Post-print of Expert Consensus on Ulinastatin for Common Acute and Critical Illnesses in Clinical Practice

Authors: Expert Group of the Expert Consensus on Ulinastatin for Common Clinical Acute and Critical Illnesses

Date: 2023-06-07T00:00:00+00:00

Abstract

Ulinastatin exerts inhibitory effects on proteolytic enzymes and modulates inflammatory responses. Currently, it is primarily indicated for acute pancreatitis, but has also been applied in other clinically common acute and critical conditions including shock, sepsis, severe pneumonia, acute respiratory distress syndrome, various acute poisonings, severe heatstroke, severe burns, severe trauma, as well as in cardiac arrest patients. Moreover, it has been recommended by multiple guidelines and expert consensuses pertaining to the management of clinically common acute and critical illnesses. However, unified opinions regarding its indications, usage, and dosage are currently lacking. Therefore, to promote the standardized application of ulinastatin, the Expert Consensus Group for "Ulinastatin in Clinically Common Acute and Critical Conditions" has compiled and summarized its mechanism of action, pharmacokinetics, indications, and application methods in common acute and critical conditions, aiming to provide a reference for the rational clinical use of ulinastatin.

Full Text

Preamble

Expert Consensus on the Application of Ulinastatin in Common Clinical Critical Illnesses

Expert Group for the Consensus on Ulinastatin Application in Common Clinical Critical Illnesses

Abstract Ulinastatin, which inhibits proteolytic enzymes and regulates inflammatory responses, is primarily used for acute pancreatitis but has also been applied in other common clinical critical conditions including shock, sepsis, severe pneumonia, acute respiratory distress syndrome (ARDS), various acute

poisonings, severe heat stroke, severe burns, severe trauma, and cardiac arrest patients. It has been recommended by multiple guidelines and expert consensus documents related to the diagnosis and treatment of these conditions. However, consensus regarding its indications, usage, and dosage remains lacking. To promote standardized application, the expert group has summarized ulinastatin's mechanisms of action, pharmacokinetics, indications, and application methods in common critical illnesses to provide a reference for its rational clinical use.

[**Keywords**] Emergency and critical diseases; Ulinastatin; Expert consensus; Acute pancreatitis; Shock; Sepsis; Severe pneumonia; Acute respiratory distress syndrome; Acute poisoning; Severe heat stroke; Severe burns; Severe trauma; Cardiac arrest

[**Chinese Classification Numbers**] R 605.975; R 926
[**Document Code**] A
DOI: 10.12114/j.issn.1007-9572.2023.0157

International Practice Guideline Registration Number: IPGRP-2022CN400

Corresponding Authors:
PAN Longfei, Associate Chief Physician/Associate Professor; E-mail: panlonf@yeah.net
ZHANG Guoqiang, Chief Physician/Professor; E-mail: zhangchong2003@vip.sina.com
MA Yuefeng, Chief Physician; E-mail: 2193017@zju.edu.cn
PEI Honghong, Chief Physician; E-mail: 18991237562@163.com

Digital Publication Date: 2023-05-25

Ulinastatin is extracted from fresh urine of healthy individuals and possesses multiple therapeutic effects including inhibition of various proteolytic enzymes, stabilization of lysosomal membranes, protection of vascular endothelium, improvement of microcirculation, reduction of apoptosis, regulation of inflammatory responses, and modulation of immune function. While widely used for acute pancreatitis, its application has recently expanded to other common critical conditions such as shock, sepsis, severe pneumonia, ARDS, various acute poisonings, severe heat stroke, severe burns, and severe trauma, with good therapeutic outcomes. It has also been used in cardiac arrest patients.

Currently, although various professional societies' guidelines and expert consensus documents for these critical illnesses recommend ulinastatin, divergent opinions remain regarding its indications, standardized application, and dosage, with a lack of comprehensive recommendations for its rational clinical use. Therefore, the Expert Group for the Consensus on Ulinastatin Application in Common Clinical Critical Illnesses has organized and developed this consensus to provide guidance for the rational application of ulinastatin in clinical practice.

1. Development Methodology

This expert consensus was developed using the consensus conference method. The editorial board of *Chinese Journal of Emergency Medicine* organized experts from emergency medicine, critical care medicine, clinical pharmacy, and other fields to form the expert group. After identifying target diseases from common critical illnesses, the group conducted three online discussion sessions and multiple rounds of correspondence review, focusing on key clinical questions regarding ulinastatin application. The process involved repeated discussions and revisions based on domestic and international research progress, guidelines, and expert consensus documents.

Following finalization, expert group members voted online on all recommendations using a Likert scale (1 = strongly not recommended, 2 = not recommended, 3 = consider recommending, 4 = recommend, 5 = strongly recommend), with the mean score determining the final recommendation strength.

The consensus structure is shown in Figure 1 [Figure 1: see original paper].

Literature Search Strategy: Databases searched included PubMed, Medline, Embase, Cochrane Library, Wanfang Data, and CNKI, with search period up to December 31, 2022.

2. Mechanism of Action and Pharmacokinetics

2.1 Mechanism of Action

Ulinastatin is a urinary trypsin inhibitor and a naturally occurring human serine protease inhibitor composed of two tandem Kunitz domains that provide broad-spectrum enzyme inhibition. Its mechanisms include five main aspects:

(1) **Protease Inhibition:** The Kunitz domains bind to serine structures of various proteases including hydrolases, trypsin, elastase, α-chymotrypsin, hyaluronidase, plasmin, and myeloperoxidase, thereby antagonizing their activity and reducing tissue/organ damage caused by these proteases during inflammatory responses [1].

(2) **Inflammatory Response Regulation:** Ulinastatin downregulates pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 while upregulating anti-inflammatory cytokines IL-10 and IL-13 by inhibiting Toll-like receptor 4 (TLR4)/nuclear factor kappa-B (NF- B) pathway activation, thereby blocking inflammatory cascade amplification and excessive inflammatory responses [2-4]. Endogenous ulinastatin can be rapidly consumed during inflammatory reactions.

(3) **Lysosomal Membrane Stabilization and Apoptosis Reduction:** Ulinastatin stabilizes lysosomal membranes for cytoprotection and inhibits apoptosis by downregulating caspase-3 expression and reducing the Bax/Bcl-2 ratio, thereby improving histopathological status [5-6].

(4) **Vascular Endothelium Protection and Microcirculation Improvement:** Ulinastatin improves vascular permeability and microcirculation by upregulating protein kinase B and endothelial nitric oxide synthase expression, increasing nitric oxide concentration and endothelial progenitor cell angiogenic capacity, while also correcting intrinsic apoptosis signals and inhibiting oxidative and inflammatory damage to vascular endothelial cells [7].

(5) **Immune Function Modulation:** Ulinastatin inhibits lymphocyte apoptosis and modulates lymphocyte subset ratios to exert immunomodulatory effects [8-9].

2.2 Pharmacokinetics

Ulinastatin in blood does not bind to plasma proteins and is primarily metabolized and excreted by the kidneys. In healthy males, blood concentration declines linearly within 3 hours after intravenous injection, with an elimination half-life of 40 minutes. Approximately 24% of ulinastatin is excreted in urine within 6 hours after intravenous administration.

3. Clinical Applications

3.1 Application in Acute Pancreatitis

Recommendation 1: For acute pancreatitis, especially severe acute pancreatitis (SAP), early application of ulinastatin (within 1 week of onset) is recommended on the basis of standard treatment (Recommendation Strength Score: 4.5).

Recommended Dosage: 100,000–200,000 U per dose, 1–3 times daily, intravenous infusion/bolus; dosage may be adjusted according to disease severity.

Abnormal activation of pancreatic enzymes causing pancreatic injury, inflammatory factor cascade release, amplified inflammatory responses, and uncontrolled inflammatory balance leading to other organ injuries and even multiple organ dysfunction are important mechanisms in the development of SAP. Ulinastatin broadly inhibits pancreatic enzyme release and activity related to acute pancreatitis progression, reducing complications. Multiple Chinese guidelines for acute pancreatitis recommend early and adequate ulinastatin use, with 200,000 U per dose, 3 times daily for SAP patients, with possible dose escalation for severe inflammatory responses [10-13].

HE et al. [14] retrospectively analyzed 130 SAP patients and found that ulinastatin improved clinical outcomes in a dose-dependent manner: patients receiving 400,000 U/d had shorter abdominal pain duration than those receiving 200,000 U/d, while those receiving 600,000 U/d had lower APACHE II scores than those receiving 200,000 U/d. ABRAHAM et al. [15] conducted a multicenter RCT (n=129) across 15 centers, finding that ulinastatin (200,000 U per dose, every

12 hours for 5 days) reduced new-onset organ dysfunction (34.3% vs. 90.6%) and 22-day all-cause mortality (2.8% vs. 18.7%) compared to placebo. LAGOO et al. [16] confirmed these findings in a retrospective study. MA et al. [17] performed a meta-analysis of 33 RCTs (n=1,786) showing that ulinastatin effectively reduced mortality in SAP patients.

3.2 Application in Shock

Recommendation 2: For shock patients, early application of ulinastatin is recommended (Recommendation Strength Score: 4.1).

Recommended Dosage: 100,000 U per dose, 1–3 times daily, intravenous infusion/bolus; dosage may be adjusted based on age and symptoms.

During shock, reduced effective circulating blood volume and acute microcirculatory hypoperfusion lead to vital organ dysfunction, metabolic disturbances, and structural damage. Activated inflammatory cells and excessive release of inflammatory and humoral factors create a "cascade effect" that exacerbates multi-organ injury [18-19]. Since excessive inflammatory responses critically contribute to organ dysfunction progression to multiple organ failure (MOF), early anti-inflammatory therapy to block inflammatory cascades is particularly important [19-20].

PARK et al. [21] found in an RCT that ulinastatin (100,000 U per dose, every 8 hours for 7 days) effectively reduced neutrophil elastase (NE) levels at 48 hours in trauma-hemorrhagic shock patients; NE causes tissue injury and activates pro-inflammatory factors like TNF-α. HE et al. [22-23] conducted meta-analyses on hemorrhagic shock (7 studies) and hypovolemic shock (13 studies), finding that early ulinastatin use (preoperative: 100,000–300,000 U per dose or 10,000 U/kg; postoperative days 2–7: 100,000–300,000 U per dose, 2–3 times daily) effectively reduced IL-6 and IL-8 levels and improved hepatic/renal function. WANG et al. [24] confirmed these findings. ZHAO et al. [25] retrospectively analyzed 128 trauma shock patients and found that ulinastatin (300,000 U per dose, 3 times daily for 7 days) ameliorated coagulation dysfunction in mild-to-moderate trauma shock.

FU et al. [26] studied 40 septic shock patients and found that ulinastatin (100,000 U per dose, every 8 hours for 5 days) reduced TNF-α, IL-6, and malondialdehyde (MDA) levels while increasing superoxide dismutase (SOD). DONG et al. [27] conducted a retrospective cohort study (n=182) showing that ulinastatin (200,000 U per dose, once daily for 7 days) reduced blood lactate, extravascular lung water index, pulmonary vascular permeability index, APACHE II score, and sequential organ failure assessment score while improving systemic vascular resistance index, cardiac output, left ventricular ejection fraction, and stroke volume.

3.3 Application in Sepsis

Recommendation 3: For sepsis patients, ulinastatin application is recommended on the basis of conventional treatment (Recommendation Strength Score: 4.3).

Recommended Dosage: 100,000–300,000 U per dose, 3 times daily, intravenous infusion/bolus.

Infection triggers inflammatory cascade amplification and pro-/anti-inflammatory imbalance, leading to organ injury and sepsis. Animal studies show ulinastatin reduces IL-6 and TNF-α while increasing IL-10 and IL-13, protecting organ function through inflammatory and oxidative stress regulation [4,28]. It also protects intestinal barrier integrity [29], reduces hepatic inflammatory cell infiltration [30], improves pulmonary capillary permeability [31], protects renal function by inhibiting autophagy and maintaining vascular endothelial cadherin expression [32], and improves sepsis-induced cardiac dysfunction by inhibiting cardiomyocyte autophagy [33]. Chinese sepsis consensus documents recommend ulinastatin (200,000 U per dose, every 8 hours) to improve tissue perfusion, microcirculation, and reduce organ injury [34-35].

MENG et al. [36] retrospectively studied 130 severe sepsis patients and found that ulinastatin (200,000 U per dose, 3 times daily for 3 days, then 100,000 U per dose, 3 times daily for 3 days) increased CD3+ and CD4+ cell ratios, improved APACHE II and MOF scores, and Glasgow Coma Scale scores without increasing adverse reactions. WANG et al. [37] performed a meta-analysis of 13 RCTs and 2 prospective studies (n=1,358), showing that ulinastatin (100,000–300,000 U per dose, every 8–12 hours for 5–8 days, or 5,000 U/kg every 12 hours for 5 days, or 1,000,000 U per dose once daily) reduced serum IL-6 and TNF-α, APACHE II score, MODS incidence [OR=0.30, 95%CI(0.18,0.49), P<0.001], and all-cause mortality [OR=0.48, 95%CI(0.35,0.66), P<0.001] while increasing IL-10 levels, without significant adverse reactions. KARNAD et al. [38] conducted a multicenter RCT (n=114) across 7 centers, finding that ulinastatin (200,000 U per dose, every 12 hours for 5 days) reduced new-onset organ failure (18.18% vs. 44.07%) and 28-day mortality (7.3% vs. 20.3%), increased ventilator-free days, and shortened hospital stay, confirming ulinastatin as an independent protective factor for 28-day mortality [OR=0.26, 95%CI(0.07,0.95), P=0.042]. XU et al. [39] found that ulinastatin [200,000 U per dose (standardized), 3 times daily] reduced 28-day mortality in severe sepsis patients.

3.4 Application in Severe Pneumonia

Recommendation 4: For severe pneumonia patients, ulinastatin application is recommended on the basis of conventional treatment (Recommendation Strength Score: 3.8).

Recommended Dosage: 200,000 U per dose, 2–3 times daily, intravenous

infusion/bolus.

Severe pneumonia patients often have immune dysfunction, and bacterial endotoxins further promote inflammatory mediator release through cascade reactions, inducing systemic inflammatory response syndrome (SIRS) and disease progression [40]. Animal studies show ulinastatin reduces serum IL-6 and IL-8 while increasing IL-10 in a rat model of severe pneumonia induced by intratracheal Klebsiella pneumoniae inoculation, demonstrating its regulatory effect on inflammation [41].

ZHANG et al. [42] studied 97 elderly severe pneumonia patients and found that ulinastatin (250,000 U per dose, twice daily for 14 days) reduced IL-1β, IL-6, TNF-α, and high-sensitivity C-reactive protein levels while improving blood gas analysis and pulmonary function parameters (FEV1, FVC, and FEV1/FVC ratio). GAO et al. [43] retrospectively analyzed 150 severe pneumonia patients and found that ulinastatin (200,000 U per dose, twice daily for 7 days) reduced inflammatory responses and surfactant proteins (SP-A, SP-B, SP-C, SP-D), improving pulmonary function indicators including peak expiratory flow, maximum mid-expiratory flow, maximal expiratory pressure, and maximal inspiratory pressure. SHE et al. [44] performed a meta-analysis of 15 RCTs (n=1,373), finding that combined ulinastatin (200,000 U per dose, 2–3 times daily for 7–10 days) effectively increased oxygenation index and shortened mean hospital stay.

3.5 Application in ARDS

Recommendation 5: For ARDS patients, ulinastatin may be considered on the basis of conventional treatment (Recommendation Strength Score: 3.8).

Recommended Dosage: 200,000 U per dose, 3 times daily, intravenous infusion/bolus; dosage may be adjusted based on age and symptoms.

Overwhelming inflammatory responses in acute pancreatitis, shock, severe pulmonary/systemic infection, poisoning, burns, severe trauma, and major surgery can damage alveolar epithelial cells and pulmonary microvascular endothelial cells, increase vascular permeability, and trigger ARDS [45]. Animal studies show ulinastatin reduces inflammation in a two-hit ARDS porcine model (smoke and MRSA-induced), improves transmembrane fluid exchange and alveolar-capillary permeability, inhibits pulmonary edema, and improves hemodynamics and gas exchange in a dose-dependent manner [46].

ZHANG et al. [47] conducted a meta-analysis of 33 Chinese RCTs (n=2,344) on ulinastatin for ARDS, showing that it (minimum 30,000 U per dose, 4 times daily; maximum 2,000,000 U per dose, twice daily; treatment duration 3–12 days) reduced serum inflammatory factors (TNF-α, IL-1β, IL-6, IL-8), respiratory rate, ventilator-associated pneumonia incidence [RR=0.50, 95%CI(0.36,0.69), P<0.001], and mortality [RR=0.51, 95%CI(0.43,0.61), P<0.001], while increasing oxygenation index and shortening mechanical ventilation, ICU, and total hospital stay. LENG et al. [48] performed a

meta-analysis of 29 RCTs (n=1,726) on ulinastatin for acute lung injury (ALI)/ARDS, showing it (minimum 50,000 U per dose once daily; maximum 600,000 U per dose, 4 times daily; treatment 2–10 days) improved oxygenation, reduced ICU mortality [RR=0.48, 95%CI(0.38,0.59), P<0.001], and shortened ICU stay. LI et al. [49] conducted a randomized double-blind trial (n=56) comparing ulinastatin (total 600,000 U/d) with methylprednisolone (120 mg/d), finding ulinastatin improved oxygenation and hemodynamics at day 7 while reducing patient mortality (28.57% vs. 42.86%), shortening hospital stay, and preventing complications like stress ulcers and hyperglycemia.

3.6 Application in Acute Poisoning

3.6.1 Acute Paraquat Poisoning Recommendation 6: For acute paraquat poisoning patients, early combined application of ulinastatin may be considered on the basis of conventional treatment (Recommendation Strength Score: 3.6).

Recommended Dosage: 200,000–300,000 U per dose, twice daily, intravenous infusion/bolus.

Although paraquat sales and use have been completely banned in China since 2020 due to high lethality and poor prognosis, sporadic cases still occur clinically. Molecular mechanisms of organ injury include redox cycling, intracellular oxidative stress, and pro-/anti-inflammatory imbalance causing cell damage, apoptosis, and autophagy [50-51]. Cellular and animal studies show ulinastatin reduces oxidative stress and type II alveolar epithelial cell injury [52] and decreases renal cell apoptosis [53].

LUO et al. [54] retrospectively analyzed 158 acute paraquat poisoning patients and found that ulinastatin (300,000 U per dose once daily or 200,000 U per dose twice daily for 7 days) prolonged survival, while higher doses (300,000 U per dose twice daily for 7 days) reduced 28-day ARDS, pulmonary fibrosis, MODS incidence, and mortality (24.2% vs. 41.4%). LIU et al. [55] retrospectively studied 392 patients with propensity score matching (n=124), finding ulinastatin (200,000 U per dose twice daily for 7 days) reduced TNF-α, IL-6, fibrosis markers (type IV collagen, ICAM-1, MMP-9), increased SOD, and decreased pulmonary fibrosis, hepatic/renal injury, and mortality (38.70% vs. 56.45%). FENG et al. [56] performed a meta-analysis of 7 case-control studies (n=400), showing ulinastatin (200,000–300,000 U per dose twice daily for 3–10 days) reduced mortality [OR=0.48, 95%CI(0.32,0.71), P<0.001] and pulmonary fibrosis incidence [OR=0.44, 95%CI(0.21,0.90), P=0.02].

3.6.2 Severe Acute Organophosphorus Pesticide Poisoning (AOPP) Recommendation 7: For severe AOPP patients, early combined application of ulinastatin may be considered on the basis of conventional treatment (Recommendation Strength Score: 3.6).

Recommended Dosage: 100,000–400,000 U per dose, 3 times daily, intravenous infusion/bolus.

Beyond neurotoxicity and acetylcholinesterase inhibition, AOPP-induced inflammatory and oxidative stress damage play important roles in neurotoxicity. Non-neural cells including pancreatic α-cells, endothelial cells, and lymphocytes expressing cholinergic components are also AOPP targets [57-59].

Studies show ulinastatin (200,000 U per dose, twice daily for 7–10 days or 200,000 U per dose, 3 times daily for 5 days) reduces TNF-α and IL-6 levels [60-61], alleviating organ injury [62]. JING et al. [63] and LIU et al. [64] confirmed that ulinastatin (100,000 U per dose, 2–3 times daily for 7 days) increased cholinesterase activity and accelerated recovery while reducing complications. SU et al. [65] confirmed in a prospective non-RCT (n=72) that ulinastatin (400,000 U per dose, 3 times daily for 7 days) combined with hemoperfusion and hemodialysis caused no drug-related adverse reactions. XU et al. [66] found ulinastatin (400,000 U per dose, 3 times daily for 7 days) reduced myocardial injury markers (cTnT, CK-MB, LDH) and liver function indicators (AST, ALT, γ-GT), decreased alveolar-arterial oxygen gradient and SP-A/SP-B levels, and increased maximal inspiratory pressure.

3.6.3 Severe Acute Carbon Monoxide Poisoning (ACOP) Recommendation 8: For severe ACOP patients, early combined application of ulinastatin may be considered on the basis of conventional treatment (Recommendation Strength Score: 3.4).

Recommended Dosage: 100,000–300,000 U per dose, 3 times daily, intravenous infusion/bolus.

In ACOP, carbon monoxide competitively binds hemoglobin causing tissue hypoxia, binds myoglobin causing cardiac dysfunction, and binds mitochondrial cytochrome C oxidase causing energy metabolism 障碍, oxidative stress, and inflammatory cascade reactions that damage heart and nerves [67-68]. Excess carbon monoxide also activates platelets to release myeloperoxidase (MPO), triggering oxidative damage and inflammatory cascade amplification.

LI [69] found ulinastatin (300,000 U per dose, 3 times daily for 5 days) inhibited TNF-α and IL-6 elevation. YANG et al. [70] prospectively studied 96 severe ACOP patients with cardiac injury requiring invasive mechanical ventilation who couldn't receive hyperbaric oxygen therapy, finding ulinastatin (100,000 U per dose, every 8 hours for 7 days) shortened coma time and improved cardiac function indicators (LVEF, LVEDD, LVFS) and CK-MB levels. WANG et al. [71] found ulinastatin (100,000 U per dose, every 8 hours for 14 days) reduced 14-day ECG abnormalities (4.84% vs. 11.48%) and mortality (1.61% vs. 6.56%).

3.7 Application in Severe Heat Stroke

Recommendation 9: For severe heat stroke patients, early combined application of ulinastatin may be considered on the basis of conventional treatment (Recommendation Strength Score: 3.8).

Recommended Dosage: 100,000–200,000 U per dose, 2–3 times daily, intravenous infusion/bolus.

During severe heat stroke, inflammatory factors including IL-1β, IL-6, and IL-10 participate in SIRS, significantly impacting MODS development and tissue recovery [72]. Animal studies show ulinastatin reduces inflammatory factor release in rhabdomyolysis rat models and improves renal function [73]; attenuates intestinal mucosal barrier injury in mouse models [74]; and reduces hypothalamic neuronal apoptosis, improving heat tolerance [75].

LI et al. [76] found ulinastatin (200,000 U per dose, every 12 hours for 5 days) exerted lung protective effects by reducing hypoxia-inducible factor 1α and macrophage migration inhibitory factor levels in peripheral blood and bronchoalveolar lavage fluid. CHEN et al. [77] prospectively studied 90 severe heat stroke patients requiring mechanical ventilation, finding ulinastatin (200,000 U per dose, twice daily for 5 days) reduced IL-6 and TNF-α levels in bronchoalveolar lavage fluid and alveolar macrophage culture supernatants at days 3 and 5, improved oxygenation index, reduced Murray lung injury score, and shortened mechanical ventilation and ICU stay. YE et al. [78] and TONG et al. [79] confirmed these findings. HAN et al. [80] verified that ulinastatin (100,000 U per dose, every 8 hours for 7 days) combined with continuous blood purification (CBP) attenuated vascular endothelial injury in heat stroke patients. LU et al. [81] confirmed that ulinastatin (100,000 U per dose, 3 times daily for 7 days) combined with CBP improved MODS recovery, survival, and reduced mortality.

3.8 Application in Severe Burns

Recommendation 10: For severe burn patients, early combined application of ulinastatin may be considered on the basis of conventional treatment (Recommendation Strength Score: 3.8).

Recommended Dosage: 100,000–600,000 U per dose, 2–4 times daily, intravenous infusion/bolus; dosage may be adjusted based on age and symptoms.

Burn patients experience thermal skin/soft tissue injury with massive release of inflammatory mediators and reactive oxygen species from lipid peroxidation, causing increased microvascular permeability, fluid extravasation, tissue hypoperfusion, and direct organ injury from overactivated inflammatory responses [82]. Shock, MOF, and sepsis are common causes of death. Animal studies show ulinastatin reduces lipid peroxidation and resuscitation fluid requirements in porcine burn models [83]; attenuates myocardial injury in severe burn rats by inhibiting systemic and myocardial inflammation and oxidative stress [84]; improves pulmonary microvascular permeability and oxygenation by inhibiting

pulmonary NE and MPO release [85]; and reduces systemic inflammation and MPO levels while improving vascular permeability and water content in heart, lung, kidney, and small intestine [86]. *Burn Medicine* recommends ulinastatin (600,000 U per dose, 4 times daily) for severe burns to reduce inflammation [87].

HUANG et al. [88] conducted an open prospective study (n=34) showing ulinastatin (100,000 U per dose, 3 times daily for 7 days) improved cTnI and CK-MB levels. SHI et al. [89] confirmed that ulinastatin (100,000 U or 400,000 U per dose, 3 times daily for 12 days) reduced serum TNF-α and SIRS incidence while increasing IL-10, with higher doses showing superior efficacy. LI et al. [90] found ulinastatin (800,000 U per dose, twice daily for 7 days) modulated immune function by regulating CD4+CD25+ regulatory T-cell proportions and CD14+ monocyte HLA-DR expression. ZHENG [91] studied 330 burn patients, finding ulinastatin (100,000 U or 200,000 U per dose, every 8 hours for 7 days) reduced wound sepsis incidence (9.09% low-dose, 5.45% high-dose vs. 15.45% control), shortened wound healing and hospital stay, with higher doses being more effective. ABHYANKAR et al. [92] retrospectively studied 97 patients with 41–80% total body surface area burns, finding that ulinastatin (100,000 U per dose, every 8–12 hours, mean 8.8 days) significantly reduced mortality (50.00% vs. 77.27%).

3.9 Application in Severe Trauma

Recommendation 11: For severe trauma patients, early combined application of ulinastatin may be considered on the basis of conventional treatment (Recommendation Strength Score: 3.6).

Recommended Dosage: 100,000–300,000 U per dose, 2–3 times daily, intravenous infusion/bolus.

Severe trauma patients develop immune suppression with paradoxical pro-inflammatory responses, leading to escalating systemic and organ-specific inflammation, immune-inflammatory imbalance, organ injury, MODS, and death [93]. Ulinastatin improves immune suppression and regulates inflammatory responses [94]. Animal studies show it reduces brain IL-1β, IL-6, TNF-α, NF- B levels and oxidative stress, decreases hippocampal apoptosis, and improves post-traumatic brain injury edema and neurological function [95]; reduces bronchoalveolar lavage neutrophil count and TNF-α in pulmonary contusion models, alleviating inflammation and oxidative stress [96].

LIU et al. [97] found early ulinastatin (100,000 U per dose, 3 times daily for 7 days) increased CD3+, CD4+, and CD4+/CD8+ ratios, promoted T-cell subset recovery, reduced IL-6 and TNF-α, shortened ICU and total hospital stay, and reduced complications (10% vs. 40%). Other studies show ulinastatin (400,000 U per dose, twice daily for 7 days) improves coagulation function and reduces MODS incidence and 30-day mortality in trauma-induced coagulopathy [98-99]. DU et al. [100] found ulinastatin (200,000 U per dose, twice daily for 7 days) reduced CRP, IL-6, endothelin, and gastrointestinal bleeding

incidence (24.39% vs. 45.65%) while increasing SOD in severe craniocerebral injury patients. HUI et al. [101] conducted an RCT (n=92) showing ulinastatin (200,000 U per dose, twice daily for 7 days) improved cerebral oxygen metabolism, reduced 30-day gastrointestinal bleeding (23.91% vs. 43.48%) and mortality (17.39% vs. 32.61%). DUAN et al. [102] meta-analyzed 7 RCTs (n=395), finding ulinastatin (100,000–300,000 U per dose, 1–2 times daily for 5–7 days) improved oxygenation and respiratory function, reducing ARDS incidence [OR=0.34, 95%CI(0.20,0.60), P<0.05] and mortality [OR=0.31, 95%CI(0.15,0.65), P<0.05].

3.10 Application in Cardiac Arrest

Recommendation 12: For cardiac arrest patients, early application of ulinastatin is recommended after return of spontaneous circulation (ROSC) on the basis of conventional treatment (Recommendation Strength Score: 3.5).

Recommended Dosage: 200,000 U per dose, twice daily, intravenous bolus; dosage may be adjusted based on age and symptoms.

During cardiac arrest, tissue ischemia-hypoxia and post-ROSC reperfusion injury, immune dysregulation, inflammatory responses, and oxidative stress cause microcirculatory and organ damage, particularly brain and cardiac dysfunction, severely affecting survival quality [103-105]. HAYAKAWA et al. [106] prospectively studied 36 out-of-hospital cardiac arrest patients with ROSC, finding NE levels correlated with arrest duration, while endogenous urinary trypsin inhibitor synthesis was insufficient, suggesting deficiency may contribute to post-resuscitation syndrome.

Animal studies show post-ROSC ulinastatin reduces serum TNF-α, IL-6, and cerebral cortex MPO/MDA levels, protects surviving neurons, and inhibits apoptosis in ventricular fibrillation rat models [107]; improves LVEF, LVFS, and E/A ratio in asphyxial cardiac arrest rat models [108]; and reduces serum IL-6, TNF-α, and multi-organ apoptosis in traumatic cardiac arrest porcine models [109].

HUANG et al. [110] confirmed that ulinastatin (200,000 U per dose, every 12 hours for 8 doses) after CPR and advanced life support reduced serum TNF-α and IL-6, improved myocardial enzymes and hepatic/renal function, reduced SIRS incidence and mortality, with better outcomes than delayed administration. MA et al. [111] found immediate post-ROSC ulinastatin (200,000 U per dose, twice daily for 7 days) improved GCS scores in elderly patients with ROSC within 10 minutes. LU et al. [112] found immediate post-ROSC ulinastatin (200,000 U per dose, every 12 hours for 3 days) improved myocardial enzymes, liver function, and lactate in patients with ROSC >10 minutes, but didn't improve 72-hour MODS incidence or final survival. HU et al. [113] found immediate high-dose ulinastatin (500,000 U per dose, every 12 hours) improved myocardial enzymes, liver/renal function, lactate, and MODS severity in patients with ROSC >10 minutes and MODS, but didn't improve 28-day neurological scores

or mortality. ZHANG et al. [114] found immediate ulinastatin (200,000 U or 400,000 U per dose, twice daily) reduced 72-hour TNF-α, IL-6, 28-day MODS incidence and mortality, and promoted IL-4/IL-10 recovery, with higher doses being more effective.

The recommendations and dosages for ulinastatin in common critical illnesses are summarized in Figure 2 [Figure 2: see original paper].

4. Safety and Adverse Reactions

Studies show high-dose ulinastatin may cause diarrhea, but patients tolerate it well with spontaneous resolution [115]. CHEN et al. [9] conducted a tolerability trial showing only 8 transient, mild adverse events (dizziness, injection site pain, leukopenia) among 42 patients, with no serious or withdrawal events. Clinical practice occasionally reveals leukopenia, eosinophilia, liver dysfunction (elevated AST/ALT), allergic symptoms, nausea, vomiting, diarrhea, and injection site pain, redness, itching, or rash. Anaphylactic shock or significant leukopenia should be considered major adverse reactions requiring immediate discontinuation and active management.

5. Summary and Outlook

Ulinastatin's ability to inhibit multiple proteases and regulate inflammatory responses makes it a therapeutic option for acute pancreatitis, shock, sepsis, severe pneumonia, ARDS, acute poisonings, severe heat stroke, severe burns, severe trauma, and cardiac arrest. However, whether its effects are attributable to monotherapy or synergistic action with other treatments remains unclear and requires further investigation. Multi-center, prospective RCTs are needed to clarify optimal dosing regimens, mechanisms, efficacy, and safety across different diseases and stages.

Expert Group Members (in alphabetical order by surname):
CAI Wenwei (Zhejiang Provincial People's Hospital), ZENG Hongke (Guangdong Provincial People's Hospital), CHEN Xiaohui (The Second Affiliated Hospital of Guangzhou Medical University), CHEN Yuguo (Qilu Hospital of Shandong University), CHONG Wei (The First Affiliated Hospital of China Medical University), DU Junkai (The First Affiliated Hospital of Xi'an Jiaotong University), FAN Chuanbo (Qingdao University Affiliated Qingdao Haici Hospital), FANG Bangjiang (Longhua Hospital Shanghai University of Traditional Chinese Medicine), FENG Qiming (Shanghai Sixth People's Hospital), GONG Ping (Shenzhen People's Hospital), HE Xiaojun (Editorial Office of *Chinese Journal of Emergency Medicine*), HONG Yucai (Sir Run Run Shaw Hospital, Zhejiang University School of Medicine), HUANG Ye (Xiyuan Hospital, China Academy of Chinese Medical Sciences), JIANG Longyuan (Sun Yat-sen Memorial Hospital, Sun Yat-sen University), LI Peiwu (The Second Hospital of Lanzhou University), LI Wenfang (Shanghai Changzheng Hospital), LIANG Tengxiao (Dongzhimen Hospital, Beijing University of Chinese Medicine), LIU Guohui (The First

Hospital of Jilin University), LU Feifei (Editorial Office of *Chinese General Practice*), LU Xiaoguang (Affiliated Zhongshan Hospital of Dalian University), MA Qingbian (Peking University Third Hospital), MA Yuefeng (The Second Affiliated Hospital, Zhejiang University School of Medicine), MAO Enqiang (Ruijin Hospital, Shanghai Jiao Tong University School of Medicine), Muyesa · Nijiati (People's Hospital of Xinjiang Uygur Autonomous Region), PAN Longfei (The Second Affiliated Hospital of Xi'an Jiaotong University), PAN Shuming (Xinhua Hospital, Shanghai Jiao Tong University School of Medicine), PAN Xinting (The Affiliated Hospital of Qingdao University), PEI Qiao (Editorial Office of *Chinese Journal of Critical Care Medicine*), PEI Honghong (The Second Affiliated Hospital of Xi'an Jiaotong University), QIAN Kejian (The First Affiliated Hospital of Nanchang University), QIN Lijie (Henan Provincial People's Hospital), SONG Zhenju (Zhongshan Hospital, Fudan University), TONG Zhihui [Jinling Hospital (Eastern Theater General Hospital)], XIE Miaorong (Beijing Friendship Hospital, Capital Medical University), XING Jihong (The First Hospital of Jilin University), XU Ping (Zigong Fourth People's Hospital), YAO Yongming (Translational Medicine Research Center, Chinese PLA General Hospital), ZHAN Hong (The First Affiliated Hospital, Sun Yat-sen University), ZHANG Bin (Qinghai Provincial People's Hospital), ZHANG Guoqiang (China-Japan Friendship Hospital), ZHANG Kanghuai (The Second Affiliated Hospital of Xi'an Jiaotong University), ZHANG Silong (Editorial Office of *Chinese Journal of Emergency Medicine*), ZHANG Xinchao (Beijing Hospital), ZHAO Huimin (The Second Affiliated Hospital of Guangxi Medical University), ZHU Huadong (Peking Union Medical College Hospital), ZHU Jihong (The Second Affiliated Hospital of Soochow University)

Contributing Authors: NIU Zequn, HONG Xin, WANG Liming, PAN Longfei

Contributing Author Unit: Department of Emergency Medicine, The Second Affiliated Hospital of Xi'an Jiaotong University

Conflict of Interest Statement: All participants declare no conflicts of interest.

References

[1] QI Anlong, CHAI Yanfen, YAO Yongming. Cellular protective effects and mechanisms of ulinastatin in sepsis [J]. *National Medical Journal of China*, 2015, 95(39): 3235-3237. DOI: 10.3760/cma.j.issn.0376-2491.2015.39.019.

[2] LIU Xiaojun, ZENG Min, FU Xiuhong, et al. Protective effect of ulinastatin on sepsis-induced acute liver injury by inhibiting NF- B pathway [J]. *Liver*, 2019, 24(8): 918-920. DOI: 10.3969/j.issn.1008-1704.2019.08.024.

…

[115] LIU Yang, WANG Qian, ZHAO Huiying, et al. Tolerability study of high-dose ulinastatin in healthy Chinese adult volunteers [J]. *Chinese Journal of Clinical Pharmacology*, 2015, 31(21): 2111-2113. DOI: 10.13699/j.cnki.1001-6821.2015.21.008.

(Received: 2023-03-27; Revised: 2023-05-12)
(Editor: LU Feifei)

Note: Figure translations are in progress. See original paper for figures.