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Review

Recommendations for managing the manifestations of severe and life-threatening mixed cryoglobulinemia syndrome

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ABSTRACT

Objective: Some of the manifestations of mixed cryoglobulinemia syndrome (MCS) can be severe or life-threatening, and should be rapidly contained but, as the therapeutic approaches to such conditions are largely based on anecdotal data, a consensus conference was organised by the Italian Group for the Study of Cryoglobulinemia (GISC) with the aim of providing a set of recommendations based on an in-depth survey of the available data and expert opinion.

Methods: The consensus panel, which included specialists working in different medical fields involved in the management of MCS patients, was first asked to divide the manifestations of MCS into severe or life-threatening conditions on the basis of their own experience, after which a complete literature review was carried out in accordance with the Cochrane guidelines for systematic reviews.

Results: Therapeutic plasma exchange (TPE) was considered the elective first-line treatment in the case of life-threatening manifestations of MCS (LT-MCS) and patients with severe clinical symptoms (S-MCS) who fail to respond to (or who are ineligible for) other treatments. The data supporting the combined use of cyclophosphamide and TPE were considered limited and inconclusive. High-dose pulsed glucocorticoid (GCS) therapy can be considered the first-line treatment of severe MCS, generally in association with TPE. Rituximab (RTX)-based treatments should be considered in patients with skin ulcers, peripheral neuropathy or glomerulonephritis, and in patients with persistent LT-MCS after TPE. In patients with hepatitis C virus-related MCS with S-MCS, viral eradication should be attempted as soon as a patient's condition allows the use of direct-acting antivirals.

1. Introduction

Mixed cryoglobulinemia syndrome (MCS) is the clinical manifestation of a form of small vessel immune complex-mediated systemic vasculitis (cryoglobulinemic vasculitis, CVa) whose clinical hallmark is the triad of Meltzer and Franklin: *i.e.* purpura, weakness and arthralgia [1–4]. Although it has a slowly progressing and relatively benign clinical course in many cases [5], severe organ damage and life-threatening manifestations (LTM-CS) can sometimes be encountered at the time of presentation or rapidly occur thereafter [3,4,6]. The most

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frequent organs are the skin, kidneys and peripheral nervous system, but the lungs, gastrointestinal tract, central nervous system (CNS) and heart may also be affected [2–4,6,7].

The protean characteristics of MCS can significantly limit treatment approaches, which depend on the severity of clinical impairment, the number of impaired organs, the extent of the damage of each, and the individual expertise of attending physicians. Furthermore, the need to intervene under emergency conditions means that many of the questions concerning the treatment of severe MCS cannot be answered by controlled studies, and the lack of classification criteria defining severity significantly hinders the development of standardised treatment strategies.

Our consensus procedure was intended to allow the sharing of experiences involving some of the less investigated aspects of MCS treatment in order to be able to define a core set of recommendations for the treatment of the severe and life-threatening manifestations of CVa.

2. Methods

The Consensus Committee consisted of specialists in internal medicine, rheumatology, haematology, nephrology, hepatology, infectious diseases, neurology and therapeutic apheresis involved in caring for patients with CVa.

After conducting a systematic literature review, the Scientific Board of the Italian Group for the Study of Cryoglobulinemias (GISC) drew up a list of conditions known to be associated with MCS and asked the members of the Consensus Committee to divide them into severe or life-threatening conditions on the basis of their experience, and subsequently formulate their treatment recommendations. The considered conditions were:

1. Severe single or multi-organ systemic impairment (S-MCS), defined as MCS with the impairment of three or more organs, particularly the kidneys, lungs, heart, gastrointestinal tract, peripheral and central nervous system, and skin.
2. Life-threatening conditions requiring immediate treatment (LT-MCS).

The literature review was carried out in accordance with the Cochrane systematic review guidelines [8]. Key words and the associated medical subject headings (MeSH) were selected and combined with the terms *mixed cryoglobulinemia* or *cryoglobulinemic vasculitis*, and the MEDLINE, EMBASE and COCHRANE CENTRAL databases were searched for papers written in English, French or Italian describing randomised controlled trials (RCTs), observational studies (prospective and retrospective cohort and case-control studies), and case series of at least three patients. Single case reports were also considered when they were needed to support expert opinion concerning otherwise neglected questions. Standardised forms were used to extract the publication details, patient characteristics, doses, therapeutic strategy and relevant outcomes from all of the selected articles, and an expert panel assessed the quality of each study using evidence-based medicine levels of evidence [9] (from level 1a [a systematic review of RCTs] to level 4 [case series], with level 5 being used for expert opinions without any explicit critical appraisal) and formulated the preliminary statements to be discussed by all of the participants at the consensus conference used to suggest the strength of the recommendations by classifying from A (substantial level 1 studies) to D (insubstantial or inconclusive studies at any level).

3. Results

The participants decided that the S-MCS related conditions requiring consideration were renal involvement with renal failure and/or nephrotic or nephritic syndrome, interstitial lung fibrosis, peripheral neuropathy, recurrent severe abdominal pain, uninfected skin ulcers, low-grade coronary arteritis, and severe liver impairment without liver failure; the LT-MCS conditions were acute renal failure with oligo-anuria and rapidly progressive renal failure, diffuse alveolar hemorrhage, acute cerebrovascular and cardiovascular events, ischemic colitis, sepsis complicating skin ulcer infection, and critical liver failure.

3.1. Severe systemic MCS

The largest study describing the clinical features of severe MCS, treatment responses and outcomes is the retrospective literature review by Retamozo et al. [6], which considered 279 patients with HCV-related LT-MCS conditions, including 232 (83%) in whom kidney failure, lung and gastrointestinal diseases, CNS disorders and heart failure were the first clinical manifestations. Emergency room admission was required in 207 cases (74%), and 63 patients (22%) died during a mean post-diagnosis follow-up period of 14 months. The main causes of death were sepsis in patients with glomerulonephritis (42%), and CVa itself in patients with gastrointestinal (60%), pulmonary (57) or CNS involvement (62%); the patients presenting with multi-organ impairment or pulmonary involvement had the poorest survival rates. One hundred and sixty-seven patients (60%) were treated with corticosteroids (GCS), 148 (53%) with therapeutic plasma exchange (TPE), 83 (30%) with immunosuppressive agents, 24 (9%) with rituximab (RTX), and two (0.7%) with infliximab. Interferon-based antiviral treatment was administered in 157 cases (57%), and the patients who received it had a better chance of survival.

Removing circulating cryoglobulins by means TPE was first proposed in the 1960s [10], and is still considered the most efficient way of improving the condition of acutely ill patients with LT-MCS [6,7,11–15]. Furthermore, data from small series of patients [16–21] and one small randomised study [22] have shown that TPE alone or associated with immunosuppressive agents or GCS can also improve S-MCS, and the 2016 Guidelines of the American Society for Apheresis (ASFA) include severe/symptomatic cryoglobulinemia as one of the disorders for which TPE should be considered as second-line treatment [23]. However, a recent systematic review of the literature has concluded that a meta-analysis of the available data is impossible because of the lack of quantitative outcomes in the available studies [24]. A recent retrospective survey [15] of 159 patients presenting severe MCS symptoms who underwent apheresis found that the patients with LT-MCS were significantly less likely to respond (adjusted odd ratio [AOR] 0.12, 95% CI 0.03–0.42; $p = .001$) and significantly more likely to die during the first year after the first apheresis session (59%) than those without LT-MCS; failure to respond to apheresis was associated with an increased risk of death (AOR 4.79; 95% CI 2.56–8.97; $p < .0001$). However, as four out of 14 patients with LT-MCS showed a good clinical response, and given the lack of valid alternatives, the authors recommended apheresis as emergency treatment in such patients.

Cyclophosphamide has frequently been used in association with TPE to reduce the post-apheresis rebound in cryoglobulin production [3], but it was only used in 19.5% of the patients described by Marson et al., mainly in association with the first TPE sessions [15]. The cost-benefit ratio of adding cyclophosphamide to TPE is currently a subject of debate, and the majority of the consensus conference participants considered it superfluous.

Data from small case series support the effectiveness of pulsed high-dose GCS therapy in controlling MCS flares [25,26], and GCS were associated with TPE at different times and doses to treat 86% of the patients included in the study of Marson et al. [15] In the majority of reported cases, pulsed high-dose GCS therapy was used in association with the first TPE session.

The only biological treatment that has proved to be beneficial in patients with MCS is RTX, which should be considered when treating patients with severe clinical manifestations [27]. A RCT including 59 MCS patients with skin ulcers and/or active glomerulonephritis and

refractory peripheral neuropathy found that those treated with RTX showed a significantly greater decrease in the Birmingham Vasculitis Activity Score (BVAS) [28] than those receiving conventional treatment with GCS, azathioprine or cyclophosphamide, and those undergoing TPE ($P < .001$), and the proportion of patients continuing their initial therapy after 12 months was significantly higher in the RTX arm (64.3% *vs* 3.5%; $P < .0001$) [29]. It has been demonstrated that TPE can waste a large amount of RTX if carried out 3–7 days after infusion of RTX [30], and so the timing of the administation of the two treatments need to be appropriately synchronised.

The still limited data concerning the effectiveness of direct-acting antivirals (DAAs) in patients with severe and life-threatening HCV-associated CVa suggest that they can significantly improve the clinical picture even in patients with severe symptoms [31]. Given the duration of treatment, the use of DAAs can be postponed until the need for first-line emergency treatment, but it should be considered as soon as a patient's condition is compatible with treatment completion.

3.1.1. Statements

1. A rapid reduction in serum cryoglobulin load is a priority in patients with S-MCS involving one or more organ, and TPE is recommended as the treatment of choice. 4C
2. On the basis of expert opinion, the treatment of LT-MCS includes TPE and high-dose (or pulsed) GCS. 4C
3. RTX is more efficacious in containing S-MCS than conventional immunosuppressive treatments. 1B
4. TPE should precede the first RTX infusion and follow further RTX infusions by at least three days. 5C
5. Patients with severe HCV-associated MCS should receive DAA treatment as soon as their condition is compatible with completing it. 5C.

3.2. Renal abnormalities

Patients with MCS frequently have kidney abnormalities [6,14,32], the most typical histopathological lesion being membranoproliferative glomerulonephritis [33–35]. MCS-related nephritic/nephrotic syndrome may be an end-stage renal disease and is a major risk factor for serious cardiovascular events [36]. Chronic renal failure (CRF = estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2 of body surface area) is associated with severe co-morbidities and increased mortality.

The treatment of cryoglobulinemic nephropathy has mainly been based on high-dose GCS, immunosuppressive drugs, biological agents (RTX) and TPE [29]. Two hundred and five (73%) of the patients in the study of Retamozo et al. [6] showed renal impairment, 47% of whom had nephrotic syndrome: the most frequently used treatment in the patients with biopsy-proven glomerulonephritis was TPE (110/205, 53.6%).

Significant improvements have been seen in patients with HCV-related MCS treated with interferon (IFN) plus ribavirin-based treatment alone or combined with different doses of RTX [26–36], but the greatest limitation of IFN-based treatment is that it cannot be used in many of the patients with the most severe clinical pictures. However, significant improvements have more recently been observed in patients treated with (DAAs), the majority of patients of whom have achieved a sustained viral response [39-43]. Nevertheless, the results of the CRESO study have shown that renal impairment is a predictor of persistent cryoglobulin production despite successful DAA treatment (M. Galli et al. Manuscript in preparation).

A number of studies have investigated the impact of RTX treatment on kidney disorders in patients with MCS using various doses and dose schedules [29,44–47]. De Vita et al. [29] compared RTX with conventional immunosuppressive therapy in a RCT in which seven of the 28 patients in the RTX group had glomerulonephritis. The treatment failed after six months in three patients, but there were two complete responses (CRs) and two partial responses (PRs), and responses were maintained after 12 and 24 months, although one of the patients needed re-treatment. Two of the eight patients with renal involvement in the control group who were switched to RTX because they did not respond to conventional therapy also failed to respond to RTX, two showed a CR and four a PR. The use of RTX has also allowed a reduction in the use of GCS and immunosuppressive drugs [44]. Another RCT [45] compared RTX with conventional therapy in patients with HCV-related MCS after the failure of antiviral therapy. Four out of 12 patients in each group had renal disorders, and only those treated with RTX improved or retained stable renal function. After six months, 10 of the 12 patients receiving RTX and one of the 10 receiving conventional therapy were in remission at 6 months, and RTX also allowed a reduction in ongoing immunosuppressive treatment. A 6-year observational study [46] including 16 patients (12 HCV+) with severe CS and glomerulonephritis treated with RTX recorded a 75% CR rate and a 19% of PR rate. Significant improvements were observed from the second month of treatment, and the 6-year survival rate was 75%.

A French study has found that patients with non-infectious MCS and glomerulonephritis have a poor long- term prognosis.[34,] This study included 80 patients (22.5%) with Sjögren's syndrome (SS), 28.7% with lymphoproliferative disorders, and 48.8% with essential MCS. The first-line treatment consisted of GCS alone (27.6%) or associated with RTX (21.1%), alkylating agents or a combination of cyclophosphamide and RTX (10.5%). About 33% of the patients also underwent TPE. During the mean 50 months of follow-up, about 30% of the patients experienced a renal flare and, at the time of the last follow-up visit, 50% of the patients had achieved complete renal remission, and only 9% had reached end-stage renal disease. Treatment with RTX plus GCS was more effective in preventing relapses than treatment with GCS alone or combined with cyclophosphamide, but was associated with a higher early death rate (not greater mortality) in the first year when used as first-line therapy, and more frequent severe infections. Severe infections and new-onset B-cell lymphoma occurred in respectively 29.1% and 8.9% of the patients, and 24% died.

In brief, long-term survival is poor in patients with non-infectious MCS and glomerulonephritis, with severe infections being the main cause of death [34]. Patients with SS-related MCS admitted to an intensive care unit because of acute respiratory insufficiency during acute renal failure may improve and recover normal renal function after treatment based on high-dose oral prednisone and a course of RTX [33]. In the retrospective study of Marson et al. [15] TPE was used in 43 patients with renal impairment and its efficacy was judged to be very good/ good in 20 cases, but it had no or unassessable effects in 14.

3.2.1. Statements

1. Nephrotic and nephritic syndrome with or without renal failure should be regarded as a manifestation of S-MCS that requires treatment as soon as possible. Rapidly progressive renal failure and acute renal failure with oligo-anuria should be considered manifestations of LT-MCS that require immediate treatment. 3B.
2. In the case of LT-MCS with renal involvement, an early aggressive therapeutic schedule should include a combination of TPE (in order to remove cryoglobulins from plasma rapidly), high-dose GCS (intravenous methylprednisolone from 200 mg to 1 g/day for three days) and RTX as a second line immunosuppressive agent. 3B.
3. The treatment of HCV-related CVa with renal involvement is based on RTX in combination with or followed by DAA treatment. 3B.
4. GCS (prednisone 0.5–1 mg/kg/day with rapid tapering) can be used in HCV-negative cases or in the case of possible evolution towards LT-MCS. 3C.

3.3. Peripheral neuropathy

Peripheral neuropathy (PN) is frequent in MCS patients [2–4] and, in 2012, the Peripheral Nerve Society issued data-driven consensus recommendations concerning the classification of vasculitic neuropathies and the diagnosis/treatment of non-systemic vasculitic neuropathy, including hepatitis C-related mixed cryoglobulinemic vasculitis, as it was concluded that cryoglobulinemic neuropathies are usually caused by vasculitis regardless of their phenotype [48].

A Cochrane review of RCTs and quasi-RCTs of IFN treatment with or without ribavirin (RBV) found that there was insufficient evidence to make evidence-based decisions concerning the treatment of peripheral neuropathy associated with HCV infection [49]. In a prospective, single-centre open-label study, RTX treatment led to the complete remission of the active manifestations of pre-treatment PN in 80% of 31 patients [46]. Significant improvements in PN symptoms have also been observed after DAA treatment in the majority of patients achieving a sustained viral response [40–43].

3.3.1. Statements

1. RTX is probably the most effective available treatment for MCS-related PN. 2B
2. DAA treatment significantly improves PN symptoms in the majority of patients with HCV-related MCS. 2B

3.4. CNS involvement

Retamozo et al. observed CNS involvement in 38/279 patients: cerebral ischemia in 47%, and CNS vaculitis in 40% [6]. Its clinical presentation consisted of hemiplegia, coma, visual impairment, encephalopathy, seizures, paraplegia, bladder disorders, and generalised pyramidal syndromes. The patients were treated with GCS (n = 33), immunosuppressants (n = 20), TPE (n = 17), antiviral agents (n = 13), and biological therapies (n = 2) and, after a mean follow-up of 16 months, five had developed established neurological impairment and three had died.

Another study found CNS involvement in approximately 6% of cryoglobulinemic HCV-infected patients. The initial manifestations of HCV infection may be acute cerebrovascular events, including ischemic stroke, transient ischemic attacks, lacunar syndromes or (rarely) haemorrhaging, and angiographic evidence of multiple focal narrowings of the cerebral arteries has been found in the case of CNS vasculitis. Treatment with GCS and cyclophosphamide has led to full recovery in some patients [50].

Acute or subacute encephalopathy syndromes (clinically characterized by cognitive impairment, confusion, altered consciousness, dysarthria, dysphagia and incontinence) have been associated with widespread involvement of the white matter in MCS patients with chronic HCV infection and, in such cases, aggressive treatment with TPE, GCS (intravenous methylprednisolone followed by oral prednisone) and either cyclophosphamide or RTX has been proposed [51]. Disease control using RTX with or without TPE is necessary before starting antiviral therapy. Other immunosuppressive drugs can be considered in the case of refractory forms, which are frequently associated with underlying B-cell lymphoma [52].

3.4.1. Statement

1. Given the severity and life-threatening nature of CNS alterations, aggressive treatment with TPE, GCS (intravenous methylprednisolone followed by oral prednisone), and either cyclophosphamide or RTX should be considered. 4B.

3.5. Gastrointestinal involvement

Gastrointestinal tract vasculitis (GTV) was the second most frequent LT-MCS in the study of Retamozo et al. [6]; there were 38 patients with intestinal ischemia (84%), three with cholecystitis (7%), three with pancreatitis (7%), and one with peritoneal vasculitis (2%). The symptoms varied from abdominal pain and general malaise to bloody stool, intestinal perforation, and hematemesis, and the diagnosis was confirmed by histopathological procedures or endoscopic clinical and laboratory data in most cases. The treatments included GCS (36 cases), immunosuppressants (17) antiviral agents (20) surgery (12), TPE (10) and RTX (9). The mortality rate was 40%.

Another retrospective single-centre study observed GTV in 12 out of 163 patients, and a mortality rate of about 20% [53]. There was a weak association between GTV and renal and cardiac involvement.

A study of a small case series treated with surgery, cyclophosphamide and GCS has found that early diagnosis and management favours better outcomes [33].

3.5.1. Statement

1. Surgery (when indicated), TPE and GCS (possibly accompanied by other immunosuppressants) followed by RTX are currently the possible treatment options in critical cases. 4C-5C

3.6. Lung involvement

Sub-clinical alveolitis is relatively frequent in patients with MCS [54], and may evolve into interstitial lung fibrosis. LT-MCS lung manifestations are less frequent and include diffuse alveolar hemorrhage, hyperviscosity-related pulmonary lesions and pulmonary edema [33]. Alveolar hemorrhage probably occurs in fewer than 5% of MCS patients and may be associated with glomerulonephritis [55] to create a pulmonary-renal syndrome. Of the 18 patients with diffuse alveolar hemorrhage described by Retamozo et al. [6], 11 (61%) had respiratory failure, nine hemoptysis (50%) and six dyspnea (33%); 13 patients (77%) also had concomitant glomerulonephritis. The patients were treated with intravenous GCS (18 cases), immunosuppressants (9), antiviral agents (6), biological drugs (2) and TPE (8).

Lung infections are also frequent, and retrospective studies have shown that they are a major cause of death in patients with MCS [56].

3.6.1. Statements

1. MCS-related diffuse alveolar hemorrhage, with or without renal impairment, is a life-threatening condition that should be urgently treated with TPE and GCS (with or without other immunosuppressants). 4 C
2. Patients with MCS, particularly those receiving RTX, other immunosuppressants or long-term GCS treatment, are probably at increased risk of severe bacterial and/or fungal lung infections. Consequently, the presence of an infection should be investigated in patients with respiratory symptoms even in the absence of fever. If an infection is suspected, consideration should be given to administering empirical antibiotic treatment in accordance with the international guidelines. 4 C
3. If concurrent infection can be reasonably excluded, persistent respiratory symptoms suggest that intensifying immunosppressive treatment should be considered. 5C

3.7. Heart involvement

Although the often advanced age of patients with MCS leads to frequent cardiac co-morbidities, severe cardiac impairment directly attributable to MC is relatively rare [33,57]. Retamozo et al. [6] reported only three cases of severe cryoglobulin-related cardiac

involvement, and a retrospective study of 165 patients with HCV-related MCS by Terrier et al. [58] found cardiac manifestations (mainly chest pain and congestive heart failure) in seven (4%). Cardiac imaging revealed dilated cardiomyopathy in five patients and hypertrophic cardiomyopathy in one. Multivariate analysis showed that the patients with cardiac manifestations more frequently had B-cell lymphoma (odds ratio 18.1, 95% confidence interval 2.8–116.7, $p = .0023$) and gastrointestinal involvement (odds ratio 14.6, 95% confidence interval 2.0–104.9, $p = .0078$). The cardiac manifestations proved to reversible soon after starting GCS and aggressive immunosuppressive therapy, but long-term survival was poorer in the patients with cardiac damage than in those without [58].

Cardiovascular co-morbidities are the third cause of death (12–17%) in patients with MCS [57]. A number of studies have described a relationship between chronic inflammation and accelerated atherosclerosis in patients with vasculitides that leads to increased morbidity and long-term mortality due to cardiovascular disease. Accelerated atherosclerosis seems to be related to chronic inflammation of the vascular intima in the case of the vasculitides of large and medium-sized vessel, whereas in anti-neutrophil cytoplasmic antibody (ANCA)-negative small vessel vasculitides such as CVa, the pathogenetic process is still largely unknown [59]. As classic cardiovascular risk factors and chronic drug therapy can both lead to excess cardiovascular risk, long exposure to GCS may increase the risk of major cardiovascular events [60]. HCV infection itself can also be considered a risk factor for the development of cardiovascular diseases [61].

Anti-inflammatory treatments of MCS may limit, but not stop MCS-related accelerated atherosclerosis [62], and cardiovascular adverse events have been occasionally reported in patients receiving RTX [63]. The classic risk factors of early atherosclerosis should also be considered and appropriately managed as hypertension and coronary heart disease are precipitating factors. On the basis of anecdotal experience and expert opinion, life-threatening acute CVa-related cardiovascular emergencies are currently treated with high- dose GCS and TPE.

3.7.1. Statements

1. As far as is currently known, CVa-related life-threatening cardiovascular emergencies should be treated with high-dose GCS and TPE. 4C
2. Cardiac condition should be carefully monitored in patients with MCS. 4C

3.8. Skin ulcers

Lower limb ulcers (LLUs) in MCS patients have a prevalence ranging from 4 to 12.5% to 30–50% [64], and represent one of the most debilitating and treatment-refractory manifestation of CVa. Data concerning the effect of DAA on LLU healing in patients with HCV-related MCS are still limited [65,66]. In the CRESO study, the LLUs of four of the 14 patients presenting them at baseline still had not healed by end of the 48-week treatment although a sustained viral response had been achieved in all cases (Galli M et al., manuscript in preparation). Many authors support th use of RTX to treat LLUs [27,38,65–67], and this could also be considered in patients with HCV-related MCS whose LLUs fail to heal even after viral elimination; however, combined treatment with low doses of RTX and high doses of GCS is controversial because it may increase the risk of severe infections [46,68,69]. Furthermore, high-dose or pulsed GCS treatment does not induce long-term clinical responses and may promote local infections, and low-dose GCS treatment is ineffective [27]. The response of LLUs to RTX is probably influenced by local co-morbidities (infections or chronic venous insufficiency) [45].

The results of studies assessing the efficacy of TPE have been conflicting [70,71] Only 22 of the 50 patients who presented LLUs in the case-file of Marson et al. [15], which included patients undergoing apheresis treatment combined with other immunosuppressive treatments, 22 showed a marked improvement, 16 showed a transient response, and 12 did not respond at all. In another study, apheresis synchronised with the administration of high- dose intravenous immunoglobulins (IVIGs) was used to treat refractory ulcers, and had a considerable immunosuppressive effect [21]. Anecdotal reports have described treating necrotising vasculitis and MCS-related digital ulcers with drugs such as iloprost and bosentan because of their possible vasodilating and anti-platelet effects, as well as the fact that they modulate lymphocyte adhesion and cytokine and endothelin expression [72,73].

In addition to the systemic treatment of MCS, local treatment is needed to prevent infections and reduce the size and severity of the skin lesions. The available information is generally anecdotal but there are reports of sharp or surgical debridement and interactive dressings depending on the condition of the wound bed and peri-lesional skin, and the possible presence of infection. Infections were detected in 29 (81%) of the 36 patients in the study of Giuggioli et al. [74], all of whom received analgesic treatment, but five with very severe, non-healing skin ulcers underwent amputation. Pain is frequent in MCS patients, particularly those with LLUs, and should be treated on the basis of the type of pain (neuropathic, mixed, nociceptive, acute or chronic), the patient's age and co-morbidities, and drug interactions. It often requires combinations of different drugs such as opioids, anti-convulsants, non-steroidal anti-inflammatory drugs and antidepressant as stated in the GISC recommendations [75].

3.8.1. Statements

1. LLU treatment is based on a combination of systemic and local interventions. 3B
2. RTX has proved to more effective than any other immunosuppressant in contributing to LLU healing. 1B.
3. Combined treatment with GCS and RTX may increase the risk of severe infections, and is not supported by the available data. 4C
4. TPE can be considered in patients not responding to other treatments, but needs to be correctly synchronised with RTX treatment. 5C

The levels of evidence and strength of the recommendations are summarised in Table 1.

4. Discussion

Although the success of DAA treatment suggests that there will be a decrease in the number of CVa patients with HCV infection, and thus a significant reduction in the incidence of MCS-related emergencies, the treatment of the latter will remain an open problem, particularly in the case of non-infectious MCS. The treatment of MCS is very challenging because of the complexity of its pathogenesis and its polymorphic and sometimes severe clinical manifestations. The aim of MCS treatment is to remove or contain the underlying cause (if known, such as in the case of HCV infection) [27,37,76], control the proliferation of the B lymphocyte clones responsible for cryoglobulin production [38,45,46], reduce the damage caused by circulating immune complexes, and relieve patient discomfort by means of immunosuppressive, symptomatic or palliative therapy [27,73]. It is widely agreed that, regardless of the severity of MCS, an attempt to eradicate HCV should be made whenever possible because suppressing viral replication may limit or, in the most favourable cases, even arrest the immunopathogenic process triggered by HCV [42,76].

Despite the very limited RCT data, RTX is considered to be the treatment of choice whenever it is necessary to containing the proliferation of the cell clones responsible for the production of cryoglobulins [38,44–47,77–82]. The main limitation of its use in LT-MCS is that treatment responses are not immediate and it is difficult fo

Table 1
Summary of recommendations for the treatment of severe (S) and life-threatening (LT) MCS, with levels of evidence and strength of recommendation according to Oxford 2001.

	Renal involvement (S)	Peripheral neuropathy (S)	Gastrointestinal vasculitis (S)	Lung involvement (S)	Heart/CNS vasculitis (S)	Skin ulcers (S)	LT-MCS (systemic disease)
Rituximab	1B Treatment of choice, coordinated with TPE in the most severe cases	1B Treatment of choice	4C After passing the critical phase in most severe conditions, coordinated with TPE if applicable	4C After passing the critical phase in most severe conditions, .coordinated TPE if applicable	NA After passing the critical phase in most severe conditions, coordinated with TPE if applicable	1B Treatment of choice as part of combined therapy	5C After passing the critical phase at immediate risk of life, coordinated with TPE if applicable
TPE	1B Part of first- line therapy in most severe cases	1B Part of first- line therapy in most severe cases	4 C Part of first-line therapy in most severe cases	4 C Part of first-line therapy in most severe cases. Limited data.	4 C Possibly part of first-line therapy in most severe cases. Limited data	1B Part of first-line therapy in most severe cases	4C Treatment of choice as part of combined therapy
Cortico- steroids	1B Short term, high doses as part of combined therapy	3 B Short term, high doses as part of combined therapy in most severe cases	4 C Short term, high doses in combination with TPE in most severe cases	4 C Short term, high doses as part of combined therapy	4 C Short term, high doses as part of combined therapy	1B Short term, high doses as part of combined therapy	4C Short term, high doses in combination with TPE
DAA in HCV+ MCS	3B As soon as compatible with patient's condition	3B As soon as compatible with patient's condition	NA As soon as compatible with patient's condition. Very limited data,	NA As soon as compatible with patient's condition. Very limited data.	NA As soon as compatible with patient's condition. Very limited data.	5C As soon as compatible with patient's condition. Limited data	5C As soon as compatible with patient's condition

NA = not applicable; TPE = therapeutic plasma exchange; DAA = direct-acting antivirals.

synchronise its use with apheresis, but it has been used in many severe or critical situations [83–90]. However, despite the considerable number of published studies, there is still a need for better defined clinical criteria concerning its use in patients with severe and life-threatening MCS. The still-open questions include its long-term effects on immune responses, the duration of the response, and possible re-treatment and maintenance strategies [12,27].

Once very extensively used, GCS are now reserved for high-dose and short-term use in situations that require an intensive and immediate intervention. The long-term use of low doses is not recommended (particularly in patients with cutaneous ulcers) because of the increased risk of infectious complications and the lack of evidence concerning their efficacy [12,27,46,68,69]. A minority of our experts felt that it was not appropriate to exclude the use of low GCS doses completely, and suggested that they should at least be considered for pain control, but the majority thought that the long-term administration of low-medium GCS doses should be discouraged and possibly avoided (particularly in naïve patients) because they are difficult to discontinue without consequences [12,27].

TPE should be used in life-threatening situations, and when other therapeutic approaches have failed or cannot be used. In 2010, Rockx and Clark looked at 11 studies involving a total of 156 patients and concluded that it was impossible to make a meta-analysis or even a systematic analysis because none of the studies had a clearly defined quantitative endpoint [24]. Nevertheless, the ASFA included severe/symptomatic cryoglobulinemia in category II ("second-line therapy") in its 2016 Guidelines [23], thus underlining the therapeutic role of apheretic techniques (TPE/immunoadsorption). Albeit with all of the limitations of such studies, our recent retrospective study of the largest case series published to date has confirmed the role of apheresis in treating the serious and life-threatening conditions associated with MCS [15]. In the case of cryoglobulinemic emergency, a treatment protocol including TPE should be started as soon as possible, preferably in an intensive care unit [15,17,33]. The 2016 ASFA Guidelines state that 3–8 procedures should be considered in the case of acute cryoglobulinemic symptoms (every 1–3 days: 1–1.5 total plasma volume, with albumin as the replacement fluid except in the case of alveolar hemorrhage where plasma use is mandatory in order to provide procoagulant factors) [23,42].

Finally, the conference strongly recommended paying attention to pain management because pain often greatly affects the quality of life of MCS patients. Unfortunately, this highly relevant aspect has not yet been considered in any RCT, but the GISC has recently produced recommendations that can be usefully adopted in everyday practice [75].

In conclusion, increasing knowledge of the pathogenesis of MCS and the current availability of new drugs (particularly DAAs) have significantly increased the possibility of treating MCS. However, given the absence of controlled trials (or because of the impossibility of conducting an RCT when treating the most serious conditions associated with MCS) physicians often need to make therapeutic choices without the support of solid data. Although they are mainly based on expert opinion, we hope the recommendations made in this paper will aid clinicians involved in treating severe and life-threatening MCS.

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This paper is dedicated to the memory of Augusto Genderini, MD.

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