

**European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome  
(EUROMENE)**

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**Joint publication manuscript on ME/CFS European practices in diagnosis and  
treatment based on survey data**

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**Abstract**

**Background.** ME/CFS is a chronic, complex, multisystem disease that often limits health and functioning of the affected patients. Diagnosing patients with ME/CFS is a challenge and many different case definitions exist and are used in clinical practice and in research. Even if patients meet the chosen criteria there is no medical treatment. Symptom relief and coping may affect how patients live with their disease and for their quality of life. There are discussions and also confusions as to which criteria should be used and which treatment strategies are working best for the patients. The results will contribute in discussion around and harmonization of diagnosis criteria and treatment for ME/CFS in Europe.

**Aims.** The purpose of the current project was to map the landscape of the Euromene countries on national guidelines and recommendations for case definition, diagnosis and clinical approaches for the ME/CFS patients.



**Methods.** A 23 items questionnaires was sent out by email to the members of Euromene. The form contained questions on existing guidelines for case definitions, treatment/management of the disease, tests and questionnaires applied, and prioritization of information for data sampling in research.

**Results** A total of 17 countries responded. Five countries reported having national guidelines for diagnosis and five countries reported having guidelines for clinical approaches. For diagnostic purpose the Fukuda criterion was most often recommended and also Canadian Consensus criteria, International Consensus Criteria and Oxford criteria were used. A mix of diagnostic criteria was applied within those countries having no guideline. Many different questionnaires and tests were used for symptom registration and diagnostic investigation.

As symptom relief, pain and anti-depressive medication were most often recommended. Cognitive Behavioral Therapy and Graded Exercise treatment were recommended as disease management and rehabilitative strategies

**Conclusion.** Based on results from the current survey and discussions within the working group, the Canadian Consensus criteria and Fukuda were recommended as case definitions to be used in the European countries. For symptom relief, self-management and coping, the most important is probably an individually tailored approach.

## **Introduction**

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is approached differently in different European countries. Selection of diagnostic criteria, treatment or methods of research may be crucial for this patient group.

The EUROMENE project aims to establish a homogeneous research network to attempt to synchronise databases, develop common standards and strategies, and initiate new research projects, in order to achieve better understanding of the disease, harmonize diagnosis and assessment methods and contribute to the development of effective treatments in the future. The network is structured in six working groups (epidemiology, biomarkers, socio-economic impact, clinical and diagnostic criteria, short term scientific mission and dissemination).

The first task of the working group on clinical and diagnostic criteria, was to analyse existing clinical criteria guidelines in order to find-out optimal criteria set allowing excluding over-diagnostic and un-diagnostic. It was decided to conduct a survey in the Euromene countries on existing gaps on ME/CFS guidelines for diagnosis and to analyse treatments of ME/CFS and its efficacy in order to find out optimal treatment approaches. Development of uniform methods for diagnosis and research as well as suggestions for treatment were the main concerns.

Around 20 different criteria are developed over the last 30-40 years in order to classify CFS and ME. The most commonly used in recent years are the Fukuda criteria [1], the Canadian Consensus Criteria (CCC, [2], the International Consensus Criteria (ICC, [3]) or the Oxford criteria [4]. Recently, a new diagnostic criteria - the SEID (Systemic Exertion Intolerance Disease) - from the Institute of Medicine (IOM, [5]), was proposed in the aftermath of a huge literature review in the field. The case definitions vary according to strictness for example the Oxford criteria are wider than the CCC or the ICC. Using different criteria restricts the possibility to estimate prevalence and incidence and to compare research results between the countries. Thus a more uniform way to diagnose and methods to map symptoms in clinic as well as in research are needed. This gives the possibility to share data and collaborate across research groups and country borders.

There is an ongoing discussion about what diagnostic criteria will work best, and preferably be used in the classification of the illness. Whether one should use broad or strict criteria or the same criteria should be used in clinical practice as in research, or whether the criteria applied should be consensus or research based. All the criteria used until today are developed by consensus discussions among researchers and clinicians, and it may be a problem that research is built upon consensus based case definitions.

That different criteria are applied by various research groups is a problem particularly for research. This indicates difficulties in comparison of research results across study samples. Although when the same criterion is applied it may be interpreted and used in different ways by physicians or other who diagnose. This is a challenge in research, but also in clinical care as diagnostic criteria are important also for the planning and management protocols and health services in general. Some countries, attempted to solve these problems by creating overarching guidelines proposing use of criteria and more specific advice in

relation to diagnosis. This discussion points to the necessity of using standardized methods for diagnosis. Using common measurement methods may also be required for mapping of symptoms, collecting other information or for subtyping of the patient group.

For symptom relief, illness coping strategies or counselling of patients, there are discussions and disagreements about what will work best. No medical cure for ME/CFS exists at this point. However, it is possible to use both pharmacological treatments and non-pharmacological strategies to alleviate unpleasant symptoms. Further, ME/CFS may benefit from various forms of coping and self-management strategies, in managing the disease and increase or maintain quality of life. There are discussions within the field of which strategies that should be used. What approaches and advice actually used in clinical practice around Europe is therefore interesting to map. Thus some questions on this topic also were added in the form.

The overall aim was to obtain a better basis for research collaborations and develop an overall European policy and harmonization of criteria and other strategies and managements offered the patients. For the current project the purpose was to map the landscape of the Euromene countries on national guidelines, specific recommendations for criteria, diagnosis, assessments and clinical approaches for the ME/CFS patients.

## **Methods**

A questionnaire was developed by the authors in collaboration with Euromene members. It consisted of 23 specific questions with the possibility of supplementary comments on each question and at the very end of the form. The form contained questions on already existing guidelines for case definitions and treatment/management of the disease. More specific, types of tests and questionnaires, themes assessed, prioritization of mappings and assessments for research, as well as existing national bio-banks, registry or research funding, were assessed. The questionnaire was sent to members of the Euromene in August 2016. As a few more countries were added to the network after this date, they also received a copy of the questionnaire. In total 19 countries received the questionnaire and 17 have at this point responded; Spain, Serbia, Denmark, Italy, Latvia, Norway, UK, Germany, Belgium, Bulgaria, Romania, France, Greece, Netherlands, Ireland, Finland as well as Belarus. All forms were reviewed by the WG4 leader and results were summarized in tables. Moreover, specific questions were further sent out for more detailed information

from the WG4 group members and from the respective WG leaders, on for example type of tests and questionnaires applied in the respective countries and how to prioritize assessments of information for data samplings.

## **Results**

### **Guidelines for diagnosis, diagnostic criteria, psychosocial or neurological investigation (Table 1).**

Twelve of the seventeen country reported having no overall national guidelines while five of them had. The following countries reported having national guidelines for diagnosis and diagnostic criteria on ME/CFS: Spain, Italy, UK, Netherlands and Norway [6,7,8,9,10]. The Fukuda criterion [1] was recommended by the Spanish and in the guideline from the Netherlands. The Norwegian guideline recommended both the CCC [2] and the Fukuda, under the condition that the applied criteria was reported in the medical journal. Both the ICC [3] and the Fukuda were suggested in the Italian guideline. In UK the NICE guidelines recommend the Oxford criteria [6]), and in addition a “*diagnostic process*” is recommended based on a few symptoms (with main reference to the Oxford criteria), and exclusion of other diseases. Both Fukuda and the Canadian Consensus Criteria are also mentioned in the Nice guidelines. In addition, one country (Belarus) reported the International Classification of Diseases -10 (ICD-10) as a guideline, but had no specific ME/CFS guideline.

Different diagnostic criteria as well as ICD-10 diagnosis are used to diagnose ME/CFS. By those countries having no national guidelines the most frequently used case definitions is the Fukuda definition (N=3) and the CCC (N=3). Also SEID (N=2), Holmes (N=1) and a mix of ICC, CCC, Fukuda and Oxford were reported used. In one country major depression and functional disease was used as diagnostic criteria. What case definition applied varies between the countries, but most countries use either Fukuda or the CCC.

Additional blood tests were recommended in the guidelines and also applied in some of the countries with no guidelines for diagnosis. What type of blood tests applied also varied between the countries.

Most often and in all the guidelines it was reported that the GP/physicians or pediatricians conducted the diagnosis. Also an array of other specialists was mentioned such as neurologist, immunologist, psychiatrist, virologists, specialist in internal medicine,

infectious disease, in physical medicine and rehabilitation or in cognitive behavioral therapy.

In all the guidelines and in three of the other countries it was recommended to also conduct an investigation of psychological/psychosocial factors. Also different neuropsychological, imaging techniques and neuro-electrophysiological investigations were mentioned by 2, 4 and 4 countries, respectively. Type of tests conducted varied between the countries.

<b>Table 1: Guidelines for diagnosis/diagnostic criteria (psychosocial, neurological investigations etc)</b>	
<b>Responders</b>	N=17
<b>National guideline for diagnosis of ME/CFS</b>	Yes= 5
<b>Case definition recommended in the guidelines</b>	Fukuda (N=2), Canada & Fukuda (N=1) Fukuda and ICC (N=1), Oxford (N=1)
<b>Additional blood samples or other tests recommended to complement the clinical investigation</b>	Yes=6
<b>Conducts the diagnosis (Physician, psychiatrist, physiotherapist, neurologist psychologist, etc)</b>	GP/physicians (N=7) specialist/specialized centers N=6
<b>Psychosocial investigation, cognitive assessment , or facilitation in relation to school etc. recommended</b>	Yes=7
<b>Neuropsychological investigations required for diagnosing and/or monitoring</b>	Yes=4
<b>Imaging techniques required for diagnosing and/or monitoring</b>	Yes=5
<b>Neuro-electrophysiological investigations (CNS evoked potentials EMG/NCV; autonomic function test) required</b>	Yes=4

**Other diagnosis, diagnostic criteria or standardized methods applied (Table 2)**

Even countries not having a national guideline do diagnose patients by using ME/CFS case definitions or other diagnosis systems. (Table 2 ). The most common diagnosis from ICD-10 applied for diagnosing ME/CFS patients are G 93.3 (N=9) and F 48 (neurasthenia, N=5). G93.4, G 90.9, F 45.3, or R 53 also were reported.

Four of the countries (Greece, Bulgaria, Finland and Russia) report using only G93.3 from the ICD-10 and one country (Serbia) reports not using any diagnosis. The Fukuda criteria is mentioned as the preferred case definitions by two of the countries (Latvia, Belgium) and the CCC is used in Germany. Otherwise a mix of all the case definitions and psychiatric diagnosis such as Fukuda, Canada, ICC, SEID, Major depression, Functional Disease, Holmes or Oxford criteria were used. It seems as the physicians who diagnose act according to their level of knowledge on ME/CFS and/or personal preferences for case definitions.

<b>Table 2: Other diagnosis, diagnostic criteria or standardized methods applied</b>	
<b>Diagnosis usually applied (for example G 93.3, F 48 etc)</b>	G93.3 (N=9): post viral fatigue syndrome, F48 (N=5):: neurasthenia, G93.4 (N=1): unspecified encephalopathy , G90.9 (N=1): unspecified disorder of the autonomic nervous system, F45.3 (N=1): somatoform autoimmune dysfunction, R 53 (N=1): malaise and fatigue, No ICD-10 diagnosis used, N= 4
<b>If no guidelines: diagnostic criteria most commonly used for ME/CFS diagnosis</b>	Fukuda (N=3), Canada (N=3), SEID (N=2), Major depression (N=1), Functional disease (N=1), Holmes criteria (N=1), USDCDCP (N=1), Mix of ICC, Canadian, Fukuda and NICE, Fatigue, Day sleepiness, Sleep disorders, hormonal imbalance, exercise intolerance
<b>Standardized methods for assessment used (questionnaires, activity assessments or electronic tools etc)</b>	N=7 Symptom questionnaires for fatigue, sleep, physical functioning, psychological aspects (varies widely between countries)  HR and BP sitting and standing for 10 min., assessment of muscle power and endothelial function within trials, Compass31: autonomic function, Modified cardiopulmonary exercise test for diagnosis

Regarding standard methods and tools for mapping symptoms seven countries reported no standardized methods while the other countries reported a variety of questionnaires applied for assessment of symptoms such as fatigue, sleep, physical functioning, anxiety or

depression. Also assessment of HR and BP, muscle power and endothelial function, as well as Compass 31: autonomic function were applied.

### **Guidelines for treatment, symptom relief and management (Table 3)**

Most of the countries do not have national guidelines for treatment of ME/CFS. The following five countries reported to have national guidelines for clinical approaches in ME/CFS: Spain, UK, Norway, Netherlands and Belgium. Two countries reported using treatment guides for mental health for these patients. As disease modifying treatment the following are suggested in the existing guidelines: painkillers (N=3), anti-viral medication (N=2), infection control (IgG, (N=1)), and medication for sleep problems (N=1). Five countries reported having follow-up after diagnosis and collaborations with the primary care, if needed.

Procedure for symptom and illness management recommended are most often Graded Exercise Therapy (GET) and Cognitive Behavioral Therapy (CBT) (N=8), pacing/activity regulation/mind-body strategies (N=4), as well as sick-leave, self-management program (8-weekly sessions) or a four-week rehabilitation stay at an institution. In most of these countries there are multidisciplinary teams involved in treatment/management of the disease. Rehabilitative strategies proposed most often are CBT, GET or some activity/exercise scheduled strategies.

<b>Table 3: Guidelines for treatment, symptom relief and management</b>	
<b>Q 13, 14, 15, 16, 17,18, 19:</b>	<b>Yes (comments)</b>
<b>National guidelines for treatment of ME/CFS</b>	N=5(2)
<b>Responsible author for guidelines</b>	National health institutions (N=6), Research ME group (N=1)
<b>Symptomatic treatment suggested (if indicated)</b>	Pain killers (N=3), antidepressive/anxiety medication (N=4), anti-viral medication (N=2), sleep (N=1), different kinds of syndromes (Sicca , trendinopathy, metabolic syndrome, thyroid dysfunction) and CBT (N=3) or GET (N=2)
<b>Follow-up after diagnosis</b>	N=6 (collaboration with primary care, yes, but only if need)



<b>Procedures for symptom management</b>	GET/CBT (N=8), activity regulation/pacing/mind-body strategies (N=3), sick-leave, psychotherapy, self-management program (8 weekly sessions), rehabilitation institutions
<b>Interdisciplinary teams involved in treatment/symptom management</b>	N=8 (differs widely , most often neurologist and psychiatrist/psychologist)
<b>Rehabilitation strategies proposed</b>	CBT, GET, pacing, mind-body strategies, exercised scheduled treatment

### **Summary and discussions**

The following gaps between countries were identified: application of diagnostic criteria, exclusion process, assessments and standardized tests and questionnaires and symptom treatment and management. National guidelines do not exist in most of the countries while five countries have comprehensive national guidelines for case definitions and diagnosis as well as recommendations for use of tests, questionnaires and for the exclusion part of diagnosis. The existing guidelines have been developed over the last ten years: 2007 (UK), 2011 (Italy), 2013 (Netherlands), 2014 (Spain) and 2015 (Norway), respectively.

### **Diagnostic criteria and case definitions**

Which diagnostic criteria to recommend for the European countries is the most important topic to be discussed. The Fukuda are most often recommended in the respective national guidelines, but also CCC and ICC are mentioned. The IOM criterion was discussed and ambivalence toward using them was revealed. These criteria was developed after an extended research literature review by the Institute of Medicine in US [5] and is in fact the only case definition that have some research foundation as opposed to the other criteria that arise from discussions among health providers and researchers.

For clinical practice the most important argument is that the criteria should be easy and not take too long time to use. Thus, for this use Fukuda might be the best choice although it is somewhat broader and may include patients with other explanations for their symptoms, than, say the CCC or the strictest ICC from 2011. Another objection to the Fukuda criteria is that they do not require PEM (post exertional malaise) which is now considered the cardinal symptom of the disease. The issue about using broad or strict criteria is tricky. To

apply the wide criteria in research when searching for subsets and bio-markers, may be a good idea. If using strict criteria such as ICC, implies that only patients satisfying this criterion and not CCC or Fukuda, would be part of the data sample. Thus comparing patients satisfying different case definitions or search for subsets in the illness population may not be possible or will be restricted. The CCC was suggested to be recommended as standard case definition for research purpose. The Fukuda criteria may also be applied for those who already use them. The newest IOM criteria labelled SEID can also be used as a complement and may a good criterion for use in clinical practice.

### **Exclusion/differential diagnosis.**

Diagnostic assessment relies on clinical interview and patient` self-reported symptoms. In addition an extended clinical evaluation to identify underlying, contributing, and comorbid somatic and psychiatric conditions that require treatments is recommended. Guidelines and standard tests for the exclusion part are unclear, vary or are completely absent in some of the countries. A few countries only, have multidisciplinary team around this patient group. Some do additional psychological/psychiatric, neurological/neuropsychological as well as other examinations. Further clinical examination often depends on what kind of specialists available in the team, at the institution or that nearby. Standardized questionnaires are applied in the exclusion part in some of the countries, but also the type of tests/questionnaires used varies between them. There seem to be lack of more specific guidelines for further examinations of the patients as well. Also this part of the diagnostic process might be harmonized between the countries. It was suggested to use the guideline for exclusion and comorbidity building on the CCC [11].

### **Test for diagnosis/symptom registrations.**

Another important discussion is which questionnaires and assessment tools are most appropriate for symptom registrations and other additional information for research. An array of questionnaires and tools for symptom assessments are applied in the different countries. Standardized and validated questionnaires for symptoms registrations and for classifying ME/CFS into different case definitions exist and are already used in four of the countries.

**Suggestions for symptom registrations and classifications for research** DePaul Symptom Questionnaire [12] is recommended for a thorough symptom registration and for

classifying into the case definitions. The DSQ is an illness specific questionnaire and at this point, the only instrument able to classify within different case definitions. DSQ is already translated into Norwegian, Spanish and Dutch and used for research on the ME/CFS patient group in these countries as well as in a research team in UK and in US. The SF-36 (Short-Form, MOS; [13]) is a generic health related questionnaire used for research in different illness populations included ME/CFS, for assessing mental, physical and social functioning. Four of the items from SF-36 are also part of the DSQ scoring system. In addition HADS (Hospital Anxiety and Depression Scale; [14]) is suggested to be used as mental health assessment and for controlling for anxiety and depression. Both DSQ, SF-36 and HAD are well-known measurement methods and often used for research on ME/CFS as well as already applied by some researchers of the Euromene countries. Additionally it is necessary to assess other health information such as family health, extended assessments on cardinal symptoms such as neurocognitive aspects or sleep etc.

### **Symptom relief, coping and self-management**

At this point no medical cure exists for ME/CFS. However, it is possible to assist patients with relief of unpleasant symptoms. Medications for pain, anxiety and depression was most commonly mentioned for symptom relief. A few countries also mentioned antiviral medication. Cognitive Behavioral therapy (CBT) and Graded Exercise Therapy (GET) were most often recommended as methods for symptom management. Also Pacing and activity regulation were mentioned and sometimes used in combination with CBT.

The patients need advice for coping and to learn self-management strategies for preventing worsening, to maintain and increase quality of life. Five of the countries have national guidelines for management of ME/CFS and all of them suggest Cognitive Behavioral Therapy, Graded Exercise Therapy, Pacing and mind-body strategies as useful as adjunct measures for patients, although the evidence for their effects have been questioned. A few countries only do have rehabilitation and self-management programs for CFS/ME patients. CBT, GET or pacing were mentioned as rehabilitative and coping management offered to the patients. Both CBT and GET is controversial and there are disagreements and uncertainty among both patients and health providers regarding the effect of the methods. That these approaches are used as treatment and self-management strategies in ME/CFS

patients may imply that even if they do not cure, they are experienced as helpful of both health-providers and patients.

Recently a review from the Spanish group in Euromene was published that should guide suggestions for symptom treatment and counselling and for symptom management. The review article [15] summarizes as following: “Nutritional supplementation is recommended in CFS/ME patients with biochemically proven deficiencies. CFS/ME treatment should also be optimized by the use of individualized pacing strategies, customization of CBT and other types of counselling and behavioral therapies so as to help relieve the symptoms. GET should be carefully modulated by an individual pacing strategy using strict case definitions to avoid the push-crash cycle. Further additional larger interventions should now incorporate personalized integrative medicine approaches for identifying CFS/ME patients most likely to respond to each type of treatment. Researchers and the medical community also need to develop new initiatives and additional forms of individualized treatment and management in CFS/ME in order to achieve significant improvements in quality of life, especially in those severely ill ME cases and bed-ridden patients”.

### **Conclusion**

A couple of diagnostic criteria are recommended for research and clinical practice. Guidelines for the exclusion part and specific suggestions for standardized mapping of symptoms and classification to be used are also suggested. Several strategies may relieve symptoms or in other ways enhance coping, self-management and quality of life, and nevertheless the best is to match the approach to the individual patient's need and challenges.

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