

# Treatment advances of sepsis-induced myopathy (Review)

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**Abstract.** Sepsis-induced myopathy (SIM) is a muscle disease caused by multiple pathological and physiological mechanisms associated with sepsis. The pathogenesis of SIM is extremely complex and still unclear, making treatment challenging. At present, clinical treatment includes early functional exercise, respiratory muscle strength training, regulation of nutritional structure and functional electrical stimulation. Drugs targeting the regulation of the ubiquitin-proteasome system, autophagy-lysosome system, calpain and caspase activation pathways, have provided potential therapeutic targets for the treatment of muscle atrophy. Stem cell transplantation therapy brings new hope for the treatment of SIM.

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## 1. Introduction

The concept of sepsis-induced myopathy (SIM) was first proposed by Professor Leigh Ann Callahan of the University of Kentucky in 2009 (1). It is a myopathy caused by sepsis. It mainly affects the muscles of the limbs, respiratory muscles and diaphragm, causing muscle strength decline, muscle atrophy and changes in muscle biological properties. This leads to decreased motor ability and muscle strength, limited

activity function, prolonged mechanical ventilation time and difficulty in weaning from ventilators, exacerbation of disease, prolonged hospitalization and increased mortality in patients (2). The pathogenesis of SIM includes signaling pathways related to skeletal muscle protein metabolism, autophagy and interactions with various cytokines, inflammatory mediators and hormonal imbalances. With the increasing incidence rate of sepsis, the effect of SIM on human beings is becoming increasingly serious. There is currently no specific treatment for SIM and the main methods currently used are early functional exercise, nutritional structure adjustment and functional electrical stimulation. Finding effective treatments for SIM is an urgent problem for modern medicine to solve. With the deepening of the understanding of the pathological mechanism of SIM, drug treatment targets for SIM have been continuously discovered.

The present review was performed by screening the Pubmed (<https://www.ncbi.nlm.gov/pubmed/>), Medline ([https://www.nlm.nih.gov/medline/medline\\_overview.html](https://www.nlm.nih.gov/medline/medline_overview.html)) and Google Scholar (<https://scholar.google.com/>) databases. The key words were 'sepsis', 'myopathy', 'treatment', 'therapy' and 'sepsis-induced myopathy'. Articles written in English, published between 2014 and 2024 and available with a full text were mainly used.

## 2. Current advances in treatment measures

**Early functional exercise.** Early functional exercise can promote the recovery of muscle strength and limb function. The Medical Research Council scale (3) can be used to assess the muscle strength in SIM patients. Meta-analyses have shown that early functional exercise can promote muscle protein synthesis, thereby enhancing the recovery of muscle strength and improving limb function in SIM patients, shortening intensive care unit (ICU) stays and reducing patient mortality rates (4-6).

Early functional exercise is also crucial for diaphragm function training and weaning from ventilators. Sepsis-induced diaphragm atrophy, coupled with mechanical ventilation, can lead to respiratory muscle weakness and difficulty weaning from ventilators. Respiratory muscle strength training can increase respiratory muscle strength, reduce the incidence of weaning difficulties and improve weaning success rates (7,8).

The effectiveness of functional exercise is positively correlated with the amount of rehabilitation. Watanabe *et al* (9) found that high-dose rehabilitation treatment groups had significantly higher exercise capacity at discharge than

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**Abbreviations:** SIM, sepsis-induced myopathy; ICU, intensive care unit; mTOR, mammalian target of rapamycin; MuRF1, muscle ring finger protein 1; MAFbx, muscle atrophy F-box; PPARs, peroxisome proliferator-activated receptors

**Key words:** sepsis-induced myopathy, treatment, advance, electrical stimulation, nutrition, drug, stem cell

low-dose rehabilitation treatment groups. The exercise capacity of patients is positively correlated with the dose of rehabilitation treatment, which is the product of the level and duration of rehabilitation training. This means a higher level of rehabilitation training does not necessarily lead to a higher exercise capacity. Early rehabilitation exercise means an increase in time, thereby increasing the dose of rehabilitation training and improving rehabilitation effectiveness.

As for the optimal intensity, time and frequency of rehabilitation treatment for patients, there is little clear evidence to guide therapists. Generally, the appropriate intensity and duration of treatment should be selected according to the patient's situation. There is currently no consensus or guideline to follow.

#### *Nutritional structure adjustment*

*Strict blood sugar control and intensive insulin treatment.* On the one hand, poor blood glucose level control is an independent risk factor for SIM and, on the other hand, sepsis causes severe insulin resistance, weakening the normal physiological response of skeletal muscle cells to insulin regulation (10). Intensive insulin treatment can reduce the incidence of SIM, but can also lead to hypoglycemia, increasing patient mortality rates (11). Therefore, blood glucose level control is particularly important.

*Supplementation of amino acids, especially branched-chain amino acids.* In sepsis patients, metabolic abnormalities result in slower nutrition initiation, with muscle synthesis rates lower than decomposition rates, leading to a decrease in total muscle mass and ultimately SIM (12). Therefore, reasonable supplementation of amino acids plays an important role. Branched-chain amino acids (including valine, leucine and isoleucine) play a crucial role in protein synthesis and energy metabolism (13). The continuous activation of the autophagy-lysosome pathway in sepsis, through the mammalian target of rapamycin (mTOR), activates AMP-activated protein kinase-related signaling pathways, inducing high levels of autophagy in skeletal muscles, which is one of the causes of muscle atrophy (14). Animal studies have found that exogenous supplementation of branched-chain amino acids can prevent sepsis-induced muscle protein degradation by inhibiting the autophagy signaling pathway in skeletal muscles, while clinical studies are still ongoing (15,16).

*Supplementation of glutathione and N-acetylcysteine.* During sepsis, a cytokine storm causes the body to produce excessive free radicals and endogenous antioxidant mechanisms are reduced (17). Muscle biopsy shows decreased glutathione levels in muscle tissue of SIM patients. Supplementing glutathione can reduce oxidative stress indices, while supplementing N-acetylcysteine (a precursor of glutathione) can not only scavenge oxygen free radicals but also increase glutathione reserves (18). Currently, using branched-chain amino acids and glutathione, including its precursors, as nutritional supplements is expected to treat SIM by promoting muscle anabolism, but current clinical studies have not yet reached consistent conclusions (19).

*Functional electrical stimulation.* Electrical stimulation of the limbs of SIM patients is beneficial for muscle strength recovery. Measuring the diameter of the cross-section of the mid-thigh and rectus femoris muscles of SIM patients through

ultrasound examination can confirm that electrical stimulation has a certain preventive and therapeutic effect on SIM (20). Another study shows that electrical stimulation cannot prevent the occurrence of SIM but can reduce the degree of muscle weakness (21). Therefore, further researches are needed on the effectiveness of electrical stimulation.

*Potential drug targets for SIM treatment.* Sepsis can lead to skeletal muscle atrophy through a combination of protein metabolism disorders, autophagy, mitochondrial dysfunction-induced oxidative stress and cytokine storms caused by inflammatory mediators. Among these influencing factors, the main factors leading to skeletal muscle atrophy are a decrease in protein synthesis and an increase in hydrolysis. There are four protein hydrolysis pathways in muscle atrophy: the ubiquitin-proteasome system, autophagy-lysosome system, calpain and caspase pathways (22). Inhibiting the corresponding activation pathways may prevent the decomposition of muscle proteins, providing potential therapeutic targets for treating muscle atrophy.

*Inhibiting protein breakdown through the regulation of the muscle ring finger protein 1 (MuRF1) and muscle atrophy F-box (MAFbx) may be a drug target for SIM treatment.* In the ubiquitin-proteasome, proteins are degraded through the ubiquitination and the combined action of the ubiquitin activating enzyme E1, ubiquitin conjugating enzyme E2 and ubiquitin ligase E3. The ubiquitin ligase E3 plays a key role. In skeletal muscle, there are two specific ubiquitin ligases, namely MuRF1 and MAFbx (23). Therefore, the degradation of proteins can be inhibited by regulating MuRF1 and MAFbx (24). Heat shock proteins (HSPs) are stress-induced proteins that are crucial for cellular homeostasis. BPG-15, an ADP-ribose polymerase inhibitor, is a co-inducer of HSP-72. In a study of early dysfunction of the soleus and diaphragm muscles in an intensive care rat model, the chaperone co-inducer BPG-15 significantly improved muscle strength in the soleus muscle by reducing the expression of MuRF1 after 5 days of ICU exposure (25).

*Vamorolone may be an ideal anti-inflammatory drug for SIM treatment.* In sepsis-induced systemic inflammation, glucocorticoids are often administered to alleviate inflammation. However, glucocorticoids can accelerate protein degradation and cause muscle wasting by promoting the expression of transcription factor FOXO. Vamorolone (a steroid anti-inflammatory drug) has a similar anti-inflammatory effect with Prednisolone, while having fewer side effects on the skeletal muscle. In rat models of ICU-acquired muscle weakness, both the Vamorolone-treated group and the Prednisolone-treated group had significantly higher survival rates compared with the control group; however, the degrees of decline on weight, muscle mass, as well as muscle fiber contraction force, were significantly lower in the control group compared with both treatment groups. The Vamorolone-treated group had a significantly higher survival rate than the Prednisolone-treated group, while the degrees of decline in weight, muscle mass, as well as muscle fiber contraction force, were significantly lower in the Vamorolone group compared with the Prednisolone group (26). The rat models of ICU-acquired muscle weakness shared similar pathophysiological mechanisms with the SIM model. Therefore, it is expected that Vamorolone could also be effective in treating SIM. Vamorolone has the potential to

replace traditional glucocorticoids and prevent muscle disease associated with glucocorticoids.

*Antioxidant therapy has been proven to inhibit muscle wasting in animal experiments.* During the production of reactive oxygen species (ROS), hydrogen peroxide is generated, which stimulates the binding of the ubiquitin to the muscle protein, leading to the muscle wasting. *Valeriana fauriei* Briq, a herbal plant containing various antioxidant flavonoids, has been shown to prevent Dexamethasone-induced muscle wasting *in vitro* and in a mouse model of muscle atrophy. *V. fauriei* not only inhibits the muscle wasting by downregulating the expression of MuRF1 and MAFbx, but also serves as a scavenger of ROS and downregulates the atrophy genes (27). Peroxisome proliferator-activated receptors (PPARs) play a key role in regulating skeletal muscle energy metabolism, contraction and inflammation. PPAR- $\delta$  agonists can increase MuRF1 mRNA expression and lead to the muscle wasting, while PPAR- $\delta$  antagonists can reduce the muscle wasting in sepsis mice treated with Dexamethasone (28). Antioxidant therapy has shown promising results in the prevention of muscle wasting in the Dexamethasone-induced mouse model of atrophy, but further studies are needed in the SIM model.

*Regulating specific transcription factors to prevent muscle wasting.* The phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt)-mammalian mTOR signaling pathway controls cell division in most cells and stimulates protein synthesis, while inhibiting protein degradation in skeletal muscle cells (29). Activation of this pathway can inhibit transcription factors such as FOXO, leading to protein synthesis. By contrast, inhibition of this pathway leads to FOXO activation and increased protein degradation, resulting in skeletal muscle atrophy. In addition, other transcription factors such as NF- $\kappa$ B and Jun-b also play important roles in regulating the muscle protein metabolism. Overexpression of NF- $\kappa$ B and Jun-b can block FOXO and reduce muscle wasting (30). Furthermore, PPAR- $\gamma$  coactivator 1 $\alpha$  also prevents skeletal muscle atrophy by inhibiting FOXO3 (31). Some proinflammatory cytokines caused by sepsis, such as IL-1, IL-6 and TNF- $\alpha$ , also play crucial roles in the process of muscle wasting by promoting the mitochondrial permeability transition, inhibiting the oxidative phosphorylation and ultimately causing the mitochondrial structure and function damage (32). Regulating specific transcription factors and inflammation factors to prevent muscle wasting is a possible treatment approach, but current research on the role of transcription factors in skeletal muscle is still limited.

The aforementioned studies provided potential therapeutic targets for the treatment of muscle atrophy. However, further experimental and clinical studies are needed and the adverse reactions and side effects also need to be further clarified.

*Stem cell transplantation therapy.* In 2015, Rocheteau *et al* (33) used mouse models of SIM to perform the intramuscular mesenchymal stem cells transplantation after the mice developed septic shock. The experiment showed that the inflammation in the SIM mice was alleviated and the related symptoms improved, including fever, atrophy (loss of muscle tone), cytokine circulation and inflammatory molecules. Histological analysis following

the transplantation showed that mesenchymal stem cell transplantation provided support for the damaged satellite cells and mesenchymal stem cells successfully repaired mitochondrial dysfunction and completely restored the metabolic and division abilities of satellite cells. The application of autologous stem cells and allogeneic mesenchymal stem cells in the refractory myositis cases could alleviate the symptoms and improve the muscle strength (34), but there have been no reports on the treatment of SIM patients with mesenchymal stem cells.

### 3. Summary and prospects

Although the understanding of SIM has been continuously deepened, the treatment of SIM has made some progress. Currently there are no consensus or guidelines to follow. Early functional exercise has certain therapeutic effects. However, there is little clear evidence to guide therapists as for the optimal intensity, time and frequency of rehabilitation. The adjustment of nutritional structure and functional electrical stimulation need further confirmation. Although the treatment of mesenchymal stem cell transplantation has surprising results, further exploration is difficult. Drugs targeting the regulation of the ubiquitin-proteasome system, autophagy-lysosome system, calpain and caspase activation pathways, have provided potential therapeutic targets for the treatment of muscle atrophy. However, further experimental and clinical studies are needed and the adverse reactions and side effects also need to be further clarified. The pathogenesis of SIM is complex and targeting the key links of the pathogenesis of SIM can provide the basis for exploring new targets for drug treatment. The treatment of SIM needs more clinical research to further explore.

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### Authors' contributions

QX and DZ wrote the manuscript. LD revised the manuscript and was in charge of the project. JZ, HW and RS performed literature search and translation. All authors read and approved the final manuscript. Data authentication is not applicable.

### Ethics approval and consent to participate

Not applicable.

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## Competing interests

The authors declare that they have no competing interests.

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