



Article

Italian Expert Consensus on Clinical and Therapeutic Management of Multiple Chemical Sensitivity (MCS)

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Abstract: Multiple chemical sensitivity (MCS) is a multisystem, recurrent, environmental disorder that flares in response to different exposures (i.e., pesticides, solvents, toxic metals and molds) under the threshold limit value (TLV) calculated for age and gender in the general population. MCS is a syndrome characterized by cutaneous, allergic, gastrointestinal, rheumatological, endocrinological, cardiological and neurological signs and symptoms. We performed a systematic review of the literature to summarize the current clinical and therapeutic evidence and then oriented an eDelphi consensus. Four main research domains were identified (diagnosis, treatment, hospitalization and emergency) and discussed by 10 experts and an MCS patient. Thus, the first Italian MCS consensus had the double aim: (a) to improve MCS knowledge among healthcare workers and patients by standardizing the clinical and therapeutic management to MCS patients; and (b) to improve and shed light on MCS misconceptions not supported by evidence-based medicine (EBM).

Keywords: multiple chemical sensitivity (MCS); chemical intolerance; threshold limit value; environmental exposure; neurogenic inflammation

1. Introduction

Multiple chemical sensitivity (MCS) is a multisystem, recurrent, environmental disorder that flares in response to different exposures (i.e., pesticides, solvents, toxic metals and molds) under the threshold limit value (TLV) calculated for age and gender in the general population [1].

From its first description in 1956 by Randolph [2], and the subsequent definition as MCS by Cullen in 1987 [3], an MCS diagnosis remains challenging for clinicians and even more so for scientists facing inclusion criteria difficulties in their studies. Remarkably, in 1999, the International Consensus on MCS [4], and then Lacour in 2005 [5], summarized a precise set of six diagnostic criteria. In the literature, MCS is described by different pseudonyms such as idiopathic environmental intolerance (IEI), environmental illness (EI), chemical intolerance (CI) or toxicant-induced loss of tolerance (TILT), which either focus on the symptoms (IEI, EI, CI) or the pathogenetic mechanisms (TILT). In the current consensus, the experts preferred the term MCS for historical and inclusive purposes.

Nowadays, MCS has an estimated prevalence of 0.5–6.5% in medically evaluated patients [6,7]; a self-reported prevalence achieves 9.0–11.2% in the general population [6,8]. In the last five years, MCS knowledge has rapidly incremented and clinical manifestations [9–20], triggers [21–27] and a patient category at risk [28–31] have been identified. These contribute to the understanding of the MCS pathogenesis [10,21,32–48] and assists in the design of dedicated MCS screening questionnaires [49–54] (Table 1).

Due to the evolution of the diagnostic criteria, the epidemiology, pathogenesis and clinical evaluation differ based on the criteria chosen. This scenario has deeply influenced the therapeutic management of MCS patients. Thus, we decided to perform a clinical and therapeutic consensus on MCS to further orient clinicians.

Table 1. Clinical and pathogenetic overview of MCS characteristics.

Pathogenetic Hypotheses	Clinical Manifestations *	Screening Questionnaires	Subjects at Risk	Triggers *
Limbic dysfunction [34–37]	Neurological disorders [1,12–17]: headache, migraine, trigeminal neuralgia, convulsions, attention deficit disorder, neurocognitive deficits, hyperacusis, insomnia, myalgic encephalomyelitis	Environmental Exposure and Sensitivity Intolerance (EESI) [49]	Industrial workers acutely or chronically exposed to recognized triggers [30]	Organic solvents and related compounds [23]
Immune disorders [36–38]	ORL disorders [1]: sinusitis, polyps, non-allergic rhinitis with eosinophilic syndrome, tinnitus, recurrent otitis, allergic rhinitis	Quick Environmental Exposure and Sensitivity Inventory (QEESI) [50]	Other workers exposed to recognized triggers (farmers, hairdressers, radiologists, anesthesiologists) [30]	Insecticides, pesticides, herbicides [23]
Biochemical mechanisms [40–43]	Cardiovascular disorders [1]: arrhythmia, tachycardia, hypotension, hypertension, Raynaud's phenomenon, lipothymia	Huppe Questionnaire [51]	Office workers [30]	Different gases (i.e., hydrogen sulfide (H ₂ S) or carbon monoxide (CO) [23]
Neurogenic inflammation [39]	Respiratory disorders [1]: asthma, tracheitis, bronchospasms, chronic tonsillitis, hyper-reactive airway syndrome, toluene diisocyanate hypersensitivity	Chemical Sensitivity Scale for Sensory Hyper-Reactivity (CSS-SHR) [52]	Residents in contaminated areas [30]	Metals (i.e., mercury) [23,30]
Neurophysiological and respiratory mechanisms [44,45]	Gastroenterological disorders [1]: irritable colon, colitis, gastroesophageal reflux (GERD), celiac disease, gluten sensitivity, food intolerances, food allergies	German Questionnaire on Chemical and Environmental Sensitivity (CGES) [53]	Gulf War veterans [30]	Molds and mycotoxins [24–28]
Vascular dysfunction [46]	Rheumatological disorders: fibromyalgia, carpal tunnel syndrome, dysfunction of the temporomandibular joint (TMJ), arthritis, connective tissue disease, systemic lupus erythematosus (SLE) [1]	Brief Environmental Exposure and Sensitivity Inventory (BREESI) [54]	Silicon or prosthesis implants carriers [10,31]	Xenobiotics in foods and beverages (i.e., sulfites) [29]
Psychiatric disorders [47,48]	Dermatological/allergic disorders [1]: eczema, systemic dermatitis, rash, urticaria/angioedema, photosensitivity, skin photosensitivity, dermatographism		Patients born by Caesarean section [33]	Combusted products (diesel exhaust, tobacco, wood) [29]
N-Methyl-D-aspartic acid or N-Methyl-D-aspartate (NMDA) sensitization and stimulation by reactive oxygen species and peroxynitrite [21]	Endocrinological disorders [1,18]: diabetes, dysthyroidism, adrenal gland disorders, pituitary disorders			Other substances (natural psoralens, terpenes) [29]
	Psychological/psychiatric disorders: anxiety, depression, manic depression, bipolar disorder, mood swings, panic attacks			
	Others [19,20]: Chronic Fatigue Syndrome, Gulf War Syndrome, Sick Building Syndrome			

* Reported in the literature; the exact causative mechanism remains elusive.

2. Materials and Methods

2.1. Scientific Committee

This consensus was designed and conducted by the MCS Italian Study Group that groups several experts and medical and non-medical researchers with a particular focus on MCS. The medical committee (>5 years of experience) comprises allergists/allergologists, dermatologists, rheumatologists, anesthesiologists, dentists and otorhinolaryngologists whereas the non-medical experts are biologists with at least five publications focusing on MCS in peer-reviewed international journals in the last five years (Table 2).

Table 2. Characteristics of the members in the pre-Delphi and Delphi consensus exercises.

Demographics and Characteristics	Pre-Delphi Exercise (N = 7)	Delphi Rounds (N = 12)
Dermatologists, N (%)	1 (14.3)	1 (8.3)
Dentists, N (%)	1 (14.3)	2 (16.6)
Otorhinolaryngologist, N (%)	1 (14.3)	1 (8.3)
Anesthesiologists, N (%)	-	1 (8.3)
Allergists/Allergologists, N (%)	1 (14.3)	1 (8.3)
Rheumatologists	-	1 (8.3)
Alternative Medicine Doctors	-	1 (8.3)
Biologists, N (%)	2 (28.6)	2 (16.6)
Representatives of Patients, N (%)	1 (14.3)	1 (8.3)
Male, N (%)	5 (71.4)	9 (75.0)
Age, Median (IQR), Years	52 (50–57.5)	55 (47–59)
Clinical/Research Experience, Median (IQR), Years	25.5 (21.3–27.5)	26 (15.5–34.5)
Academic Experience, N (%) *	5 (71.4)	5 (41.7)
Hospital or Private Practice Experience, N (%)	4 (57.1)	9 (75.0)
Both, N (%)	6 (85.7)	11 (91.7)

IQR: Interquartile range. * Among the experts, five had an academic position: 1 Postdoctoral Fellow (G.D.), 1 Assistant Professor (A.M.) and 3 Associate Professors (A.M., D.C. and P.D.M.P.).

2.2. Study Design

Due to the growing body of literature on MCS and the coronavirus 2 (SARS-CoV-2) infection pandemic, experts were involved in a Delphi process shaped in a pre-Delphi with three rounds divided by 2 months each to promote an interdisciplinary discussion and a critical literature evaluation.

To define MCS, we adopted the Lacour revised criteria: (a) a chronic condition (>6 months duration) with a worsening of both quality of life and organic functions; (b) recurrent and reproducible symptoms also involving the nervous system with a characteristic hypersensitivity to odors; (c) symptoms involving the central nervous system and at least one other symptom; (d) reproducible responses to triggers at a low concentration; (e) a response to unrelated chemicals; and (f) an improvement of symptoms or even a complete resolution after the removal of the trigger [5]. Remarkably, a diagnosis can be made if the patient fulfills all six criteria.

2.2.1. Pre-Delphi Exercise

A systematic review was conducted in PubMed and EMBASE using the keywords “Multiple Chemical Sensitivity”, “MCS”, “Idiopathic Environmental Intolerances”, “Environmental Illness”, “Chemical Intolerance”, “Toxicant-Induced Loss Of Tolerance”, “TILT”, “EI” and “IEI” by two MCS Study Group members (G.D. and P.D.M.P.) on 21 May 2020.

In line with Lacour’s MCS extended criteria [5] and the clinical manifestations, we decided to create four main research domains, namely, diagnosis, therapy, hospitalization and emergency treatment (Figure 1).

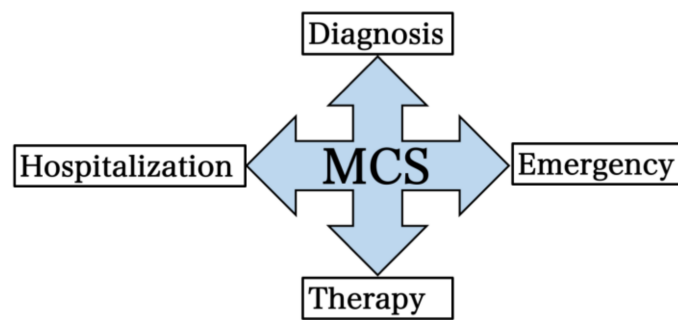


Figure 1. Research domains identified during the pre-Delphi. MCS: multiple chemical sensitivity.

2.2.2. Delphi Rounds

The eDelphi exercise was designed from the feedback of the pre-Delphi exercise and proposed to 11 Italian MCS experts with a median experience of 26 (15.5–34.5) years plus a representative of the patients (Table 2). All participants rated the questions from 0 (strong disagreement) to 10 (complete agreement) and the agreement was established as $\geq 70\%$. A comment space was present after each question as well as a link to the reference used to prepare the voting statement. During all rounds, the results of the previous round were reported.

After each round, a meeting took place to discuss the potential criticisms and disagreements.

2.2.3. Statistics

The continuous data were reported as a median and interquartile range and the agreement was calculated with the Fleiss Kappa coefficient (≤ 0 , no agreement; 0.01–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, an almost perfect agreement). We reported in the results section only statements that achieved an agreement. All statistical analyses were performed by the commercial software “Statistical Package for Social Sciences” (SPSS for Windows, version 24.0, IBM, Armonk, NY, USA).

3. Results and Discussion

3.1. Pre-Delphi and eDelphi Exercises

During the pre-Delphi, the results of the systematic review were collegially discussed among six stakeholders but no agreement was reached. In every round, all 11 stakeholders and the representative of the patients were present and voted.

3.2. Diagnosis

The diagnostic and clinical management parameters are summarized in Table 3. The third round eDelphi agreements are summarized in Figure 2.

Table 3. Diagnostic and clinical parameters of MCS patients.

Screening and Diagnosis (Level 0)	1st Level Assessments	2nd Level Assessments
– First consultation and preliminary exams	– Allergologic/dermatologic assessment	
– Screening tests	– ORL assessment *	
– Exclusion of the main differential diagnoses	– Dental assessment	
	– Neurologic assessment	– Genetic assessment
	– Endocrinologic assessment	– Metabolic assessment
	– Cardiologic assessment	
	– Rheumatologic assessment	
	– Anesthesiologic assessment	
	– Public health/occupational medicine assessment	

* ORL: Otorhinolaryngology.

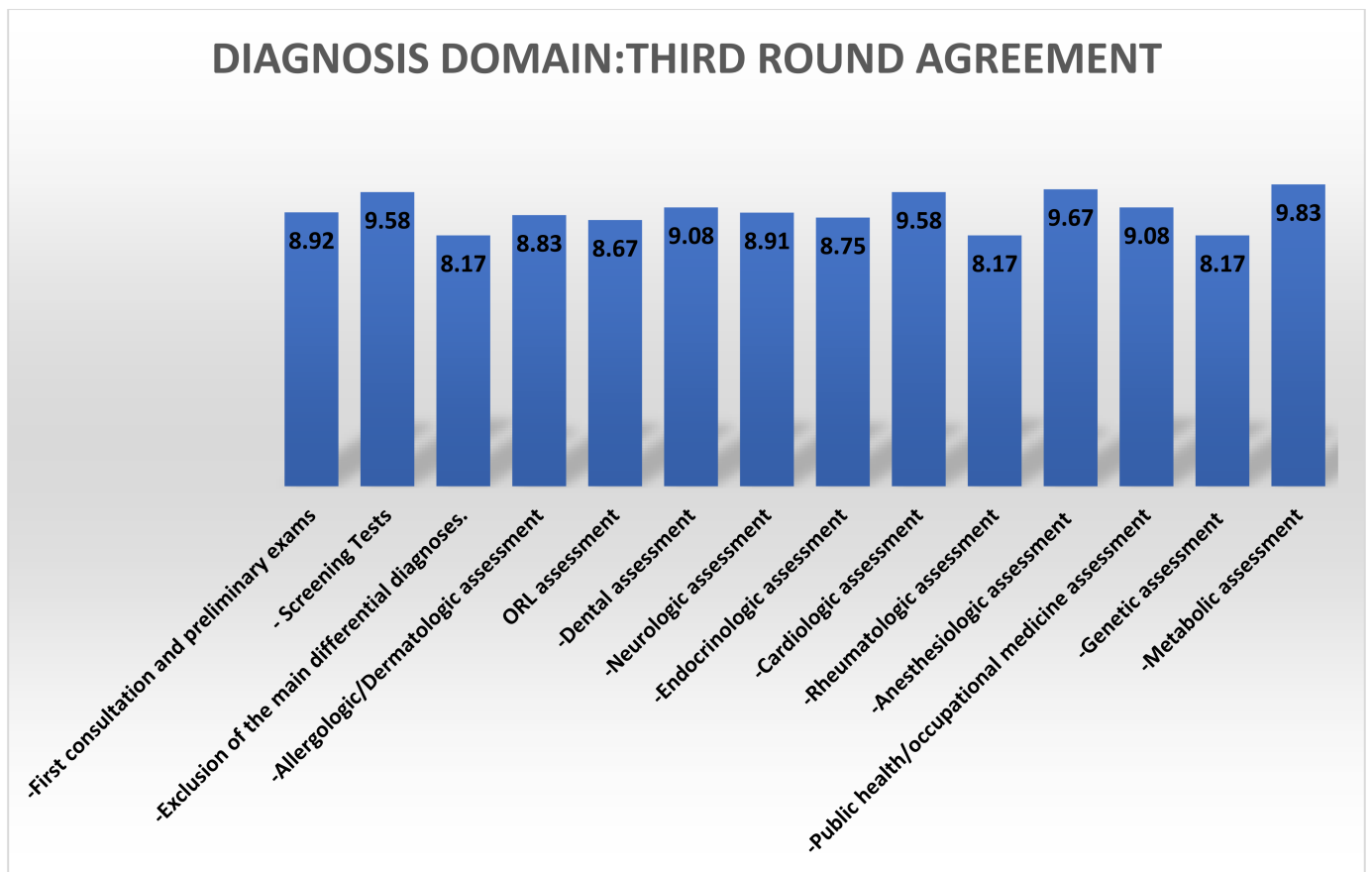


Figure 2. Third round agreement summary for the diagnosis domain.

3.2.1. First Consultation Exam to Prescribe

Medical history is of paramount importance in starting the evaluation of a potential MCS patient and may enable clinicians to set up a preliminary blood exam list. We achieved an agreement for these blood test sets according to the literature [1]:

1. Serum protein electrophoresis;
2. Ferritin serum;
3. Sodium (Na), magnesium (Mg), zinc (Zn) serum;
4. Creatine phosphokinase (CPK) serum;
5. Cholinesterase serum/plasma/erythrocyte;
6. Erythrocyte sedimentation rate (ESR);
7. C-reactive protein (CRP) serum;
8. Immunoglobulin E (Total IgE) serum;
9. Interleukin-2 receptor (sIL2r) serum;
10. Basal serum cortisol;
11. Basophil activation test on chemicals known for adverse reactions.

3.2.2. Screening Tests

The Brief Environmental Exposure and Sensitivity Inventory (BREESI), validated in 2020 by Palmer et al., is a three-question, fast and easy-to-perform screening tool that screens patients with possible MCS [54] and who, consequently, must undergo the Quick Environmental Exposure and Sensitivity Inventory (QEESI©) for diagnostic purposes [50].

The QEESI©, validated in 1999 by Miller and Prihoda, was chosen to maintain international comparability and adequate accuracy [50,51]. The questionnaire has four scales of values to establish the severity of the symptoms, chemical intolerances, other intolerances and environmental impact on the health of the subject. Each scale provides a score from

0 to 10 and also includes the evaluation of the masking index or of the possible lack of awareness on the part of the interviewed subject of their intolerance and of their responses to environmental exposures [50].

In a study carried out by Miller and colleagues on 421 subjects including four exposure groups and a control group, the QEESI© had a sensitivity of 92% and a specificity of 95% in discriminating chemically sensitive people and the common population [55].

Both the BREESI and QEESI© were translated into Italian by the MCS Italian Study Group and are currently under validation.

3.2.3. Main Diagnoses to Exclude

Other systemic diseases capable of fulfilling all the Lacour criteria [5] should be ruled out with particular attention paid to porphyria and macrocytosis, which have a defined set of diagnostic criteria [56,57].

3.2.4. Specialist Evaluations in Patients with MCS

Allergologic/Dermatologic Assessment (I Level)

Despite MCS not being classified as an allergic disease, the evidence sustains an epidemiological association with an allergic disorder [58,59]. Thus, clinicians should encourage potential MCS patients to maintain a diary of symptoms. During the third eDelphi round, we achieved an agreement on the following set of tests:

1. Total immunoglobulin E (IgE) dosage and, only in the case of a clinical suspect, specific or recombinant IgE assays (Immuno Solid-Phase Allergen Chip (ISAC®) and in vitro multiplex allergy (i.e., Allergy Explorer-ALEX® and ALEX²®) tests).
2. Patch tests are regarded as a second choice as they can cause MCS flares to the patients.
3. A lymphocyte transformation test (LTT) is optimal only for testing metal allergies and has approval/approbatory medical-legal validity only for metal allergies.

The experts agreed on the assessment and treatment of allergic and dermatologic diseases in MCS patients following the Italian Society of Allergological, Occupational and Environmental Dermatology (SIDAPA), the Italian Society of Dermatology (SIDeMaST) and the Italian Respiratory Society (SIP/IRS) guidelines.

Otorhinolaryngology (ORL) Assessment (I Level)

This evaluation has a pivotal role in evaluating both the functionality and reactivity of the upper airways together with the sensory pathway. The agreement was reached with this set of exams:

1. Upper airway endoscopy [11,60–66];
2. Olfactometry with ‘Sniffin’ Stick’ stick tests (threshold, discrimination and odor identification) and olfactory-related questionnaires [11,60–66];
3. An otoneurological evaluation (pure-tone audiometry and impedance examination, auditory brainstem response and otoacoustic emissions, hyperacusis and dizziness-related questionnaires, posturographic examination) [62–66];
4. Positron emission tomography (PET) with a pure olfactory stimulus only in selected cases with borderline or ambiguous results [11,60–66].

The experts agreed on the assessment and treatment of ORL diseases in MCS patients following the Italian Society of Otolaryngology and Head and Neck Surgery (SIO-CCF) guidelines.

Dental Assessment (I Level)

Mercury-containing dental amalgam fillings release metal ions (i.e., mercury, silver, tin, copper, gold and nickel) in the oral cavity, resulting in toxicity (i.e., neurotoxicity, immune-toxicity and hormonal dysfunction) and potential allergic reactions [67,68]. Dental prostheses and metal crowns may release gold, palladium, chromium, beryllium, cobalt

and titanium. Ceramics and dental porcelain can release aluminum into the saliva and dental resin-based composite restorations can release zirconium [69].

The eDelphi results suggested that blood/serum, urine and saliva analyses should be performed to check metal toxicity [70–72].

Toxic Metals Screening in Blood:

1. Mercury (Hg) whole blood.
2. Lead (Pb) whole blood.
3. Aluminum (Al) whole blood/serum.
4. Cadmium (Cd) whole blood.
5. Nickel (Ni) whole blood.

Toxic Metals Screening in Urine:

1. Mercury (Hg) 24 h urine specimens.
2. Arsenic (As) 24 h urine specimens.

The chewing-gum-stimulated saliva test represents a non-invasive and accurate method of detecting metals released in the saliva. Unfortunately, it is not currently available in Italy [73,74].

The experts agreed on the assessment and treatment of oral diseases in MCS patients following the Italian Society of Periodontology and Implantology (SIDP), the Italian Endodontic Society (SIE), the Italian Academy of Conservative Dentistry (AIC), the Italian Academy of Osseointegration (IAO), the Italian Society of Oral Pathology and Medicine (SIPMO), the Italian Academy of Endodontics (AIE), the Italian Society of Orthodontics (SIDO) and the Academy of Non-Transfusional Hemo-Components (ANTHEC) guidelines.

Neurological Assessment (I Level)

Despite MCS patients often displaying a normal neurological exam, environmental exposures may negatively modulate the nervous system (spatial disorientation, short-term memory loss, tinnitus, tremors, convulsions) in susceptible subjects [1]. Thus, the neurological armamentarium may also include the following clinical and instrumental tests:

1. Pupillography [75];
2. Simple and choice reaction time tasks [76];
3. Balance tests [77];
4. Visual contrast tests [78–81];
5. Visual color tests [82];
6. Tests of the perception of vibrations [77];
7. Electroencephalography (EEG) [82];
8. Single-photon emission computed tomography (SPECT) [83–86].

An assay of the serum S100B protein is recommended to evaluate the permeability of the blood–brain barrier that may be altered by MCS triggers [87]. A neuron-specific enolase (NSE) assay in serum is suggested to evaluate current or even previous mercury-related neurological signs and symptoms [88,89].

The experts agreed on the assessment and treatment of neurological diseases in MCS patients following the Italian Society of Neurology (SIN) guidelines.

Endocrinologic assessment (I Level)

Several metals as well as chemicals may interfere with physiology of the endocrine glands; in particular, the thyroid [90] and hypothalamic-pituitary-adrenal axis [72]. Recently, epidemiologic studies further confirmed the association between MCS and endocrinological disorders (i.e., hyposurrealism, dysthyroidism and hyperprolactinemia) [18,50,91,92].

The experts agreed on the assessment of endocrinopathies in MCS patients following the Italian Association of Clinical Endocrinologists (AME) or the Italian Society of Endocrinology (SIE) guidelines.

Cardiological assessment (I Level)

MCS patients display a wide range of comorbidities including cardiovascular ones [40,93]. As well as the epidemiological associations between MCS and tachycardia, arrhythmia, a mitral valve prolapse [94] and electrocardiogram abnormalities [95,96], the cause–effect link is far from being elucidated. Rea and colleagues postulated a synergic detrimental effect of a dysregulated autonomous central nervous system with vasoconstriction due to MCS triggers in susceptible patients (i.e., diabetes and/or hypertension) [97,98].

The experts agreed on the assessment of cardiovascular disorders in MCS patients following the Italian Federation of Cardiology (IFC), the Italian Society of Cardiology (SIC) and the Italian Association for Cardiovascular Prevention and Rehabilitation (AICPR) guidelines.

Rheumatologic Assessment (I Level)

Several MCS patients may display an association with autoimmune diseases (Hashimoto's thyroiditis, systemic lupus erythematosus (SLE), Sjogren's syndrome) [38,99,100], corroborating the MCS immunological pathogenetic hypothesis [36–39].

The experts agreed on the assessment of rheumatological disorders in MCS patients following the Italian Society of Rheumatology (SIR) guidelines.

Anesthesiologic Assessment (I Level)

The anesthesiologic management of MCS patients remains challenging in real-life and should avoid all environmental exposures capable of triggering an MCS flare [101–103] (see Section 3.3 Therapy Domain).

Remarkably, MCS patients do not display an increased risk of anaphylaxis related to anesthetics (both local and systemic ones), but may experience transient postoperative symptoms currently interpreted as self-limiting flares [104]. Anesthesiologists should carefully collect the pharmacological history of MCS patients to avoid anesthetics that previously provoked anaphylaxis and/or intraoperative signs and symptoms. Pre-operative anesthetic-related allergy tests should not be performed to avoid sensitization phenomena.

The experts agreed on the assessment of potential anesthesiologic disorders in MCS patients following the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) guidelines.

Public Health/Occupational Medicine Assessment (I Level)

Chemical, physical and biological evaluations should be performed at the working site and at home to detect any recognized MCS triggers [1] for patients with a positive QEESI©.

The experts agreed on the assessment of occupational and environmental-related disorders in MCS patients following the Italian Society of Occupational Medicine (SIML) and the Italian Society of Hygiene, Preventive Medicine and Public Health (SITI) guidelines.

Genetic Assessment (II Level)

Although the MCS genetic fingerprint is far from being fully elucidated, phase I and II detoxification enzymes (cytochromes P450 (CYPs), glutathione S-transferases (GSTs), N-acetyltransferases (NATs)) and antioxidant enzyme (SOD2) gene polymorphisms have been linked to MCS [105–109]. These polymorphisms may decrease xenobiotic catabolism and increase oxidative stress [21,105]. Thus, the gene expression is epigenetically modulated by exposure, both internal and external, leading to potential hypersensitivity and MCS [105–109].

Thus, the experts agreed that MCS-related polymorphism screening remains not diagnostic but only a complementary test.

Metabolic Assessment (II Level)

Metabolism perturbations due to or provoked by environmental exposures are currently under evaluation and the preliminary data suggest abnormalities in the detoxification metabolism (i.e., glutathione transferase, catalase, superoxide dismutase), energetic

metabolism (i.e., intracellular adenosine triphosphate (ATP) in erythrocytes and platelets) and inflammatory response (pro-inflammatory serum cytokines) [43,87,105,109–114]. These promising biomarkers evaluated on serum, whole blood and peripheral blood mononuclear cells (PBMCs) are detected with methods validated only in experimental conditions and are not applicable to daily clinical practice. Thus, the experts agreed that biochemical tests should be reserved for an experimental setting.

3.3. Therapy Domain

Due to the wide range of clinical manifestations of MCS and the fragility of patients, a multidisciplinary approach (including a combination of dietetic [59] and psychological treatment strategies [110]) is mandatory. Furthermore, MCS determines disability, limiting interactions and forcing patients to purchase several medical devices to prevent MCS flares [115,116]. The agreements on this domain are summarized in Figure 3.

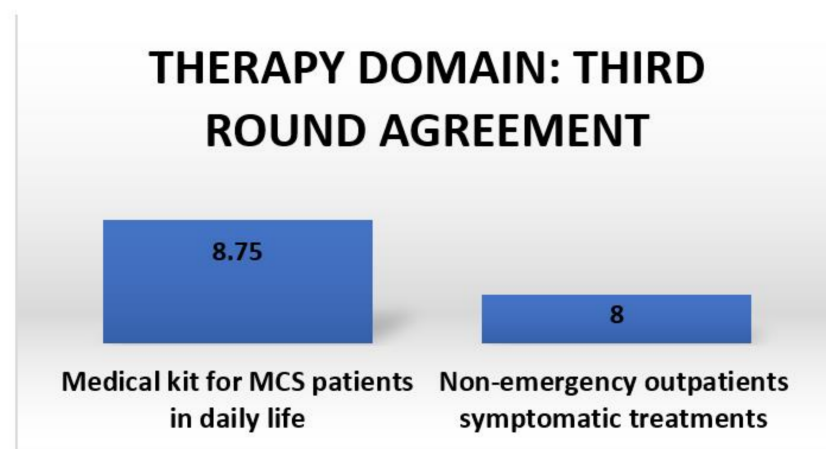


Figure 3. Third round agreement summary for the therapy domain.

3.3.1. Medical Kit for MCS Patients in Daily Life

During the COVID-19 pandemic, the use of medical devices (i.e., masks) has become a mandatory preventive strategy but mask choice is of paramount importance in patients with pre-existent facial dermatoses and especially in MCS patients [117–119]. Thus, the experts agreed to suggest this kit of medical devices for MCS patients according to their clinical profile to prevent daily flares:

1. Masks (latex-free paper face masks or cotton masks and filters and/or masks with a high-efficiency particulate absorbing filter (HEPA) and activated carbon filters).
2. Air purifiers (portable household air in metal with HEPA filters with activated carbon and a percentage of rubber gaskets < 3% and relative filters and/or air purifiers for cars in metal with HEPA filters with activated carbon and a percentage of rubber gaskets < 3% and relative filters. Air filters should be supplied with an oxygen tank and a glass oxygen bubbler and be phthalate-free and flexible with an oxygen tube with a ceramic mask and latex-free glasses).
3. Water purifiers (an active carbon water purifier with a percentage of rubber gaskets < 3%).

All devices should have the CE (Conformité Européenne) mark and masks may guarantee SARS-CoV-2 protection at least equal to surgical masks. If the mask does not display surgical mask protection characteristics, it should be supplemented with a surgical mask on top to prevent a SARS-CoV-2 infection.

3.3.2. Symptomatic Treatments for Non-Emergency Outpatients

Due to the fragility of MCS patients and frequent allergies, a careful evaluation of prescribed drugs (i.e., avoid colored tablets and assess non-active components) and the assessment of medical devices (i.e., avoid plastic and glass ones) are mandatory [1].

Pharmacological therapy must start at half the dosage and carefully increase until the adequate dose is reached to ensure the tolerability of the MCS patient to the drug.

The oximetry should be carefully evaluated in MCS patients and also during MCS flares before delivering any oxygen therapy. An intranasal administration of hyaluronic acid may alleviate olfactory discomfort [63].

3.4. Hospitalization Domain

Healthcare workers should undergo dedicated MCS training to safely manage MCS patients at every step of hospitalization (i.e., environment, admission, access policy, pharmacy and canteen) [1,115]. The agreements on this domain are summarized in Figure 4.

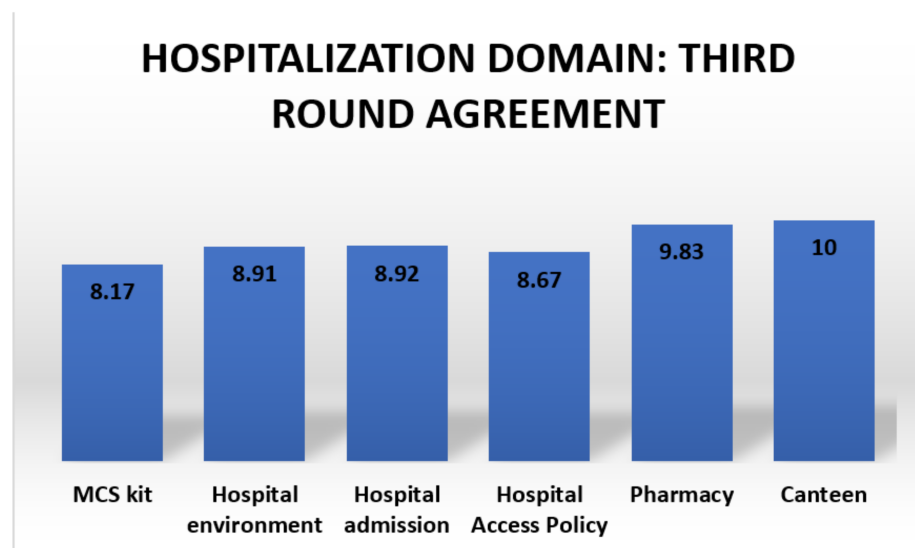


Figure 4. Third round agreement summary for the hospitalization domain.

The eDelphi experts agreed that an MCS kit marked with a distinct color should be established in hospitals to maximize the therapeutic management efficacy and it should include:

1. Latex-free surgical gloves;
2. Cleaning products without perfumes and hydrogen peroxide;
3. Hydrogen peroxide for disinfection;
4. 5% dextrose (glucose-intravenous) in a 1000 cc 0.9% NaCl glass drip;
5. Porcelain oxygen mask;
6. Phthalate-free, flexible oxygen tube;
7. Latex-free glasses;
8. Inverted sugar solution in a 1000 cc 0.9% NaCl glass drip;
9. Sodium bicarbonate solution in glass vials (500 cc);
10. Intravenous administration kit in glass;
11. Sheets, pillowcases, tablecloths, sterile cotton towels, washed cotton pillows with non-perfumed detergents and without softener (not dry-cleaned);
12. Disposable cotton tunics washed with fragrance-free detergents;
13. Disposable headgear, shoe covers and tunics;
14. Latex-free paper plasters;
15. Intravenous butterfly valve;
16. Velcro tourniquet/cuff sphygmomanometer;
17. Fragrance-free soap for healthcare workers in contact with MCS patients;
18. Latex-free paper masks for healthcare workers in contact with MCS patients;
19. A 0.9% NaCl 1000 cc solution drip in glass.

3.4.1. Hospital Environment

The eDelphi experts found a substantial agreement between the following statements. MCS patients should be conducted in the ambulatory, if possible, without crossing waiting rooms and from a different entrance. Furthermore, the MCS ambulatory should be far from sterile processing facilities, laundries, waste rooms or any sources of internal and external potential MCS triggers. Solvents, pesticides and herbicides or any other potentially toxic chemical agent dispersions should be avoided in the external area adjacent to the MCS ambulatory. The ambulatory should be covered by unpolished natural stoneware majolica on the floor and walls to decrease the cleaning time and prevent chemical absorbance. Natural light is preferred to artificial light.

3.4.2. Hospital Admission

The experts agreed that healthcare workers should:

1. Arrange MCS patients in a private room marked with a dedicated color (i.e., the MCS kit) with advice prohibiting the access of any person with perfumes;
2. Prioritize the arrangement in ventilated rooms far from sources of MCS-recognized triggers (i.e., streets);
3. Decontaminate the room in advance (>6 h before the admission);
4. Clean the room with water, bicarbonate and fragrance-free detergents;
5. Use sheets, pillowcases and 100% cotton towels;
6. Mark in the clinical history any allergies, previous drug reactions and tolerated drugs with particular attention paid to antibiotics, anesthetics and disease-modifying antirheumatic drugs (DMARDs);
7. Pre-alert the hospital pharmacy, healthcare workers and the canteen service;
8. Provide water only in glass bottles with glass cups.

3.4.3. Hospital Access Policy

The experts agreed that every person who accesses the MCS room should:

1. Avoid any perfumes, spray or hair products;
2. Wash hands with fragrance-free soap or white soap;
3. Change their clothes in a dedicated pre-entrance vestibule or a locker room, disinfected and cleaned as an MCS room;
4. Have a dedicated MCS kit that contains shirts, gloves (powder-free vinyl or nitrile), latex-free and phthalate-free oxygen tubes and a latex-free oxygen mask.

3.4.4. Pharmacy

The experts agreed on these statements about the hospital pharmacy facility:

1. Use only glass bottles for intravenous solutions;
2. Do not replace tolerated drugs with generic pharmaceutical products or even with biosimilars (for target therapies);
3. Galenic preparations are preferred to packaged drugs due to their lower concentration of preservatives;
4. Carefully monitor the drug intake of MCS patients.

3.4.5. Canteen

The eDelphi experts agreed on these statements about the hospital canteen:

1. Pre-alert the canteen;
2. Refer previous food reactions to the canteen;
3. Do not cook in aluminum or copper pots;
4. Use only glasses, iron cutlery and glass transparent plates (no colored glassware);
5. Report any adverse events in the medical history regarding food or beverages.

3.5. Emergency Domain

MCS patients display a higher risk than the general population of being hospitalized [1] so first aid, ambulance transportation and the arrival at the emergency room should be standardized. The MCS management during an emergency should be integrated in both volunteer and professional healthcare workers. The agreements on this domain are summarized in Figure 5.

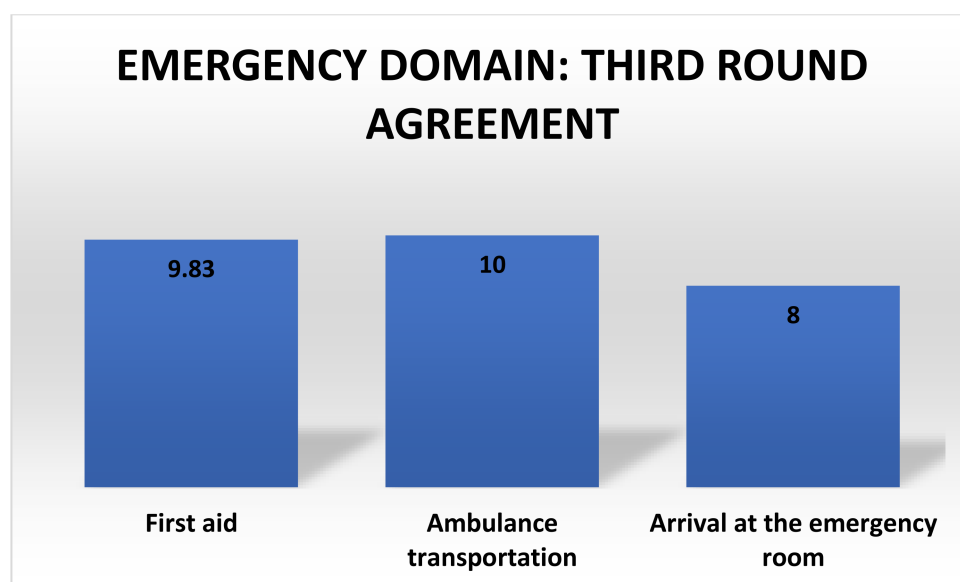


Figure 5. Agreements summary for the emergency domain.

3.5.1. First Aid

During the eDelphi, the experts agreed on the creation of an Emergency Kit for MCS that includes:

1. Latex-free and powder-free gloves;
2. Latex-free materials for healthcare workers;
3. Latex-free oxygen glasses for the patient;
4. Hydrogen peroxide solution to decontaminate;
5. Glass drip bottles;
6. Aluminum roll to seal off any parts of medical equipment (i.e., tubes, rubber gaskets) potentially contaminated by MCS-recognized triggers;
7. Ice gown;
8. Headgear;
9. Disposable paper shoe covers.

3.5.2. Ambulance Transportation

Experts suggest the following tips for ambulance transportation:

1. Avoid environmental deodorants;
2. Healthcare workers should avoid smoke, perfumes, hair gel or deodorants 6 h before an ambulance shift;
3. Use the emergency kit for MCS.

3.5.3. Arrival at the Emergency Room

The eDelphi experts agreed on the following suggestions for MCS patients arriving at the emergency room:

1. Isolate MCS patients from the other patients and place visitors into a separate room;

2. Decontaminate the separate room and remove all potential MCS triggers (i.e., solvents, rubber parts);
3. Assign a priority code to the MCS patients;
4. Use the MCS kit.

4. Conclusions

This is the first Italian consensus and one of the few consensuses worldwide on MCS that aims to orient daily practice and improve the quality of delivered treatments to MCS patients. The MCS evidence in the literature remains scant so future studies should evaluate in deeper detail the clinical, epidemiological and therapeutic unmet needs.

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