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Mini Review

Clinical Prospects of Ulinastatin in the ICU: Opportunities and Challenges—A Mini Review

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Abstract

Ulinastatin, a broad-spectrum serine protease inhibitor widely used in Asia, has attracted increasing interest for its potential role in critical care. This review summarizes current evidence on its efficacy and safety in acute pancreatitis, severe acute pancreatitis, sepsis, acute respiratory distress syndrome, and perioperative management in cardiac surgery with cardiopulmonary bypass. Meta-analyses suggest that ulinastatin may improve outcomes by reducing mortality, shortening intensive care unit and hospital stays, and attenuating inflammatory responses. In severe acute pancreatitis, its use has been associated with reduced mortality and shorter hospitalization. In sepsis and septic shock, ulinastatin appears to lower all-cause mortality, decrease organ dysfunction scores, and reduce inflammatory markers. Evidence in acute respiratory distress syndrome indicates improvements in the oxygenation index and possible mortality reduction. Perioperative administration during cardiac surgery may mitigate postoperative inflammation and shorten the duration of mechanical ventilation. Despite these encouraging findings, most available studies originate from Asia and are limited by small sample sizes, heterogeneous designs, and inconsistent dosing regimens, which restrict generalizability and prevent standardized recommendations. Additionally, although ulinastatin demonstrates a favorable safety profile with a low incidence of adverse drug reactions, long-term and multinational pharmacovigilance data remain limited. Well-designed international, multicenter randomized controlled trials are required to clarify optimal dosing strategies, confirm clinical efficacy across diverse populations, and determine its independent effects compared with combination therapies. Overall, ulinastatin shows promise as a potential adjunctive therapy in critical care through modulation of inflammation and organ protection, but broader global adoption will depend on higher-quality evidence addressing current methodological gaps.

Introduction

Ulinastatin, a broad-spectrum serine protease inhibitor, is predominantly utilized in Asia—particularly in China, Japan, South Korea, and India—for managing acute pancreatitis (AP) and severe acute pancreatitis (SAP). Its off-label applications in China extend to sepsis, acute respiratory distress syndrome (ARDS), and perioperative care during cardiac surgery with cardiopulmonary bypass (CPB).[1] While emerging evidence highlights its anti-inflammatory, immunomodulatory, and organ-protective properties, current research remains constrained by geographic bias, methodological inconsistencies, and a limited number of high-quality trials. This mini-review presents a narrative synthesis of recent clinical evidence regarding ulinastatin use in intensive care unit (ICU) settings, with an emphasis on meta-analyses, systematic reviews, and large-scale real-world studies to highlight both its therapeutic potential and existing evidence gaps.

We performed a focused literature search in PubMed, Web of Science, and Scopus using the terms "ulinastatin," "ICU," "critically ill patients," "guidelines," "meta-analysis," "systematic reviews," "real-world study," and "post-marketing surveillance." The search targeted studies addressing ulinastatin's emerging clinical applications, therapeutic efficacy, and safety concerns within intensive care settings. Eligible literature included peer-reviewed clinical guidelines, meta-analyses, systematic reviews, and real-world studies. Articles unrelated to ulinastatin's ICU applications were excluded. In this review, we primarily focused on evidence from clinical guidelines,

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systematic reviews, and meta-analyses to provide a comprehensive and up-to-date synthesis of ulinastatin use in critical care. Although randomized controlled trials (RCTs) exist, their findings have been largely synthesized in previous meta-analyses and therefore were not individually analyzed here. This concise review synthesizes current evidence to provide a comprehensive and up-to-date perspective on ulinastatin use in critical care.

Mechanism of action and pharmacokinetics

Ulinastatin is a broad-spectrum serine protease inhibitor that exerts multiple protective effects in critical illness. It inhibits proteases such as trypsin, elastase, α-chymotrypsin, hyaluronidase, and myeloperoxidase, thereby reducing protease-mediated tissue injury. Ulinastatin suppresses excessive inflammatory responses, downregulating pro-inflammatory cytokines while enhancing anti-inflammatory cytokines. It stabilizes lysosomal membranes, decreases caspase-3 activity, and attenuates apoptosis. Furthermore, ulinastatin protects vascular endothelial function by enhancing nitric oxide production and reducing oxidative and inflammatory damage, thereby improving microcirculation. It also modulates immune responses by preventing lymphocyte apoptosis and regulating lymphocyte subset distribution.[1]

Pharmacokinetically, ulinastatin does not bind to plasma proteins and is primarily metabolized and excreted via the kidneys. After intravenous administration in healthy males, plasma concentrations decline rapidly within 3 h, with an elimination half-life of approximately 40 min; around 24% of the dose is excreted in urine within 6 h.[1]

AP and SAP

SAP is a common and life-threatening condition in the ICU, often complicated by ARDS, acute kidney injury, or multiple organ dysfunction syndrome (MODS), necessitating intensive management. Ulinastatin has been widely explored as a potential therapeutic agent for AP and SAP. A meta-analysis based on RCTs suggested that the combination of ulinastatin with standard treatment significantly reduces mortality, improves the total effective rate, and shortens hospital stay compared with standard treatment alone. However, this conclusion is primarily drawn from studies conducted in China, with limited representation from other regions. The overall quality of the included RCTs was low due to inadequate allocation concealment and blinding, which might introduce selection and performance biases.[2]

Another meta-analysis based on cohort studies reported that ulinastatin significantly reduces serum C-reactive protein, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) levels in Asian patients with AP. Although these findings suggest an anti-inflammatory effect of ulinastatin, the included studies exhibited high heterogeneity, indicating potential inconsistencies in patient populations, treatment regimens, or measurement methodologies. Additionally, the studies predominantly relied on short-term inflammatory marker changes without long-term clinical outcome assessment.[3]

More recently, a comprehensive systematic review and meta-analysis evaluated the efficacy of ulinastatin in patients with SAP, incorporating both prospective and retrospective studies published up to December 2024. This analysis demonstrated a significant reduction in mortality associated with ulinastatin-based therapy, with concurrent improvements in inflammatory markers (including C-reactive protein, IL-6, and TNF-α) and faster resolution of abdominal pain. However, no statistically significant benefit was observed for hospital length of stay or Acute Physiology and Chronic Health Evaluation II scores, suggesting that biochemical and symptomatic improvements may not consistently translate into short-term severity score reduction. The certainty of evidence was rated as low, primarily due to the observational nature of the included studies, moderate to substantial heterogeneity, and methodological limitations in study comparability. Most studies originated from China and India, which may limit the generalizability of the findings to other regions due to differences in patient populations, healthcare systems, and clinical practices. In addition, variations in ulinastatin dosing regimens, treatment duration, and concomitant therapies limited the feasibility of subgroup and dose–response analyses. Potential publication bias was also suggested for mortality outcomes, further tempering confidence in the pooled estimates. Collectively, while this updated meta-analysis strengthens the signal that ulinastatin may confer mortality and anti-inflammatory benefits in SAP, the overall quality of evidence remains insufficient to support definitive, globally generalizable clinical recommendations.[4]

In Asian countries, particularly China and Japan, ulinastatin is frequently combined with somatostatin or its analog octreotide for treating AP and SAP. A meta-analysis demonstrated that this combination therapy significantly reduces the incidence of complications such as ARDS, MODS, and acute kidney injury compared with somatostatin or octreotide monotherapy. In addition, the combination therapy reduced the duration of abdominal pain and hospital stay. Nevertheless, the included studies were limited by small sample sizes, a lack of multinational validation, and potential publication bias, as studies with negative results may not have been published. Furthermore, the meta-analysis did not evaluate potential adverse effects or drug interactions, limiting its clinical applicability.[5]

A large-scale meta-analysis comparing ulinastatin plus octreotide with octreotide alone reported significant reductions in mortality, hospital stay, and inflammatory markers. Despite this, the evidence was classified as low quality due to the predominance of single-center studies, the absence of high-quality multicenter trials, and a lack of standardized dosing regimens. Furthermore, whereas statistical significance was observed for most outcomes, the clinical relevance of these improvements may remain uncertain, especially considering variations in treatment protocols across different institutions.[6]

In summary, clinical studies indicate that ulinastatin, whether used alone or in combination with somatostatin analogs, may exert beneficial effects on AP/SAP through its anti-inflammatory, anti-apoptotic, and immunomodulatory properties. Nevertheless, the overall certainty of evidence remains low, primarily due to methodological limitations and variability across studies.

Perioperative management during cardiac surgery with CPB

In recent years, the perioperative use of ulinastatin in cardiac surgery with CPB has increased, primarily to prevent complications and organ damage. A meta-analysis shows that ulinastatin can reduce pro-inflammatory cytokine levels and enhance anti-inflammatory cytokine levels in patients undergoing cardiac surgery with CPB. It also significantly lowers myocardial injury markers, intubation time, and mechanical ventilation duration (MVD), without increasing the frequency of spontaneous cardiac resuscitation after CPB. Nonetheless, despite these promising findings, the study's conclusions are limited by several factors, including the predominance of studies from East Asia, substantial heterogeneity

in dosing regimens, and the reliance on small, single-center studies with variable methodologies. Notably, the meta-analysis did not find statistically significant differences in hemodynamics, cardiac function, ICU stay, or postoperative complications.[7]

Similarly, a meta-analysis of RCTs examining the impact of ulinastatin on patients undergoing coronary artery bypass grafting found that ulinastatin reduces pro-inflammatory cytokines and boosts anti-inflammatory cytokines while improving respiratory function and the oxygenation index (OI). However, the included trials exhibited varying levels of methodological rigor, with some lacking proper randomization or blinding procedures. In addition, although improvements in inflammatory markers were observed, their direct correlation with long-term clinical outcomes remains unclear, as many studies focused solely on short-term biochemical changes without assessing overall patient survival, quality of life, or major postoperative complications.[8]

Earlier meta-analyses conducted between 2013 and 2015 also reported that intraoperative or perioperative ulinastatin reduced postoperative inflammatory cytokines and shortened extubation time or MVD but had no significant impact on ICU stay, hospital mortality, or major complications. These findings reinforce the notion that while ulinastatin exerts consistent anti-inflammatory and short-term protective effects, its influence on hard clinical outcomes remains inconclusive.[9,10]

Another meta-analysis incorporating 12 RCTs assessed the impact of ulinastatin on ICU stay, MVD, and renal failure incidence in CPB patients. The findings suggested that ulinastatin may reduce ICU stay and MVD, with some indication of a protective effect against renal failure. Nevertheless, significant heterogeneity was noted across studies, and the clinical significance of these reductions remains uncertain. Furthermore, the analysis failed to demonstrate a clear benefit of ulinastatin in reducing hospital stay or all-cause mortality. Importantly, the meta-analysis highlighted the lack of standardized dosing protocols for ulinastatin, raising concerns about the reproducibility of results and the feasibility of integrating ulinastatin into standardized perioperative management strategies.[11]

Cardiac surgery with CPB induces a systemic inflammatory response that negatively impacts clinical outcomes. While current evidence suggests that ulinastatin has potential benefits in modulating this response and reducing certain postoperative complications, its overall clinical efficacy remains uncertain, particularly given the inconsistency in clinical outcomes and variability in perioperative management across studies.

Sepsis and septic shock

A meta-analysis including 13 RCTs and two prospective studies suggests that ulinastatin significantly reduces all-cause mortality, lowers Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and decreases the incidence of MODS in patients with sepsis and septic shock. In addition, ulinastatin modulates the inflammatory response by reducing pro-inflammatory cytokines, such as IL-6 and TNF-α, while increasing anti-inflammatory cytokines, such as interleukin-10 (IL-10). However, the findings should be interpreted with caution due to several limitations. First, the included studies primarily originated from China and India, raising concerns about geographical bias and limiting generalizability to other populations with different healthcare systems. Second, although statistical improvements in mortality and inflammatory markers were observed, the overall sample size remains relatively small, and several included studies had methodological limitations, such as inadequate blinding, inconsistent control groups, and varying dosing regimens. Additionally, high heterogeneity in the reported outcomes, particularly in inflammatory marker levels, suggests variability in study designs and patient populations, making it difficult to establish standardized clinical recommendations.[12]

A recent systematic review focusing specifically on septic shock reported that ulinastatin significantly reduced mortality and MODS incidence, shortened ICU and hospital length of stay, and improved APACHE II and Sequential Organ Failure Assessment scores, alongside marked reductions in inflammatory markers. However, the evidence base is limited by the predominance of Chinese-language trials and modest sample sizes, with many studies lacking detailed randomization and blinding and having incomplete outcome reporting; several secondary outcomes also showed substantial heterogeneity. Signals of publication bias were detected for key cytokine outcomes, and adverse events were sparsely and inconsistently reported (only four RCTs, qualitative descriptions), further tempering confidence in the pooled estimates.[13]

A 2025 systematic review and meta-analysis evaluated the efficacy of adding ulinastatin to continuous blood purification (CBP) in patients with sepsis and septic shock. Across 34 studies, the combination therapy significantly reduced all-cause mortality and improved multiple inflammatory biomarkers. Nevertheless, these findings should be interpreted with caution. First, the included studies were geographically restricted to China and were mostly single-center with small sample sizes, limiting the generalizability of results. Second, there was considerable heterogeneity in cytokine outcomes, partly due to differences in ulinastatin dosing, CBP modalities, and relatively short treatment courses. Third, the pooling of RCTs and retrospective studies with inconsistent blinding, inadequate randomization, and incomplete outcome reporting may have introduced bias. Fourth, adverse events were rarely reported, and publication bias was detected, further tempering confidence in the findings. Additionally, the observed decrease in IL-10 might reflect nonselective cytokine removal by CBP and differences in sampling time points.[14]

Most recently, an umbrella review synthesizing evidence from multiple meta-analyses evaluated the effects of ulinastatin on clinical outcomes in patients with sepsis. This umbrella review included nine meta-analyses assessing ulinastatin alone or in combination with immunomodulatory agents such as thymosin α1 or Xuebijing, with outcomes including 28-day mortality, ICU stay, MVD, APACHE II score, and inflammatory biomarkers (IL-6 and TNF-α). Overall, the pooled evidence suggested that ulinastatin-based therapies—particularly when used in combination regimens—were associated with reductions in short-term mortality, ICU stay, MVD, and inflammatory marker levels. However, the methodological quality of the included meta-analyses was predominantly rated as low, and all underlying studies were conducted exclusively in China, raising substantial concerns regarding geographical bias and external validity. In addition, most favorable outcomes were driven by combination therapies, making it difficult to isolate the independent effect of ulinastatin. Considerable heterogeneity was observed across outcomes, and variations in dosing regimens, treatment duration, and concomitant interventions further limited comparability. Collectively, this umbrella review highlights that while ulinastatin may confer clinical benefits in sepsis—especially as part of combination therapy—the overall certainty of evidence remains limited, underscoring the need for high-quality, multinational RCTs to clarify its independent efficacy and generalizability.[15]

Taken together, current evidence indicates that ulinastatin, either alone or in combination with CBP, may improve clinical outcomes in sepsis and septic shock through modulation of the inflammatory response and reduction of organ dysfunction. However, these benefits are primarily supported by small, single-center studies with methodological limitations, underscoring the need for large, high-quality, multicenter trials to establish definitive recommendations.

ARDS

A meta-analysis encompassing 33 RCTs demonstrates that ulinastatin reduces mortality rates in ARDS patients, as well as the incidence of ventilator-associated pneumonia, MVD, ICU stay, and overall hospitalization time. Moreover, ulinastatin enhances the OI and lowers pro-inflammatory cytokine levels. These benefits of ulinastatin in ARDS may be attributed to its anti-inflammatory mechanisms. Despite this, several limitations should be noted. The included studies were primarily conducted in China, raising concerns about geographical bias and the applicability of findings to broader patient populations. In addition, although significant reductions in inflammatory markers were observed, the high heterogeneity in continuous outcomes, such as ICU stay and hospital stay, suggests variability in treatment protocols, patient populations, and supportive care measures. Moreover, most included studies were small-scale and had methodological limitations, such as inadequate blinding, inconsistent dosing regimens, and a lack of long-term follow-up, limiting the strength of the conclusions.[16]

Acute lung injury, previously used to describe milder forms of lung injury, has now been incorporated into the broader definition of ARDS according to the Berlin criteria.[17] A systematic review and meta-analysis of 29 randomized trials in acute lung injury/ARDS found that ulinastatin significantly improved the OI, reduced ICU mortality, and shortened ICU stay, while 28-day mortality was not significantly different between groups. Despite these benefits, several limitations warrant caution: trials were almost exclusively conducted in China, typically small and single-center, with generally low methodological quality (limited reporting of randomization, allocation concealment, and blinding), no systematic adverse-event reporting, and substantial heterogeneity in continuous outcomes; funnel plots also suggested publication and language bias.[18]

In addition to ulinastatin monotherapy, recent evidence has explored its use in combination with continuous renal replacement therapy (CRRT) in ARDS. A systematic review and meta-analysis of RCTs involving 384 patients demonstrated that, compared with CRRT alone, the combination of ulinastatin and CRRT significantly reduced mortality, shortened ICU stay and MVD, and improved disease severity (as reflected by APACHE II scores), as well as oxygenation parameters including the OI and partial pressure of oxygen (PaO_2). However, these findings should be interpreted with caution. The included studies were small, single-center trials conducted exclusively in China, with limited methodological rigor and absence of detailed reporting on CRRT modalities. In addition, the lack of safety data and long-term outcomes further limits the strength of the evidence. Despite these limitations, the observed improvements suggest a potential synergistic effect of combining ulinastatin with extracorporeal blood purification strategies in ARDS.[19]

Beyond ARDS, a systematic review and meta-analysis has evaluated the effects of ulinastatin in patients with pulmonary edema.[20] However, pulmonary edema is a heterogeneous condition that includes both permeability-related and hydrostatic forms.[21] Given that ulinastatin primarily exerts anti-inflammatory and endothelial-protective effects, its potential benefit is more biologically plausible in permeability-related pulmonary edema (e.g., ARDS), whereas its role in hydrostatic pulmonary edema remains uncertain. A systematic review and meta-analysis of RCTs in pulmonary edema found that, compared with conventional care, ulinastatin reduced the incidence of pulmonary edema, decreased the extravascular pulmonary water index (EVLWI), shortened MVD, and reduced ICU stay. However, the evidence is limited by all trials being single-center studies from China with small sample sizes; suboptimal methods (randomization reported in four studies, allocation concealment in one, no blinding); substantial heterogeneity for ventilator time; nonuniform EVLWI/pulmonary vascular permeability index (PVPI) measurement approaches; and variable ulinastatin dosing and duration with insufficient data for dose subgroups.[20]

Overall, current evidence suggests that ulinastatin may provide clinical benefit in ARDS by improving oxygenation and short-term outcomes, both as monotherapy and in combination with extracorporeal blood purification strategies such as CRRT.[16,18,19] While a systematic review and meta-analysis have also reported improvements in pulmonary edema and related resource use (e.g., MVD and ICU stay), these findings should be interpreted with caution, as pulmonary edema is a heterogeneous condition. The potential benefit of ulinastatin is more biologically plausible in permeability-related edema (e.g., ARDS), whereas its role in hydrostatic pulmonary edema remains uncertain.[20] Therefore, high-quality, multicenter RCTs with standardized dosing strategies, robust safety monitoring, and longer follow-up are required to clarify its efficacy across different clinical contexts.

Safety

A multicenter retrospective real-world study involving 11,252 patients indicated that ulinastatin has a low incidence of adverse drug reactions (ADRs) and adverse drug events (ADEs), demonstrating considerable tolerability and safety. The reported ADRs/ADEs included liver function abnormalities, thrombocytosis, thrombocytopenia, leukocytosis, leukopenia, and rash, with an overall incidence rate of <5‰. Most adverse events were mild to moderate and resolved after drug discontinuation. Nevertheless, several limitations should be considered. The study was conducted exclusively in China, limiting the generalizability of its findings to other populations. Additionally, only 327 patients received ulinastatin strictly according to the drug specifications, with the majority of cases involving off-label use, which complicates the assessment of true ADR rates. The study also found that the combined use of other medications was associated with a higher likelihood of ADRs/ADEs, raising concerns about potential drug interactions. Despite these limitations, the available data suggest that ulinastatin is generally well-tolerated in critical care settings.[22] Despite this, continued post-marketing surveillance and further studies with larger, more diverse populations are necessary to comprehensively assess its safety profile and optimize its clinical application.

Table 1 shows the applications of ulinastatin in the ICU along with the relevant studies, key findings, dose, frequency, duration, included studies and participants, and evidence quality.[2–16,18–20,22]

Discussion

In 2023, numerous emergency, intensive care, and clinical pharmacy experts in China jointly developed an expert consensus on

Table 1. Summary of applications and safety of ulinastatin in ICU

Applications/Study	Key findings	Intervention details			Included studies and participants	Quality of evidence (GRADE)
		Dose	Frequency	Duration		
AP and SAP						
Ma *et al.*, 2018[2]	Ulinastatin combined with standard treatment significantly lowers mortality, improves efficacy, and reduces hospital stays compared to standard treatment alone	NA	NA	NA	33 RCTs (n = 1,786)	Very low
Zhang *et al.*, 2016[3]	Ulinastatin significantly reduces serum CRP, IL-6 and TNF-α levels in Asian patients with AP	NA	NA	NA	10 Cohort studies (n = 424)	Very low
Bandyopadhyay *et al.*, 2025[4]	Ulinastatin was associated with reduced mortality and inflammatory markers in severe acute pancreatitis, but showed no significant improvement in hospital stay or APACHE II scores	100,000–600,000 U IV	QD-Q12H	5–10 days	12 Prospective and retrospective studies (n = 1,244)	Low
Zeng *et al.*, 2025[6]	For SAP, combining ulinastatin with OCT may improve symptoms, CT findings, and lab markers (inflammation, oxidative stress, immunity, and hemorheology) more than OCT alone. It may also reduce mortality, complications, and hospital stay duration	50,000–300,000 U IV	QD-QID	3–28 days	145 RCTs (n = 13,605)	Very low
Horváth *et al.*, 2022[5]	Ulinastatin combined with somatostatin or octreotide for the treatment of AP and SAP significantly reduced the incidence of complications such as ARDS, MODS, and AKI compared to somatostatin or octreotide alone, and also shortened the duration of abdominal pain and hospital stay	50,000–200,000 U IV	QD-Q12H	3–14 days	9 RCTs (n = 1,037)	Very low
Perioperative management during cardiac surgeries with CPB						
He *et al.*, 2014[9]	Ulinastatin reduced extubation time, improved OI (day 1), lowered troponin-I, and inhibited TNF-α, PMN elastase, IL-6, and IL-8	NA	NA	NA	15 RCTs (n = 509)	Low
Zhang *et al.*, 2014[7]	Ulinastatin reduces pro-inflammatory cytokines and boosts anti-inflammatory cytokines in CPB cardiac surgery patients, while significantly decreasing myocardial injury markers, intubation time, and MVD	5,000 IU/kg–24,000 IU/kg IV	NA	NA	52 RCTs (n = 2,025)	Low
He *et al.*, 2015[10]	Ulinastatin reduced cytokine levels during/after CPB and shortened MVD	2.5 kU/kg–60 kU/kg or 300 kU IV	PS or AO or AI	NA	11 RCTs (n = 339)	Low
He *et al.*, 2020[8]	Ulinastatin in CABG patients reduces pro-inflammatory cytokines, increases anti-inflammatory cytokines, and improves respiratory function and OI	NA	NA	NA	15 RCTs (n = 646)	Low
Hu *et al.*, 2022[11]	Ulinastatin may reduce ICU stay and MVD in CPB patients, with potential protective effects against renal failure	100,000–300,000 U IV or 1,000 U/kg–15,000 U/kg IV	NA	1–3 days	12 RCTs (n = 1,620)	Low

(continued)

Table 1. *(continued)*

Applications/Study	Key findings	Intervention details			Included studies and participants	Quality of evidence (GRADE)
		Dose	Frequency	Duration		
Sepsis and septic shock						
Tong *et al.*, 2024[13]	Ulinastatin significantly reduces mortality, MODS incidence, ICU and hospital stay, APACHE II and SOFA scores, and lowers inflammatory markers	NA	NA	NA	48 RCTs (n = 3,714)	Very low
Gao *et al.*, 2025[14]	Adding ulinastatin to CBP significantly reduced mortality, improved APACHE II/SOFA scores, shortened ICU stay, and decreased inflammatory markers	NA	NA	NA	28 RCTs (n = 2,442) and 6 retrospective studies (n = 488)	Very low
Wang *et al.*, 2019[12]	Ulinastatin significantly reduces all-cause mortality, APACHE II scores, and MODS incidence in sepsis and septic shock patients. It also modulates inflammation by lowering pro-inflammatory cytokines like IL-6 and TNF-α and increasing anti-inflammatory cytokines	100,000–300,000 IU	QD-Q8H	3–8 days	13 RCTs (n = 1,358)	Very low
Cao *et al.*, 2025[15]	Ulinastatin-based therapies, especially in combination regimens, were associated with improved short-term outcomes and reduced inflammatory markers in patients with sepsis	166,000–570,000 IU	QD-Q12H	3–8.5 days	9 Meta-analyses (n = 7,793)	Very low
ARDS						
Leng *et al.*, 2014[16]	Ulinastatin improved OI, reduced ICU mortality, shortened ICU stay, and lowered inflammatory markers	50,000–600,000 U IV	QD-TID	2–10 days	4 RCTs (n = 236) and 25 NRCTs (n = 1,490)	Low to very low
Zhang *et al.*, 2019[18]	Ulinastatin reduces mortality, VAP rate, MVD, ICU stay, and hospital stay in ARDS patients, while improving OI and decreasing pro-inflammatory cytokines	30,000–2,000,000 U IV	QD-Q6H	3–14 days	33 RCTs (n = 2,344)	Low
Zeng *et al.*, 2026[19]	CRRT combined with ulinastatin, compared with CRRT alone, may reduce mortality, ICU stay, MVD, and APACHE II scores, while improving OI and PaO_2 in patients with ARDS	200,000 U	Q8H or TID	7 days	5 RCTs (n = 384)	Low to very low
Tan *et al.*, 2025[20]	Ulinastatin reduced pulmonary edema incidence, EVLWI, MVD, and ICU stay	NA	NA	NA	9 RCTs (n = 577)	Low to very low
Safety						
Li *et al.*, 2022[22]	Ulinastatin shows low ADRs/ADEs incidence, indicating high tolerability and safety	NA	NA	NA	Multicenter retrospective study (n = 11,252)	Low

ADEs, adverse drug events; ADRs, adverse drug reactions; AI, injected intravenously after anesthesia induction; AO, injected intravenously around aortic opening; AP, acute pancreatitis; APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; CBP, continuous blood purification; CT, computed tomography; CPB, cardiopulmonary bypass; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; EVLWI, extravascular lung water index; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; ICU, intensive care unit; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IV, intravenous; MODS, multiple organ dysfunction syndrome; MVD, mechanical ventilation duration; NA, not applicable; NRCTs, non-randomized controlled trials; OCT, octreotide; OI, oxygenation index; PaO_2, partial pressure of oxygen; PMN, polymorphonuclear neutrophil; PS, injected in prime solution; QD, once daily; Q6H, every 6 hours; Q8H, every 8 hours; Q12H, every 12 hours; QID, four times daily; RCTs, randomized controlled trials; SAP, severe acute pancreatitis; SOFA, Sequential Organ Failure Assessment; TID, three times daily; TNF-α, tumor necrosis factor-α; U, unit; VAP, ventilator-associated pneumonia.

the application of ulinastatin in critical and severe conditions. This consensus recommends the use of ulinastatin for SAP, sepsis, shock, severe pneumonia, ARDS, severe burns, severe trauma, cardiac arrest, severe heatstroke, and various acute poisonings based on existing research. This consensus reflects the growing clinical interest in ulinastatin as a multi-target anti-inflammatory and organ-protective agent in ICU settings. However, it is important to note that these recommendations are largely based on heterogeneous studies with variable dosing regimens and a lack of high-quality RCTs.[1]

Limitations

The clinical potential of ulinastatin in ICU settings is promising, particularly given its broad-spectrum anti-inflammatory and organ-protective properties. However, the current body of evidence is limited by several important methodological challenges. First, the predominance of studies conducted in East and South Asia introduces geographical bias, as differences in healthcare systems, clinical practices, patient characteristics, and baseline disease severity may limit the generalizability of these findings to other regions. Second, substantial heterogeneity across studies—particularly in outcomes such as ICU stay, MVD, and inflammatory markers—likely reflects variations in ulinastatin dosing regimens, timing of administration, disease severity, and concurrent supportive therapies, which reduces the comparability and reliability of pooled estimates. In addition, many of the included meta-analyses are predominantly based on small, single-center trials with limited methodological rigor, which further reduces the overall certainty of the evidence.

Importantly, the relationship between the mechanistic effects of ulinastatin and observed clinical outcomes warrants further consideration. Ulinastatin exerts its therapeutic effects primarily through modulation of the inflammatory response, stabilization of endothelial function, and attenuation of protease-mediated tissue injury. These mechanisms are closely linked to key pathophysiological processes in critical illness, particularly in conditions such as sepsis and ARDS, where excessive inflammation and endothelial dysfunction contribute to organ failure.[1] However, while improvements in inflammatory markers and oxygenation parameters are consistently reported, their translation into hard clinical outcomes—such as mortality reduction or long-term functional recovery—remains less robust and more variable across studies. This discrepancy may reflect the complex and multifactorial nature of critical illness, where clinical outcomes are influenced not only by inflammation but also by factors such as timing of intervention, organ support strategies, and underlying disease severity.

Future directions

Future research should prioritize well-designed, international, multicenter RCTs to establish standardized treatment protocols, optimize dosing strategies, and assess the long-term clinical impact of ulinastatin across diverse patient populations. The current evidence base is largely derived from East and South Asia, reflecting the fact that ulinastatin was first developed and approved in Japan and China, with limited availability and regulatory approval in other regions. This geographical concentration raises important concerns regarding global applicability. Differences in ICU infrastructure, clinical practices, and implementation of evidence-based protocols—such as lung-protective ventilation strategies in ARDS or sepsis management bundles—may substantially influence treatment effects across regions. This context underscores the need for international collaborations to evaluate ulinastatin in diverse healthcare systems and patient populations. Future studies should not only address methodological rigor but also specifically investigate whether the efficacy and safety observed in Asian cohorts are consistent across different ethnic, genetic, and demographic groups. By bridging this gap, future trials could enhance the global relevance of ulinastatin evidence and pave the way for broader integration into international guidelines.

Moreover, exploring its synergistic effects when combined with other anti-inflammatory and organ-supportive therapies could help refine its clinical applications. With its increasing use beyond Asia, evaluating its efficacy and safety in varied demographic and ethnic groups will be crucial for broader adoption. Furthermore, integrating ulinastatin within precision medicine frameworks, such as biomarker-guided therapy or artificial intelligence-driven patient monitoring, may enhance its therapeutic potential and enable more personalized critical care management. Ongoing pharmacovigilance efforts and post-marketing surveillance will also be essential to monitor rare adverse events and refine its safety profile.

By addressing these challenges, future studies can help position ulinastatin as a well-established therapy in ICU settings, potentially transforming its role from a regionally used agent to a globally recognized therapeutic option in critical care medicine.

Conclusions

Ulinastatin demonstrates biological plausibility and consistent signals of benefit in critical care, with an overall favorable safety profile. However, the current evidence remains limited by substantial heterogeneity, variable study quality, and the predominance of studies conducted in Asian populations, which restricts the certainty and generalizability of these findings. Future well-designed international multicenter RCTs are warranted to establish standardized dosing strategies and confirm its efficacy and safety in broader populations.

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Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

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