, identify diagnostic markers, and develop targeted therapeutic interventions.

1. Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a multisystemic disorder, classified as a neurological condition (ICD-10 G93.3). In most cases, it is triggered by viral infections, such as with Epstein-Barr virus (EBV), influenza viruses, or, more recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Core symptoms include fatigue, sleep disturbances, autonomic and cognitive dysfunction, pain, and post-exertional malaise (PEM). The latter refers to an inappropriate worsening of symptoms following physical or mental exertion. ME/CFS affected an estimated 0.2-1.4% of the population pre-pandemic, [1,2], with prevalence strongly increasing due to the coronavirus disease 2019 (COVID-19) pandemic [3]. Around 50% of patients with ME/CFS are unable to work, 25% are severely affected, and a subset is bedbound. Despite the substantial burden, there is still no specific treatment or adequate medical care [4–8]. While the pathophysiology remains incompletely understood, increasing evidence implicates dysregulation of the immune, nervous, metabolic, and vascular systems. There is an overlap with post-acute infection syndromes (PAIS) which demonstrate similar symptom profiles irrespective of the infectious agent [7,9]. The striking similarities in the clinical picture of post-COVID syndrome (PCS) – also termed Long COVID or post-acute sequelae of COVID-19 (PASC) – with a subset fulfilling diagnostic criteria of ME/CFS have boosted scientific and public attention to ME/CFS and offers an unprecedented opportunity to advance understanding, identify biomarkers, and develop effective therapies. Building on the

insights summarized in the 2023 conference report [10], this year's two-day-meeting started on May 12, 2025 – international ME/CFS awareness day – and aimed to further consolidate emerging research and foster interdisciplinary exchange on ME/CFS and PCS.

2. Post-infectious syndromes – lessons from the COVID-19 pandemic

David Putrino opened the conference by outlining key insights into infection-associated chronic illnesses (IACIs) gained during the COVID-19 pandemic. IACIs are an umbrella term for long-term conditions that are triggered by infections and include PAIS. During hospital overload in the early stages of the COVID-19 pandemic, the use of remote patient monitoring (RPM) technology facilitated patient care while enabling the collection of clinical data, revealing persistent symptoms in approximately 15% of cases [11,12]. Emerging evidence for multi-organ involvement in Long COVID [13] supported hypotheses of pathobiological mechanisms, including immune dysregulation, viral persistence and reactivation, microbiota dysbiosis, autoimmunity, as well as vascular and nervous system impairment [14]. Hallmarks of IACIs such as endothelial dysfunction and associated coagulopathy – with increased fibrinogen deposition, platelet hyperactivity, and red blood cell abnormalities – were identified [15]. Neurological deficits attributed to neuroinflammation were observed even after mild acute illness [16] and immunoglobulins isolated from patients with persistent symptoms lasting longer than six weeks after SARS-CoV-2 infection showed increased reactivity against neural tissue [17]. Putrino also presented preliminary data on sex differences in Long COVID symptom presentations, showing that low testosterone levels were associated with

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female-typical and low estradiol levels with male-typical symptomatology, with hormone levels correlating with respective symptom severity. To advance treatment options, he emphasized the need to address viral persistence and the reactivation of latent viruses [18–20], the recognition of metabolic dysfunction rather than deconditioning as the driver of post-exertional symptoms [21], and concluded by underscoring the complexity of IACIs, emphasizing the necessity of individualized profiling for effective patient care.

ME/CFS has long been neglected and underfunded, but the emergence of PCS as a PAIS has accelerated research progress. As presented by **Carmen Scheibenbogen**, this shift has led to increased public awareness, funding, and the establishment of new biomedical studies and research groups. PEM and fatigue, core symptoms of ME/CFS, were identified early on as frequent symptoms in PCS as well [22]. A 2022 observational study at the Charité Fatigue Center in Berlin, Germany, showed that approximately half of the patients presenting with persistent moderate to severe fatigue and exertional intolerance following mild to moderate COVID-19 after World Health Organization (WHO) criteria fulfilled the Canadian Consensus Criteria (CCC) for diagnosis of ME/CFS [23], with a 2-year follow-up showing little improvement and persistent chronic symptomatology [24]. Current evidence suggests that dysregulation of the immune system, including the presence of autoantibodies, and an imbalance of the autonomic nervous system are key underlying pathomechanisms of the condition. Autoantibodies targeting G-protein coupled receptors (GPCRs) such as adrenergic or muscarinic receptors, have been shown to correlate with symptom severity in PCS and ME/CFS [25–30]. PCS studies have also contributed to a better understanding of ME/CFS associated metabolic dysfunction, with most intriguing findings originating from skeletal muscle studies showing severe impairment of muscle force [23,24,31] as well as metabolic [21,32–34], mitochondrial, and microvascular dysfunction [21,35]. Scheibenbogen emphasized the urgent need for international collaboration and presented a declaration advocating for coordinated efforts in research and therapeutic development. Advances in ME/CFS research are increasingly driven by insights from post-infectious cohorts, including PCS, offering a unique opportunity to advance understanding and treatment of ME/CFS. According to the ME/CFS Research Foundation, PCS and ME/CFS resulted in more than €60 billion in societal costs in Germany in 2024, and modelling suggests persistently high ongoing costs in 2025 and beyond [36]. This considerable cost burden highlights that investing in research is not only urgently needed but also very cost-effective in the long run.

3. Care for ME/CFS

Uta Behrends outlined the work of PEDNET-LC, a nationwide pediatric network in Germany that aims to establish sustainable, state-of-the-art care and research for children and adolescents living with PCS, similar post-acute infection and vaccination syndromes (PAIVS), and ME/CFS [37]. Key pillars of the project are the establishment of 20 interdisciplinary “Comprehensive Care Centers of Long COVID” (CCC-LC), two specialized pediatric pain clinics, three specialized rehabilitation clinics, and eight institutes for medical informatics and health services research. PEDNET-LC focusses on multidisciplinary, sustainable national research and telemedical infrastructure, evidence generation and translation, educational programs, the perspectives of medical professionals, patients, and parents, clinical and translational studies, as well as linked analysis of registry and health insurance data. Patients with complex symptoms that caused participation deficits, PEM, and/or ME/CFS will be referred to their regional CCC-LC for screening and needs-based diagnostics. Structured patient-reported data and data from medical visits are being fed into the network’s PAIVS-MECFS-Registry, which integrates and expands upon the preceding, state-funded German ME/CFS registry (MECFS-R) [38] and the Multicenter Long COVID Registry (MLC-R) [39]. Large medical datasets together with standardized biosamples from patients with PAIVS and/or ME/CFS as

well as from disease controls with similar symptoms but other diagnoses provide the basis for the identification of biomarkers and therapeutic targets in translational studies. In sum, the network integrates more than 90 research partners, including clinicians, scientists, health insurance companies, medical and professional associations, as well as patient organizations.

An introduction to the National Reference Center for Post-viral Syndromes in Austria was provided by **Kathryn Hoffmann** [40]. Hosted by the Medical University of Vienna, and sponsored by the Austrian Federal Ministry of Health, this first-of-its-kind center brings together expertise from multiple medical disciplines working in close cooperation with social insurance providers and patient organizations. Its interdisciplinary work is focused on knowledge processing, the promotion of national and international collaboration, and support for clinical and research exchange. While the center itself does not provide direct medical care to patients, it aims to serve as a central knowledge hub to indirectly improve overall medical care and research by offering training to medical professionals – including assessors – and by disseminating information, such as the recently released consensus-based treatment recommendations, to both practitioners and patients [41,42]. Given the urgent need for standardized care for people living with post-viral syndromes in Austria, the center aims to foster the establishment of dedicated treatment structures.

Another effort to improve the medical care situation of people living with ME/CFS on a national level was presented by **Fridbjörn Sigurdsson**. The Akureyri Clinic in Iceland provides medical care to patients across the country and coordinates healthcare services nationwide, partnering with the national university hospital, rehabilitation centers, and medical professionals. The clinic takes its name from the town of Akureyri, where a localized and well-documented outbreak of ME/CFS occurred in the late 1940s, sparking some of the earliest debates around the disease’s etiology and appropriate terminology [43–47]. To date, the clinic’s interdisciplinary staff has seen around 400 new patients referred to them, mostly from general practitioners, with around half diagnosed with PCS. While the clinic has been tasked with developing a nationwide ME/CFS and PCS registry and currently collects clinical data, using well-established instruments, such as the Functional Capacity Questionnaire (FUNCAP55) [48], additional funding and personnel are required to enable the implementation of a fully operational registry and biobank, as well as the establishment of a collaborative research center.

Claudia Kedor introduced the CFS_CARE study at the Charité Fatigue Center in Berlin, Germany, which investigated the effectiveness of an interdisciplinary care model for patients fulfilling the CCC for diagnosis of ME/CFS [49]. Interventions included diagnostic assessments, and personalized therapy such as pacing, sleep and pain management, nutritional guidance, and social support, aiming to ameliorate symptoms and improve physical health and occupational participation. A total of 240 ME/CFS patients with a disease duration between 6 months and 5 years were randomly assigned to an intervention or a matched control group. Therapeutic implementation included a 5-week stay at the Bavaria Kreischa rehabilitation clinic, and regular evaluations at the ME/CFS outpatient clinic for the intervention group, while controls remained under the care of the referring physicians. Although the rehabilitation program was tailored to ME/CFS with pacing and individualized flexibility, over 50% of patients reported experiencing a PEM episode during their stay. A total of 77% felt that their condition had improved as a result of the rehabilitation, and 74% reported feeling more capable of coping with their illness. Despite this positive assessment, preliminary results indicate that physical functioning assessed via the Short Form 36 (SF-36) health survey did not improve at 12 months [50]. These findings suggest that rehabilitation programs are not universally beneficial for individuals with ME/CFS, and that symptomatic therapy has no significant impact on the clinical course of the disease. A comprehensive analysis of the study is currently ongoing to identify patient subgroups more likely to benefit from rehabilitation interventions as well as those for whom such interventions may be

contraindicated or ineffective.

Michael Stingl outlined his experience in the neurological outpatient care of ME/CFS patients in Vienna, Austria, having evaluated more than 1,000 suspected cases. His approach to diagnosing ME/CFS focuses on the assessment of PEM – the hallmark symptom of ME/CFS – using questionnaires and hand grip strength (HGS) testing [51], alongside a thorough evaluation of differential diagnoses and comorbidities. Stingl routinely discusses PEM with patients over the course of their disease, and repeatedly educates them on the concept of pacing, including the psychological implications of adhering to a strict pacing regime. Identifying and treating common comorbidities, such as postural orthostatic tachycardia syndrome (POTS), small fiber neuropathy (SFN), mast cell activation syndrome (MCAS), immunodeficiencies, hypermobility, and psychological conditions, can reduce the individual symptom burden [41]. Given the limited evidence for pharmacological interventions in ME/CFS, off-label drug treatment should be critically evaluated with regards to its efficacy and tolerability and should be tapered or discontinued if no benefit is evident. If pharmacological intervention results in a stable, gradual improvement, additional treatments may only be administered restrictively. The overall therapeutic goal is to raise the threshold for PEM and improve quality of life. Lastly, the documentation of functional impairments using the FUNCAP55 questionnaire [48], and the evaluation of the need for care assistance, particularly in severely affected patients, are additional building blocks in the holistic care for ME/CFS patients.

The challenge of off-label drug use for PCS in Germany was addressed by **Bernhard Wörmann**. Coordinated by the German Federal Institute for Drugs and Medical Devices (BfArM), an expert commission has been convened to develop recommendations for the pharmacological treatment of symptoms associated with PCS [52]. Several pharmaceutical candidates were evaluated in an evidence-based research approach for their potential efficacy in the treatment of PCS. A literature review of the selected drugs yielded 41 articles suitable for inclusion, out of a total of more than 1,600 initially identified publications, highlighting the significant research gap in PCS drug treatment. Wörmann presented evidence for the potential symptom relief and/or improvement of health-related quality of life of antidepressants (vortioxetine, agomelatine) [53–57], ivabradine [58,59], and low-dose naltrexone [60]. Additionally, a small number of clinical studies were identified investigating beta-blockers, glucocorticoids, midodrine, and pyridostigmine in related conditions, such as ME/CFS and POTS. In contrast, no studies fulfilling the inclusion criteria were found evaluating statins, aripiprazole, and metformin in PCS or related conditions. However, the commission reviewed studies reporting a significant protective effect of low dose metformin against the development of PCS when administered during acute COVID-19 [61]. Upon finalizing their recommendations, the expert commission's decision will be submitted to the federal joint committee (G-BA) for inclusion into the pharmaceutical guideline.

Kristian Sommerfelt presented findings from an online survey on the situation of people living with severe and very severe ME/CFS in Norway, as diagnosed by their physicians [62]. His team developed the Activities of Daily Living Score (ADLS), which evaluates energy expenditure across 15 activities in four domains: motor (e.g. leaving the house), communication (e.g. having a conversation), general daily activities (e.g. unassisted eating), and basic hygiene (e.g. showering). Each item is weighted by energy use and frequency. Severity classification is based on the International Consensus Criteria (ICC) for ME/CFS [63]. Among 491 respondents, 47 were classified as very severe, 444 as severe, and 95 as moderate. Most (88%) were female, 11% 19 years or younger, 43% aged 20–39, and 46% over 40. Notably, 19% of very severely affected were under 19 years, and 43% reported disease onset before age 15. Nearly half (45%) lived with their parents. Fatigue, pain, brain fog, sleep disturbance, and sensory intolerance were the most burdensome symptoms. Intolerance to sunlight or sound worsened with disease severity. Key differentiators between severe and very severe ME/CFS were the ability to get out of bed, dress, or shower. Only 60% of

severely and very severely affected received health or social care, with many reporting negative experiences and only 15% satisfied with specialists' services. In contrast, home nursing services, general practitioners, and therapists were evaluated more positively. Family caregivers had a predominantly negative perception of their own situation.

4. Pathophysiology of ME/CFS

An overview of the pathophysiological mechanisms discussed at the conference and their corresponding speakers is provided in [Figure 1](#).

4.1. Cardiovascular dysregulation and mitochondrial pathology

David M. Systrom elaborated on circulatory dysfunction in ME/CFS. Invasive cardiopulmonary exercise testing (iCPET), originally developed to detect early cardiac disease and pulmonary hypertension, has proven exceedingly valuable in investigating exertional intolerance among ME/CFS and PCS patients. During iCPET, patients perform upright exercise on a stationary bicycle, while undergoing continuous monitoring of ventilation and respiratory gas exchange via mouthpiece and comprehensive physiological assessment through catheters placed in the pulmonary and radial arteries. The invasive measurements are particularly crucial for identifying abnormalities in blood flow and oxygen extraction. Systrom described a reduced maximal oxygen uptake (VO_2 max) in ME/CFS patients and two types of neurovascular dysregulation as potential contributing factors. The reduction in VO_2 max was attributed either to a reduced preload, characterized by diminished venous return that results in inadequate ventricular filling prior to cardiac contraction, or to impaired oxygen extraction, likely due to vascular dysregulation or small fiber neuropathy in patients diagnosed with ME/CFS according to Institute of Medicine (IOM) criteria [32]. In a promising randomized controlled trial, pyridostigmine (Mestinon) treatment demonstrated improvements in exercise capacity among ME/CFS patients with preload failure who met IOM criteria [64]. These findings support the potential of neuroactive therapies as an approach for addressing exercise-induced fatigue and impaired oxygen-supply.

Christian Puta emphasized that the ME/CFS key symptom PEM likely involves multiple pathophysiological mechanisms rather than a single cause. This is indicated by the variability in PEM onset, duration, severity and the complex interaction between physical and cognitive exertion [13]. Currently discussed potential mechanisms underlying PEM include microvascular dysfunction leading to hypoperfusion and hypoxia, mitochondrial dysregulation, and (auto)immune dysregulation triggered by exercise or infection or the interaction of exercise and infection [65]. In PCS, an impaired cardiopulmonary response with systemic and peripheral oxygen extraction is evident [32,66], along with abnormal erythrocyte morphology and increased oxygen affinity driving hypoperfusion [67–69]. Metabolic and mitochondrial dysfunction worsen with induction of PEM in PCS patients, potentially due to viral reactivation and interference with mitochondrial proteins and gene expression, as seen in acute COVID-19 [21,70]. Additionally, altered frequency of regulatory T cells, which normally protect muscle mitochondria from interferon- γ -mediated damage [71], might contribute to mitochondrial dysfunction in PCS patients [72].

Rob C. I. Wüst presented his group's recent findings on skeletal muscle dysfunction in ME/CFS and PCS with particular emphasis on PEM. The researchers took skeletal muscle biopsies both before and one day after maximal cardiopulmonary exercise testing (CPET), to assess exercise capacity and to study the effects of exercise and PEM. Based on this methodology, they demonstrated worsened muscle abnormalities following exercise in 23 PCS patients who met WHO diagnostic criteria [21]. Several key factors that may contribute to reduced exercise capacity have been identified, including impaired mitochondrial respiration, elevated concentrations of fatigue-related metabolites, increased prevalence of glycolytic fiber and diminished power-output per muscle

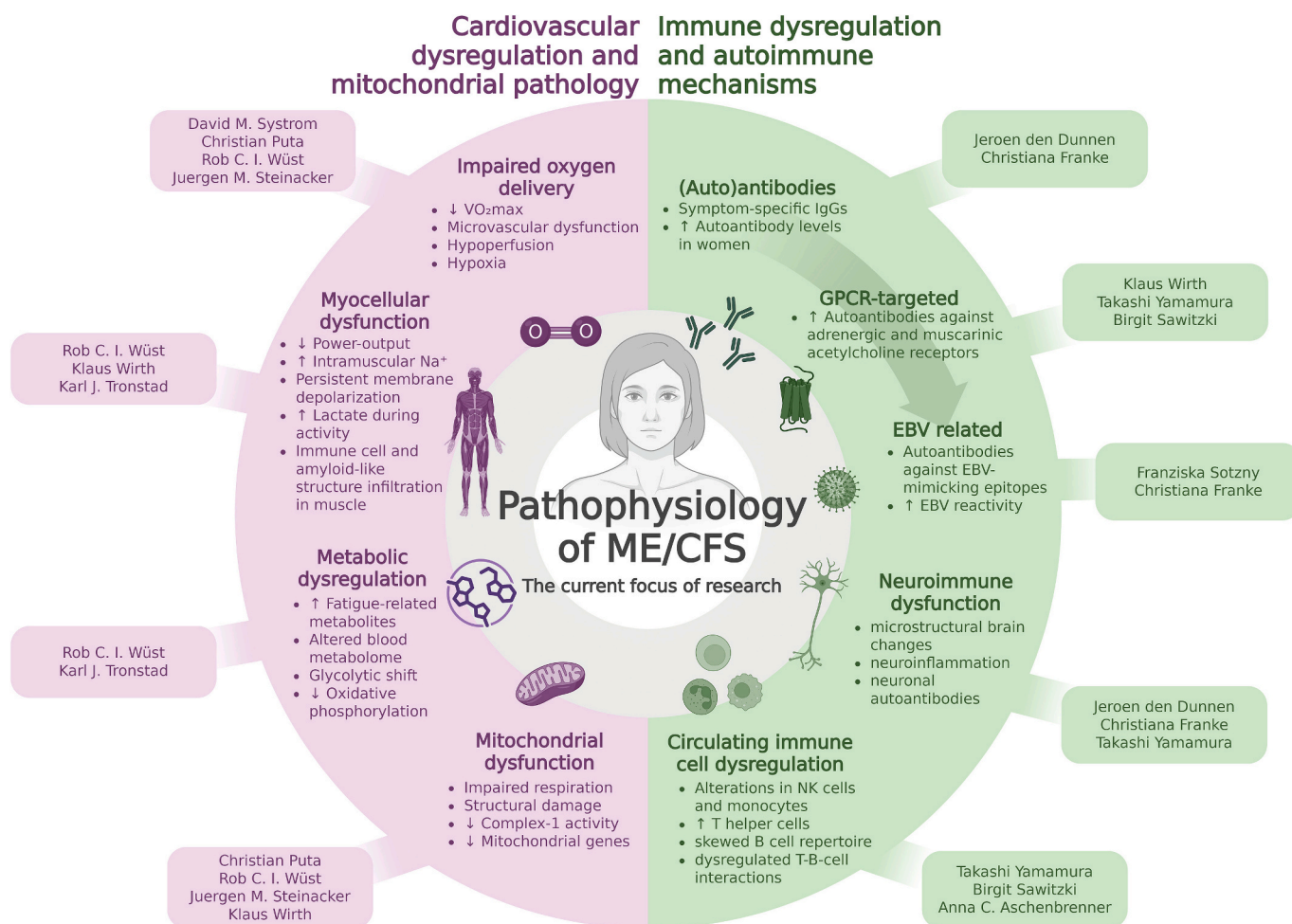


Fig. 1. Pathophysiological mechanisms of ME/CFS as discussed at the 3rd international ME/CFS conference. Topics are assigned to their respective speakers. [160]

cross-sectional area. Moreover, PEM was linked to rapid local and systemic metabolic changes, exercise-induced markers for muscle damage, and infiltration of immune cells and amyloid-like structures into skeletal muscle. A recent follow-up study comparing muscle changes caused by exercise in PCS and ME/CFS patients fulfilling the CCC versus a 60-day bed rest healthy control group found a comparable reduction in VO₂ max [73]. However, compared to bed rest-induced alterations, fiber types were differentially affected. In addition, patients, particularly those with ME/CFS, exhibited reduced capillary density and decreased capillary-to-fiber ratio, potentially impairing metabolite removal, as well as oxygen and nutrient delivery to tissue. These findings suggest that PEM stems from specific pathological mechanisms rather than simple deconditioning. This conclusion was further supported by preliminary data on microvascular alterations, particularly basement membrane thickening and reduced lumen size in ME/CFS and PCS patients, which may serve as potential diagnostic biomarkers.

Juergen M. Steinacker presented recent findings on muscle mitochondrial dysfunction identified via muscle biopsies, mitochondrial oxidative phosphorylation (OXPHOS) capacity measurements, electron microscopy, and CPET protocols in patients with fatigue or post-COVID-19 pathology diagnosed with either ME/CFS according to the CCC or classified as PCS [74]. Structural mitochondrial damage, including cristae loss, reduced mitochondrial area, and sarcomere damage, was found in both ME/CFS and PCS. Notably, OXPHOS capacity measurements revealed significantly decreased complex-1 activity among PCS patients. In a complementary study comparing performance of athletes before and after SARS-CoV-2 infection, Steinacker's group demonstrated that even convalescent athletes exhibited a VO₂ max reduction of

approximately 5%, while athletes with persistent symptoms showed even more severe decreases [75]. Given the absence of significant cardiac pathology, mitochondrial and consecutive slight muscular dysfunction appear to be plausible. Supporting evidence from Guarnieri et al. demonstrated SARS-CoV-2-infection-induced downregulation of mitochondrial genes [70]. Consequently, mitochondrial dysfunction may interfere with cellular metabolism, transport systems, and intracellular ion homeostasis and points to post-acute viral mechanism common in PCS and ME/CFS.

Klaus Wirth presented a comprehensive disease concept for PCS and ME/CFS, centered on exercise intolerance and PEM, along with a derived therapeutic strategy [76]. The model focuses on a vicious circle involving perfusion disturbances, intracellular sodium and calcium overload, and mitochondrial dysfunction in skeletal muscle. Impaired microcirculation in skeletal muscle leads to proton accumulation and sodium influx via NHE1, while insufficient stimulation of Na⁺/K⁺-ATPase due to β₂-adrenergic receptor dysfunction and reduced calcitonin-gene related peptide (CGRP) further promote sodium overload [77]. Elevated intracellular sodium reverses the sodium-calcium exchanger (NCX), resulting in calcium influx and mitochondrial calcium overload, which impairs ATP production and increases reactive oxygen species [78]. Over time, this leads to cumulative mitochondrial damage, reduced regenerative capacity, and progressive muscle dysfunction [21]. Clinical and imaging data support this model, showing elevated intramuscular sodium in ME/CFS patients after exercise, correlating with fatigue and loss of force [34]. The model links transient membrane depolarization during PEM to persistent depolarization in severely affected patients, explaining symptoms such as fatigue,

fasciculations, and muscle cramps. Risk factors such as autoantibodies against regulatory GPCRs [79] modulate individual vulnerability, potentially by contributing to receptor dysfunction. The proposed therapeutic strategy aims to interrupt the vicious circle by restoring membrane potential and mitochondrial function, for example through pharmacological stimulation of Na^+/K^+ -ATPase and mitochondrial calcium efflux.

In his presentation, **Karl J. Tronstad** discussed recent findings on alterations in blood metabolites and proteins in ME/CFS patients, addressing both acute and persistent changes. Beyond previously documented exertion-triggered abnormalities such as lactate overproduction during activity [80], persistent metabolic modifications including alternative energy source utilization, altered key enzymes and proteins, and dysregulated metabolic hormones have been reported [81,82]. These metabolic changes are typically triggered by exercise, starvation, hypoxia, or chronic diseases, and therefore possibly suggest amplified hypoxic effects in ME/CFS. These result in a metabolic shift toward increased glycolysis and reduced oxidative phosphorylation, creating persistent energy stress adaptations through intrinsic regulatory mechanisms. Here, the hypoxia-inducible factor 1 α (HIF1 α) could play a central role as a transcriptional regulator suppressing mitochondrial oxidative phosphorylation and inhibiting pyruvate dehydrogenase [81]. Cellular counteractive mechanisms attempt to compensate by maintaining ATP production and providing alternative fuel sources [81]. Tronstad presented preliminary proteome data revealing alterations in over 1,800 serum protein targets in ME/CFS patients, demonstrating multiorgan impact, immune dysregulation, and metabolic adaptations [83]. These multiscale patterns converge toward a unified mechanism involving immune, vascular, and metabolic dysregulation in ME/CFS pathophysiology.

4.2. Immune dysregulation and autoimmune mechanisms

Jeroen den Dunnen presented evidence supporting autoimmunity as a central mechanism in PCS and ME/CFS. Building on prior models in fibromyalgia [84], his group reproduced PCS symptoms in mice via passive transfer of patient derived serum immunoglobulin G (IgG) [85]. A total of 34 PCS patients were diagnosed according to WHO criteria, recruited at the post-COVID-19 clinic of the Amsterdam University Medical Center, and stratified into subgroups based on biomarker profiles: one with elevated neuronal damage markers, another with elevated type I interferons (IFNs) and dysregulated muscle markers, and a third with no elevated markers. IgG from the second group reduced mobility in mice and IgG from all subgroups induced varying levels of increased pain sensitivity, leading to the conclusions that IgG plays a causative role in the pathomechanism of PCS and is symptom-specific. Similar studies from other groups have validated these findings [17,86]. Proteomics analysis of over 21,000 autoantigens revealed heterogeneous specificity profiles for PCS patients with diverse neuronal and muscle antigen targets. Additionally, den Dunnen presented findings of in vitro impairment and cell death of skeletal muscle cells cultured in the presence of 5% plasma from PCS patients. As an outlook, he expressed his ambitions to establish in vivo and in vitro models for PCS and ME/CFS to serve as platforms for testing therapies, screening drugs, and developing diagnostic tools, including autoantibody panel tests for individual phenotyping of patients.

In an effort to further characterize autoantibodies in ME/CFS and PCS, **Franziska Sotzny** presented data on autoantibodies targeting potential epitopes that mimic EBV antigens [79]. These findings were based on high-throughput peptide microarrays identifying elevated antibody responses against arginine rich peptides derived from EBV proteins in ME/CFS patients diagnosed using the CCC [87,88]. Sequence homologies to human proteins involved in vascular, metabolic, and neurological signaling, were identified. A total of 45 PCS patients suffering from moderate to severe fatigue and exertion intolerance at least six months after COVID-19, of whom 26 fulfilled the CCC for

diagnosis of ME/CFS, were recruited at the Charité Fatigue Center in Berlin, Germany, to investigate IgG responses to the identified peptide sequences. This revealed enhanced IgG reactivity against several arginine rich human peptides (derived from ion channel SLC24A3, TSPYL2, TSPYL5, and the neuronal antigen SRRM3) and in a subsequent step also to α -adrenergic receptor and TSPYL2 protein. Correlation analysis showed that IgG reactivity against most arginine-rich peptides was associated with fatigue, PEM, and autonomic dysfunction. IgG reactivity against a peptide sequence of the neuronal antigen SRRM3 correlated with cognitive impairment and against full-length TSPYL5 with cognitive impairment, muscle pain and headache [79].

Christiana Franke discussed the growing relevance of autoantibodies targeting neuronal surface antigens in neurological disease research [89]. She highlighted their increasing influence on diagnostics and treatment, whether their role is causative, contributory, or unclear. In patients with neurological symptoms during acute COVID-19, a high frequency of cerebrospinal fluid autoantibodies, but no COVID-19 specific pattern was identified [90]. Similar findings, alongside persistent complement activation and thromboinflammation, were reported in PCS patients with cognitive dysfunction [91,92]. Based on this, two double-blinded, randomized clinical trials were initiated at the Charité in Berlin, Germany: the placebo-controlled PoCoVIT trial testing methylprednisolone in PCS patients with predominant cognitive dysfunction [93,94], and the sham-controlled IA-PACS-CFS trial, evaluating immunoadsorption in 66 post-infectious ME/CFS patients fulfilling the CCC [95,96]. Results from the two trials are pending.

Although COVID-19 vaccinations offer partial protection against PCS [97], some individuals develop persistent symptoms, termed post-COVID vaccination syndrome (PCVS). Franke presented data demonstrating autoantibodies binding to peripheral nerve structures in PCVS patients with peripheral sensory deficits [98]. In ME/CFS, prior studies identified neuronal autoantibodies [99,100]. However, a recent report investigating 7,542 autoantibody-antigen interactions found no overall group differences, although ME/CFS patients showed increased reactivity to herpesviruses, including EBV, and generally higher autoantibody levels in women [101]. Franke concluded by emphasizing the heterogeneity of PCS and ME/CFS and the need for biomarker-based subtype classification in clinical care.

Takashi Yamamura discussed recent findings on GPCR autoantibodies in ME/CFS from a neuroimmunological perspective. In 2019, his group identified microstructural brain changes potentially linked to cognitive dysfunction in ME/CFS patients fulfilling the CCC, Fukuda, and IOM diagnostic criteria, particularly in the right superior longitudinal fasciculus, by diffusional kurtosis imaging (DKI) and neurite orientation dispersion and density imaging (NODDI) [102]. To explore autoimmune mechanisms, they examined autoantibodies against $\beta 1/\beta 2$ -adrenergic and M3/M4-muscarinic acetylcholine receptors and confirmed elevated levels in Japanese patients, consistent with prior findings from Germany [25,99]. Furthermore, levels of autoantibodies correlated with brain abnormalities; adrenergic receptor autoantibody levels were positively associated with betweenness centrality in the right dorsolateral prefrontal cortex and negatively with characteristic path length in the right precentral gyrus, based on gray matter network analysis from routine magnetic resonance imaging (MRI) [103]. Neuroinflammation and degeneration in the right frontal operculum, detected via free-water-corrected diffusion tensor imaging (FW-DTI), were linked to levels of autoantibodies and disease duration [30]. These findings suggest a connection between GPCR autoantibody levels, cognitive dysfunction, and pain in ME/CFS. Additionally, Yamamura presented next-generation sequencing data showing a skewed B cell repertoire, particularly with biased IGHV gene usage in ME/CFS patients fulfilling the CCC, Fukuda, and IOM diagnostic criteria [104], and an increase in Neuropilin-1⁺ self-reactive T helper cells in ME/CFS, PCS, and other autoimmune disorders [105]. He emphasized the need for longitudinal studies, further clinical correlation, and investigation of other autoantibodies.

Birgit Sawitzki proposed that a subset of ME/CFS patients exhibits increased frequencies of activated B and T cells due to dysregulated T-B interactions, with the degree and molecular characteristics of this activation offering potential for treatment stratification and identification of therapeutic targets. A critical aspect is distinguishing between extrafollicularly-derived short-lived plasmablasts and long-lived plasma cells that undergo somatic hypermutation in the germinal center, as this enables tracing the cellular origin and molecular pathways involved in the development of autoreactive B cells. Sawitzki presented preliminary data from a post-COVID ME/CFS cohort ($n=20$), diagnosed using the CCC, with elevated β_2 -adrenergic receptor autoantibodies that underwent immunoadsorption as part of a clinical trial at the Charité Fatigue Center in Berlin, Germany [106]. The study aimed to compare patients with healthy controls, patients pre- versus post-treatment, and responders versus non-responders. In treatment responders, deep immunophenotyping revealed elevated frequencies of strongly activated CXCR5^{high} B cells – indicative of germinal center activity – which were significantly reduced after treatment in the same patients, suggesting a pathological role. In addition, ME/CFS patients showed increased frequencies of activated T follicular helper cells compared to healthy controls as well as elevated plasma concentration of markers indicative of ongoing follicular T-B cell interactions. These markers were also reduced after treatment, supporting a role for dysregulated germinal center responses in disease pathology. Ongoing and future studies aim to examine B cell receptor (BCR) clonal overlap in activated B cells and plasmablasts, identify targeted autoantigens, and characterize the molecular signals driving pathological T and B cell activation.

Anna C. Aschenbrenner further elaborated on immune cell signatures in post-COVID ME/CFS with preliminary single-cell RNA-sequencing data. A total of 40 PCS patients with persistent fatigue and exertion intolerance six months after COVID-19 with or without ME/CFS, diagnosed using the CCC, after mild to moderate COVID-19 were recruited at the Charité Fatigue Center in Berlin, Germany. Analysis of peripheral blood mononuclear cells (PBMCs) revealed alterations in circulating immune cells, especially in the natural killer (NK) cell and monocyte compartment, compared to 20 recovered healthy controls. These entailed altered gene expression profiles distinguishing post-COVID ME/CFS patients from recovered healthy controls including changes in compositions of NK and monocyte subpopulations with dysregulation of pro-inflammatory markers. First insights into a second study on 46 post-infectious ME/CFS patients, including cases with other prior infectious triggers than SARS-CoV-2, such as EBV or influenza viruses, revealed no major differences in the single-cell transcriptome profiles between the infection-based clinical groups. In contrast, similar alterations in NK cell subpopulation compositions were observed across all ME/CFS patients compared to recovered controls, consistent with findings from the first cohort. Furthermore, transcriptome profiles stratified this patient cohort into two subgroups, one of which appeared to have a more pronounced clinical phenotype with a higher PEM score, lower Bell score, and a longer disease duration. These findings support the use of clinical omics approaches for patient stratification and the development of targeted therapeutic strategies in future clinical trials.

5. Treatment of ME/CFS

An overview of all presented clinical trials, including available identifiers, study design, and status, can be found in [Table 1](#).

5.1. Clinical trials

Nina Babel provided an overview of the current knowledge on IgG therapy in ME/CFS and PCS. She outlined the clinical use of intravenous and subcutaneous immunoglobulin (IVIG and SCIG), approved in Germany as substitution therapy for immune deficiencies and as modulatory therapy for autoimmune disorders. For the latter, the mechanism of action is unresolved but may involve blocking of antigen- or Fc-

receptors, neutralizing autoantibodies and cytokines, and enhanced degradation of autoantibodies via neonatal Fc-receptor saturation. A 1990 study with 49 ME/CFS patients treated with 3 IVIG infusions of 2 g/kg bodyweight showed significant physical improvement after 3 months [107], not replicated in a 1997 follow-up [108]. Another study from 1997 in 70 adolescents, showed significant functional improvement after 3 IVIG infusions of 1g/kg of bodyweight [109]. A 2020 study using SCIG (0.8 g/kg for 12 months), showed fewer infections, as well as improvement of fatigue score and physical activity after 12 months in patients who met the CCC [110]. Babel's own group reported on IVIG (3 infusions of 0.5 g/kg) in PCS patients with severe symptoms persisting longer than three months after COVID-19, showing significant reduction in self-reported fatigue and cognitive deficits after 24 weeks with a broader therapeutic effect than budesonide or non-pharmacological therapy [111]. In conclusion, while IgG therapy shows promise for ME/CFS and PCS, optimal dosing, effectiveness, and identification of biomarkers for patient stratification require further large-scale studies.

Laura Kim presented results from an ongoing study on hyperbaric oxygen therapy (HBOT) at the Charité Fatigue Center in Berlin, Germany [112]. Patients received 100% oxygen at 2.0 atmosphere absolute (ATA) in a pressurized chamber over 40 sessions. HBOT induces an unphysiological state of hyperoxia, increasing tissue oxygenation. With repeated exposure, this triggers adaptive cellular responses, known as the hyperoxia-hypoxia paradox, including activation of hypoxia-inducible factors, angiogenesis, and improved mitochondrial function and tissue repair [113–115]. The trial included 30 ME/CFS patients fulfilling the CCC following viral infections. The treatment was well tolerated, with only mild, transient side effects. The primary outcome, physical functioning measured by SF-36, showed significant improvement one month after treatment. Additionally, improvements were observed in secondary outcomes, including pain (SF-36), fatigue (Chalder Fatigue Questionnaire), and neurocognitive function (Symbol Digit Modalities Test, SDMT). These findings support HBOT as a potentially effective intervention for a subgroup of ME/CFS patients. However, questions remain regarding the durability of benefit, and the identification of biomarkers to determine which patients are most likely to benefit from the treatment.

Alan Cash presented findings on oxaloacetate treatment in ME/CFS patients. Oxaloacetate, a key metabolite in the Krebs cycle, is often depleted in ME/CFS patients fulfilling Fukuda criteria, as shown by metabolomic data from a Cornell University cohort [116]. Preclinical research on anhydrous enol-oxaloacetate (AEO) shows it reduces chronic inflammation by suppressing NF- κ B [117], decreases glycolysis and lactate production [118], enhances mitochondrial biogenesis [117], and improves cellular glucose uptake and NAD⁺/NADH redox balance [119]. Two clinical trials in ME/CFS patients who met Fukuda criteria revealed that oxaloacetate is well tolerated and significantly reduces fatigue, with an average improvement of 33.3% in the first trial ($n=76$) [120,121] and 25–35% in the second trial ($n=82$) [122,123]. Notably, 40.5% of patients were classified as “enhanced responders”, reporting an average fatigue reduction of 63%. Cognitive function, measured by Simple Reaction Time, also improved significantly compared to controls [120,122]. These findings suggest that oxaloacetate may offer a promising therapeutic approach for physical and mental fatigue symptoms in ME/CFS.

David M. Systrom presented the study protocol for the Life Improvement Trial (LIFT), a randomized controlled trial on the therapeutic potential of low-dose naltrexone (LDN) and pyridostigmine (Mestinon) in 160 patients with ME/CFS diagnosed using the CCC, recruited at the Massachusetts General Hospital, Brigham and Women's Hospital, and through Open Medicine Foundation's StudyME registry [124,125]. LDN, a μ -opioid receptor antagonist, downregulates proinflammatory signaling via toll-like receptor 4 inhibition, reducing cytokines such as TNF- α and IL-6, when administered at subtherapeutic doses (0.5–4.5 mg) [126]. Previous studies in fibromyalgia showed a 65% improvement in pain [127], and a Finnish ME/CFS chart review

Table 1

Overview of presented clinical studies or trials with presenter, title, intervention/treatment, study design, and status listed.

Presenter	Clinical Study/ Trial	(Short) Title	Intervention/ Treatment	Study Design	Status	Ref.
Nina Babel	Lloyd et al., 1990	A double-blind, placebo-controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue syndrome	Intravenous immunoglobulin	Interventional, randomized, double-blind, placebo-controlled trial	Completed	[107]
Nina Babel	Vollmer-Conna et al., 1997	Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome	Intravenous immunoglobulin	Interventional, randomized, double-blind, placebo-controlled trial	Completed	[108]
Nina Babel	Rowe et al., 1997	Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents	Intravenous immunoglobulin	Interventional, randomized, double-blind, placebo-controlled trial	Completed	[109]
Nina Babel	Scheibenbogen et al., 2021	Tolerability and Efficacy of s.c. IgG Self-Treatment in ME/CFS Patients with IgG/IgG Subclass Deficiency: A Proof-of-Concept Study	Subcutaneous immunoglobulin	Interventional, open-label proof-of-concept trial	Completed	[110]
Nina Babel	Hogeweg et al., 2023	Intravenous immunoglobulins in the treatment of post-COVID: A case-control study	Intravenous immunoglobulin	Observational case-control study	Completed	[111]
Laura Kim	NCT06118138, 2023	Hyperbaric High Pressure Oxygen Therapy in Post-COVID Syndrome and ME/CFS	Hyperbaric oxygen therapy (HBOT)	Observational study	Ongoing, recruitment ended	[112]
Alan Cash	NCT04592354, 2020 Cash et al., 2022	Anhydrous Enol-Oxaloacetate (AEO) on Improving Fatigue in Post-COVID-19 Survivors (AEO)	Oxaloacetate	Interventional, open-label, non-randomized, dose-escalation proof-of-concept trial	Completed	[120,121]
Alan Cash	NCT05273372, 2022 Cash et al., 2024	RESTORE ME - RCT of Oxaloacetate on Improving Fatigue in ME/CFS	Oxaloacetat	Interventional, randomized, double-blind, placebo-controlled trial	Completed	[122,123]
David M. Systrom	NCT06366724, 2024 Meadows et al., 2024	LIFT: Life Improvement Trial (LIFT)	Pyridostigmine/Low-Dose Naltrexone	Interventional, randomized, double-blind, placebo-controlled phase II trial	Recruiting	[124,125]
David Putrino	NCT06960928, 2025	Low Dose Sirolimus in People With Post-Acute Sequelae of COVID-19 (PASC) Long COVID-19	Low-dose Sirolimus	Interventional, randomized, double-blind, placebo-controlled phase III trial	Recruiting	[131]
Michael J. Peluso	Peluso et al., 2022	Effect of Oral Nirmatrelvir on Long COVID Symptoms: 4 Cases and Rationale for Systematic Studies	Nirmatrelvir	Observational case series	Completed	[136]
Michael J. Peluso	NCT05668091, 2022 Sawano et al., 2025	A Decentralized, Randomized Phase 2 Efficacy and Safety Study of Nirmatrelvir/Ritonavir in Adults with Long COVID	Nirmatrelvir/ Ritonavir	Interventional, randomized, double-blind, placebo-controlled phase II trial	Completed	[137,138]
Michael J. Peluso	Schepke et al., 2024	Remission of severe forms of long COVID following monoclonal antibody (MCA) infusions: A report of signal index cases and call for targeted research	Casirivimab/ Imdevimab	Observational case report	Completed	[139]
Michael J. Peluso	NCT05576662, 2022 Geng et al., 2024	Paxlovid for Treatment of Long Covid (STOP-PASC)	Nirmatrelvir/ Ritonavir	Interventional, randomized, double-blind, placebo-controlled phase II trial	Completed	[140,141]
Clinical trials targeting autoantibodies						
Olav Mella	Fluge et al., 2009	Clinical impact of B-cell depletion with the anti-CD20 antibody rituximab in chronic fatigue syndrome: a preliminary case series.	Rituximab	Observational case series	Completed	[142]
Olav Mella	NCT00848692, 2008 Fluge et al. 2011	B-Lymphocyte Depletion in Myalgic Encephalopathy/Chronic Fatigue Syndrome	Rituximab	Interventional, open-label phase II trial	Completed	[143,144]
Olav Mella	NCT01156909, 2010 Fluge et al., 2015	B-cell Depletion Using the Monoclonal Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome	Rituximab	Interventional, open-label phase II trial	Completed	[145,146]
Olav Mella	NCT02229942, 2014 Fluge et al., 2019	B-lymphocyte Depletion Using Rituximab in Chronic Fatigue Syndrome/Myalgic Encephalopathy (CFS/ME). A Randomized Phase-III Study (RituxME)	Rituximab	Interventional, randomized, double-blind, placebo-controlled phase III trial	Completed	[147,148]
Olav Mella	NCT02444091, 2015 Rekeland et al., 2020 Rekeland et al., 2024	Cyclophosphamide in Myalgic Encephalopathy/Chronic Fatigue Syndrome (ME/CFS) (CycloME)	Cyclophosphamide	Interventional, open-label phase II trial	Completed	[149–151]
Øystein Fluge	EudraCT 2022-000281-18, 2022 Fluge et al., 2025	Treatment with daratumumab injections in moderate to severe ME/CFS	Daratumumab	Interventional, open-label phase II trial	Completed	[153,154]

(continued on next page)

Table 1 (continued)

Presenter	Clinical Study/Trial	(Short) Title	Intervention/Treatment	Study Design	Status	Ref.
Øystein Fluge	EUCT 2024-520094-13-00, 2025	Plasma cell targeting in ME/CFS	Daratumumab	Interventional, randomized, double-blind, placebo-controlled phase II trial	Recruiting	[155]
Wakiro Sato	NCT06952413, 2025	Study of the Efficacy and Safety for Rituximab in Myalgia Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)	Rituximab	Interventional, randomized, double-blind, placebo-controlled phase II trial	Recruiting	[156]
Elisa Stein	Stein et al., 2025	Efficacy of repeated immunoadsorption in patients with post-COVID myalgic encephalomyelitis/chronic fatigue syndrome and elevated β 2-adrenergic receptor autoantibodies: a prospective cohort study	IgG depletion via Immunoadsorption	Observational study	Completed	[106]

reported a 73.9% positive self-reported response, especially in cognitive vigilance [128]. Mestinon, an acetylcholinesterase inhibitor that enhances cholinergic signaling at synapses [129,130], will be evaluated for its effect on autonomic dysfunction. The study incorporates non-invasive cardiopulmonary exercise testing (Shape Test) to assess physiological and functional outcomes. Dosing strategies and combination therapy (LDN + Mestinon) were explored. Preliminary findings indicate synergistic benefits in symptom relief and functional capacity, supporting the clinical use of combined LDN and Mestinon treatment in ME/CFS and PCS.

David Putrino's presentation outlined a clinical trial that will investigate low-dose rapamycin for Long COVID treatment at the Icahn School of Medicine at Mount Sinai in New York, USA [131], targeting key pathophysiological features including latent viral reactivation (EBV, Human Herpesvirus (HHV) 1-6, Cytomegalovirus (CMV), etc.), immune dysregulation (T cell exhaustion, B cell dysregulation), and chronic inflammation (altered interferon expression) [19]. Preclinical and clinical evidence from other populations suggest that low-dose rapamycin can reverse immunosenescence and enhance T cell function [132], stabilize inflammatory cytokine secretion [133], and reduce infection rates. In the ongoing double-blind, randomized, placebo-controlled trial 80 participants with physician-diagnosed Long COVID and at least six months of persisting symptoms after SARS-CoV-2 infection, including moderate fatigue and PEM, were randomized 1:1 to receive rapamycin (escalating doses: 1mg, 2mg, 4mg) or placebo. Deep immunophenotyping will be performed at baseline, midpoint, intervention end and post-interventional follow-up. The study aims to identify responders and associated biomarkers, guiding future larger-scale and combination therapy studies.

Michael J. Peluso presented an overview of current findings and open questions regarding viral persistence and its treatment in PCS. He reviewed evidence of long-term SARS-CoV-2 RNA and antigen detection in various tissues, such as gut, brain, blood, and stool, up to 24 months post-infection, using data from multiple studies across different platforms [18,134,135]. Peluso emphasized that viral persistence was clearly observed in the early phase of the pandemic, when population immunity was low and infections were often more severe. However, its current role remains uncertain, and it is not yet clear whether viral persistence is a cause or a consequence of PCS. The presentation addressed both the challenges and potential of targeting viral persistence therapeutically. Case reports and early trials using antivirals (e.g. nirmatrelvir-ritonavir) and monoclonal antibodies show mixed results, with some improvements in individual cases but no consistent benefit in controlled studies [136–141]. Limitations include short treatment duration, insufficient tissue penetration, and lack of validated viral persistence. Peluso stressed the need for dedicated biomarker development and scalable diagnostics and called for coordinated, cross-institutional efforts to investigate persistent viral reservoirs and their therapeutic relevance.

5.2. Clinical trials targeting autoantibodies

Olav Mella presented early findings from the Haukeland University Hospital in Bergen, Norway, showing that some cancer patients with comorbid ME/CFS experienced symptom improvement after chemotherapy, particularly with cyclophosphamide and rituximab. This led to trials exploring ME/CFS immunopathogenesis and the therapeutic potential of immune-modulating agents. Early studies on rituximab, a CD20+ B cell-depleting monoclonal antibody, including a 2009 case series and two phase II trials (2011, 2015), showed benefits in a subset of ME/CFS patients diagnosed based on Fukuda criteria [142–146]. However, the subsequent phase III RituxME trial, involving 151 patients who met the CCC, failed to demonstrate significant differences between rituximab and placebo [147,148]. Potential explanations included sub-optimal endpoints, insufficient dosing, or low efficacy in unselected cohorts. Meanwhile, a phase II cyclophosphamide trial in 40 moderate-to-severe ME/CFS patients fulfilling the CCC reported a 55% response rate after six infusions over 23 weeks [149,150]. Short-term toxicity was notable, long-term side effects were limited, with durable responses at 6-year follow-up in many responders [151]. Clinical improvements across symptoms support an underlying immunopathogenic mechanism involving dysfunctional autoantibodies affecting circulatory, neurological, and gastrointestinal function. Rituximab responses appeared 4-9 months post-treatment, while cyclophosphamide responses were more variable (2-8 months) and acute [147,149]. Persistent and recurring symptoms may relate to long-lived plasma cells producing pathological autoantibodies, residing in immune-privileged niches and evading CD20 depletion [152]. Overall, those findings emphasize immune dysregulation as a central component of ME/CFS, with therapeutic success reliant on precise targeting of immune components. This experience has led to current plasma cell depleting trials.

Øystein Fluge presented a pilot study investigating daratumumab treatment, a CD38-targeting monoclonal antibody, in ME/CFS patients diagnosed based on the CCC and recruited at the Haukeland University Hospital in Bergen, Norway [153,154]. Based on prior findings implicating the involvement of functional autoantibodies in ME/CFS and inconclusive results from B cell-depletion therapy with rituximab, this study targeted plasma cells to reduce immunoglobulins and persistent pathogenic autoantibodies. Ten female patients with moderate to severe ME/CFS and a mean disease duration of 12 years (range 3-35 years) participated. The primary aim was to assess feasibility and tolerability. Secondary endpoints included immunological parameters and clinical measures like physical function and fatigue. Daratumumab was well tolerated with only mild adverse events. Clinical improvement occurred in 60% of patients, lasting up to 24 months to date in five cases. Responders showed increased physical activity, a mean 56% IgG reduction, and higher baseline NK cell counts. This suggests that antibody-dependent cellular cytotoxicity (ADCC), a mechanism by which NK cells eliminate antibody-coated target cells via Fc receptor interaction, might contribute to the therapeutic effects. Non-responders (40%) showed no significant changes in symptoms or biomarkers. The results

support the assumption that functional autoantibodies contribute to ME/CFS pathophysiology and suggest that a subset of patients could benefit from plasma cell depletion. A randomized, double-blind, placebo-controlled phase II trial (KTS11) is currently being prepared to validate these findings [155].

Wakiro Sato presented a recently initiated exploratory placebo-controlled, double-blind, phase II study to evaluate the efficacy and safety of rituximab in ME/CFS at the National Center of Neurology and Psychiatry in Tokyo, Japan [156]. The study includes 30 ME/CFS patients aged 18-65 years with moderate to severe functional impairment (Performance Status (PS) [157] of 4 or higher), diagnosed according to the CCC. Subjects are randomized into rituximab-first and placebo-first groups, receiving rituximab at 375 mg/m²/week intravenously for 4 weeks, with primary evaluation at 24 weeks and secondary evaluation at 48 weeks. Primary endpoint is the proportion of patients with a PS improvement of at least one point at 24 weeks, adjusted for baseline severity, prior infectious-episode onset, and anti- β 2-adrenergic receptor antibody status. Secondary endpoints include detailed clinical evaluations (e.g., supine time, activities, fatigue, sleep quality) and biomarkers (e.g., gut microbiome, brain imaging, immune profiling, metabolomics). Sato highlights the potential role of B cell dysregulation and autoantibodies in ME/CFS pathophysiology and aims to identify biomarkers predictive of treatment response to rituximab.

Judith Bellmann-Strobl presented the setup for the PIONEER B cell depletion trial in patients with post-infectious autoimmune ME/CFS at the Charité in Berlin, Germany. The trial will investigate the efficacy of inebilizumab (anti-CD19 monoclonal antibody) compared to ocrelizumab or ublituximab (anti-CD20 monoclonal antibody), following pre-treatment with immunoadsorption. A total of 55 participants fulfilling the CCC will be randomized into three treatment groups: placebo ($n=25$), anti-CD20 ($n=15$), and anti-CD19 ($n=15$) treatment. Key inclusion criteria comprise infection-triggered disease onset, a functional disability Bell score of 30–60, the presence of autoantibodies directed against β 2-adrenergic receptor or neuronal antigens, and evidence of a clinical response to pre-treatment with immunoadsorption. Monoclonal antibodies are administered intravenously in three doses – an initial infusion, a second dose after 2 weeks, and a third at 6 months – in accordance with their use in routine clinical practice. Bellmann-Strobl presented preliminary data from two patients who received B cell depleting therapy with inebilizumab following a clinical response to immunoadsorption [106], both of whom demonstrated notable symptom improvement. These findings support the pathophysiological relevance of B cells in ME/CFS and PCS, at least in a subset of patients, and provide a strong rationale for further exploration of CD19- and CD20-targeted immunotherapy in post-infectious ME/CFS.

Elisa Stein presented an observational study conducted at the Charité Fatigue Center in Berlin, Germany, which investigated the efficacy of repeated immunoadsorption in post-COVID ME/CFS patients with elevated levels of β 2-adrenergic receptor autoantibodies [106]. A total of 20 patients fulfilling the CCC (median age 40 years, median illness duration 22 months) underwent five sessions of immunoadsorption within 10 days, with a second treatment cycle offered upon symptom relapse. Primary endpoint was defined as a ≥ 10 -point improvement in physical functioning score as assessed by the SF-36 at 4 weeks post-intervention. By day 5, significant reductions in serum immunoglobulins (IgG -79%, IgA -68%, IgM -76%) and autoantibody titers were observed. Clinical responses varied with a subset of 14 patients demonstrating rapid improvements in SF-36 physical functioning score and related symptoms, while six others did not respond. A repeated cycle in ten responders conferred no additional benefit. Findings from this study are consistent with previous studies suggesting that immunoadsorption may offer therapeutic potential for patients with autoimmune profiles. However, variable responses highlight the need for markers to predict treatment efficacy, and the limited durability underscores the need for maintenance therapy. Studies on deep B cell subtyping and markers of immune dysregulation are ongoing.

Sequential therapies combining immunoadsorption with subsequent depletion of autoantibody-producing B cells are in preparation.

Georg Schlieper reported clinical observations on immunoadsorption in severely affected ME/CFS patients, particularly after SARS-CoV-2 infection or vaccination, treated at Dialysis Hannover – Center for Kidney, Hypertension and Metabolic Diseases in Hannover, Germany. Several case reports and a patient series ($n=24$) were presented. Across all case reports immunoadsorption led to improvements in fatigue, PEM and cognitive symptoms such as brain fog. Some patients progressed from bedridden to walking or returning to daily activities. In some patients, improvements began already after 3–5 immunoadsorption sessions, in others a few weeks after treatment, with benefits lasting for several months in the majority of patients. However, responses varied, and not all patients improved (response rate 70-75%). For analysis of the patient series, individuals were stratified by baseline Bell scores (15–30 vs. 40–70), with both subgroups improving in fatigue severity and health questionnaires, especially in the more severely affected group (Bell score 15-30). No severe adverse effects were reported. This case series suggests immunoadsorption may offer therapeutic benefit in ME/CFS patients with autoimmune features. However, the uncontrolled nature of the study and the absence of a placebo group underscores the need for randomized controlled trials to validate efficacy and identify predictors of response.

6. Research in progress – highlights from selected poster presentations by early-career scientists

This section highlights selected poster presentations by early-career scientists, curated by **Martina Seifert** and **Wolfram Doehner**, showcasing ongoing research projects presented during the conference.

Guido Cammà presented data on structural and functional brain alterations in ME/CFS patients identified via MRI before and after hyperbaric oxygen therapy (HBOT) as part of a clinical trial at the Charité Fatigue Center in Berlin, Germany [112]. The study included 30 ME/CFS patients fulfilling the CCC and 30 matched controls who underwent 40 sessions of 100% oxygen treatment in hyperbaric chambers, intended to enhance microcirculation, mitochondrial function, and reduce neuro-inflammation. Pre-HBOT, ME/CFS patients showed increased thalamic functional connectivity with motor, somatosensory, and visual regions, suggesting altered sensory and motor processing. After HBOT, thalamic functional connectivity normalized. The absence of volumetric changes indicates that ME/CFS symptoms are more closely associated with functional network changes than with structural abnormalities.

Wiebke Löhden investigated gut microbial alterations in 106 ME/CFS patients who met the CCC compared to 91 matched healthy controls using metabolic modeling of stool metagenomic data. Participants were recruited at five geographically-diverse ME/CFS clinics across the USA [158]. ME/CFS patients had decreased α -diversity and amino acid auxotrophy abundances, suggestive of an altered gut microbiome composition. An increased production of the tryptophan metabolites tryptamine, indole-3-acetic-acid, and indole-3-lactic acid with a potential influence on the gut-brain-axis was observed. Moreover, a reduced bacteria-mediated production of the anti-inflammatory indole-3-propionic-acid was reported. Therefore, Löhden concluded that the altered gut microbial metabolism in ME/CFS might be in favor of pro-inflammatory reactions.

Lorenz L. Mihatsch assessed the feasibility, disease severity correlations, and predictive value of hand grip strength (HGS) for diagnosis of ME/CFS in children, adolescents, and young adults, using an established protocol with an electric dynamometer [51]. For this, 83 ME/CFS patients fulfilling the CCC aged 10-25 years were recruited at the Munich Chronic Fatigue Center for Young People (MCFC) in Munich, Germany. The study demonstrated a significant reduction in muscular strength in ME/CFS patients compared to 82 healthy controls, but not specific to ME/CFS when compared to 63 disease controls who presented to the MCFC for probable post-viral or post-vaccination fatigue. Despite

fatigue and PEM, HGS testing was feasible in all patients and had a predictive diagnostic value of 50-56%. Both maximum and mean HGS showed significant correlations with markers of disease severity. These findings show that HGS testing is a promising additional diagnostic tool for ME/CFS in children and adolescents.

Christian Puta presented data from **Anuradha Ramoji** investigating the differentiation of ME/CFS through Raman spectroscopic profiling of PBMCs from 18 ME/CFS patients experiencing PEM and 16 healthy controls recruited at the Interdisciplinary Center for Post-Infectious Long-Term Consequences (ICPL, University Hospital Jena, Germany). Samples were collected immediately before and 24 hours after a one-minute sit-to-stand-test. A Raman-based principal component and linear discriminant analysis (PCA-LDA) model and difference-Raman spectra revealed significant alterations of protein and lipid content in PBMCs of ME/CFS patients post-exertion, demonstrating the profound impact of minimal physical activity on the immune system. Furthermore, the PCA-LDA model enabled successful discrimination between pre- and post-exertion samples in ME/CFS patients, but not in healthy controls, with approximately 70% accuracy. Notably, the analysis revealed two distinct patient subgroups based on divergent immune cell profiles, highlighting the clinical heterogeneity of ME/CFS.

Anouk Slaghekke investigated microvascular dysfunction and basement membrane thickening in skeletal muscle in ME/CFS patients fulfilling the CCC and PCS patients diagnosed by experienced physicians, recruited at Amsterdam Medical Center (AMC), the Netherlands. For this, skeletal muscle oxygenation during maximal exercise was assessed, and microvasculature structure and function in muscle biopsies from the vastus lateralis were analyzed histologically and by electron microscopy. Both patient groups (ME/CFS $n=26$; PCS $n=24$) exhibited decreased oxygen uptake and vasodilatory capacity compared to 30 healthy controls, while only ME/CFS patients showed additional lower capillarization. Moreover, patients had increased Collagen IV deposition in the capillary basement membrane, characterized through a thicker basement membrane and reduced lumen space. Further, patients exhibited microvascular ultrastructural abnormalities including endothelial activation and dysfunction, abundance of vacuoles and signs of endothelial cell degeneration. These pathological alterations likely result in insufficient oxygen and nutrient supply alongside impaired waste product clearance.

Timon Kuchler presented insights from the All Eyes on PCS study at the University Hospital of the Technical University Munich, Germany, analyzing dynamic and static retinal vessel parameters in 102 PCS patients, experiencing persisting symptoms for at least two months after SARS-CoV-2 infection, compared to 96 SARS-CoV-2-infection-naïve as well as 102 SARS-CoV-2-infection-recovered healthy controls [159]. Patients showed significantly reduced venular flicker-induced dilation (vFID), narrower retinal arterioles and reduced arterio-venous-ratio (AVR). These findings indicate persistent alterations in retinal microcirculation among PCS patients. Correlation analysis revealed associations between both vFID and AVR with clinical severity scores, suggesting that ongoing endothelial dysfunction contributes to symptom burden. Within the PCS cohort, patients meeting the CCC for diagnosis of ME/CFS ($n=63$) exhibited more severe microvascular impairment compared to those without ME/CFS. These findings support the diagnostic potential of retinal vessel analysis.

7. Conclusion and outlook

In summary, the conference provided a comprehensive overview of state-of-the-art research on ME/CFS, covering recent advances in patient care and mechanistic insights into cardiovascular dysregulation, metabolic dysfunction, and immune dysregulation. Clinical trials targeting these pathophysiological pathways were presented, underlining the field's ongoing efforts to translate foundational research into targeted therapies.

Future challenges in ME/CFS research remain substantial. Key

priorities include the identification of reliable biomarkers for diagnosis, a better understanding and resolution of disease heterogeneity, and the translation of preclinical findings into well-designed clinical studies to identify effective treatment options. In addition, systemic challenges such as stigma and persistent underfunding continue to hinder progress. Addressing these issues will require improved physician education as well as sustained and coordinated research funding. A promising example for the latter is the National Decade for Post-Infectious Diseases, a long-term research program launched by the German Federal Ministry of Research, Technology and Space (BMFTR) to strengthen and coordinate research, infrastructure, and clinical translation for diseases that can occur after infections, such as ME/CFS and PCS, over a ten-year period. Addressing these scientific and systemic challenges will be critical to advancing the field and ultimately improving diagnosis and treatment for those affected by ME/CFS and related post-infectious diseases.

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

During the preparation of this work, the authors did not use generative AI and AI-assisted technologies in the writing process, which go beyond improving readability and language.

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Alan Cash is an executive in the pharmaceutical company Terra Biological LLC developing oxaloacetate for the treatment of ME/CFS.

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Klaus Wirth is Managing Director of Mitodicure GmbH that develops a drug for the treatment of ME/CFS.

The remaining authors declare no known competing interests.

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AF, LW, SSc and SSt prepared the initial draft of the manuscript. All other authors contributed substantially to the scientific content during the conference through presentations and discussions of their research, which is reflected in this report. All authors critically revised the manuscript and approved the final version for submission.

Data availability

No data was used for the research described in the article.

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