Traditional Chinese medicine bundle therapy for septic acute gastrointestinal injury: A multicenter randomized controlled trial

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ABSTRACT

Objective: Current conventional treatments for sepsis associated with acute gastrointestinal injury (AGI) have limited efficacy. This study aimed to study traditional Chinese medicine (TCM) bundle therapy (based on TCM syndrome differentiation) as add-on to conventional treatments on the incidence of AGI and on the prognosis of patients with sepsis.
Design: This was a prospective multicenter randomized single-blind controlled trial.
Setting: Intensive care units (ICUs) of five university teaching hospitals in Zhejiang Province (China) from December 2012 to December 2014.
Interventions: The control group received conventional treatment for sepsis and AGI. The intervention group received the conventional treatment combined with TCM bundle therapy.
Measurements and main results: The primary outcome was 28-day mortality. The secondary outcomes included the clinical indicators of sepsis. The 28-day mortality (35.3% vs. 48.3%, P = 0.01) and AGI-attributable mortality (15.1% vs. 36.2%, P = 0.02) in the intervention group were significantly lower than in controls. Duration of mechanical ventilation (17.4 ± 10.4 vs. 19.9 ± 11.1 days, P = 0.049) and duration of ICU stay (17.3 ± 10.2 vs. 20.1 ± 11.5 days) were significantly shorter in the intervention group compared with controls. On days 7 and 14, D-lactate, diamine oxidase, lipopolysaccharides, tumor necrosis factor-α, intra-abdominal pressure, and abdominal circumference in the intervention group were significantly lower than in controls, and serum MTL levels and bowel sounds were significantly higher (all P < 0.05).
Conclusions: TCM bundle therapy in the early stage of sepsis can improve survival and the markers of gastrointestinal function in patients with sepsis associated with AGI.

1. Background

Sepsis is a critical condition caused by an infection. Sepsis can result in serious complications such as septic shock and multiple organ dysfunction syndrome (MODS), which is one of the main reasons for death in the intensive care unit (ICU).[1] The incidence of severe sepsis is about one per 1000 inpatients, but about 1 per 10 ICU patients.[2] In the United States, the prevalence of sepsis is about 4.3% of hospitalized patients and in-hospital mortality is 21.9%.[3]

Acute gastrointestinal injury (AGI) plays an important role in sepsis

and participates in sepsis initiation[4] Indeed, sepsis itself causes intestinal dysfunction, decreased motility, and intestinal barrier function injury, resulting in the translocation of gut microbiota and endotoxin, and finally leading to the induction and aggravation of MODS. The occurrence of MODS will induce and aggravate AGI, and accelerate patient death.[5,6]

Current therapies for sepsis include anti-infection therapy, early fluid resuscitation, mechanical ventilation, and nutritional support [7-11] The prevention and treatment of AGI include early enteral nutrition and acid inhibitor to protect the gastrointestinal mucosa.[7-12] The current

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treatment approaches have limited efficacy in patients with sepsis and AGI and in-hospital mortality is still around 21.9% despite the best efforts.[3] Complementary and novel approaches are needed to improve the outcomes of sepsis.

Traditional Chinese medicine (TCM) has some efficacy against AGI.[13,14] In TCM, the patients can be categorized according to the principles of syndrome differentiation, and this classification has been shown to be appropriate to guide treatments in patients with AGI.[13,14] In addition, since the etiology of sepsis and AGI is complex and critical, a single therapy approach is not appropriate for all patients.[7–9,12] The use of a bundle TCM therapy based on each patient's specific condition might improve the general outcomes of the patients with sepsis. A previous observational study by our group suggested that the TCM syndrome differentiation (syndrome of interior accumulation of dampness and turbid, obstruction of fu-qi, syndrome of qi stagnation, and blood stasis and spleen-stomach deficiency) could be used to categorize the patients to the appropriate treatments.[15] According to the TCM syndrome differentiation, pill of fructus cannabis, dachengqi decoction, chaihushugan powder, and buzhongyiqi decoction were used, and drugs with effects such as heat-clearing and detoxifying, bowel-relaxing, blood circulation promotion to remove meridian obstruction, and strengthening vital qi were used according to the syndromes.

The exact effect of TCM bundle therapy has not been studied using a well-designed randomized controlled trial. Therefore, the aim of the present study was to examine the effect of TCM bundle therapy based on TCM syndrome differentiation on the incidence of AGI and clinical prognosis of patients with sepsis.

2. Methods

2.1. Subjects and study design

This was a prospective multicenter, randomized (1:1), parallel, single-blind, controlled trial of patients with sepsis and AGI admitted to the ICU (the First Affiliated Hospital, Zhejiang Chinese Medical University; Xinhua Hospital of Zhejiang Province; Integrated Traditional Chinese and Western Medical Hospital of Zhejiang Province; Hangzhou Hospital of Traditional Chinese Medicine; Tongde Hospital of Zhejiang province) between December 2012 and December 2014.

The study was approved by the ethics committee of the First Affiliated Hospital, Zhejiang Chinese Medical University (central ethics committee), and the ethics committees of the four other participating hospitals acknowledged the approbation. All procedures performed in studies involving human participants were in accordance with the ethical standards of the research committee and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards. All enrolled patients signed an informed consent form. This study was registered in the Chinese Clinical Research Registry (Registration number: ChiCTR-IOR-15007625; Date of Registration: 2015-11-18). There were no changes to the protocol after trial initiation.

2.2. Diagnostic criteria

The diagnostic criteria for sepsis complied with the International Guidelines for Sepsis (2008)[16] confirmed or suspected infection, with acute organ dysfunction secondary to infection, and with septic shock (severe sepsis plus hypotension not reversed by fluid resuscitation).

According to the criteria proposed by the European Society of Intensive Care Medicine in 2012[11] AGI was diagnosed as a gastrointestinal dysfunction caused by acute disease in critically ill patient, showing mild or severe abdominal distension, weak or absent bowel sound, paralytic ileus, stress ulcer, and/or gastrointestinal bleeding. The patients were diagnosed with AGI in the presence of any one of the above criteria.

AGI can be divided into four grades. Grade I: there is risk of

gastrointestinal failure and presence of temporary gastrointestinal symptoms with clear cause, but the patients can spontaneously recover. Grade II, digestion and absorption functions do not meet the body requirements for nutrients and water, but without influencing patients' systemic conditions; the intra-abdominal pressure is 12–15 mmHg. Grade III: the gastrointestinal function is lost; the gastrointestinal function cannot be recovered, even with therapy; the intra-abdominal pressure is 15–20 mmHg. Grade IV: gastrointestinal function fails and severely impairs the other organs, leading to MODS and shock. AGI Grade I is reversible and can recover spontaneously without any intervention; therefore, patients with AGI Grade II, III, or IV were enrolled in the present study.

2.3. Inclusion and exclusion criteria

The inclusion criteria were: 1) diagnosis of sepsis; 2) AGI grade II, III, or IV occurring after sepsis; and 3) 18–80 years of age. The exclusion criteria were: 1) patients with predicted ICU time < 3 days; 2) primary gastrointestinal diseases (such as gastrointestinal ulcer or inflammatory bowel disease); 3) history of gastrointestinal surgery; 4) pregnant or lactating women; 5) terminal-stage malignant tumor; 6) patients whose hemodynamics were not stable after 48 h of ICU stay; 7) could not be treated by TCM nasal feeding or acupuncture; 8) allergy to TCM; or 9) participating in another clinical trial.

2.4. Randomization

The patients were randomized after the hemodynamics had been stabilized (MAP ≥ 65 mmHg, noradrenaline dose < 0.2 μg/kg/min, and blood lactic acid < 4 mmol/L). Patients were randomized into the control and intervention groups (1:1 ratio, without blocks) using a central computerized randomization system prepared by an independent statistician. The patients had to be enrolled in the study and registered in the system before allocation was provided. Study registration was performed by the study nurse.

2.5. Blinding

The patients, physicians, and nurses could not be blinded because of the nature of the interventions. The patients (if unconscious, their family members were asked for consent) and their family members were informed of the possible therapeutic regimens prior to the study. Many patients were under coma or sedation during their ICU stay, and were not aware of the therapy being applied. The staff evaluating the gastrointestinal function was not involved in the day-to-day care of the patients and was blind to the treatment regimen.

2.6. Therapy, control group

Conventional therapy was carried out according to the International Guidelines for Sepsis 2012 and included antimicrobial therapy, infection source control, fluid therapy, vasopressors therapy, inotropic therapy, blood product administration, mechanical ventilation therapy, glucose control, renal replacement therapy, nutrition, and stress ulcer prophylaxis.[7]

2.7. Therapy, intervention group

TCM bundle therapy was added to the conventional therapy every day. Each patient received the appropriate TCM decoction by nasal feeding based on their syndrome differentiation. The patients with intra-abdominal pressure > 20 mmHg, gastrointestinal bleeding, or intestinal obstruction did not receive TCM decoction by nasal feeding. As per the exclusion criteria, no patient with coagulopathy received acupuncture. Two TCM physicians (at least deputy director) diagnosed the syndrome differentiation of the patients based on the Diagnostic
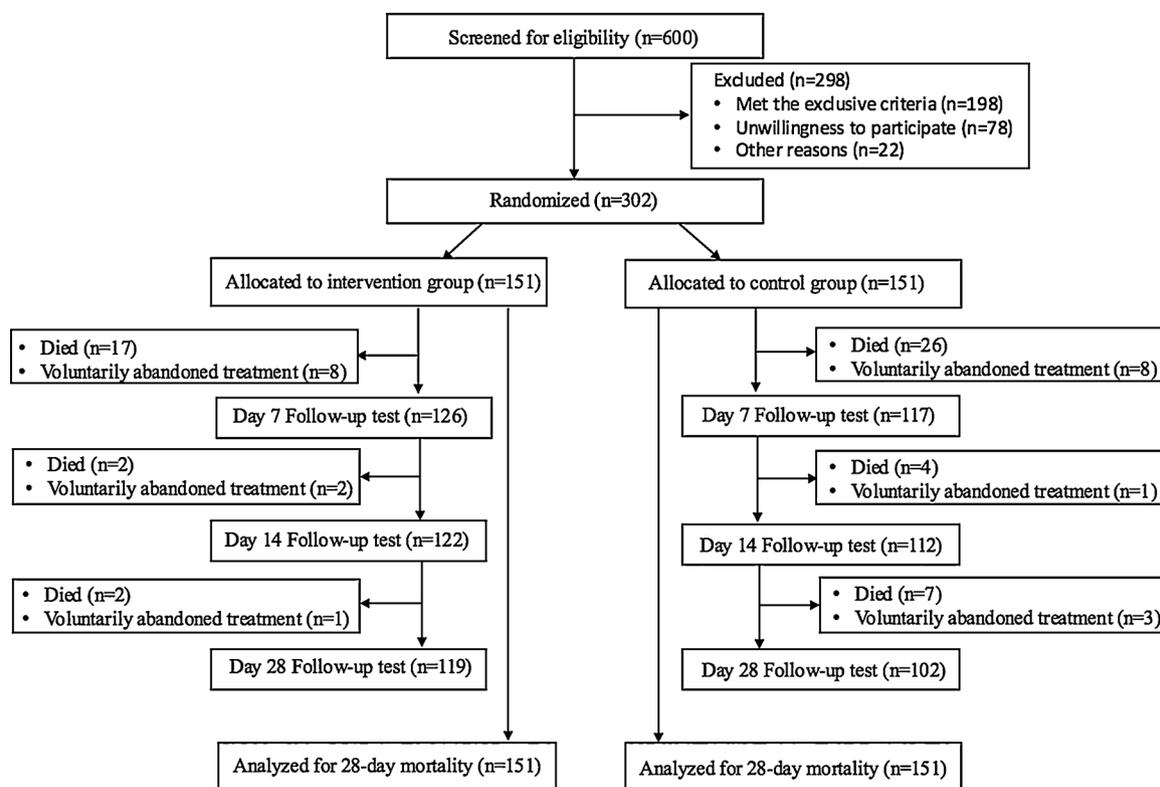
Fig. 1. Patient flowchart.

Criteria of Traditional Chinese Medicine.[17]

1) For syndrome of interior accumulation of dampness and turbidity, the patients were given pills of fructus cannabis: *Rheum officinale* 9 g, linum 12 g, *Fructus aurantiiimmaturus* 12 g, *Radix paeoniaealba* 10 g, *Magnolia officinalis* 10 g, *Semen armeniacaeamarum* 12 g, and whitish honey 6 g.

2) For obstruction of fu-qi, the patients were given modified dachengqi decoction: *Fructus aurantiiimmaturus* 15 g, *Magnolia officinalis* 20 g, *Rheum officinale* 10 g (decocted later), and mirabilite 10 g (administered after dissolving in water or mixed with other drugs, not decocted).

3) For syndrome of qi stagnation, the patients were given modified chaihushugan powder: *Bupleurumchinense* 12 g, *Fructus aurantii* 12 g, *Rhizoma ligustici chuanxiong* 12 g, *Radix paeoniaealba* 12 g, *Rhizomacyperi* 12 g, tangerine peel 9 g, and *Radix glycyrrhizaepreparata* 6 g.

4) For syndrome of spleen and stomach deficiency, the patients were given buzhongyiqi decoction: *Astragalus membranaceus* 15 g, *Panax ginseng* 15 g, *Rhizoma atractylodismacrocephalae* 15 g, *Angelica sinensis* 15 g, *Bupleurumchinense* 15 g, ginger 9 g, jujube 9 g, tangerine peel 12 g, *Rhizoma cimicifugae* 10 g, and *Radix glycyrrhizaepreparata* 6 g.

The differentiation syndrome was reevaluated after 7 days and the patients were treated for another 7 days according to the new diagnosis if it changed or the same treatment was continued if the syndrome remained the same. The total TCM treatment period was 14 days. No TCM was given thereafter.

For decoction, the ingredients were weighted in a non-woven bag. Water was added and the ingredients were immersed for 30 min in a decoction machine (Donghuayuan, Beijing). All decoctions were prepared at the First Affiliated Hospital, Zhejiang Chinese Medical University. The decoction was concentrated, measured, filtered, and packed (100 mL). The decoction was administrated once daily in two doses of 50 mL by nasal feeding, for 14 days.

2.8. TCM decoction by enteroclysis

Enteroclysis was performed only in patients with yang or yin syndrome. The application of enteroclysis for the intervention group was performed according to the yang and yin syndromes. If the patients reported internal accumulation of dampness toxin and blockage of bowel qi, it belonged to the yang syndrome, while spleen-stomach weakness, qi stagnation, and blood stasis belonged to the yin syndrome. If the patients showed stomach or abdominal obstruction, dry stool or constipation, abdominal pain refusing pressing, severe fever and coma, yellow thick and dry tongue, and sunken and solid pulse, they were diagnosed with yang syndrome, and were given clearing heat and detoxicating catharsis, and modified dachengqi decoction: *Fructus aurantiiimmaturus* 15 g, *Magnolia officinalis* 20 g, raw rhubarb 10 g, and mirabilite 10 g. If the patients showed abdominal distension and constipation, twisting below the umbilicus, cold extremities, white tongue, and deep wiry pulse, they were diagnosed with yin syndrome, and they were given yang-warming benefiting qi bowel-relaxing TCM. The modified dachengqi decoction was added with aconite root 15 g, *Panax ginseng* 6 g, dried ginger 9 g, and *Radix glycyrrhizae* 6 g. Each decoction was 100 mL, and retention enema was 10–15 min. The decoctions were administrated once daily. If the bowel frequency were > 3 times daily, the decoction was withdrawn for 1 day. The therapy lasted from 14 days. Other treatment for enteroclysis was forbidden.

2.9. Acupuncture

Acupuncture was performed in patients with different differentiation syndromes using the same method. The acupuncture points in this study were the common ones for the treatment of gastrointestinal dysfunction. Among them, Zhōngwǎn (CV12) is the front-*mu* point of the stomach, and the four acupoints of Zúsānlǐ (ST36), Tiānshū (ST25), Shàngjùxū (ST37), and Xiàjùxū (ST39) are all the foot-yangming

Table 1
Characteristics of the subjects.

General information	Control group					Intervention group					P*
	Total (n = 151)	Syndrome of interior accumulation of dampness and turbid (n = 45)	Syndrome of obstruction of fu-qi (n = 33)	Syndrome of qi stagnation and blood stasis (n = 41)	Syndrome of spleen-stomach deficiency (n = 32)	Total (n = 151)	Syndrome of interior accumulation of dampness and turbid (n = 38)	Syndrome of obstruction of fu-qi (n = 37)	Syndrome of qi stagnation and blood stasis (n = 35)	Syndrome of spleen-stomach deficiency (n = 41)	
Age (years)	75.4 ± 12.2	75.5 ± 12.0	75.5 ± 13.5	75.3 ± 12.5	75.0 ± 11.3	75.5 ± 11.7	74.8 ± 12.6	75.8 ± 12.7	75.5 ± 11.3	75.8 ± 10.6	0.981
BMI (kg/m^2)	22.7 ± 4.3	22.8 ± 4.3	23.4 ± 4.3	21.6 ± 4.4	23.2 ± 4.2	23.4 ± 4.7	24.2 ± 4.3	24.1 ± 4.6	23.4 ± 4.3	21.8 ± 5.1	0.198
Sex: male, n (%)	97 (64.2%)	37 (82.2%)	22 (66.7%)	20 (48.8%)	18 (56.3%)	101 (66.9%)	25 (65.8%)	31 (83.8%)	23 (65.7%)	22 (53.7%)	0.257
APACHE II score	22.3 ± 3.6	21.3 ± 3.0	22.1 ± 3.5	22.1 ± 3.3	24.2 ± 4.3	21.7 ± 3.8	20.5 ± 3.8	23.2 ± 3.6	20.0 ± 3.1	23.0 ± 3.5	0.170
SOFA score	24.8 ± 3.2	24.4 ± 3.5	24.8 ± 3.2	25.0 ± 3.4	24.8 ± 2.7	24.8 ± 3.5	24.6 ± 3.2	23.5 ± 3.4	26.1 ± 3.3	25.1 ± 3.8	0.865
MODS score	6.6 ± 1.4	6.6 ± 1.4	6.6 ± 1.5	6.7 ± 1.4	6.4 ± 1.5	6.4 ± 1.5	7.1 ± 0.8	5.7 ± 1.1	5.9 ± 1.6	6.5 ± 1.8	0.205
GIF score	2.6 ± 0.6	2.4 ± 0.5	2.5 ± 0.5	2.9 ± 0.6	2.7 ± 0.7	2.6 ± 0.6	2.6 ± 0.5	2.5 ± 0.5	2.6 ± 0.7	2.7 ± 0.6	0.847
Reason for ICU stay, n (%)											
Respiratory failure	32 (21.2%)	5 (11.1%)	5 (15.2%)	12 (29.3%)	10 (35.3%)	28 (18.5%)	4 (10.5%)	7 (18.9%)	6 (17.1%)	11 (26.8%)	0.665
Circulatory failure	43 (28.5%)	12 (26.7%)	8 (24.2%)	15 (36.6%)	8 (25.0%)	49 (32.5%)	6 (15.8%)	12 (32.4%)	15 (42.9%)	16 (39.0%)	0.532
Nervous system (epilepsy, stroke)	17 (11.3%)	5 (11.1%)	5 (15.2%)	3 (7.3%)	4 (12.5%)	19 (12.6%)	8 (21.1%)	4 (10.8%)	3 (8.6%)	4 (9.8%)	0.859
Trauma	23 (15.2%)	10 (22.2%)	5 (15.2%)	4 (9.8%)	4 (12.5%)	22 (14.6%)	9 (23.7%)	4 (10.8%)	5 (14.3%)	4 (9.8%)	> 0.999
Other	20 (13.2%)	7 (15.6%)	6 (18.2%)	4 (9.8%)	3 (9.4%)	18 (11.9%)	6 (15.8%)	5 (13.5%)	3 (8.6%)	4 (9.8%)	0.862
Postoperative patient (except gastrointestinal surgery), n (%)	16 (10.6%)	6 (13.3%)	4 (12.1%)	3 (7.3%)	3 (9.4%)	15 (9.9%)	5 (13.2%)	5 (13.5%)	3 (8.6%)	2 (4.9%)	> 0.999
TCM type, n (%)											
Syndrome of interior accumulation of dampness and turbid	45 (29.8%)					38 (25.2%)					0.439
Syndrome of obstruction of fu-qi	33 (21.9%)					37 (24.5%)					0.683
Syndrome of qi stagnation and blood stasis	41 (27.2%)					35 (23.2%)					0.507
Syndrome of spleen-stomach deficiency	32 (21.2%)					41 (27.2%)					0.282
TCM bundle therapy, n(%)											
TCM decoction by nasal feeding	135 (89.4%)	39 (86.7%)	30 (90.9%)	37 (90.2%)	29 (90.6%)	132 (87.4%)	33 (86.8%)	31 (83.8%)	30 (85.7%)	38 (92.7%)	0.72
enteroclysis	126 (83.4%)	40 (88.9%)	29 (87.9%)	34 (82.9%)	23 (71.9%)	129 (85.4%)	32 (84.2%)	31 (83.8%)	34 (97.1%)	32 (78.0%)	0.751
acupuncture therapy	141 (93.4%)	42 (93.3%)	31 (93.9%)	38 (92.7%)	30 (93.8%)	135 (89.4%)	32 (84.2%)	33 (89.2%)	34 (97.1%)	36 (87.8%)	0.305
acupoint application	142 (94.0%)	42 (93.3%)	30 (90.9%)	39 (95.1%)	31 (96.9%)	145 (96.0%)	36 (94.7%)	35 (94.6%)	34 (97.1%)	40 (97.6%)	0.598
Fluid therapy (mL)											
Day 1	4404 ± 1140	4330 ± 1262	4526 ± 941	4552 ± 1156	4193 ± 1136	4480 ± 1209	4438 ± 1197	4509 ± 1245	4476 ± 1272	4496 ± 1175	0.576
Day 3	3418 ± 1128	3374 ± 1227	3526 ± 941	3552 ± 1156	3193 ± 1136	3507 ± 1199	3438 ± 1197	3509 ± 1245	3590 ± 1226	3496 ± 1175	0.507

BMI: body mass index; APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; MODS: multi-organ dysfunction syndrome; GIF: gastrointestinal function failure; ICU: intensive care unit; TCM: traditional Chinese medicine.

* P values were for comparison between the total intervention group vs. the total control group.

Table 2
Comparison of the prognosis between the two groups.

Index	Control group					Intervention group					P*	95% CI
	Total (n = 151)	Syndrome of interior accumulation of dampness and turbid (n = 45)	Syndrome of obstruction of fu-qi (n = 33)	Syndrome of qi stagnation and blood stasis (n = 41)	Syndrome of spleen-stomach deficiency (n = 32)	Total (n = 151)	Syndrome of interior accumulation of dampness and turbid (n = 38)	Syndrome of obstruction of fu-qi (n = 37)	Syndrome of qi stagnation and blood stasis (n = 35)	Syndrome of spleen-stomach deficiency (n = 41)		
Duration of mechanical ventilation (days)	22.4 ± 11.4	20.0 ± 11.4	21.6 ± 10.1	24.1 ± 11.9	24.3 ± 12.1	19.9 ± 10.1	16.2 ± 9.6	17.7 ± 8.4	22.2 ± 11.5	23.2 ± 9.2	0.044	0.070,4.950
Duration of ICU stay (days)	24.4 ± 12.5	21.3 ± 12.6	24.3 ± 11.5	26.6 ± 12.6	26.1 ± 13.0	21.4 ± 11.1	17.2 ± 10.8	18.6 ± 9.4	23.9 ± 12.0	25.6 ± 10.0	0.025	0.383,5.723
28-day mortality[a]	24.5%	26.7%	21.2%	19.5%	31.3%	13.9%	18.4%	13.5%	17.1%	7.3%	0.026	0.149,0.241

* P values were for comparison between the total intervention group vs. the total control group.
a This mortality statistic includes patients who are automatically discharged from the ICU.

stomach meridians, according to the Name and Location of Acupoints 2006 (GB/T12346-2006). Some studies have shown that these acupuncture points were effective for patients with gastrointestinal dysfunction from various TCM syndromes.[18–22] Therefore, point selection according to the pattern differentiation grouping was not necessary in this study. In the present study, different manipulations were used according to their excess and deficiency syndromes during acupuncture. If excess syndromes (internal accumulation of dampness toxin, blockage of bowel qi, qi stagnation and blood stasis) were confirmed, reducing methods were used. If deficiency syndromes (spleen-stomach weakness) were confirmed, reinforcing methods were used. All acupoints were treated with 1.5 cun acupuncture needles (Jiachen, Wujiang) connected to an electroacupuncture system (HT-2, electro-acupuncture therapeutic equipment, Huanyin, Changzhou) by a trained TCM physician. The system was set as continuous-wave and frequency of 4 Hz. The treatment was performed twice daily for 15 min each time, for 14 days.

2.10. Acupoint application

Acupoint application was performed in patients with different differentiation syndromes using the same method. *Fructus evodiae* and cinnamon (3 g each) were ground and mixed with vinegar. The mixture was applied on the patients' Shenque point, covered by a small piece of plastic film and a sterile gauze (external), and fixed by an adhesive plaster. The treatment was performed once daily for 12 h each time, for 14 days.

2.11. Outcomes

The primary outcome was 28-day mortality. The secondary outcomes were D-lac, serum levels of diamine oxidase (DAO), lipopolysaccharides (LPS), motilin (MTL), and tumor necrosis factor (TNF)-α, APACHE II score, sequential organ failure assessment (SOFA) score, MODS score, intra-abdominal pressure, bowel sounds, abdominal circumference, duration of mechanical ventilation, duration of ICU stay, and gastrointestinal function (GIF) score on day 14.

Age, sex, and the cause of ICU stay were recorded. On days 1, 3, 7, and 14, serum samples were collected in the fasting state (discontinued intestinal and parenteral nutrition for > 4 h). All samples were stored at the First Affiliated Hospital, Zhejiang Chinese Medical University, and tested using enzyme-linked immunosorbent assays (ELISA, Xitang, Shanghai) for D-lac, DAO, LPS, MTL, and TNF-α. APACHE II score, AGI grade, SOFA score, MODS score, GIF score (assessed by blinded trained personnel), intra-abdominal pressure, abdominal circumference, bowel sound, duration of mechanical ventilation, duration of ICU stay, and 28-day mortality were determined on days 1, 3, 7, and 14.

For bowel sound examination, the patient was placed in the supine position and a stethoscope was placed on the umbilical region. The number of gurgling sounds within 1 min was recorded. For intra-abdominal pressure measurement, the patient was placed in the supine position. A Foley urinary catheter was connected to a urine storage bag and a piezometer tube. The bladder was emptied and the urinary bag was closed; 0.9% NaCl solution (20 mL) was added into the piezometer tube. The piezometer tube was connected to a transducer. The symphysis pubis was set as zero to measure the intra-abdominal pressure in the bladder.[23]

The adverse events of TCM and conventional therapy were recorded, including anaphylactic reaction (such as rash, shock, etc.), liver function injury, vomiting after TCM administration, fainting during acupuncture, and ecchymosis. If there was an anaphylactic reaction, the suspicious drug was stopped, and appropriate treatment was given. If TCM was vomited, the TCM was prepared again and administered more slowly. If fainting occurred during acupuncture and ecchymosis appeared, the acupuncture needles were taken out immediately. If there were severe adverse reactions to TCM (such as severe liver and kidney damage), the TCM intervention was stopped immediately.
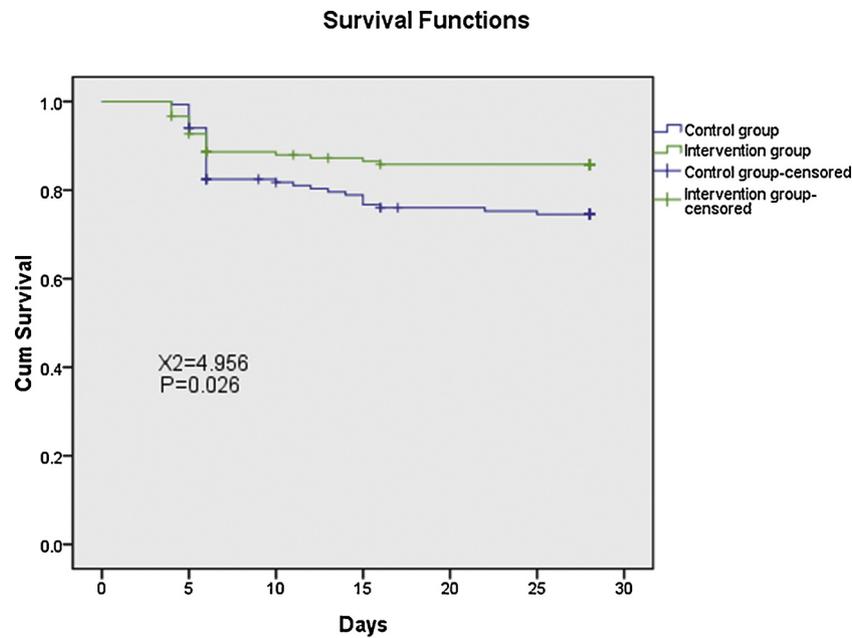
Survival Functions

Fig. 2. Kaplan-Meier analysis of the 28-day survival of the intervention and control groups.

Table 3
Comparison of the clinical efficacy between the two groups.

Index	Time	Control group (n1 = 151) (n3 = 151) (n7 = 117) (n14 = 102)	Intervention group (n1 = 151) (n3 = 151) (n7 = 126) (n14 = 122)	P
D-lac (μg/L)	Day 1	519.8 ± 157.4	515.2 ± 152.4	0.778
	Day 3	471.1 ± 130.6	458.4 ± 136.4	0.411
	Day 7	445.7 ± 121.5	404.9 ± 126.6	0.011
	Day 14	379.2 ± 132.0	344.8 ± 121.0	0.043
DAO (U/ml)	Day 1	12.7 ± 5.5	12.8 ± 5.5	0.968
	Day 3	12.1 ± 3.8	12.0 ± 3.7	0.828
	Day 7	10.9 ± 3.3	9.8 ± 3.5	0.015
	Day 14	8.8 ± 2.4	8.0 ± 2.6	0.018
LPS (eu/ml)	Day 1	0.84 ± 0.16	0.82 ± 0.12	0.826
	Day 3	0.81 ± 0.13	0.82 ± 0.12	0.782
	Day 7	0.73 ± 0.15	0.69 ± 0.17	0.010
	Day 14	0.47 ± 0.13	0.43 ± 0.11	0.013
MTL (pg/ml)	Day 1	149.3 ± 95.3	149.2 ± 98.9	0.993
	Day 3	182.5 ± 127.2	193.2 ± 119.8	0.454
	Day 7	219.6 ± 115.0	253.3 ± 119.5	0.026
	Day 14	278.9 ± 169.0	336.9 ± 181.4	0.014
TNF-α (ng/L)	Day 1	224.7 ± 137.3	225.3 ± 138.1	0.967
	Day 3	207.2 ± 116.3	205.0 ± 105.3	0.863
	Day 7	176.4 ± 68.0	162.0 ± 70.1	0.007
	Day 14	122.7 ± 36.5	112.3 ± 31.8	0.025
Intra-abdominal pressure (cmH2O)	Day 1	14.2 ± 1.9	14.6 ± 2.1	0.052
	Day 3	13.0 ± 3.2	12.9 ± 3.4	0.800
	Day 7	13.2 ± 3.3	12.1 ± 3.4	0.019
	Day 14	11.9 ± 3.6	11.0 ± 3.0	0.033
Bowel sound (times/ min)	Day 1	1.05 ± 0.93	1.18 ± 0.76	0.177
	Day 3	1.10 ± 0.79	1.13 ± 0.76	0.767
	Day 7	1.24 ± 0.75	1.56 ± 0.82	0.014
	Day 14	1.88 ± 0.95	2.21 ± 0.97	0.011
Abdominal circumference (cm)	Day 1	90.3 ± 10.7	90.6 ± 9.7	0.844
	Day 3	89.9 ± 10.4	89.7 ± 9.7	0.837
	Day 7	89.0 ± 9.2	85.9 ± 8.0	0.036
	Day 14	86.0 ± 8.7	83.4 ± 9.5	0.038

Note: n1, n3, n7, n14 represented the survived case number on Day 1, 3, 7 and 14.
D-lac: D-lactic acid; DAO: diamine oxidase; LPS: lipoplysaccharides; MTL: motilin; TNF-α: tumor necrosis factor α.

2.12. Sample size

Sample size estimation was based on the 28-day mortality, a superiority design, and 1:1 randomization. The estimated 28-day mortality was 35% and 20% for the control and experimental groups, respectively. Type I error (α) was set at 0.05, and power was set at 0.80. Assuming a drop-out rate of 15%, a total sample size of 302 was required.

2.13. Statistical analysis

Data were analyzed using SPSS 17.0 (IBM, Armonk, NY, USA). Two-sided P-values ≤ 0.05 were considered statistically significant. Continuous data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous data are presented as means ± standard deviation, and were analyzed using the Student *t*-test Skewed continuous data are presented as medians (range), and were analyzed using the Mann-Whitney U test. Categorical data are presented as number (n), and percentage or rate (%), and were analyzed using the chi-square test, corrected chi-square test, or Fisher's exact test, as appropriate. Overall survival (OS) was analyzed by the Kaplan-Meier method and the log-rank test. We assessed the 28-day mortality, duration of mechanical ventilation and hospital stay, and adverse events in the full analysis set, and the other variables in the per-protocol set. Considering the severity of sepsis with AGI, subjects who voluntarily chose to discontinue treatment and leave the hospital, or who were lost to follow-up were presumed dead.

3. Results

3.1. Characteristics of the patients

A total of 600 patients with sepsis and AGI and admitted to the ICU of five hospitals between December 2012 and December 2014 were screened; 302 patients were enrolled according to the eligibility criteria (Fig. 1).

There were no significant differences in age, sex, APACHE II score, SOFA score, MODS score, reason for ICU stay, and TCM syndrome differentiations between the two groups (all P > 0.05) (Table 1).

Table 4
Comparisons of the GIF and APACHE II scores in subgroups of different AGI grades.

Group		AGI Grade II			AGI Grade III			AGI Grade IV		
		Control group (n1 = 71, n14 = 51)	Intervention group (n1 = 70, n14 = 55)	P	Control group (n1 = 64, n14 = 49)	Intervention group (n1 = 66, n14 = 55)	P	Control group (n1 = 16, n14 = 12)	Intervention group (n1 = 15, n14 = 12)	P
GIF score	d1 d14	2.44 ± 0.50	2.56 ± 0.50	0.155	2.80 ± 0.65	2.64 ± 0.62	0.152	2.69 ± 0.70	2.67 ± 0.72	0.936
		1.37 ± 0.63	1.11 ± 0.71	0.047	1.73 ± 0.70	1.42 ± 0.76	0.030	1.75 ± 0.62	1.67 ± 0.89	0.792
APACHE II score	d1 d14	21.92 ± 3.16	21.87 ± 4.01	0.942	22.06 ± 3.45	21.27 ± 3.43	0.195	25.06 ± 4.84	23.07 ± 3.77	0.212
		15.37 ± 3.35	13.75 ± 3.31	0.013	14.22 ± 3.44	12.55 ± 3.56	0.016	19.25 ± ,4.65	14.25 ± 4.03	0.010

3.2. Primary outcome

In the control group, 37 patients died and 12 who voluntarily abandoned treatment and discharged from hospital were presumed dead. The causes of death in 37 patients in the control group were respiratory failure (n = 6), circulatory failure (n = 10), failure of the central nervous system (n = 6), trauma (n = 7), and hepatic failure (n = 8). In the intervention group, 21 patients died and 11 who voluntarily abandoned treatment and discharged from hospital were presumed dead. The causes of death in 21 patients in the intervention group were respiratory failure (n = 3), circulatory failure (n = 6), failure of the central nervous system (n = 5), trauma (n = 4), and hepatic failure (n = 3). There was no difference between the two groups regarding the causes of death. No patient died from treatment-related causes. The 28-day mortality (21.2% vs. 32.5%, P = 0.038) in the intervention group was significantly lower than in the control group (Table 2 and Fig. 2).

3.3. Secondary outcomes

There were no significant differences in all indexes between the two groups on days 1 and 3 after enrollment (all P > 0.05) (Table 3). On the other hand, serum D-lac, DAO, LPS, TNF-α, intra-abdominal pressure, and abdominal circumference in the intervention group were all significantly lower than in the control group on days 7 and 14, and serum MTL and bowel sounds were significantly higher (all P < 0.05) (Table 3).

The patients in the intervention and control groups were divided into three subgroups according to the AGI grade at enrollment. On day 1, the GIF and APACHE II scores in each subgroups of the two groups were similar (all P > 0.05). On day 14, the GIF and APACHE II scores of the patients with AGI grades II and III were significantly lower in the intervention group compared with controls (P < 0.05). The patients with AGI grade IV had similar GIF scores (P > 0.05), but the APACHE II scores in the intervention group were lower than in the control group (P < 0.05) (Table 4).

Duration of mechanical ventilation (19.9 ± 10.1 vs. 22.4 ± 11.4 days, P = 0.044) and duration of ICU stay (21.4 ± 11.1 vs. 21.4 ± 12.5 days, P = 0.025) were significantly shorter in the intervention group compared with the control group (Table 2).

3.4. Adverse events

Apart from sepsis-related events leading to mortality, three patients vomited when receiving the decoction. Two patients had ecchymosis after acupuncture. No patient stopped treatment because of adverse events.

4. Discussion

Currently, the treatment approaches used to treat patients with sepsis and AGI have limited efficacy. The present randomized controlled trial aimed to examine the effect of TCM bundle therapy based on TCM syndrome differentiation added to Western treatments on the prognosis of patients with sepsis. The results suggest that TCM bundle therapy in the early stage of sepsis can improve the gastrointestinal function and clinical prognosis of patients with sepsis and AGI.

Sepsis-associated AGI displays high mortality, around 20–25%[3] indicating that the conventional therapeutic approaches[7–9,12] are still far from being optimal. TCM has been shown to have some efficacy against AGI when using the principles of syndrome differentiation to categorize and treat the patients.[13,14] A previous observational study by our group[15] showed that prevention bundle therapy tailored to the specific syndrome differentiation and added to the conventional therapy could improve patients' outcomes. The results of this observational study were confirmed by the present multicenter randomized controlled trial. Indeed, the 28-day mortality was significantly improved in the intervention group. The secondary outcomes were improved as well.

Fructus cannabis pills can increase humor and promote gastrointestinal motility.[24] The dachengqi decoction administrated by nasal feeding or early enteroclysis can help gastrointestinal emptying, decrease intra-abdominal pressure, and improve gastrointestinal function recovery.[25] Chaihushugan powder can increase the secretion of MTL, and decrease the release of adrenocorticotropic hormone.[26] Buzhongyiqi decoction has good efficacy on treating gastritis, constipation, diarrhea, functional dyspepsia, and colitis.[27] Fructus evodiae dispels cold, relieves pain, and decreases counter-flow, nausea, and diarrhea.[28] Cinnamon tonifies fire, helps the yang, dispels cold, relieves pain, warms channels, frees the vessels, and conducts the fire back to its origin, and it is the main medicine for treating yang-function insufficiency of kidney zang.[29] Fructus evodiae combined with cinnamon on the Shenque point can decrease abdominal distension in ICU patients.[30]

Zusanli, ST37, ST39, and ST25 all belong to the stomach meridian of foot-yangming.[31] Acupuncture at the Zusanli point can harmonize the stomach for descending adverse qi and promote bowel movements. Acupuncture on ST37 can calm and regulate the intestines. Acupuncture on ST25 can regulate the intestines and qi-flowing for activating stagnancy, and help digestion. Acupuncture on ST39 can regulate the intestines. Acupuncture on Zhongwan can regulate the middle energizer and supplement middle qi. Above all, acupuncture on these five acupoints can promote the recovery of the gastrointestinal function.[31,32] The Shenque point lies in Qizhong, which can dredge meridians and collaterals, regulate viscera and bowels, moisten intestine, and relax the bowels.[31,32]

D-lac is a metabolite of bacterial fermentation in the gastrointestinal tract. In severe sepsis, acute ischemia/hypoxia occurs in the intestinal tract, leading to increased permeability of the intestinal mucosa. The D-lac generated by the intestinal bacteria can enter into blood circulation through the damaged mucosa.[33] DAO is a highly active enzyme in the cytoplasm of mammalian intestinal epithelial cells. DAO is highly stable in the peripheral blood and is a marker of severe intestinal stress or trauma.[34] Therefore, serum DAO and D-lac levels can indicate the integrity and injury degree of the intestinal mucosal barrier. LPS is a component on the cell wall of Gram-negative bacteria and can pass through the intestinal wall into blood when the gastrointestinal

mucosal barrier function is injured. Thus, LPS can be used as a marker to evaluate intestinal barrier function.[35] MTL is a gastrointestinal hormone secreted by M cells in the duodenum and upper mucosa of the jejunum, and can promote gastrointestinal motility. Under critical disease, the intestinal mucosa is injured, and the M cell secretion function is gradually lost, leading to decrease in MTL secretion and peristalsis, or even intestinal paralysis.[36] This state causes further over-growth and translocation of bacteria, which aggravates the disease. TNF-α is a pro-inflammatory mediator secreted by Th1 cells and activated monocytes/macrophages, and it is also the most important multifunctional pro-inflammatory cytokine. TNF-α increases the expression of myosin light chain kinase (MLCK), increases the permeability of para-intestinal epithelial cells, and aggravates the damage and apoptosis of intestinal mucosa and intestinal epithelial cells by inducing the activation of nuclear transcription factors.[37] In the present study, these markers were secondary outcomes and were found to be improved after 7 and 14 days of bundle therapy, but no differences were seen at 1 and 3 days, suggesting that the effect of the bundle therapy on these parameters is relatively slow and gradual. Hence, the gastrointestinal dysfunction was gradually improved with treatment time. The intestinal mucosal barrier eventually recovered, permeability decreased, and the release into circulation of toxins and inflammatory mediators also decreased. Furthermore, the gastrointestinal motility was improved and intra-abdominal pressure and secretion of gastric acid were reduced, which might improve septic AGI. Above all, the improvements in the intervention group were superior to the changes observed in the control group, suggesting that the TCM bundle therapy possesses some advantages in improving gastrointestinal dysfunction of critical disease.

The APACHE II score is a quantitative scoring index indicating the severity and prognosis of severe diseases. Higher scores indicate more severe disease and poorer prognosis, and it is widely used in the ICU[38] GIF is another score considered to evaluate patients' prognosis.[39] In the present study, after TCM bundle intervention, the GIF and APACHE II scores of patients with AGI grades II and III were significantly lower than those in the corresponding control subgroups. The GIF scores of patient with AGI Grade IV in the intervention group had no significant difference compared with the control group (P > 0.05), but APACHE II scores were significantly lower than in the control group (P < 0.05). These results suggest that TCM bundle therapy had better efficacy on improving mild-to-moderate gastrointestinal dysfunction. With disease aggravation, the factors influencing gastrointestinal function are increased, and the effect of treating AGI could not be optimal. Additional studies are necessary to examine the best approach for severe AGI.

The present study has limitations. Because the observation period was short and most of the enrolled patients were old, some biases might be present and limit the generalizability of the results. Because of the nature of the interventions, the patients, nursing staff, and physicians could not be blinded to grouping. In addition, many patients did not meet the eligibility criteria. Finally, because of the variability in clinical presentation and reference from clinics and other hospitals, it was impossible to determine which, between AGI and sepsis, occurred first. Future studies should include a longer follow-up and explore the involved mechanisms.

5. Conclusions

In conclusion, our study suggests that TCM bundle therapy in the early stage of sepsis can improve the survival and the markers of gastrointestinal function of patients with sepsis and AGI.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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