Intensive care unit—acquired weakness (ICUAW) and muscle wasting in critically ill patients with severe sepsis and septic shock

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Abstract Sepsis presents a major health care problem and remains one of the leading causes of death within the intensive care unit (ICU). Therapeutic approaches against severe sepsis and septic shock focus on early identification. Adequate source control, administration of antibiotics, preload optimization by fluid resuscitation and further hemodynamic stabilisation using vasopressors whenever appropriate are considered pivotal within the early—golden—hours of sepsis. However, organ dysfunction develops frequently in and represents a significant comorbidity of sepsis. A considerable amount of patients with sepsis will show signs of severe muscle wasting and/or ICU-acquired weakness (ICUAW), which describes a frequently observed complication in critically ill patients and refers to clinically weak ICU patients in whom there is no plausible aetiology other than critical illness. Some authors consider ICUAW as neuromuscular organ failure, caused by dysfunction of the motor unit, which consists of peripheral nerve, neuromuscular junction and skeletal muscle fibre. Electrophysiologic and/or biopsy studies facilitate further subclassification of ICUAW as critical illness myopathy, critical illness polyneuropathy or critical illness myoneuropathy, their combination. ICUAW may protract weaning from mechanical ventilation and impede rehabilitation measures, resulting in increased morbidity and mortality. This review provides an insight on the available literature on sepsis-mediated muscle wasting, ICUAW and their potential pathomechanisms.

Keywords ICU-acquired weakness · Critical illness myopathy · Systemic inflammation · Immunity · Multiple organ failure · CIP/CIM

1 Sepsis

1.1 Epidemiology and definition of sepsis

Sepsis is a leading cause of death in intensive care units (ICU) [1–3]. In order to establish consensus definitions, the terms systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock have been proposed [4–7]. These terms define gradual stages of disease severity that correlate with mortality. Whereas SIRS defines a rather unspecific inflammatory host response due to both infectious and non-infectious origin, severe sepsis refers to a proven systemic infection associated with acute organ dysfunction. Criteria of septic shock are met once additional volume-refractory hemodynamic failure occurs [4, 5]. Recently, there has been great effort in studying the epidemiology of sepsis [2]. Data from the United States report 750,000 cases/year of severe sepsis [8] and an overall mortality of 29% for 2001. A 9% annual increase of severe sepsis incidence between 1977 and 2000 was reported [9]. Epidemiological trials from Germany indicate that 79,000 inhabitants (116/100,000) will suffer from sepsis each year and an additional 75,000 inhabitants (110/100,000) will be diagnosed with severe sepsis. Ninety-day mortality of severe
sepsis amounts to 54%. With 60,000 sepsis-related deaths per year in Germany, sepsis remains a leading cause of death and a considerable burden for health care systems [10–12].

1.2 Fundamental clinical and pathophysiological considerations in sepsis

Treatment of patients with sepsis should be implemented according to international guidelines and recommendations, e.g., as proposed by the Surviving Sepsis Campaign [4]. Early identification and therapy initiation seem of pivotal importance and were shown to significantly improve patients’ prognoses. In general, guidelines for the treatment of severe sepsis or septic shock aim to initiate early symptomatic organ support therapies; e.g. early optimization of cardiac preload, afterload and contractility in order to balance oxygen delivery with oxygen demand influences survival rates in sepsis [13]. Over the past years, several treatment approaches have been associated with beneficial outcomes in large-scale, mostly single-centre trials, including low-dose hydrocortisone [14], glycemic control [15, 16] and recombinant activated protein C [17]. Yet, these benefits could not be replicated by confirmative studies [18–20].

Pathophysiologically, the first response to a severe infection consists in the activation of antigen-presenting immune cells. This occurs via pattern recognition receptors [1, 21–23] and is accompanied by other immune mechanisms such as cytokine liberation, endothelium and complement activation, and release of oxygen radicals. Cytokines (tumour-necrosis factor alpha (TNF-α), interleukin (IL)–6 and IL–1) and complement factors (C3a and C5a) may then act as key mediators during this stage of inflammation [21]. Clinical signs of infection such as leukocytosis, increased respiratory rate or acute organ failure may then develop [1] and, as a protective measure, the immune system coordinates an immunological and endocrine counter-regulation which is mediated by up-regulation of key anti-inflammatory cytokines (e.g. IL–10, tumour-growth factor-β) [7, 24–27]. This may lead to prolonged hypo-inflammatory states (“immunoparalysis”) [27], which have been linked to secondary/nosocomial infection, prolonged ICU stay, chronic multiple organ failure and an increased mortality [21–31]. Ongoing clinical trials investigate measures of immunostimulation [28–30] or removal of inhibitory factors [31] to reverse this immunological condition.

Inflammation-mediated organ dysfunction represents a detrimental comorbidity of sepsis. As sepsis is frequently accompanied by short- and long-term affection of neuromuscular function, it has been postulated that the “motor unit” presents another system affected by inflammation-mediated multiple organ dysfunction: Sepsis is not only associated with involuntary loss of muscle mass, which is frequently referred to as muscle wasting, but also severe neuromuscular dysfunction resulting in “ICU-acquired weakness” (ICUAW). Patients with acute respiratory distress syndrome show a particularly high incidence for ICU-acquired weakness [32].

2 Sepsis-induced muscle wasting and ICUAW: an imbalance in protein metabolism

William Osler first commented on the “rapid loss of flesh” that occurs with severe sepsis in 1892 [33]. Today, this phenomenon remains a frequent complication of critical illness—particularly sepsis—and is often referred to as muscle wasting. However, because sepsis led to a fairly rapid death in Osler’s days, the primary focus was rather survival than sepsis-associated long-term complications. Yet, once ICU and artificial organ support therapies are available, more patients survive the initial stages of systemic inflammation/sepsis and critical care specialists are increasingly confronted with profound muscle weakness, which is often accompanied by difficulties in weaning from respiratory support. Sepsis-induced multiple organ failure has been identified as one of the primary risk factors for this major and frequent complication of critical illness [34]. As a confusing number of various terminologies referred to similar or identical clinical presentations of this neuromuscular disorder, a recent round table conference held in 2009 proposed the mutual term “ICUAW” [35]. Whereas ICUAW is usually accompanied by muscle wasting, muscle wasting does not necessarily lead to neuromuscular dysfunction, since overall muscle strength depends both on total muscle mass and force generating capacity (force per cross-sectional area), which is affected in ICUAW but not necessarily in muscle wasting syndromes [36] (Fig. 1).

2.1 Sepsis-associated muscle wasting

As mentioned above, muscle force capacity may remain stable in muscle wasting syndromes [36]. Muscle wasting can be triggered by other conditions than sepsis, including disuse, denervation, fasting, cancer, cardiac failure and renal dysfunction. As these conditions frequently coincide with sepsis, systematic research of sepsis-specific muscle wasting and ICUAW may be challenging in humans. This seems especially the case as sepsis is often accompanied by prolonged bedrest/immobilisation, application of sedatives, acute or chronic organ dysfunction, malignancy as an underlying disease, medication using glucocorticoids and others.

An imbalance between muscle protein synthesis and muscle protein degradation causing net loss of muscle mass...
is considered to present the main mechanism of muscle atrophy in muscle wasting and may result from decreased protein synthesis and/or increased protein degradation [36] (Fig. 1).

2.2 Decreased muscle protein synthesis during sepsis

Even though studies on sepsis-induced muscle protein degradation received more attention, animal models of sepsis clearly indicate that sepsis also decreases protein synthesis in skeletal muscles [37] and preferentially inhibits myofibrillar and sarcoplasmatic protein synthesis within fast twitch muscles [38].

One central mechanism is decreased protein translation by lower amounts of active translation initiation factor complex eIF4E/eIF4G, possibly resulting from decreased phosphorylation of eIF4G and mammalian target of rapamycin (mTOR) [37]. Interestingly, mTOR activation presents an important downstream target of anabolic insulin/insulin like growth factor 1 (IGF-1) signalling, which may be impaired in sepsis since decreased insulin sensitivity presents a frequently observed complication of sepsis [39–44]. Further indirect evidence for contribution of impaired insulin signalling to decreased protein synthesis comes from the observation that the proinflammatory cytokines IL-6 and TNF-α have been linked to both insulin resistance [45, 46] and muscle atrophy [47–50] and that local IGF-1 application prevents sepsis-induced muscle atrophy [37], possibly by inhibition of sepsis-induced increases of muscle atrogin-1 and the proinflammatory cytokine IL-6 [51]. IL-1 may lead to decreased protein synthesis as well, as an animal model of abdominal sepsis showed cytokine-dependent decreases of phosphorylated eIF4G that was primarily attributed to this cytokine [52]. There is evidence that systemic cytokine response in sepsis results in local amplification of proinflammatory cytokines within muscle [36], possibly aggravating decreased protein synthesis in skeletal muscle during sepsis.

Nutritional aspects may contribute to decreased muscle protein synthesis as well. Administration of the essential branched chain amino acid leucine has been shown to increase protein synthesis in rat skeletal muscles during ageing, exercise or food-deprivation [53–56]. However, under certain conditions including sepsis, the muscle may be resistant to leucine-stimulated protein synthesis [37]. Although the exact mechanisms of sepsis-induced leucine resistance remain to be elucidated, this phenomenon was accompanied by an 80% reduction in the amount of active eIF4E/eIF4G complex (besides other factors) and could be completely reversed by the combination of TNF binding protein and glucocorticoid receptor antagonist RU486 [57]. Exploring the underlying mechanism of sepsis-induced resistance to leucine-stimulated protein synthesis may contribute to a better understanding of the mechanisms involved in sepsis-mediated reductions of active translation initiation factor complexes, particularly the eIF4E/eIF4G complex.
Critical illness, confronting intensivists around the globe

ICUAW presents a severe and frequent complication of critical illness, confronting intensivists around the globe with various difficulties. It is believed that ICUAW can affect more than half of all ICU patients [77]. This substantial neuromuscular complication of critical illness is associated with increased rates of morbidity and mortality, substantially affecting both short- and long-term clinical outcomes in septic patients [78–85]. By causing prolongation of ICU stay and rehabilitation, ICUAW leads to an increased risk of secondary complications and a higher demand on already limited resources of health care systems. ICUAW is further associated with decreases in health-related quality of life (HRQOL) which may be impaired for years after ICU discharge [85, 86]. Modern critical care must therefore no longer solely focus on survival, but particularly consider HRQOL after ICU discharge.

3 ICUAW: clinical presentation, relevance, risk factors, treatment options and subclassifications

3.1 General considerations on ICUAW

ICUAW presents a severe and frequent complication of critical illness, confronting intensivists around the globe.
interobserver reliability in patients with Guillan–Barré syndrome [87]. Values of <11-kg force for men and <7-kg force for women at dominant-hand dynamometry have also been described to identify ICU-acquired weakness in previously healthy individuals [88]. Nevertheless—and in spite of daily wake up calls, both approaches share one major limitation—the requirement for patient cooperation and consciousness, which may be inadequate due to delirium resulting from sedation and/or septic encephalopathy. Electrophysiologic testing offers an additional approach to estimate neuromuscular dysfunction in unconscious patients incapable of voluntary contraction. Moreover, electrophysiologic testing after direct muscle stimulation can be conducted in unconscious/sedated patients and has been shown to predict ICUAW with high sensitivity and specificity in mechanically ventilated, sedated patients and differentiates between primary nerve or muscle dysfunction [89]. However, as it requires some expertise and certain devices to perform these measurements, use of this technique is currently restricted to larger facilities or experts.

3.3 Risk factors involved in ICUAW

While the exact molecular mechanisms contributing to ICUAW remain to be elucidated, five central risk factors of ICUAW have been repeatedly reported [34]. As there are currently no specific therapies, minimising exposure to these risk factors is crucial in order to prevent this devastating neuromuscular complication. Possibly the most important risk factor complex comprises conditions leading to multiple organ failure, particularly severe sepsis and septic shock. Some authors actually consider ICUAW an additional organ failure following severe sepsis and septic shock. The other four risk factors of ICUAW involve muscle inactivity, disturbances of glucose metabolism resulting in hyperglycaemia, administration of corticosteroids, and use of neuromuscular blocking agents (Fig. 1).

3.4 Implications for minimising risk factor exposure and treatment options

3.4.1 Sepsis

In addition to the optimum realisation of early goal-directed sepsis therapy [13], there are a number of hypothetical approaches targeting inflammation-mediated multiple organ failure, such as reducing levels of distinct cytokines by extracorporeal measures [31, 90–94] or restoring the immunological equilibrium by pharmaceutical immunomodulation [28–30]. However, the current literature on ICUAW has not considered sepsis-induced affections in cellular immunity to participate directly in the induction of neuromuscular dysfunction.

3.4.2 Immobilisation

Schweickert and colleagues [95] recently reported that patients undergoing an ambitious protocol of early and determined mobilisation were more frequently able to get out of bed, stand and occasionally walk with assistance during mechanical ventilation whereas standard regimens of physical therapy led to longer impairment of functional status and recovery time. Besides, early mobilisation was associated with a shorter duration of delirium. It is possible, that additional electrical muscle stimulation (EMS) assists in preventing ICUAW, since studies indicate that EMS partially prevents muscle atrophy in critically ill patients [96] and mitigates increased proteasome activation besides stimulating insulin like growth factor in patients after major abdominal surgery [97]. Preliminary data of our ongoing trial on ICUAW prevention by daily EMS supports this, as it indicates improvement of muscle membrane excitability in critically ill patients at high risk for ICUAW (unpublished data). Importantly, EMS can be initiated immediately after ICU admission and could facilitate faster mobilisation progress. Implementation of protocol-based sedation and weaning measures may further reduce the incidence of ICUAW and weaning failure (Fig. 2).

3.4.3 Intensive insulin therapy

Increased serum glucose levels are typical findings in patients with severe sepsis and septic shock. Studies from van den Berghe and colleagues reported that intensive insulin therapy (IIT) was associated with a lower incidence of ICUAW [98, 99]. However, recent data from the NICE-SUGAR trial demonstrates that 90-day mortality rate is significantly lower in critically ill patients with liberal glycemic control (serum glucose ≤180 mg/dl) vs. those patients receiving IIT, the risk of severe hypoglycemia being significantly higher in the IIT group [19, 20]. Although tight glycemic control as a general approach in ICU patients is currently controversial, it seems reasonable that protocol-based glycemic control targeting prevention of excessive blood glucose levels and variability help reduce the incidence of ICUAW.

3.4.4 Glucocorticoid exposure

Although de Jonghe et al. identified corticosteroid administration as the strongest predictor for ICU-acquired weakness [100], data from a recent meta-analysis does not indicate a clear relationship between systemic levels of corticosteroids and myotoxic effects in patients with sepsis [81]. Development of steroid induced myopathy [101, 102] may be dependent on steroid doses applied, which is in line with findings from our group, that do not indicate an
association between low-dose hydrocortisone application and impaired muscle membrane excitability—one of the key features in ICUAW patients with predominant myopathy [103]. Yet, as this observation has to be confirmed by other groups, strict indication is still warranted considering low-dose hydrocortisone administration.

### 3.4.5 Neuromuscular blockers

Treatment with neuromuscular blocking agents has been reported to contribute to ICUAW development. Initial reports stated that vecuronium and pancuronium may be particularly harmful in regard to critical illness neuromuscular abnormalities [104]. It remains unclear, however, whether this is simply attributable to the rather widespread use of these substances at that time. Importantly, renal function must be taken into account, as some neuromuscular blocking agents undergo excretion via the kidneys. As firm conclusions regarding specific deleterious effects of neuromuscular blockers are precluded, cautious use is still warranted [34].

#### 3.5 Subclassification of ICUAW

Depending on electrophysiologic or histological documentation of neuropathy and/or myopathy, ICUAW can be further subclassified as critical illness myopathy (CIM), critical illness polyneuropathy (CIP), or critical illness myoneuropathy (CIMN), which is more frequent than previously thought and applies to ICUAW patients with coinciding neuropathy and myopathy [35]. Myopathy is likely to present the predominant feature of ICUAW and has been shown to precede neuropathy in patients with CIMN [89]. Yet, as both histology and electrophysiology are currently not obtained during clinical routine, subclassification of ICUAW may seem of less importance to clinicians dealing with this complication. We just recently demonstrated that myopathy occurs earlier and more frequent, whereas additional polyneuropathy develops later and less frequent. By showing that additional polyneuropathy was associated with longer ICU length of stay, we suggest that differential diagnosis of ICUAW becomes more important to clinicians [105].
3.6 Sepsis-induced myopathy: CIM and CIMN

Three characteristics are commonly described in patients with CIM or CIMN [106–108]:

- Selective thick filament loss
- Predominant type II muscle fibre atrophy (Fig. 3)
- Muscle membrane inexcitability

Unspecific but predominant type II (fast twitch) muscle fibre atrophy has been repeatedly described within muscle tissue from CIM/CIMN biopsies [35]. Selective but patchy loss of myosin filaments can be visualised by electron microscopy and is considered a hallmark of CIM, explaining its additional terminology of thick filament myopathy [35]. In contrast to these morphologic alterations, non-excitile muscle membrane is detected by electrophysiologic testing [43, 108, 109] and has been shown to predict ICUAW in mechanically ventilated, sedated patients with high sensitivity and specificity [89]. All three characteristics may result in different mechanisms leading to ICUAW, as loss of muscle mass (atrophy) correlates with decreased maximum force, thick filament loss represents an additional reduction of force generating capacity by additional myofilament dysfunction, and non-excitile muscle membrane may be considered as an incapability of the muscle to generate contraction-preceding action potentials. Less frequently described histologic signs of CIM/CIMN include acute necrosis [110, 111], regeneration [112] as well as loss of myofibrillar ATPase staining [113], the latter affecting both type I and II muscle fibres.

3.7 Suggested subcellular abnormalities in sepsis-induced myopathy

A number of subcellular sites involved in excitation-contraction coupling may be affected in sepsis-induced myopathy [36]. These include the sarcolemma, the sarcoplasmatic reticulum, the contractile apparatus and the mitochondria. As described above, one of the key features of CIM/CIMN is that skeletal muscle becomes electrically inexcitable, which has led to the concept that CIM/CIMN could represent an acquired channelopathy involving dysregulation of sodium channels located at the sarcolemma. Experimental studies describe sarcolemmal injuries in diaphragm and limb muscle that were in part associated with excessive nitric oxide generation [114–116]. Altered calcium homeostasis has been observed in a number of studies on skeletal muscle during sepsis with calcium level increases in some subcellular compartments and decreases in others [36]. Contractile protein dysfunction resulting in reduced force pCa relationship has been reported in diaphragm and limb muscle in a number of sepsis models [117–120]. It is likely that free radical generation is involved in this mechanism, as either a superoxide scavenger or NO synthesis inhibitor significantly attenuated reduced endotoxin-induced force pCa relationships. TNF-α has been linked to decreases in titanic force generation due to changes in myofilament function, as well [121, 122]. A considerable amount of data indicates that sepsis also causes profound alterations in respiratory muscle mitochondrial function [36]. Limb muscle biopsies from septic patients show decreased mitochondrial content and lower concentrations of energy rich phosphates [123].

4 Conclusions and outlook

In conclusion, sepsis and systemic inflammation may lead to multiple organ failure, which is associated with loss of muscle mass and/or onset of ICUAW. ICUAW presents a significant clinical problem and is thought to affect up to 50% of all ICU patients. As an increasing amount of patients survives sepsis, long-term complications of critical care are likely to gain in significance. Short term complications of ICUAW include...
secondary complications due to prolonged ICU stay, protraction of rehabilitation measures, failure in weaning from mechanical ventilation and others. Currently, there is no causal therapy of ICUAW and measures are restricted to minimising risk factor exposure. Risk factors besides multiple organ failure—which is most likely due to sepsis and systemic inflammation—include excessive blood glucose levels, immobilisation, exposure to neuromuscular blockers and corticosteroid application. Therefore, measures such as identification of risk patients, avoidance of unnecessarily deep sedation, promotion of early mobilisation and EMS, prevention of excessive blood glucose levels, rational administration of glucocorticoids and/or neuromuscular blockers as well as early goal-directed therapy of sepsis seem to reduce the severity and incidence of ICUAW. Nutritional approaches, immunomodulatory interventions, antioxidant treatment or others might furthermore lower the incidence of muscle wasting and ICUAW in critically ill patients.

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