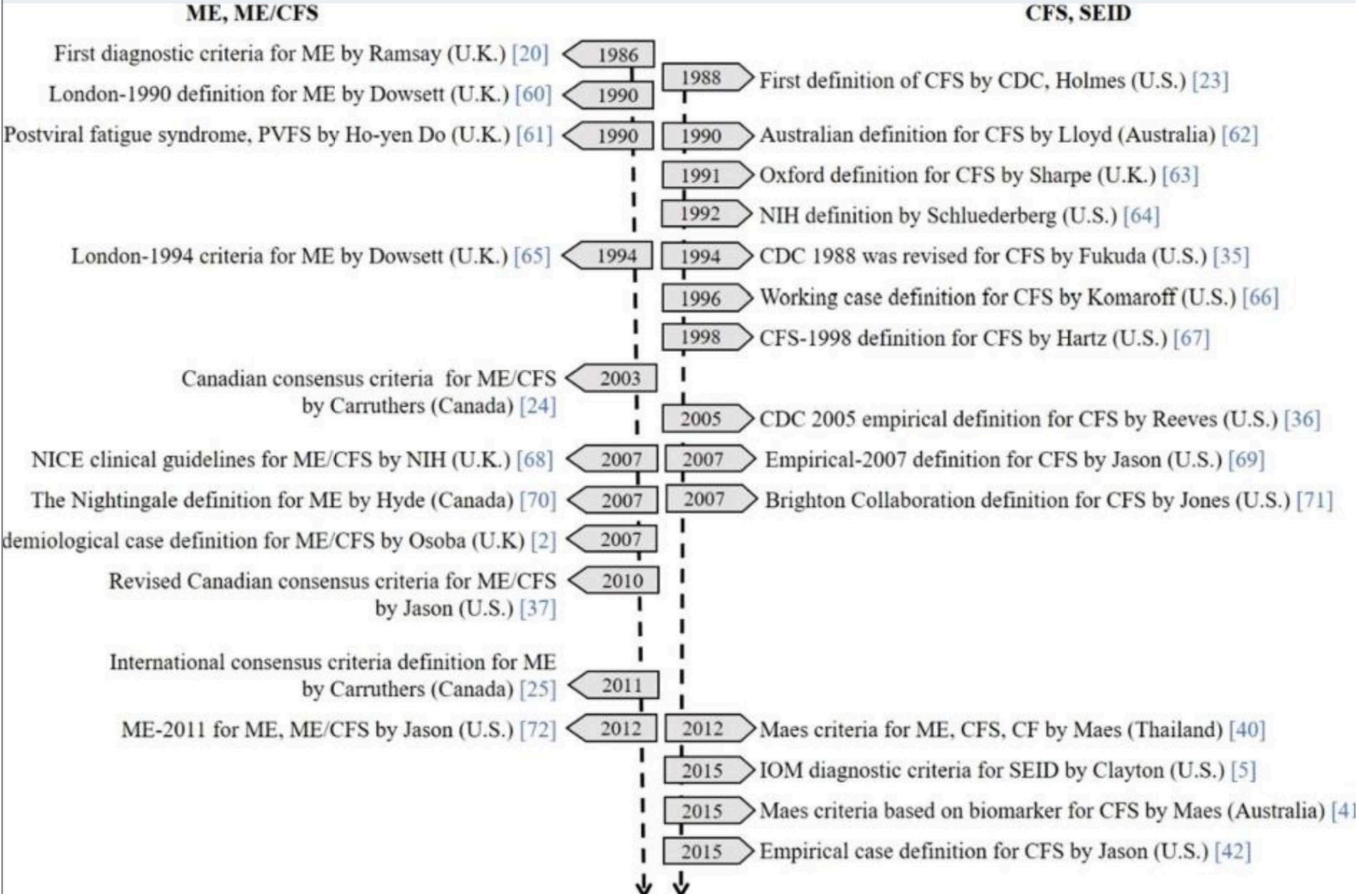
Caseness: The ME/CFS Experience and Long COVID

Nancy Klimas, MD
Professor & Chair Department of Clinical Immunology,
Director, Institute for Neuro-Immune Medicine
Dr. Kiran C. Patel College of Osteopathic Medicine,
Nova Southeastern University
Director, Clinical Immunology Research, Miami VAMC
Professor Emerita, University of Miami Miller School

Long COVID case definition learning from the the ME/CFS experience: basic principles

- The importance of an easily taught clinical case definition that is more inclusive. (impact on confidence of clinicians in recognizing he illness, as well as impact on patient in other issues e.g. disability eligibility)
- The need of a research case definition to be tighter with potential subgrouping criteria that assist in finding key pathogenesis features and defining subgroups that would be more likely to respond to proposed treatments (eg autoimmune or viral reactivation subgroup criteria in trial designs that target these mediators)
- The Common Data Elements (NINDS) process also greatly assisted the research process in requiring comparable measures of domains, severity and outcomes. The ME/CFS studies remain complicated by having several acceptable research case definitions



Lim EJ, Son CG. Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). J Transl Med. 2020 Jul 29;18(1):289.

2015 IOM Clinical Case Definition: Evidence based

- The 2015 IOM diagnostic criteria for ME/CFS in adults and children state that **three symptoms and at least one of two additional manifestations are required** for diagnosis. The three required symptoms are:

1. **A substantial reduction or impairment in the ability to engage in pre-illness levels of activity** (occupational, educational, social, or personal life) that:
    1. lasts for more than 6 months
    2. is accompanied by fatigue that is often profound, of new onset, not relieved by rest and not caused by excessive exertion
2. **Post-exertional malaise (PEM)*** —worsening of symptoms after physical, mental, or emotional exertion that would not have caused a problem before the illness.
3. **Unrefreshing sleep*—**patients with ME/CFS may not feel better or less tired even after a full night of sleep despite the absence of specific objective sleep alterations.

- At least one of the following **two additional manifestations** must be present:

1. **Cognitive impairment*—**patients have problems with thinking, memory, executive function, and information processing, as well as attention deficit and impaired psychomotor functions. All can be exacerbated by exertion, effort, prolonged upright posture, stress, or time pressure, and may have serious consequences on a patient's ability to maintain a job or attend school full time.
2. **Orthostatic intolerance—**patients develop a worsening of symptoms upon assuming and maintaining upright posture as measured by objective heart rate and blood pressure abnormalities during standing, bedside orthostatic vital signs, or head-up tilt testing.

1994 International Research Case Definition

Overview of Inclusions

- Fatigue + 4 out of 8 case-defining symptoms:
- PEM lasting more than 24 hours
- Unrefreshing sleep
- Significant impairment of short-term memory or concentration
- Muscle pain
- Pain in the joints without swelling or redness
- Headaches of a new type, pattern, or severity
- Tender lymph nodes in the neck or armpit
- A sore throat that is frequent or recurring

Duration

- ≥ 6 months (clinical evaluation starts at one month – prolonged fatigue)

References

Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. *Ann Intern Med* 121:953-959, 1994.

Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, Evengard B, White PD, Nisenbaum R, Unger ER; International Chronic Fatigue Syndrome Study Group. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Serv Res. 2003 Dec 31;3(1):25

2003 Canadian Consensus

Overview of Inclusions

Fatigue, post-exertional malaise ±fatigue, sleep dysfunction, and pain; have 2 or more neurological/cognitive manifestations and 1or more from 2 categories of autonomic, neuroendocrine and immune manifestations

Duration

- ≥ 6 months (preliminary diagnosis can be earlier)

Fatigue

Significant new onset persistent or recurrent physical or mental fatigue

- Unexplained after clinical evaluation
- Substantially reduces activity level

Post-exertional malaise

- Required

Minimum number of symptoms—8

Reference
Carruthers BM, Jain AK, DeMeirleir KL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: Clinical working case definition, diagnostic and treatment protocols. *J Chronic Fatigue Syndrome* 11:7-115, 2003.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Data Standards

Organized by domains and subdomains often used in clinical studies, data standards include:

- CDEs — Classified as Core, Supplemental–Highly Recommended, Supplemental, or Exploratory
- CRF Modules — Template forms that logically organize CDEs for data collection
- Guidance Documents — Provide further information about the CDEs
- Instrument Notice of Copyright (NOC) Documents — Include pertinent information on recommended instruments (Instrument Notice of Copyright Information)

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Start-up Resource Listing: All Core and Supplemental–Highly Recommended CDEs recommended for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome study start-up

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Highlight Summary: Overview of all Myalgic Encephalomyelitis/Chronic Fatigue Syndrome-specific CDE recommendations as they appear on the website

ME/CFS Common Data Elements Project Frequently Asked Questions

Click **Expand All** to view the CDEs associated with the CRF modules, organized by domain and subdomain.

COVID-19: Understanding the Post-Viral Phase (COVID UPP)

- Nancy Klimas, MD (PI); Kristina Aenlle, PhD, Devra Cohen, MPH, Ilya Pavlov, MD, Aryan Lajevardi, Julio Llanga, Patrick Hardigan, PhD; Institute for Neuro-Immune Medicine, Nova Southeastern University, Davie, Florida, U.S.A; and Miami VAMC GRECC
- Ana Palacio, MD,(CoPI) University of Miami, Coral Gables, Florida, U.S.A.; and Miami VAMC GRECC
- Lily Chu, MD, Stanford ME/CFS Initiative, Stanford, California, U.S.A.;

- Jeanne Bertolli, PhD, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia, U.S.A.; Jin-Mann Lin, PhD, Elizabeth R Unger, PhD, MD , Quan Vu, MD, U.S. Chronic Viral Diseases Branch, Division of High Consequence Pathogens and Pathology; National Center for Zoonotic and Emerging Infectious Diseases, Centers for Disease Control and Prevention, Atlanta GA

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COVID UPP

Recognizing the inherent heterogeneity of the illness, our focus in COVID-UPP is on applying standardized measures of symptoms and function, along with biologic measures, to allow patients to be compared with other illness groups, and to identify subgroups based on underlying pathogenesis.

Questions that are a main focus of COVID-UPP are

- How do individuals who have a prolonged fatiguing illness following SARS-CoV-2 infection differ from those who are fully recovered?
- How does their clinical profile differ from that of individuals diagnosed with ME/CFS?
- Focus is on those with syndromic illness, not long-term symptoms that are secondary to COVID, like post-ICU syndrome, or defined conditions caused by the infection that have established diagnoses—like myocarditis, lung fibrosis, stroke, acute and chronic kidney disease.

COVID-19: Understanding the Post-Viral Phase (COVID UPP)

- Among a large, racially/ethnically diverse population who tested positive for SARS-CoV-2 infection and who report Post-acute COVID-19 symptoms:
- Describe the function, quality of life, and symptom complex (frequency and severity).
- Assess the rate of self-reported symptom persistence and extent to which the symptom profile matches that of ME/CFS.
- Describe the trajectory of Post-acute COVID symptoms and associated risk factors of population who continue to report being unrecovered from the infection over time.
- Perform in-depth clinical and biologic phenotyping to describe the clinical presentation and laboratory findings of unrecovered individuals compared with individuals who have fully recovered.

Compare to the existing data set in ME/CFS from the CDC MCAM study of 750 individuals with ME/CFS (deigned with many of the same assessment features)

COVID UPP Case Definition. Inclusion Criteria

Between 18 to 65 years of age (consideration re age >65: distinguishing cognitive symptoms associated with COVID vs associated with age)

Self-report confirmation of positive COVID-19 test at least 3 months prior to enrollment Positive test required to minimize factors complicating interpretation of results. If closer than 6 months from infection, would include many people whose symptoms will resolve

Satisfactory completion of Recruitment Screen which includes: Reported symptom of fatigue, tiredness, or exhaustion post COVID and at least one additional symptoms of seven in the screen

NO' to "Symptom before the recent health concern that caused you to get a COVID-19 test,*"

Symptoms "Good bit of time", "Most of time", or "All of Time"

Long COVID symptoms in common with ME/CFS are common in the general population, e.g. fatigue. It's the frequency and severity of some of these symptoms among people with PCC that are unusual, suggesting that frequency and severity are important considerations in the definition.

- **Exclusion criteria**
- Self-report intensive care unit (ICU) stay due to COVID-19 infection
- Self-report ME/CFS diagnosis prior to positive COVID-19 test
- Self-report, did not receive a positive COVID-19 test
- Chronic lung disease reported developed or worsened after COVID-19 infection
- Alzheimer's disease or Dementia reported
- Excluding organ specific sequelae to acute OCIVD 19:
- Cardiac fibrosis or cardiomyopathy with an ejection fraction less than normal (assessed during clinical visit).
- Chronic lung disease, developed or worsened after SARS-CoV-2 infection (assessed during clinical visit).
- O2 saturation of 92 or below on the 6-minute walk (assessed during clinical visit).
- • Abnormal spirometry that does not resolve after bronchodilator (assessed during clinical visit).

- **From here the exclusions follow the recommendations of the ME/CFS case definition ambiguities paper by Reeves et al 2003**
- Hospitalization in past 12 months due to chronic disease (Diabetes, high blood pressure, kidney disease, cancer, depression, substance abuse, heart failure, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, other auto-immune disease)
- Medical or psychiatric conditions diagnosed prior to testing positive for SARS-CoV-2 infection that would reasonably explain their prolonged fatiguing illness and the degree of impairment seen. such as severe chronic obstructive pulmonary disease (COPD), organ failure, chronic infections, rheumatic and chronic inflammatory diseases, major neurologic diseases, etc.

Case Definition and Assessment Platform

- We wanted our case ascertainment to be reproducible (be able to be applied consistently by other researchers).
- We tried to balance inclusivity and specificity. Broad enough to reflect the heterogeneity of Long COVID syndromic illness, but specific enough that all research subjects have medically unexplained symptoms that affect their physical functioning.
- Along these lines, we aimed for inclusion/exclusion criteria to be unambiguous (based on standardized assessments with thresholds for interpreting results as meeting or not meeting criteria). Since we were comparing with ME/CFS, we chose standardized assessments validated in ME/CFS patients, drawn from the Common Data Elements of ME/CFS and our prior MCAM (Multi-Site Clinical Assessment of ME/CFS) study.

PROMIS 29 (ME/CFS CDE functional scale) Our cutoff is informed by ME/CFS research. The mean score of Physical Function of PROMIS-29 Profile for the MCAM ME/CFS cohort was approximately 40 and the general population norm is 50. We decided to have the middle-point as the screening cutoff for the unrecovered group in addition to case-defining symptoms. We chose 45 as the cutoff because a five-point difference in Physical Function on the PROMIS-29 Profile is considered a clinically meaningful difference.

Phenotyping study focuses on moderate to severe illness

- Unrecovered group: Moderate to severe illness as indicated by PROMIS 29 score of 45 or lower on the physical subscale, and have fatigue that does not resolve with rest, and one additional symptom from the CDC SI screener.

- Recovered Group: Individual reports recovery from SARS-CoV-2. PROMIS 29 score of 46 or higher on the physical subscale, does not report fatigue which is not resolved by rest or list symptom on the Health Screen

COVID UPP Longitudinal Study

Inclusion criteria

Funding Source: Centers for Disease Control
Contract # 75D30120C09554

1.- Between 18 to 65 years

2.- Sign Inform Consent

3.- Positive COVID-19 test at least 3M prior to enrollment

4.- **RECOVERED COHORT:** Recovery from SARS-COV-2 and does not report fatigue after infection

5. **UNRECOVERED COHORT:** Reported Fatigue, Tiredness or Exhaustion after COVID

PLUS

One Additional Symptom present: **Good bit of the time**, **Most of the time** or **All the time**

- Sore Throat
- Tender Lymph Nodes
- Diarrhea
- Fatigue after Exertion
- Muscle Aches and Pains
- Joint Pain
- Fever
- Chills
- Unrefreshing Sleep
- Sleeping Problems
- Headaches
- Memory Problems
- Concentration problems
- Nausea
- Stomach or Abdominal pain
- Sinus or Nasal problems
- Sensitivity to Light
- Depression
- Dizziness

COVID UPP Longitudinal Study

Exclusion Criteria

Funding Source: Centers for Disease Control
Contract # 75D30120C09554

1. Self report ICU stay due to COVID-19 Infection

2. Self report ME/CFS diagnosis prior to positive COVID-19 test

3. Self report did not receive a positive COVID-19 test

4. Chronic lung disease , heart or kidney disease reported as developed or worsened after COVID-19 infection

5. Alzheimer's disease or Dementia reported

6. Before diagnosis with COVID-19, hospitalization in past 12 months due to chronic diseases

- Diabetes
- HTN
- Kidney Disease
- Cancer
- Depression
- Substance Abuse
- CHF
- COPD
- Rheumatoid Arthritis
- Other Auto-Immune Disease

COVID UPP Phenotyping Study

Inclusion criteria

Funding Source: Centers for Disease Control
Contract # 75D30120C09554

RECOVERED COHORT: Recovery from SARS-COV-2 and does not report fatigue after infection
Promise 29 score >46

UNRECOVER COHORT:

- Moderate to severe Illness as indicated by PROMIS 29 Score of 45 or lower on the Physical Subscale
- Have Fatigue

PLUS

One Additional Symptom present: **Good bit** of the time, **Most** of the time or **All** the time

- Sore Throat
- Tender Lymph Nodes
- Diarrhea
- Fatigue after Exertion
- Muscle Aches and Pains
- Joint Pain
- Fever
- Chills
- Unrefreshing Sleep
- Sleeping Problems
- Headaches
- Memory Problems
- Concentration problems
- Nausea
- Stomach or Abdominal pain
- Sinus or Nasal problems
- Sensitivity to Light
- Depression
- Dizziness

COVID UPP Phenotyping Study

Exclusion Criteria

Evidence of organ specific damage as a consequence of acute COVID 19 infection

- Abnormal diastolic function or Cardiomyopathy with EF less than normal.
- Oxygen saturation of 92% or below on the 6- minute walk
- Abnormal Spirometry that does not resolve after bronchial dilator

Funding Source: Centers for Disease Control
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Conclusion

- Early consensus on research case definitions and common data element platforms are early consensus will prevent long delays in comparable studies and meta analyses in a rapidly evolving literature
- Clinical case definitions are equally important in allowing medical education to go forward and allowing patients from experience long delays and misdiagnoses.
- ME/CFS research methodologic advances should be a starting point, the evolution of case definitions and the Common Data Elements Platform have allowed critical advances
- COVID-UPP data and conclusions will be an a important resource to understand the overlap with ME/CFS and developing clinical subsets of syndromic Long COVID
- Note the ME/CFS Clinicians Coalitions position statements on ME/CFS

https://mecfscliniciancoalition.org/