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IM-POINT OF VIEW

Handling shock in idiopathic systemic capillary leak syndrome (Clarkson's disease): less is more

Maddalena Alessandra Wu[1] · Riccardo Colombo[2] · Gian Marco Podda[3] · Marco Cicardi[4]

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Abstract

Idiopathic systemic capillary leak syndrome (ISCLS) presents with recurrent potentially life-threatening episodes of hypovolemic shock associated with severe hemoconcentration and hypoproteinemia. Timely recognition is of paramount importance because ISCLS, despite resembling other kinds of hypovolemic shock, requires a peculiar approach, to prevent life-threatening iatrogenic damage. Due to the rarity of this condition with only scattered cases described worldwide, evidence-based recommendations are still lacking. Here, we summarize our 40 years' experience in treating shock in ISCLS patients to derive a therapeutic algorithm. Records from 12 ISCLS patients (mean follow-up is 6 years, with a mean age at symptoms' onset of 51.5 years) were informative for treatment modalities and outcome of 66 episodes of shock. Episodes are divided in three phases and treatment recommendations are the following: prodromal symptoms-signs (growing malaise, oligo-anuria, orthostatic dizziness) last 6–12 h and patients should maintain rigorous bed rest. The acute shock phase lasts 24–36 h. Patients should be admitted to ICU, placed on restrictive infusion of fluids favoring cautious boluses of high-molecular-weight plasma expanders when SAP < 70 mmHg; monitored for cerebral/cardiac perfusion, myocardial edema and signs of compartment syndrome. The post-acute (recovery) phase may last from 48 h to 1 week. Monitor for cardiac overload to prevent cardiac failure; in case of persistent renal failure, hemodialysis may be necessary; consider albumin infusion. Complications listed by frequency in our patients were acute renal failure, compartment syndrome and neuropathy, rhabdomyolysis, myocardial edema, pericardial–pleural–abdominal effusion, cerebral involvement, acute pulmonary edema and deep vein thrombosis.

Keywords Idiopathic systemic capillary leak syndrome · Clarkson's disease · Shock · Diagnosis · Treatment

Introduction

Systemic capillary leak syndrome (SCLS) may complicate malignancies, exposure to toxic agents and chemotherapy, engraftment syndrome, post-surgery and post-trauma conditions, hemophagocytic lymphohistiocytosis, ovarian hyperstimulation syndrome, hemorrhagic fever, skin disorders (e.g. psoriasis) and infections. However, in a few patients systemic capillary leak syndrome recurs episodically in the absence of an identified cause. This condition is identified as idiopathic systemic capillary leak syndrome (ISCLS), also known as Clarkson's Disease [1]. It presents with recurrent, potentially life-threatening episodes of hypovolemic shock due to leakage of plasma from the intravascular into the extravascular compartment [2]. The increased endothelial permeability underlying plasma leakage allows passage of water, solutes and plasma proteins up to the size of 300 kDa [3]. The diagnosis relies on the occurrence of unexplained shock accompanied by deep hemoconcentration and severe

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✉ Maddalena Alessandra Wu
maddalena.wu@unimi.it; maddalena.ale.wu@gmail.com

[1] Department of Biomedical and Clinical Sciences "Luigi Sacco", ASST Fatebenefratelli Sacco, Luigi Sacco Hospital, University of Milan, Via Giovanni Battista Grassi, 74, 20157 Milan, Italy

[2] Intensive Care Unit, ASST Fatebenefratelli Sacco, Milan, Italy

[3] Medicina III, Dipartimento Di Scienze Della Salute, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy

[4] IRCCS-Istituti Clinici Scientifici Maugeri, University of Milan, Milan, Italy

hypoproteinemia. Up to 90% of patients carry a monoclonal gammopathy of uncertain significance (MGUS), mostly IgG [3]. Failure to differentiate ISCLS-related shock from sepsis or anaphylaxis and other types of distributive shock leads to dire iatrogenic complications and death [4].

The etiology and pathogenesis of ISCLS are mostly unknown. Circulating permeability factors in acute but not convalescent ISCLS sera induce endothelial permeability in vitro by disrupting endothelial adherens junctions and causing cell retraction without inducing cell death (with attenuation of membrane VE-cadherin and actin stress fiber formation)[5]. Among circulating factors, a pivotal role seems to be played by angiopoietin 2 (Angpt2), which is a negative regulator of Tie2, a tyrosine kinase receptor located predominantly on vascular endothelial cells, able to stabilize the vasculature [6].

The rarity of the disease (less than 300 cases described) precludes evidence-based shared medical management. Currently used therapeutic approaches derive from case reports or case series obtained from registries collecting retrospective data from independent clinical centers [7–9].

The experience of our group on ISCLS patients goes back to the 70s when we published the first two patients [10]. From then on, we had the opportunity to observe and manage 22 patients, 12 of whom repeatedly seen during shock emergency.

Twelve of the 22 patients (9 men and 3 women) were managed by the authors during 1 or more hospitalizations for shock and their complete records were analyzed. The mean age at symptoms' onset was 51.5 years (range 36–61 years); the mean follow-up lasted 6 years (range 1 month–18 years). All patients carried a quantitatively irrelevant monoclonal component (MGUS). Eight patients are alive (mean age 59.1 years, range 36–70), four patients died at the mean age of 57 years (range 49–65 years). The total number of shock episodes recorded was 66, with a mean of 6.0 shocks per patient (range 1–20).

Description of shock episodes

Prodromal phase

It is controversial whether episodes of shock in ISCLS patients have specific triggers. There are reports showing that intense physical effort elicits attacks [7]. One of our patients died for irreversible shock after extreme skiing activity [11]. Six out of 12 patients reported the impression that strenuous physical exercise may have triggered the onset of symptoms. For six patients in our cohort, mild inflammatory-infectious conditions (e.g. flu, upper respiratory and gastrointestinal infections) were identified to precede at least one episode.

Prodromes of an upcoming shock consist of arterial hypotension, asthenia, dizziness, nausea and vomiting, edema, dyspnea, skin mottling, myalgias, and abdominal pain [12]. In our series, they were: arterial hypotension (11/12 patients), oligo-anuria (10/12), profound fatigue (10/12), worsening edema (9/12), weight gain (7/12), presyncopal/syncopal episodes (6/12), abdominal pain (6/12), sore throat, dysphonia, cough (5/12), nausea, vomiting, diarrhea (5/12), arthromyalgia (5/12), high temperature (4/12), dizziness (4/12), thirst/polydipsia (3/12), dyspnea (3/12), diaphoresis (3/12), altered consciousness (3/12), headache (2/12), and livedo reticularis (1/12).

Interestingly, despite being variable from patient to patient, the type of prodromal symptoms and signs experienced by each patient tend to be constant, with even non-specific symptoms showing peculiar characteristics when announcing an upcoming attack.

Shock (leak) phase

Shock develops after the prodromal phase [8], thus it is mandatory that patients should be promptly admitted to hospital. In our experience, the mean time from symptoms' onset to hospital admission is 16 h (range 3–48 h). Upon arrival, systolic arterial blood pressure (SAP) is 40–60 mmHg below the patients' usual values and they present with oligo-anuria that usually persists for 48 h. Puffiness in the lower limbs is present in 100% patients, less frequently also in the periorbital region; mean weight gain above the usual body weight is 8 kg (range 4–17 kg).

Blood tests are characterized by hemoconcentration, which leads to dramatic increase of hemoglobin (Hb), hematocrit (Hct) (up to more than 70%) and blood cell count (RBC $\geq 6\times10^6$, WBC $\geq 3\times10^4$, platelets $\geq 5\times10^5$), carrying the risk of misdiagnosis of primary polycythemia.

Total serum proteins decrease (to 50%) and albumin can be as low as 9 g/L in the absence of protein reducing conditions such as proteinuria, enteric protein-loosing syndromes, malnutrition or chronic inflammatory disorders. Discrepancy between hemoconcentration and hypoproteinemia is nearly pathognomonic of hypovolemia due to capillary leakage.

Table 1 reports baseline vital parameters together with Hct and albumin values and worst measured values during hospital stay. Hypotension and tachycardia can be extremely remarkable (e.g. in two of our cases SAP 60 mmHg, heart rate up to 160 beats per minute for several hours).

Rhabdomyolysis (above 100-fold creatine kinase increase), lactic acidosis (lactate > 7 mmol/L) and decreased glomerular filtration rate (eGFR < 30 mL/min) commonly accompany the shock phase.

Before diagnosis of ISCLS is established, the picture of hypovolemic shock, marked leukocytosis and sometimes mild fever can induce to consider septic shock as most likely

Table 1 Baseline and acute-attack vital parameters, together with hematocrit and albumin values recorded at baseline and during attacks

Patient	Baseline BP (mmHg)	Baseline HR (bpm)	Minimum BP during attack (mmHg)	Maximum HR during attack (bpm)	Baseline Hct (%)	Minimum Hct during crisis (%)	Maximum Hct during crisis (%)	Baseline albumin (g/dL)	Minimum albumin during crisis (g/dL)
1	125/70	84	70/50	130	44	56	66	4.2	2.5
2	140/80	72	85/70	100	37	51	72	4.3	3.4
3	140/70	76	80/60	112	35	55	68	n.a.	2.7
4	140/90	76	80/60	100	41	50	67	4.5	2.3
5	120/70	76	80/60	120	30	64	64	n.a.	2.3
6	140/80	70	80/n.a.	160	39	59	74	4	2.7
7	130/80	60	90/50	120	35	29	67	n.a.	1.7
8	140/90	71	80/50	104	44	31	62	3.3	1.9
9	135/80	70	60/35	120	30	45	66	4.1	1.5
10	130/80	70	85/60	125	39	53	60	n.a.	2.7
11	120/75	72	60/n.a.	160	33	55	> 60	4.2	0.9
12	130/70	60	70/n.a	96	42	51	58	4.2	2.8

As for basic vital parameters, the minimum value of blood pressure and the maximum value of heart rate during ISCLS-related shocks are indicated for each patient. As for biochemical parameters, baseline together with minimum and maximum hematocrit level and baseline together with minimum albumin value are specified for each patient during acute crises

BP blood pressure, *HR* heart rate, *Hct* hematocrit, *n.a.* not available

diagnosis [12]. Anaphylaxis also needs to be excluded. Main clues are past and current medical history (with no relation to foods, medications and insect stings) and laboratory tests (no significantly increased Hct values, normal albumin values and usually elevated tryptase levels in anaphylaxis).

Our experience confirms that fluids do not restore the intravascular volume, do not affect hemoconcentration/hypoperfusion-related complications while, due to extravasation, they worsen edema, facilitating compartment syndrome [12]. This is a major difference compared to shock in sepsis and anaphylaxis, and should be always considered to properly deal with ISCLS patients. Trying to counteract symptoms with aggressive fluid replacement results in a dangerous overfilling and increase in body weight (e.g. up to 17 kg in our cohort). The related edema becomes massive with non-pitting features. It usually involves upper and lower limbs' muscles, with a net increase of their circumference and "stone-like" consistency. It leads to functional defect and accompanying paresthesia and/or pain. When not adequately prevented or treated, compartment syndrome may lead to permanent damage [13]. A recent multicenter retrospective study highlighted that high-volume fluid therapy (cumulated fluid volume greater than 10.7 L) was independently associated with poorer outcomes in patients admitted to ICU for ISCLS flares [odds ratio, 16.8 (1.6–180); $p = 0.02$] [12].

Over the last years, we pragmatically adopted a strategy which minimizes the infusion of fluids, with crystalloids ≤ 25 mL/h adding 200 mL boluses of high-molecular-weight plasma expanders when SAP fell below 70 mmHg. This strategy of "permissive hypotension" is consistent with findings from other case series [8, 12]. During the shock phase, the choice between an aggressive fluid replacement aiming at restoring tissue perfusion and a restrictive fluid use aiming at avoiding severe tissue edema is a very difficult challenge for the physicians. During the capillary leakage, awareness of the futility of any attempt to restore the intravascular volume should lead to tolerate a "permissive hypotension". It should be pointed out that respiratory failure is rare, metabolic acidosis is mild to moderate and anuria time limited. The clinicians should hold back their impulse to "optimize" the hemodynamics as soon as possible in what they think are the golden hours. Due to the absence of tools to revert the increased permeability, they should move from "doing" to "watching": ISCLS is the paradigmatic setting where "less is more". Usually, the shock phase fully resolves within 24–36 h.

Treatment of the shock phase requires monitoring of cardiovascular parameters. We recommend early admission to ICU in case of hypotension with SAP < 100 mmHg because life-threatening shock may develop within a few hours. Timely insertion of a central vein catheter, invasive arterial pressure and urine output monitoring are warranted. Continuous cardiac output (CO) monitoring might be useful, although the absolute value of CO should not be considered as a mandatory target in this phase. In case of invasive CO monitoring, we recommend the use of volumetric techniques (i.e. PICCO) instead of a pulmonary artery catheter. The CO, estimated through thermodilution technique in two patients, was reduced (range 1.8–2.5–3 L/min). A 49-year-old man with no previous cardiac medical history had a stroke volume of barely 20 mL. The vasoactive amines are usually administered during this phase, but their usefulness

is questionable and on high doses they can induce left ventricular (LV) outflow tract dynamic obstruction in empty ventricles. Therefore, now we limit or completely avoid their use. Terlipressin was prescribed in one patient during six separate episodes of shock crises to redistribute blood mass reducing splanchnic circulation. With 0.17 mg/h of terlipressin SAP returned > 80 mmHg in five episodes while in one the same regimen had no effect.

Marked thickening (up to fourfold the normal size) of the myocardial wall has been frequently reported during the shock phase [14, 15] suggesting that its regular assessment every 6–12 h by transthoracic cardiac ultrasound may be helpful to promptly detect cardiac failure. Myocardial edema was identified in five patients, with increased LV wall thickness (septal and posterior LV wall end-diastolic thicknesses) associated with systolic and diastolic dysfunction. As expected, myocardial magnetic resonance (MR), performed in one patient early during the recovery phase, confirmed that myocardial apparent hypertrophy was due to edema. When massive, edema markedly impairs myocardial function: one case with cardiogenic shock was treated by extracorporeal circulatory support through peripheral veno-arterial extracorporeal membrane oxygenation (ECMO).

Pericardial effusion was detected in five patients and resolved uneventful in four. A 60-year-old man with recurrent weekly episodes of mild to moderate shock since 4 months presented pericardial effusion that persisted over 1 month. We could clearly record that the effusion increased during episodes of shock to a point that required percutaneous pericardiocentesis for risk of tamponade. Six hundred milliliters of fluid were drained, whose albumin concentration was the same as in plasma (31 g/L). In this case, MR showed absence of myocardial edema. None of our patients developed major arrhythmias.

Pleural and/or abdominal effusions appear to be rare in the acute shock phase. Serosal effusions were also detected in our patients in the late phase of the attack when the Hct was decreasing, being apparently related to the magnitude of fluid overload.

Deep venous thrombosis (DVT) may occur due to severe hemoconcentration, increased serum viscosity, and stasis; its actual frequency is unclear. We observed the case of a 36-year-old man who, despite an initial aggressive fluid replacement strategy adopted in another Center, experienced bilateral ilio-femoropopliteal and superior vena cava thrombosis, requiring oral anticoagulation for 4 months. For this reason and for the extreme hemoconcentration, heparin prophylaxis is indicated.

Involvement of the blood–brain barrier, cerebral infarction and ischemic cerebral edema, although uncommon, can complicate ISCLS and in one patient decompressive surgery was needed [9]. In our series, two patients had severe brain complications during acute episodes. A 57-year-old woman died for cerebral edema occurred during an acute episode. Being the patient in a deep coma for cerebral edema at admission to our ED, no clear evidence exists as to whether it was related to local hyperpermeability or to fluid overload. A 57-year-old man experienced thromboembolic ischemic stroke during the shock phase, with residual cerebral ischemia.

Deep sedation should be avoided for two main reasons: (1) to avoid the need of mechanical ventilation which carries hemodynamics derangement due to increased intrathoracic pressure and (2) to allow monitoring of consciousness as parameter of brain perfusion. Opioids may be necessary to reduce anxiety, stress, and to provide adequate analgesia. To achieve better control of vital parameters in severe episodes, three of our patients, in five episodes, underwent orotracheal intubation with sedation and neuromuscular blockade for mechanical ventilation. All five episodes had severe complications, but we cannot conclude whether the aggressive approach or the severity of the episodes were responsible for the unfavorable outcome. Our current policy is to maintain the patient conscious unless major problems of ventilation or need for ECMO are documented. In fact, "pure" respiratory failure is infrequent, being oro-tracheal intubation applied basically for neurologic and hemodynamic reasons [12].

We tested several additional therapies, aimed at antagonizing mediators and pathways known to induce increased vascular permeability. Methylene blue may counteract the vasoactive effect of nitric oxide; therefore, it was administered in repeated episodes, but evidence of its efficacy remained controversial. Similar inconclusive results were obtained with the use of drugs developed to revert bradykinin-mediated edema [16] as the bradykinin B2 receptor antagonist icatibant and plasma-derived C1-inhibitor. Likewise, the anti-VEGF monoclonal antibody bevacizumab was administered without clear benefit. Efficacy of i.v. immunoglobulins (i.v. Ig) for the prevention of attacks is fairly well documented [17, 18] and one report suggests that they can be beneficial in the acute phase [18]. In one of our patients, 1 g/kg i.v. Ig did not modify the shock state. The size of i.v. Ig suggests that they are not expected to stay inside the vessels during the capillary leak phase and recent studies warn on their association with poorer prognosis (possibly for nephrotoxic effects) [12]. Thus, we tried to assess the usefulness of IgM-enriched products, for potential advantage due to their higher molecular weight. However, we observed that, when administered in a very early phase of the acute shock, they tend to extravasate, while stable intravascular increase was detected only later, paralleling the improvement of vital parameters, probably related to initial restoration of the inter-endothelial junctions. Further data will clarify whether IgM-enriched preparations can be recommended as effective treatment to counteract shock (and, if useful, what timing should be chosen).

Despite remarkable edema, diuretics are strongly contraindicated throughout the entire shock phase.

Over the time, patients may learn to recognize the course of the symptoms and, from the very early prodromes, adapt their behavior to minimize damage (e.g. reducing fluid intake and physical activity). A 36-year-old man experienced a 13 kg body weight increase during the first attack and then no more than 4 kg increases during the subsequent crises thanks to adaptive behaviors.

Interestingly, six patients reported the possibility to control minor attacks with complete rest.

Of 66 hospital admissions reported in our cohort, the most severe ones occurred during the first months-years from symptoms' onset. This undeniable improvement is probably related to the adapting patients' attitude and better management in the healthcare setting rather than to the natural course of the disease.

Post-shock (recovery) phase

The transient nature of the shock phase accounts for a merely functional, reversible, endothelial junctions' loosening. The mean duration of the acute shock phase, evaluated as restoration of baseline Hct values, was 61 h (range 24–96 h). The shift from the shock to the recovery phase is announced by progressive Hct reduction. Since this parameter has minimal fluctuations, even two small consecutive decreases may indicate that endothelial permeability is reverting to normal. This is a turning point that changes patients' needs. Attention should move from shock to overfilling-related risks. In a few hours, water and ions return into the intravascular space and patients switch from hemoconcentration to various degrees of hemodilution depending on the amount of fluid administered. The mean time elapsing from highest to lowest hematocrit value was 59 h (range 24–96 h). Instead, the reversal of serum protein count takes days (mean 9 days, range 6–14 days) since it realizes through the lymphatic circulation. During this period, the low oncotic plasma pressure may worsen edema. In this phase, albumin administration may be recommended.

Restoration of the intravascular volume is usually accompanied by progressive increase of diuresis. However, the two processes do not always occur simultaneously. Awareness of the pending risk of acute cardiac failure and life-threatening pulmonary edema (two cases from our cohort) may lead clinicians to consider hemofiltration or dialysis. Acute kidney injury developed during the shock phase mainly due to hypoperfusion, but it may require days to recover [19, 20]. Rhabdomyolysis and possibly administration of excessive amounts of colloids may further contribute to renal damage and delay its recovery.

Ten patients in our cohort had signs of renal failure during attacks and in four patients continuous veno-venous hemofiltration was applied, being prolonged in one case for many days after the resolution of the ISCLS flare. These data are consistent with those from the EurêClark Registry, showing that renal dysfunction occurred in 88.1% episodes recorded and 86.5% patients with renal SOFA scores ≥ 1 in severe ISCLS flares [12].

Compartment syndrome [13] is a quite frequent complication of massive muscles' edema. It developed in seven patients from our cohort, requiring decompressive surgery once. Judicious fluid administration during shock is the only preventing strategy. Seven of our 12 patients suffered from mono/multiple neuropathy due to lower limbs' compartment syndrome. Permanent peroneal/tibial nerve palsy was observed in three patients from our cohort. Electromyography of the lower limbs shows variable degrees of distal sensory-motor nerve impairment, with patterns consistent with demyelination/neurapraxia, likely due to ischemic injury. Magnetic resonance can also be useful to highlight muscles' edema ruling out the presence of abscesses or necrosis. Functional consequences are walking difficulties for impaired flexion/extension of metatarsus and mild/moderate sensory defect. Involvement of the upper limbs can lead to cubital/carpal tunnel syndromes (one patient in our cohort). Paresthesia–dysesthesia (often with sock-like distribution) may persist after resolution of the functional defect. A patient from our cohort was transferred to the Rehabilitation Unit for lower extremity paraparesis with bilateral equinism. Four years later he walks without any device, drives his car and has no need for painkillers, whereas electromyography shows only partial re-innervation.

Conclusions

The aim of our study is to provide recommendations on the most appropriate diagnostic–therapeutic approach to acute shock in patients with ISCLS, whose rarity and acute presentation prevents designing controlled clinical trials.

On the basis of our clinical experience that includes years of meticulous patient follow-up and of our review of the available literature, we propose the following "key points" for healthcare professionals and patients facing this challenging disease. Such suggestions, far from being dogmatic, derive from the current understanding of the complexity of this condition and must be "tailored" to each specific patient:

- Alert patients to rest at prodromes and limit fluid intake.
- Upon SAP < 100 mmHg and/or increase in hematocrit $\geq 20\%$ usual values, the patient must be admitted to ICU.
- Consider early patient transfer to hospitals experienced in managing ISCLS and with expertise in multidisciplinary approach. In case of worsening myocardial

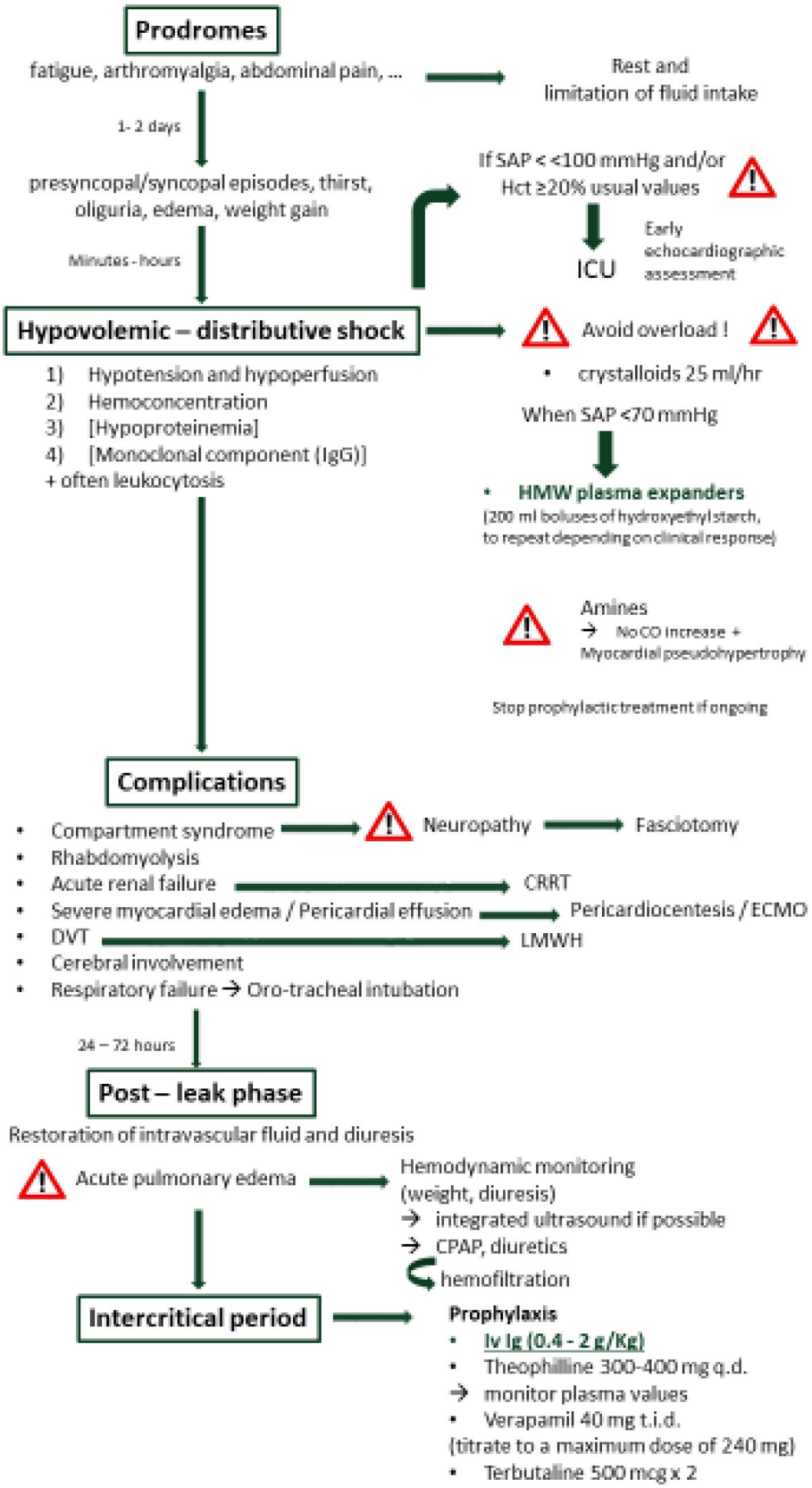

Fig. 1 Diagnostic–therapeutic algorithm of ISCLS**.** The picture shows a step-by-step approach to patients affected by ISCLS in its different stages: prodromes, acute phase with hypovolemic shock and the subsequent complications which may last also in the post-leak phase and intercritical period. Several warnings are visually indicated by a triangular roadside signal (for instance, the suggestion to send the patient to the Intensive Care Unit when systolic arterial pressure decreases under 70 mmHg and/or hematocrit value raises over 20% of its usual values). These critical points are discussed in the text. *SAP* systolic arterial pressure, *Hct* hematocrit, *ICU* intensive care unit, *HMW plasma expanders* high-molecular-weight plasma expanders, *CO* cardiac output, *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *DVT* deep vein thrombosis, *LMWH* low-molecular weight heparin, *CPAP* continuous positive airway pressure, *iv Ig* intravenous immunoglobulins

edema, consider referral to a center with venous-arterial ECMO capability.
- Monitor cardiorespiratory parameters and urine output continuously.
- Evaluate blood cell count with focus on Hct every 4 h, because this is the only parameter which gives a real insight into the course of the crisis and guides therapy.
- Measure total serum proteins/albumin, creatinine, BUN, CK, AST, ALT and blood gas analysis every 24 h.
- Perform ultrasound evaluation of serosal effusions, thickness of myocardial wall and clinical evaluation of upper and lower limbs' muscles and repeat every 6–12 h if effusion/edema are present.
- Start crystalloids (suggested infusion rate of 25 mL/h). Remember that aggressive fluid replacement does not restore intravascular volume, does not prevent hypoperfusion/hemoconcentration-related damage and can induce severe complications due to overload.
- Administer 200 mL boluses of colloids when SAP < 70 mmHg.
- When signs of worsening compartment syndrome are detected, perform decompressive surgery to prevent peripheral nerve injuries.
- Deep sedation, neuromuscular blocking drugs, orotracheal intubation and mechanical ventilation in the absence of severe respiratory failure should be avoided.
- If anuria and hypoproteinemia persist ≥ 6 h after Hct and SAP normalization, consider albumin supplements and loop diuretics (e.g. ethacrynic acid starting at 50 mg/day or furosemide 120 mg mg/day). In the presence of pulmonary edema, apply continuous positive airway pressure ventilation and, if oligo-anuria persists, consider extracorporeal fluid removal (continuous or intermittent renal replacement therapy).

Figure 1 shows our proposal for a diagnostic–therapeutic algorithm of ISCLS.

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Compliance with ethical standards

Conflict of interest No conflicts of interest to disclose.

Human and animal rights statement Patients' anonymity has been carefully protected.

Informed consent All patients provided informed consent for the publication of anonymized data.

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