Traditional Chinese medicine for septic patients undergoing ulinastatin therapy
A meta-analysis

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Abstract

Purpose: This study aimed to assess the efficacy of traditional Chinese medicine (TCM) in septic patients treated with ulinastatin.

Methods: PubMed, EmBase, and the Cochrane library were searched up to January 2021 to identify randomized controlled trials. The weight mean difference (WMD) and relative risk (RR) with 95% confidence intervals were used with the random-effects model.

Results: Twenty-three randomized controlled trials with 1903 septic patients were included. TCM significantly reduced the APACHE II score (WMD: −5.18; P < .001), interleukin-6 (WMD: −63.00; P < .001), tumor necrosis factor-α (WMD: −8.86; P < .001), c-reactive protein (WMD: −3.47; P < .001), mechanical ventilation duration (WMD: −3.98; P < .001), intensive care unit stay (WMD: −4.18; P < .001), procalcitonin (WMD: −0.53; P < .001), lipopolysaccharide (WMD: −9.69; P < .001), B-type natriuretic peptide (WMD: −159.87; P < .001), creatine kinase isoenzyme MB (WMD: −45.67; P < .001), cardiac troponin I (WMD: −0.66; P < .001), and all-cause mortality risk (RR: 0.55; P < .001).

Conclusions: TCM lowers inflammation levels and reduces the risk of all-cause mortality for septic patients.

Abbreviations: CI = confidence interval, ICU = intensive care unit, RCT = randomized controlled trial, RR = relative risk, TCM = traditional Chinese medicine, WMD = weight mean difference.

Keywords: Chinese traditional, medicine, meta-analysis, septic, ulinastatin

1. Introduction

Sepsis is defined as a life-threatening organ dysfunction syndrome that develops as the host response to infection.[1,2] Studies have reported that the prognosis of sepsis is poor, and mortality in severe sepsis is around 25%, with septic shock occurring in nearly 50%.3,4 The prevalence of sepsis increases by 1.5% annually, and the number of sepsis cases reached 49 million in 2017.5-7 The diagnosis of sepsis is based on infection-related dysfunction of the lung, kidney, liver, cardiovascular system, blood, or central nervous system. The progression of sepsis is rapid and it is considered as a high-risk condition in the intensive care unit (ICU).

There is currently no standard approach for sepsis management. Ulinastatin is a urinary trypsin inhibitor considered an important protease inhibitor that exists in urine, blood, and other tissues; it is widely used for sepsis.5,8,9 The use of ulinastatin in sepsis can modulate pro-inflammatory mediators and cytokines, and can provide a protective effect on several organs.10-12 The suggested mechanism of ulinastatin is a decrease of inflammatory mediators and the frequency of immune cell apoptosis in sepsis models.13 However, the treatment effects of ulinastatin for sepsis in clinical studies remained conflicting.14,15 In traditional Chinese medicine (TCM), Xuebijing is widely used for treatment of sepsis. Its main components are safflower yellow pigment A and protocatechudehyde, which can inhibit the inflammation level, improve microcirculation, and regulate immune function. Xuebijing consists of Carthamus tinctorius L, Paeonia lactiflora Pall, Ligusticum chuanxiong Hort, Salvia miltiorrhiza Bge, and Angelica sinensis (Oliv.) Diels. The herb of C. tinctorius L can activate blood circulation and remove blood stasis. P. lactiflora Pall and L. chuanxiong Hort act as accessory drugs playing an important role in cooling the blood, dispersing blood stasis, and detoxifying. S. miltiorrhiza Bge and A. sinensis (Oliv.) Diels can enrich the blood and disperse stasis.16

The combined use of TCM and ulinastatin for septic patients has already been illustrated. Whether TCM can yield superior effects for septic patients undergoing ulinastatin treatment remains controversial. We therefore performed this randomized controlled trial (RCTs) to assess the treatment efficacy of TCM for septic patients treated with ulinastatin.
2. Methods

2.1. Data sources, search strategy, and selection criteria
This study was performed and guided by the reporting items for systematic reviews and meta-analysis. RCTs that investigated the efficacy of TCM plus ulinastatin versus ulinastatin alone for septic patients were eligible for our study. No restrictions were placed on publication language and status. We searched PubMed, EmBase, the Cochrane library, and China National Knowledge Infrastructure for eligible trials up to January 2021. The following search terms were applied: “sepsis” OR “severe sepsis” OR “pyemia” OR “pyohemia” OR “pyohemias” OR “pyaemia” OR “pyaemias” OR “septicaemia” OR “septicemias” OR “poisoning, blood” OR “blood poisoning” AND “xuebing” AND “ulinastatin.” The reference lists were reviewed to identify any new eligible trial.

Two reviewers independently performed the study selection, and conflicts between reviewers were settled mutually by discussion. The study was included if: patients: sepsis, irrespective of the severity of disease; intervention: TCM and ulinastatin; control: ulinastatin; outcomes: APACHE II, interleukin (IL)-6, tumor necrosis factor (TNF)-α, C-reactive protein (CRP), mechanical ventilation (MV) duration, ICU stay, all-cause mortality, procalcitonin (PCT), lipopolysaccharide (LPS), B-type natriuretic peptide (BNP), creatine kinase isoenzyme MB (CK-MB), cardiac troponin I (cTnI), or lactic dehydrogenase (LDH); and study design: the study had to have a RCT design. This study did not contain any participates and ethics approval and informed consent are not applicable.

2.2. Data collection and quality assessment
Two reviewers independently abstracted the following items from each trial, first author, publication year, country, sample size (number of patients in intervention and control groups), mean age, male proportion, baseline APACHE II, disease status, intervention and control, and treatment course. These 2 reviewers then assessed the quality of the included trials using the Jadad scale, which is based on 5 items. The scoring system for each trial ranged from 0 to 5. Any disagreement between reviewers was resolved by the primary reviewer reviewing the full text of included trials.

2.3. Statistical analysis
The effects of TCM on septic patients were assigned as continuous and categorical outcomes, then weighted mean difference (WMD) and relative risk (RR) with a 95% confidence interval (CI) were analyzed in individual trials. The random-effects model was used to calculate the pooled effect estimate, which could consider underlying variants across included trials. The I² and Cochran Q statistic were used to assess the heterogeneity of each outcome; the significant heterogeneity was defined as an I² > 50.0% or P < .10. The robustness of the pooled conclusion for each outcome was evaluated using sensitivity analysis. Subgroup analysis for APACHE II, IL-6, TNF-α, CRP, MV duration, ICU stay, and all-cause mortality were performed based on mean age, male proportion, and treatment duration. Then an interaction t test was used to compare differences between subgroups. All P-values are 2-sided, and the inspection level was .05. All of the analyses in this study were performed with STATA software (Version 10.0; StataCorp, TX).

3. Results

3.1. Literature search
The literature search in electronic databases yielded 891 articles after duplicate articles were removed. A total of 812 studies were removed because these articles reported irrelevant topics. A total of 79 studies were downloaded for full-text evaluation, and 56 studies were removed because patients were not treated with ulinastatin (n = 29), they were not RCT (n = 21), and review papers (n = 6). Reviewing the reference lists, we identified 11 potentially relevant articles, while no new eligible study was found. Finally, 23 RCTs were included in the final meta-analysis (Fig. 1).

3.2. Study characteristics
The characteristics of the identified studies are summarized in Table 1. Of the 23 included trials, there were 1903 septic patients. All the studies were performed in China, and the sample size ranged from 40 to 240. The mean age of patients across trials ranged from 33.2 to 66.2 years, and the male proportion for each trial ranged from 48.3% to 84.8%. The treatment duration ranged from 3 to 14 days. Study quality was evaluated by the Jadad scale, 9 trials had 3 scores, 10 trials, 2 scores, and the remaining 4 trials, 1 score. The details of the abstracted data for the investigated outcomes are shown in Supplementary material 1, http://links.lww.com/MD/G388.

3.3. APACHE II
Nine trials reported the effect of TCM on the APACHE II score. The pooled result indicated that the use of TCM was associated with a lower APACHE II score for septic patients treated with ulinastatin (WMD: −5.18; 95% CI: −7.05 to −3.31; P < .001; Fig. 2). Moreover, a significant heterogeneity was observed (I² = 90.6%; P < .001). The pooled conclusion was robust and not changed (Supplementary material 2, http://links.lww.com/MD/G389). The significant difference with TCM on the APACHE II score were observed in all subgroups. Mean age (P < .001) or male proportion (P = .002) could affect the treatment efficacy of TCM on APACHE II (Table 2). No significant publication bias for APACHE II was detected (P_Egger: .071; P_Begg: .118; Supplementary material 3, http://links.lww.com/MD/G390).

3.4. IL-6
Fourteen trials reported the effect of TCM on IL-6 levels. The pooled result suggested TCM significantly reduced IL-6 (WMD: −63.00; 95% CI: −75.27 to −50.72; P < .001; Fig. 3). Moreover, we noted significant heterogeneity for IL-6 (I² = 95.5%; P < .001). Sensitivity analysis indicated the pooled conclusion was not altered (Supplementary material 2, http://links.lww.com/MD/G389). The subgroup analysis found that TCM was associated with lower IL-6 in all subgroups, and that the male proportion (P < .001) or treatment duration (P < .001) could affect the efficacy of TCM on IL-6 (Table 2). The Begg test showed no publication bias for IL-6 (P = .324), while potential significant publication bias was observed with the Egger test (P = .001) (Supplementary material 3, http://links.lww.com/MD/G390).
3.5. TNF-α

Thirteen trials reported the effect of TCM on TNF-α level. TCM significantly reduced TNF-α levels (WMD: −8.86; 95% CI: −12.31 to −5.41; \( P < .001 \); Fig. 4), and a significant heterogeneity was obtained (\( I^2 = 96.4\%; P < .001 \)). The pooled conclusion was robust and stable (Supplementary material 2, http://links.lww.com/MD/G389). We noted that TCM significantly reduced TNF-α in mostly subgroups, while TCM was not associated with a TNF-α level if treatment duration >7 days. Moreover, mean age (\( P < .001 \)), male proportion (\( P < .001 \)), and treatment duration (\( P < .001 \)) could affect the efficacy of TCM on TNF-α (Table 2). The Begg test showed no evidence of publication bias, while potential significant publication bias existed for TNF-α using the Egger test (\( P < .001 \)) (Supplementary material 3, http://links.lww.com/MD/G390).

3.6. CRP

Eight trials reported the effect of TCM on CRP levels. The pooled result suggested TCM significantly reduced the CRP level (WMD: −9.47; 95% CI: −12.17 to −6.78; \( P < .001 \); Fig. 5). We noted significant heterogeneity for CRP (\( I^2 = 85.6\%; P < .001 \)), and the pooled conclusion was stability after sequentially removing a single study (Supplementary material 2, http://links.lww.com/MD/G389). The significant differences between groups for CRP levels were observed in all subgroups, and male proportion (\( P = .010 \)) or treatment duration (\( P < .001 \)) could affect the efficacy of TCM on CRP (Table 2). There was no evidence of publication bias for CRP (\( P_{\text{Egger}} = .640; P_{\text{Begg}} = .902; \) Supplementary material 3, http://links.lww.com/MD/G390).

3.7. MV duration

Eleven trials reported the effect of TCM on MV duration. The pooled result found that TCM was associated with a shorter MV duration (WMD: −3.98; 95% CI: −4.74 to −3.21; \( P < .001 \); Fig. 6). We noted significant heterogeneity for MV duration (\( I^2 = 64.9\%; P = .002 \)) and the pooled conclusion was stability (Supplementary material 2, http://links.lww.com/MD/G389). Subgroup analysis indicated TCM significantly reduced MV duration in all subgroups (Table 2). No evidence of publication bias for MV duration was observed (\( P_{\text{Egger}} = .517; P_{\text{Begg}} = .876; \) Supplementary material 3, http://links.lww.com/MD/G390).

3.8. ICU stay

Twelve trials reported the effect of TCM on ICU stay. The pooled result suggested TCM was associated with a shorter ICU stay...
## Table 1
The baseline characteristics of included studies and involved patients.

| Study            | Country | Sample size | Age, yr | Male (%) | APACHE II | Disease status | Intervention | Control | Treatment duration, d | Study quality |
|------------------|---------|-------------|---------|----------|-----------|----------------|--------------|---------|----------------------|---------------|
| Mao, et al 2008  | China   | 114 (57/57) | 50.8    | 84.8     | 16.8      | Severe sepsis | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7        | 3                    |
| Sun, et al 2010  | China   | 40 (20/20)  | NA      | NA       | NA        | Severe sepsis | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 10       | 1                    |
| Ye, et al 2010   | China   | 50 (27/23)  | 40.0    | 66.0     | 16.9      | Sepsis        | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7        | 2                    |
| Abu, et al 2013  | China   | 30 (15/15)  | 47.1    | 61.8     | NA        | Severe sepsis | TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (300,000 U/12 h) plus basic treatment | Ulinastatin (300,000 U/12 h) plus basic treatment | 7        | 1                    |
| Zeng, et al 2013 | China   | 54 (27/27)  | 47.2    | 55.6     | 44.8      | Septic shock  | TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7        | 2                    |
| Jiang, et al 2013| China   | 86 (43/43)  | 49.4    | 53.5     | NA        | Severe sepsis | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7        | 3                    |
| Zhao, et al 2013 | China   | 88 (44/44)  | 62.6    | 55.3     | 24.4      | Sepsis        | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7–10      | 2                    |
| Zhou, et al 2013 | China   | 122 (61/61) | 43.5    | 54.2     | NA        | Sepsis        | TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (900,000 U/12 h) plus basic treatment | 14       | 2                    |
| Cao, et al 2015  | China   | 240 (135/105)| 64.7   | 57.8     | 17.4      | Sepsis        | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (900,000 U/12 h) plus basic treatment | Ulinastatin (100,000 U/12 h) plus basic treatment | 7        | 2                    |
| Li, et al 2015   | China   | 80 (40/40)  | 48.2    | 55.8     | NA        | Severe sepsis | TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (100,000 U/12 h) plus basic treatment | Ulinastatin (300,000 U/12 h) plus basic treatment | 7        | 2                    |
| Shan, et al 2016 | China   | 70 (35/35)  | 42.5    | 60.0     | 30.8      | Septic shock  | TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (300,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7        | 3                    |
| Ji, et al 2016   | China   | 60 (30/30)  | 66.2    | 48.3     | 23.5      | Sepsis        | TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7        | 1                    |
| Li, et al 2016   | China   | 80 (40/40)  | 36.9    | 57.5     | NA        | Sepsis        | TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (100,000 U/12 h) plus basic treatment | Ulinastatin (100,000 U/12 h) plus basic treatment | 7        | 2                    |
| Bian, et al 2017 | China   | 52 (26/26)  | 39.0    | 63.5     | NA        | Sepsis        | TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (100,000 U/12 h) plus basic treatment | Ulinastatin (100,000 U/12 h) plus basic treatment | 10       | 3                    |
| Chen, et al 2017 | China   | 69 (35/34)  | 33.2    | 59.4     | NA        | Sepsis        | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 10       | 2                    |
| Lu, et al 2018   | China   | 45 (25/20)  | 59.8    | 62.2     | 23.3      | Sepsis        | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (400,000 U/12 h) plus basic treatment | Ulinastatin (400,000 U/12 h) plus basic treatment | 5        | 3                    |
| Zhang, et al 2018| China   | 60 (30/30)  | 58.0    | 63.3     | NA        | Sepsis        | TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 6        | 2                    |
| Yu, et al 2018   | China   | 84 (42/42)  | 49.2    | 55.6     | 16.7      | Sepsis        | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7        | 3                    |
| Li, et al 2018   | China   | 80 (40/40)  | 38.6    | 60.0     | NA        | Sepsis        | TCM (Xuebijing, 50 mL/12 h) plus ulinastatin (300,000 U/12 h) plus basic treatment | Ulinastatin (300,000 U/12 h) plus basic treatment | 7        | 1                    |
| Wei, et al 2018  | China   | 150 (75/75) | 57.5    | 59.3     | 25.6      | Sepsis        | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7        | 3                    |
|                 | China   | 86 (43/43)  | 45.8    | 52.3     | NA        | Sepsis        | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7        | 3                    |
Table 1 (continued).

| Study       | Country | Sample size | Age, yr | Male (%) | APACHE II | Disease status | Intervention | Control | Treatment duration, d | Study quality |
|-------------|---------|-------------|---------|----------|-----------|----------------|--------------|---------|-----------------------|---------------|
| Xu, et al 2019 [47] | China | 67 (35/32) | 44.9    | 59.4     | NA        | Septic shock | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (300,000 U/12 h) plus basic treatment | Ulinastatin (300,000 U/12 h) plus basic treatment | 3        | 3                     |               |
| Zhang, et al 2020 [48] | China | 96 (48/48) | 55.9    | 60.4     | NA        | Sepsis | TCM (Xuebijing, 100 mL/12 h) plus ulinastatin (200,000 U/12 h) plus basic treatment | Ulinastatin (200,000 U/12 h) plus basic treatment | 7        | 2                     |               |

(WMD: −4.18; 95% CI: −5.39 to −2.97; P < .001; Fig. 7). We noted significant heterogeneity for ICU stay (I² = 76.8%; P < .001). Sensitivity analysis indicated the pooled conclusion was stability (Supplementary material 2, http://links.lww.com/MD/G389). Significant differences between groups for ICU stay were observed in all subgroups, and mean age (P = .012) or male proportion (P = .006) could affect the efficacy of TCM on ICU stay (Table 2). No significant publication bias for ICU stay was detected (P_Egger = .166; P_Begg = .451; Supplementary material 3, http://links.lww.com/MD/G390).

3.9. All-cause mortality

Twelve trials reported the effect of TCM on all-cause mortality risk. We noted that the TCM significantly reduced all-cause mortality risk (RR: 0.55; 95% CI: 0.43–0.70; P < .001; Fig. 8). There was no significant heterogeneity for all-cause mortality (I² = 0.0%; P = .989). The pooled conclusion was not changed when excluding any specific trial (Supplementary material 2, http://links.lww.com/MD/G389). Subgroup analysis found that TCM was associated with a lower risk of all-cause mortality in all subgroups (Table 2). No evidence of publication bias for all-cause mortality was seen (P_Egger = .116; P_Begg = .244; Supplementary material 3, http://links.lww.com/MD/G390).

3.10. PCT, LPS, BNP, CK-MB, cTnI, and LDH

The effects of TCM on PCT and LPS were available in 11 and 5 trials, respectively. TCM significantly reduced the levels of PCT (WMD: −0.53; 95% CI: −0.67 to −0.39; P < .001; Fig. 9), and LPS (WMD: −9.69; 95% CI: −11.19 to −8.19; P < .001; Fig. 10). Moreover, we noted significant heterogeneity for PCT (I² = 97.3%; P < .001), but no evidence of heterogeneity for LPS (I² = 0.0%; P = .983).

The number of trials that reported the effects of TCM on BNP, CK-MB, cTnI, and LDH were 6, 4, 4, and 3, respectively (Fig. 11). We noted TCM significantly reduced the levels of BNP (WMD: −159.87; 95% CI: −230.26 to −98.48; P < .001), CK-MB (WMD: −45.67; 95% CI: −64.67 to −26.68; P < .001), and cTnI (WMD: −0.66; 95% CI: −0.94 to −0.39; P < .001), while it did not affect LDH levels (WMD: 22.31; 95% CI: −150.88 to 195.51; P = .801). There was significant heterogeneity for BNP (I² = 85.6%; P < .001), CK-MB (I² = 68.4%; P = .024), cTnI (I² = 99.7%; P < .001), and LDH (I² = 99.1%; P < .001).

![Figure 2. The effect of TCM on APACHE II in septic patients treated with ulinastatin. TCM = traditional Chinese medicine.](http://example.com/fi2.png)
4. Discussion
This study assessed the treatment efficacy of TCM for septic patients undergoing ulinastatin treatment. A total of 1903 septic patients across a broad range of characteristics from 23 RCTs were selected in the final meta-analysis. This study found that the TCM use of Xuebijing significantly improved APACHE II, IL-6, TNF-α, CRP, MV duration, ICU duration, all-cause mortality, PCT, LPS, BNP, CK-MB, and cTnI, while it had no significant effect on LDH for septic patients. Subgroup analyses found the treatment efficacy of TCM for septic patients could be affected by mean age, male proportion, and treatment duration.

A prior meta-analysis identified 16 RCTs and found that supplementation of TCM Xuebijing could improve the risk of 28-day mortality, lower APACHE II scores, the WBC count, and body temperature in septic patients without serious adverse events, while it had no significant effect on mortality during treatment. However, patients enrolled in this meta-analysis underwent various treatment strategies. Xiao et al.[51] found the combined use of TCM Xuebijing and ulinastatin could improve MV duration, ICU stay, PCT, APACHE II, IL-6, TNF-α, reduce the risk of 28-day mortality, and multiple organ dysfunction syndrome in septic patients. However, one of the included studies did not mention septic patients treated with ulinastatin.[52] Moreover, several additional RCTs were published recently,[42-49] and the treatment efficacy of TCM for septic patients undergoing ulinastatin needs to be re-evaluated. Furthermore, whether the treatment efficacy of TCM in septic patients differs according to mean age, male proportion, and treatment duration needs further evaluation.

Therefore, the current study was performed to compare the effects of TCM plus ulinastatin with ulinastatin alone for septic patients. The summarized results indicate that TCM Xuebijing can significantly improve the severity of disease, inflammation, MV duration, ICU stay, and all-cause mortality in septic patients.
undergoing ulinastatin therapy. Most of the included studies reported similar results, while 2 studies did not find a significant effect of TCM on ICU stay.\[28,42\] Most studies did not find a significant effect of TCM on the risk of all-cause mortality. The reason for this could be that events occurred less than expected, and the 95% CI for all-cause mortality in an individual study was broad. The significant effects of TCM Xuebijing in septic patients treated with ulinastatin could be because Xuebijing removes toxins, it detoxifies, dredging the veins, promoting blood circulation, and removing blood stasis.\[53\] The main components of Xuebijing activate blood circulation, remove blood stasis, clear toxins, and strengthen body resistance.\[16\] Several mechanisms of Xuebijing for treating sepsis include: anti-inflammatory; Xuebijing can inhibit pro-inflammatory cytokine release, or the production of high mobility group box-1 protein, promote anti-inflammatory cytokine release in early-stage sepsis, and downregulate the expression of the TLR4/NF-\(\kappa\)B signaling pathway; an anticoagulant effect; Xuebijing plays an important role in anti-inflammatory, anti-coagulation, and removing blood stasis.\[53\] The main components of Xuebijing activate blood circulation, remove blood stasis, clear toxins, and strengthen body resistance.\[16\] Several mechanisms of Xuebijing for treating sepsis include: anti-inflammatory; Xuebijing can inhibit pro-inflammatory cytokine release, or the production of high mobility group box-1 protein, promote anti-inflammatory cytokine release in early-stage sepsis, and downregulate the expression of the TLR4/NF-\(\kappa\)B signaling pathway; an anticoagulant effect; Xuebijing plays an important role in anti-inflammatory, anti-coagulation, and removing blood stasis.
role in tissue factor release, procoagulant, anticoagulant, and fibrinolytic pathways; immunomodulation; Xuebijing can polarize the immune response of Th2 to Th1, enhance Treg apoptosis, and reduce the apoptosis of immune cells; protection of the vascular endothelium; antioxidative stress function, and other mechanisms, including inhibiting intercellular adhesion molecule-1 expression and vascular cell adhesion molecule-1 in liver tissue and intercellular adhesion molecule-1 in lung tissue.\textsuperscript{[54]}

Therefore, combined use of Xuebijing and ulinastatin can alleviate the symptoms of sepsis, reduce the progression of multiple organ failure and collapse caused by the body’s endogenous inflammatory mediators, and reduce the probability of sepsis continuing to deteriorate.\textsuperscript{[55,56]}

Subgroup analyses found that the treatment effects of TCM in septic patients treated with ulinastatin can be affected by age, male proportion, and treatment duration. We noted the effects

| Study               | Mean difference (95% CI) | % Weight |
|---------------------|--------------------------|----------|
| Cao, et al 2015     | −5.90 (−7.58,−4.22)      | 15.6     |
| Shan, et al 2016    | −11.95 (−16.91,−6.99)    | 10.6     |
| Ji, et al 2016      | −10.80 (−13.86,−7.74)    | 13.7     |
| Li, et al 2016      | −11.10 (−13.69,−8.51)    | 14.4     |
| Bian, et al 2017    | −4.20 (−6.99,−1.41)      | 14.1     |
| Lu, et al 2018      | −20.57 (−35.00,−6.14)    | 2.9      |
| Zhang, et al 2018   | −12.58 (−14.32,−10.84)   | 15.6     |
| Wei, et al 2018     | −8.10 (−11.54,−4.66)     | 13.1     |
| Overall             | −9.47 (−12.17,−6.78); P<0.001 | (I-square: 85.6%; P<0.001) |

Figure 5. The effect of TCM on CRP in septic patients treated with ulinastatin. CRP=C-reactive protein, TCM=traditional Chinese medicine.

| Study               | Mean difference (95% CI) | % Weight |
|---------------------|--------------------------|----------|
| Mao, et al 2008     | −4.16 (−5.59,−2.73)      | 9.7      |
| Sun, et al 2010     | −2.11 (−4.01,−0.21)      | 7.7      |
| Abu, et al 2013     | −4.11 (−6.00,−2.22)      | 7.7      |
| Jiang, et al 2013   | −2.60 (−4.51,−0.69)      | 7.7      |
| Zhao, et al 2013    | −4.07 (−5.16,−2.98)      | 11.2     |
| Li, et al 2015      | −3.50 (−4.87,−2.13)      | 9.9      |
| Ji, et al 2016      | −4.30 (−6.20,−2.40)      | 7.7      |
| Li, et al 2016      | −4.50 (−6.15,−2.85)      | 8.7      |
| Zhang, et al 2018   | −2.40 (−3.44,−1.36)      | 11.5     |
| Yu, et al 2018      | −6.18 (−7.81,−4.55)      | 8.8      |
| Wei, et al 2020     | −5.80 (−7.26,−4.34)      | 9.5      |
| Overall             | −3.98 (−4.74,−3.21); P<0.001 | (I-square: 64.9%; P=0.002) |

Figure 6. The effect of TCM on MV duration in septic patients treated with ulinastatin. MV=mechanical ventilation, TCM=traditional Chinese medicine.
of TCM on symptom of sepsis. The improvement in inflammation in younger septic patients was greater than in elderly septic patients, while ICU stay in elderly septic patients was shorter than in younger septic patients. The potential reason for this could be that the mortality risk in elderly patients is higher. Moreover, the improvement in disease severity and inflammation in male patients might be superior to women, which could be caused by disease severity. Finally, we noted that a shorter treatment duration was associated with better prognosis, which could be explained by disease severity and the smaller number that reported a treatment duration >7 days.

Figure 7. The effect of TCM on ICU duration in septic patients treated with ulinastatin. ICU = intensive care unit, TCM = traditional Chinese medicine.

| Study            | Mean difference (95% CI) | % Weight |
|------------------|--------------------------|----------|
| Mao, et al 2008  | −3.39 (−4.99,−1.79)      | 9.4      |
| Sun, et al 2010  | −1.76 (−4.14, 0.62)      | 7.8      |
| Abu, et al 2013  | −3.91 (−6.08,−1.74)      | 8.3      |
| Jiang, et al 2013| −3.70 (−5.77,−1.63)      | 8.5      |
| Zhao, et al 2013 | −3.97 (−5.50,−2.44)      | 9.5      |
| Li, et al 2015   | −2.10 (−4.16,−0.04)      | 8.5      |
| Ji, et al 2016   | −4.40 (−7.12,−1.68)      | 7.2      |
| Li, et al 2016   | −4.60 (−6.96,−2.24)      | 7.9      |
| Lu, et al 2018   | −2.13 (−5.95, 1.69)      | 5.3      |
| Zhang, et al 2018| −8.90 (−10.43,−7.37)     | 9.5      |
| Yu, et al 2018   | −5.29 (−7.21,−3.37)      | 8.8      |
| Wei, et al 2020  | −4.53 (−6.22,−2.84)      | 9.2      |
| Overall          | −4.18 (−5.39,−2.97); P<0.001 (I-square: 76.8%; P<0.001) | 100.0    |

Figure 8. The effect of TCM on all-cause mortality in septic patients treated with ulinastatin. TCM = traditional Chinese medicine.

| Study            | Risk ratio (95% CI) | % Weight |
|------------------|---------------------|----------|
| Mao, et al 2008  | 0.69 (0.35, 1.35)   | 13.8     |
| Ye, et al 2010   | 0.37 (0.11, 1.25)   | 4.1      |
| Jiang, et al 2013| 0.67 (0.30, 1.47)   | 10.1     |
| Zhao, et al 2013 | 0.57 (0.27, 1.22)   | 10.8     |
| Cao, et al 2015  | 0.39 (0.07, 2.08)   | 2.2      |
| Ji, et al 2016   | 0.45 (0.18, 1.15)   | 7.3      |
| Li, et al 2016   | 0.38 (0.15, 0.98)   | 7.2      |
| Chen, et al 2017 | 0.46 (0.24, 0.87)   | 15.4     |
| Zhang, et al 2018| 0.33 (0.04, 3.03)   | 1.3      |
| Yu, et al 2018   | 0.58 (0.25, 1.34)   | 9.1      |
| Wei, et al 2018  | 0.78 (0.33, 1.84)   | 8.4      |
| Wei, et al 2020  | 0.57 (0.26, 1.24)   | 10.5     |
| Overall          | 0.55 (0.43, 0.70); P<0.001 (I-square: 0.0%; P=0.989) | 100.0    |
The shortcomings of this study should be acknowledged: the quality of included trials was low to moderate, and the evidence level for pooled conclusion was restricted; the conclusions should be considered with caution since all trials were performed in China; the conclusions could be biased due to disease severity and underlying treatment strategies; the detailed analyses were restricted because they were based on pooled data; and publication bias was inevitable because the analysis is based on published articles.

This study found that TCM plus ulinastatin could yield additional benefits in APACHE II score, IL-6, TNF-α, CRP, MV duration, ICU stay, all-cause mortality, PCT, LPS, BNP, CK-MB, and cTnI in septic patients, while it has no significant effect on LDH levels. Furthermore, RCTs should be performed to

| Study            | Mean difference (95% CI) | % Weight |
|------------------|--------------------------|----------|
| Mao, et al 2008  | −0.83 (−1.16,−0.50)      | 8.4      |
| Ye, et al 2010   | −0.10 (−0.40, 0.20)      | 9.0      |
| Jiang, et al 2013| −0.82 (−1.18,−0.46)      | 7.7      |
| Zhao, et al 2013 | −0.68 (−1.06,−0.30)      | 7.3      |
| Zhou, et al 2013 | −0.30 (−0.36,−0.24)      | 15.5     |
| Cao, et al 2015  | −0.19 (−0.21,−0.17)      | 15.9     |
| Lu, et al 2018   | −3.98 (−6.60,−1.36)      | 0.3      |
| Zhang, et al 2018| −7.20 (−8.44,−5.96)      | 1.2      |
| Yu, et al 2018   | −0.83 (−1.12,−0.53)      | 9.2      |
| Wei, et al 2018  | −0.04 (−0.06,−0.02)      | 15.9     |
| Wei, et al 2020  | −0.86 (−1.14,−0.58)      | 9.7      |
| Overall          | −0.53 (−0.67,−0.39); P<0.001 | 100.0 |

(I-square: 97.3%; P<0.001)

Figure 9. The effect of TCM on PCT in septic patients treated with ulinastatin. PCT = procalcitonin, TCM = traditional Chinese medicine.

| Study            | Mean difference (95% CI) | % Weight |
|------------------|--------------------------|----------|
| Mao, et al 2008  | −9.50 (−12.60,−6.40)     | 23.4     |
| Jiang, et al 2013| −9.25 (−12.93,−5.57)     | 16.6     |
| Zhao, et al 2013 | −10.59 (−13.79,−7.39)    | 21.9     |
| Yu, et al 2018   | −9.50 (−13.11,−5.90)     | 17.3     |
| Wei, et al 2020  | −9.47 (−12.77,−6.17)     | 20.7     |
| Overall          | −9.69 (−11.19,−8.19); P<0.001 | 100.0 |

(I-square: 0.0%; P=0.983)

Figure 10. The effect of TCM on LPS in septic patients treated with ulinastatin. LPS = lipopolysaccharide, TCM = traditional Chinese medicine.
determine the effects of TCM Xuebijing plus ulinastatin for septic patients with specific characteristics.

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References
[1] Prescott HC, Angus DC. Enhancing recovery from sepsis: a review. JAMA 2018;319:62–75.
[2] Dugar S, Choudhary C, Duggal A. Sepsis and septic shock: guideline-based management. Cleve Clin J Med 2020;87:53–64.
[3] Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.
[4] Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369:840–51.
[5] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Fontanarosa BP. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303–10.
[6] Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis. current estimates and limitations. Am J Respir Crit Care Med 2016;193:259–72.
[7] Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med 2007;35:1244–50.
[8] Liu D, Yu Z, Yin J, et al. Effect of ulinastatin combined with thymosin alpha1 on sepsis: a systematic review and meta-analysis of Chinese and Indian patients. J Crit Care 2017;39:259–66.
[9] Wang H, Liu B, Tang Y, et al. Improvement of sepsis prognosis by ulinastatin: a systematic review and meta-analysis of randomized controlled trials. Front Pharmacol 2019;10:1370.
[10] Atal SS, Atal S. Ulinastatin - a newer potential therapeutic option for multiple organ dysfunction syndrome. J Basic Clin Physiol Pharmacol 2016;27:91–9.
[11] Inoue K, Takano H, Shimada A, et al. Urinary trypsin inhibitor protects against systemic inflammation induced by lipopolysaccharide. Mol Pharmacol 2005;67:673–80.
[12] Li YM, Chen H, Li X, et al. A new immunomodulatory therapy for severe sepsis: ulinastatin plus Thymosin [alpha] 1. J Intensive Care Med 2009;24:47–53.
[13] Shi H, Liu K, He Q, et al. Ulinastatin, a protease inhibitor, may inhibit allogeneic blood transfusion-associated pro-inflammatory cytokines and systemic inflammatory response syndrome and improve postoperative recovery. Blood Transfus 2014;12(suppl):s109–18.
[14] Feng Z, Shi Q, Fan Y, Wang Q, Yin W. Ulinastatin and/or thymosin α1 for severe sepsis: a systematic review and meta-analysis. J Trauma Acute Care Surg 2016;80:335–40.
[15] Uchida M, Abe T, Ono K, Tamaya N. Ulinastatin did not reduce mortality in elderly multiple organ failure patients: a retrospective observational study in a single center ICU. Acute Med Surg 2018;5:90–7.
Xuebijing treatment is associated with decreased mortality risk of patients with moderate parasitic poisoning. PLoS One 2015;10:e0123504.

[14] Mohr D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[15] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.

[16] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

[17] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[18] Deeks JJ, Higgins JP, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[19] Tobias A. Assessing the influence of a single study in the meta-analysis estimate. Stata Tech Bull 1999;47:1–7.

[20] Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. Med Decis Making 2005;25:646–54.

[21] Deeks JJ, Higgins JP, Altman DG. Higgins JPT, Green S. Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions 2008;243–96.

[22] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[23] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629.

[24] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

[25] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[26] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[27] Mao XS, Lv T, Meng DL, et al. Study on the efficacy and safety of ulinastatin combined with Xuebijing in severe sepsis. Chin J Crit Care Med 2008;28:1077–80.

[28] Sun Q, Yang L, Ai ZZ. The efficacy and clinical observation of ulinastatin combined with Xuebijing in severe sepsis. Chin Commun Doctors 2010;12:108.

[29] Ye DW, Wu JG. Clinical observation of ulinastatin combined with Xuebijing in the treatment of sepsis. Chin J Primary Med Pharm 2010;17:514–5.

[30] Bktm ZYL, Nu E. The efficacy and safety of Xuebijing combined with ulinastatin in patients with severe sepsis. Chin Health Ind 2013;10:78.

[31] Zeng FJ, Chen FL, Chen SM, Xu XW, Peng N. Ulinastatin combined with Xuebijing injection for septic shock patients protective effects of myocardial injury. J Guangdong Med Univ 2013;34:616–8.

[32] Jiang L, Mao RS. Chinese medicine preparation adjudvant treatment of severe sepsis efficacy evaluatio. Chin J Hosp Pharm 2013;33:1078–80.

[33] Zhao GK, Liu YH. Clinical study of Xuebijing combined with ulinastatin on myocardial injury in sepsis. Lab Med Clin 2013;10:2718–20.

[34] Zhou CE, Fang ZC. Effect of Xuebijing combined with ulinastatin on immune function in patients with sepsis. Mod J Integr Trad Chin West Med 2013;22:131–2.

[35] Cao CH, Fang XH, Wu XH. Clinical observation of Xuebijing combined with ulinastatin in the treatment of sepsis. Shanxi J Trad Chin Med 2015;36:850–2.

[36] Li XY. Evaluation of the clinical effect of ulinastatin combined with Xuebijing in the treatment of severe sepsis. Contemp Med Symp 2015;13:161–2.

[37] Shan JL. Effect of Xuebijing injection combined with ulinastatin on myocardial injury in patients with septic shock. Mod J Integr Trad Chin West Med 2016;25:1166–71.

[38] Ji BH, Cheng WL, Yang FT. Effect of ulinastatin combined with Xuebijing in treating sepsis. Chin J Rural Med Pharm 2016;23:30–1.

[39] Li CN. The efficacy of ulinastatin combined with Xuebijing in the treatment of thyroid sepsis. Strait Pharm J 2016;28:175–6.

[40] Bian DH, Chen MR, Yu RY. Clinical analysis of Xuebijing injection in the treatment of severe burn with sepsis. Mod Med J 2017;45:483–6.

[41] Chen LX. Effect of Xuebijing injection combined with ulinastatin on cardiac function in patients with multiple organ dysfunction of sepsis. Yunnan J Trad Chin Med Mater Mater Med 2017;38:28–9.

[42] Lu J, Xiao B, Su TS, Xu Q, Li W. Study on the protective effect of Xuebijing combined with ulinastatin on myocardial injury in sepsis. Mod J Integr Trad Chin West Med 2018;27:2633–6.

[43] Zhang Y, Zhao M, Sheng Z, et al. Effect of Xuebijing injection combined with ulinastatin on sepsis induced ARDS patients. XX 2018.

[44] Yu W, Chen Y. Analysis of the effect of hemodiazepine combined with oxytocin on patients with ICU sepsis. China Contin Med Educ 2018;10:143–5.

[45] Li G, Zhang J, Liu Z. Effect of ulinastatin combined with Xuebijing in the treatment of coagulation function and systemic inflammatory response in patients with sepsis. China Med Engin 2018;24:16–8.

[46] Wei J, Wang YH, Jiang JH, Feng DQ. Xuebijing injection combined with ulinastatin in the treatment of severe sepsis patients and its influence on serum factors, T cell subgroup and D-dimer. Drug Eval Res 2018;41:1077–81.

[47] Xu AP, He XL. Effect of Ulinastatin combined with Xuebijing on serum inflammatory cytokines in patients with sepsis. World Latest Med Inform 2019;19:168–71.

[48] Zhang Z. Effect of Xuebijing combined with Ulinastatin injection on myocardial injury in patients with severe septic shock. Prac J Med Pharm 2020;37:425–9.

[49] Wei XL. Analysis of the effect of Xuebijing combined with ulinastatin on ICU sepsis patients. China Foreig Med Treat 2020;8:10–3.

[50] Li C, Wang P, Zhang L, et al. Efficacy and safety of Xuebijing injection (a Chinese patent) for sepsis: a meta-analysis of randomized controlled trials. J Ethnopharmacol 2018;224:512–21.

[51] Xiao SH, Luo L, Liu XH, Zhou YM, Liu HM, Huang ZF. Curative efficacy and safety of traditional Chinese medicine xuebijing injections combined with ulinastatin for treating sepsis in the Chinese population: a meta-analysis. Medicine (Baltimore) 2018;97:e10971.

[52] Liu DH, Liu J, Mo Y, et al. Treatment of sepsis with Xuebijing injection. Med Recap 2016;22:161–3.

[53] Xu HH, Jin LN, Cao ZQ. Clinical effectiveness comparison of Xuebijing or Ulinastatin combined with conventional treatment for chronic obstructive pulmonary disease with acute exacerbation complicated with systemic inflammatory response syndrome. China Pharmacist 2017;20:864–6.

[54] Li C, Wang P, Li M, et al. The current evidence for the treatment of sepsis with Xuebijing injection: Bioactive constituents, findings of clinical studies and potential mechanisms. J Ethnopharmacol 2021;265:113301.

[55] Liu HW. Effect of ulinastatin combined with Xuebijing on clinical efficacy, prognosis and inflammatory status in sepsis patients with severe acute pancreatitis. Shandong Med 2018;58:53–5.

[56] Zhang W. Effects of Ulinastatin combined with Xuebijing and anti-tuberculosis drugs on arterial blood gas and lactate clearance in patients with pulmonary tuberculosis complicated with acute respiratory distress syndrome. Hebei Med 2017;23:1652–6.