

# Early traditional chinese medicine bundle therapy for the prevention of sepsis acute gastrointestinal injury in patients with severe sepsis

## Abstract

To study the role of early traditional Chinese medicine bundle therapy on the prevention of sepsis-associated acute gastrointestinal injury (AGI). This was a multicenter, prospective cohort study of 296 consecutive patients with severe sepsis between 2013/3 and 2014/11; 150 patients received standard treatments (controls) and 146 received traditional Chinese medicine bundle therapy (intervention group) (herbal decoction gavage based on syndrome differentiation, acupuncture, application of mirabilite, and defecation mixture). D-lactic acid, diamine oxidase, endotoxin, gastrin, and intra-abdominal pressure were measured. AGI was classified into four levels. Compared with controls, D-lactic acid, diamine oxidase, endotoxin, gastrin, and intra-abdominal pressure in the intervention group were decreased and motilin was increased on day 7 ( $P<0.05$ ). AGI incidence in the intervention group was lower than in controls ( $P<0.05$ ). GIF scores of the intervention AGI II and III groups were lower than in controls ( $P<0.05$ ). The APACHE II scores of intervention AGI II, III, and IV groups were lower than in controls ( $P<0.05$ ). Compared with controls, mechanical ventilation time and ICU stay in the intervention group were shorter ( $P=0.011$  and  $P=0.035$ ); and 28-day overall and AGI-attributed mortality were lower ( $P=0.048$  and  $P=0.043$ ). For patients with severe sepsis, early traditional Chinese medicine bundle therapy could decrease AGI incidence and improve prognosis.

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## Introduction

Sepsis is a crucial clinical issue in critical care medicine. There are millions of new cases of sepsis every year globally and >25% of these patients die.<sup>1</sup> The immune function of patients with sepsis is depressed, which can easily lead to multiple organ dysfunction syndrome (MODS).<sup>2</sup>

The main manifestations of sepsis include gastrointestinal dysfunction or failure and gastrointestinal mucosa injury, which lead to the translocation of gastrointestinal bacteria and toxin, leading to septic shock 3,4. Furthermore, aggravation of the septic shock condition will lead to gastrointestinal mucosa function being further impaired, leading to a vicious circle.<sup>3</sup>

Studies have shown that early enteral nutrition (EN) support can improve the nutritional status and prognosis.<sup>5,6</sup> In 2014, sepsis treatment guidelines suggested that patients with stable hemodynamics should receive EN support as soon as possible (within 48h). This early stage EN support could maintain the integrity of the intestinal mucosa, prevent bacterial translocation and organ dysfunction, and decrease the infection rate.<sup>7</sup> However, in stressful situation, the gastrointestinal tract is depressed and its function is significantly weakened, resulting in difficult EN support.<sup>7-9</sup> Impaired gastrointestinal motility will cause reflux and aspiration, increasing the risk of ventilator-associated pneumonia (VAP) and will lead to longer mechanical ventilation time, ICU stay, and total hospitalization. Some randomized controlled trials (RCT) found that 24-48h of EN treatment for ICU patients with trauma could significantly decrease mortality and hospitalization expenses.<sup>6,9</sup>

Treatments for sepsis include early resuscitation, anti-infection therapy, mechanical ventilation, nutritional support, immunoregulation, and symptomatic support.<sup>6</sup> Prevention measures for gastrointestinal dysfunction include the use anti-acids to protect

the gastrointestinal mucosal barrier, supplement glutamine, and microbial ecological agents. Based on the early goal-directed therapy (EGDT)<sup>10</sup> and bundle therapy theories proposed in recent years (herbal decoction gavage based on syndrome differentiation, acupuncture, application of mirabilite, and defecation mixture),<sup>11-13</sup> the modern Chinese medicine differentiates syndrome, pays equal attention to strengthening body resistance and eliminating pathogenic factors, and proposes the concept of traditional Chinese medicine (TCM) bundle therapy from the concept of "wholism". According to the TCM theory, the six fu-organs function well when the gastrointestinal tract unobstructed. For patients with sepsis, TCM aims to maintain unobstructed daily stool elimination, good tolerance of EN, normal borborygmus, and normal intra-abdominal pressure. However, clinical data are still lacking about the efficiency of this approach in patients with sepsis.

Therefore, this study aimed to study the role of early traditional Chinese medicine bundle therapy on the prevention and treatment of sepsis after acute gastrointestinal injury (AGI). Patients received bundle intervention that included herbal decoction gavage according to syndrome differentiation, acupuncture at acupoints of Stomach Meridian of Foot-Yangming, application of mirabilite on the umbilicus, and enema with defecation mixture.

## Results

### Characteristics of the patients

From the 551 eligible patients, 296 patients were enrolled and included in the analysis (Figure 1). Table 1 presents the characteristics of these patients. There was no significant difference between the two groups for age, gender, APACHE II score, SOFA score, MODS score, source of infection, and reason of ICU admission (all  $P>0.05$ ).

### Index of gastrointestinal function and intra-abdominal pressure

Table 2 presents the laboratory indexes of gastrointestinal function of the patients. On day1, there was no significant difference between the two groups for D-lac, DAO, endotoxins, MTL, GAS, and intra-abdominal pressure (all  $P>0.05$ ). On day3, compared with controls, the intra-abdominal pressure was lower in the intervention group ( $P<0.01$ ) and MTL levels were higher ( $P<0.05$ ), but there was no difference for D-lac, DAO, endotoxin, and GAS (all  $P>0.05$ ). On day 7, D-lac, DAO, endotoxin, GAS, and intra-abdominal pressure were all lower in the intervention group than in controls (all  $P<0.05$ ), and MTL levels were higher ( $P<0.05$ ).

### AGI incidence

Within 7days after admission, there were 88 patients with AGI in the control group and 69 patients in the intervention group. The incidence of AGI in the intervention group was lower than in the control group ( $P<0.05$ ) (Table 3).

### General condition of the patients

There was no difference in the distribution of patients with AGI II, III, and IV between the intervention and control groups ( $P>0.05$ ). The GIF scores of the AGI II and III subgroups of the intervention group were significantly lower than the AGI II and III subgroups of the control group ( $P<0.05$ ). APACHE II scores of the AGI II and III subgroups of the intervention group were lower than in the AGI II and III subgroups of the control group ( $P<0.05$ ) (Table 4).

The patients were divided into three groups according to their APACHE II score at admission:  $<10$ ,  $10-20$ , or  $>20$ . When comparing the AGI incidence, the AGI incidence of the  $<10$  and  $10-20$  subgroups in the intervention group were lower than in the  $<10$  and  $10-20$  subgroups of the control group ( $P<0.05$ ) (Table 5).

The mechanical ventilation time and ICU stay in the intervention group were significantly shorter than in the control group (both  $P<0.05$ ). The 28-day and AGI-related mortality in the intervention group were lower than in the control group ( $P<0.05$ ) (Table 6) (Figure 1).

**Table 1** Characteristics of the 296 patients with sepsis

	Control group (n=150)	Intervention group (n=146)	P
Age (years)	76.4±13.9	76.5±14.0	0.927
Male, n (%)	109 (72.7%)	109 (74.7%)	0.792
SOFA score	8.72±1.51	9.02±1.40	0.081
APACHE II score	15.5 ± 2.0	15.9 ± 2.0	0.085
<b>Original infection sites, n (%)</b>			
Respiratory system	80 (53.3%)	76 (52.1%)	
Digestive System	37 (24.7%)	29 (19.9%)	
Urinary system	7 (4.7%)	10 (6.9%)	0.787
Hematogenous infection	9 (6.0%)	12 (8.2%)	
Intracranial infection	5 (3.3%)	4 (2.7%)	
Other sites	12 (8.0%)	15 (10.3%)	
<b>Reason of ICU admission, n (%)</b>			
Respiratory failure	69 (46.0%)	75 (51.4%)	
Circulatory failure	20 (13.3%)	18 (12.3%)	
Nervous system (epilepsy, apoplexy)	21 (14.0%)	16 (11.0%)	0.918
Trauma	17 (11.3%)	18 (12.3%)	
Others	3 (2.0%)	2 (1.4%)	
Postoperative patient	20 (13.3%)	17 (11.6%)	
<b>Traditional chinese medicine syndrome</b>			
Qi activity stagnation	52 (34.7%)	45 (30.8%)	
Qi stagnation and blood stasis	40 (26.7%)	36 (24.7%)	0.773
Spleen-stomach weakness	30 (20.0%)	35 (24.0%)	
Internal accumulation of damp-heat	28 (18.7%)	30 (20.6%)	

**Table 2** Laboratory indexes of gastrointestinal function

Indexes	Time point	Control group (n1=150) (n3=150) (n7=136)	Intervention group (n1=146) (n3=146) (n7=138)	P
D lactic acid (mg/L)	Day 1	508.25 ± 285.03	506.54 ± 279.74	0.960
	Day 3	392.21 ± 186.26	373.01 ± 163.78	0.406
	Day 7	377.79 ± 204.93	321.65 ± 138.78	0.044
Diamine oxidase (U/ml)	Day 1	12.98 ± 7.31	12.97 ± 7.31	0.992
	Day 3	10.65 ± 5.32	11.11 ± 5.84	0.530
	Day 7	12.36 ± 6.43	10.09 ± 4.55	0.010
Endotoxin (eU/ml)	Day 1	0.77 ± 0.23	0.78 ± 0.21	0.630
	Day 3	0.68 ± 0.18	0.63 ± 0.19	0.097
	Day 7	0.64 ± 0.17	0.59 ± 0.17	0.035

Table Continued...

Indexes	Time point	Control group (n1=150) (n3=150) (n7=136)	Intervention group (n1=146) (n3=146) (n7=138)	P
Motilin (ng/L)	Day 1	273.05 ± 198.18	268.55 ± 198.18	0.844
	Day 3	274.08 ± 165.02	324.12 ± 201.30	0.041
	Day 7	320.54 ± 230.24	423.02 ± 318.69	0.021
Gastrin (ng/L)	Day 1	221.82 ± 177.96	216.42 ± 177.63	0.794
	Day 3	216.24 ± 120.75	183.79 ± 113.08	0.041
	Day 7	214.32 ± 121.37	176.54 ± 99.14	0.037
Intra-abdominal pressure (mmHg)	Day 1	9.77 ± 4.02	10.30 ± 2.86	0.193
	Day 3	11.23 ± 4.11	9.16 ± 4.12	<0.001
	Day 7	11.59 ± 3.80	10.28 ± 2.61	0.012

Table 3 Comparison of AGI incidence

Groups	Control group (n=150)	Intervention group (n=146)	P
AGI (%)	88 (58.67%)	69 (47.26%)	0.041
No AGI (%)	62 (41.33%)	77 (52.74%)	

Table 4 General condition of the patients

	Control group (n7=88)	Intervention group (n7=69)	P
AGI II			
n	13 (14.8%)	18 (26.1%)	0.077
GIF score	2.7 ± 1.0	2.2 ± 0.9	0.006
APACHE II score	12.2 ± 2.5	11.3 ± 2.0	0.011
AGI III			
n	68 (77.3%)	48 (69.6%)	0.275
GIF score	2.9 ± 1.0	2.4 ± 1.0	0.007
APACHE II score	11.1 ± 2.0	10.2 ± 1.9	0.013
AGI IV			
n	7 (8.0%)	3 (4.4%)	0.358
GIF score	4.7 ± 0.7	4.6 ± 0.8	0.552
APACHE II score	13.7 ± 1.9	13.2 ± 1.6	0.023

Table 5 Comparison of the AGI incidence according to APACHE II scores

	APACHE II <10, n (AGI incidence)	APACHE II 10-20, n (AGI incidence)	APACHE II >20, n (AGI incidence)
Control group (n=150)	24 (25.0%)	70 (51.4%)	56 (82.1%)
Intervention group (n=146)	21 (0%)	67 (31.3%)	58 (82.8%)
P	0.023	0.024	1.000

Table 6 Comparison of prognosis between the two groups

Parameter	Control group (n=150)	Intervention group (n=146)	P
Mechanical ventilation time (days)	10.4 ± 3.7	9.3 ± 3.8	0.011
ICU stay (days)	18.5 ± 10.6	14.2 ± 7.9	0.035
28-day mortality	43.3%	31.5%	0.048
AGI-attributable mortality	8.7%	2.7%	0.043

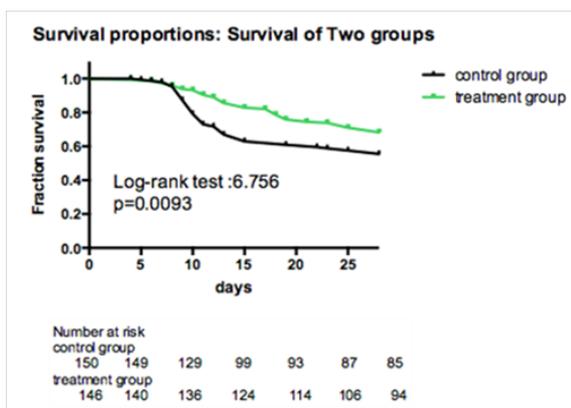
## Discussion

The aim of the present study was to study the role of early traditional Chinese medicine bundle therapy on the prevention and treatment of sepsis-associated AGI. Results showed that compared with controls, D-lactic acid, diamine oxidase, endotoxin, gastrin, and intra-abdominal pressure in the intervention group was decreased on day 7; motilin was increased on day 7. AGI incidence in the intervention group was lower than in controls. GIF scores of the intervention AGI II and III groups were lower than in controls. The APACHE II scores of intervention AGI II, III, and IV groups were lower than in controls. Compared with controls, mechanical ventilation time in the

intervention group was shorter; ICU stay was shorter; and 28-day overall and AGI-attributed mortality was lower.

Severe ischemia and anoxia observed in patients with sepsis often lead to gastrointestinal mucosal barrier dysfunction, allowing intestinal bacteria and endotoxin translocation. In the last decade, critical disease monitoring and organ function support technologies improved greatly, but mortality from sepsis is still as high as 20-50%.<sup>1</sup> The therapeutic approach of western medicine on sepsis gastrointestinal dysfunction is still limited to symptomatic treatment. On the other hand, the spleen-stomach theory of TCM pays attention to the spleen-stomach function, which is a crucial principle of syndrome differentiation. In the Treatise on Spleen and Stomach, Li indicated

that internal impairment of the spleen and stomach will cause various diseases, suggesting the significant role of spleen and stomach on disease development. TCM believes that there cannot be any survival without stomach Qi. Some randomized clinical trials showed that in the first 24-48h, EN treatment for the patients with critical illness could significantly decrease mortality and hospitalization expenses of patients in the ICU.<sup>8,14</sup> Reintam et al.,<sup>15</sup> suggested that because of the complex and various functions of the gastrointestinal tract, a single treatment would not improve the gastrointestinal tract in cases of severe illness.



**Figure 1** 28-day survival curve between the control group and intervention group.

TCM bundle therapy includes nasal feeding, tongbian mixture enema, umbilicus compress of mirabilite, acupuncture, and moxibustion. According to TCM, sepsis gastrointestinal dysfunction can be divided into four types: Qi activity stagnation, Qi stagnation and blood stasis, asthenia of spleen and stomach, and dampness and heat from interior. These syndromes are treated with Simo Yinzi, taohe chengqitang, six gentlemen decoction, and peptic powder, respectively. The main component of tongbian mixture enema is rheum officinale, which have various pharmacological actions and can protect gastrointestinal mucosal barrier, promote gastrointestinal motility,<sup>16</sup> alleviate inflammatory reaction, decrease intestinal permeability, inhibit the absorption of endotoxin and growth of pathogenic bacterium, and improve cellular immunity and proliferation of lymphocyte to prevent GIF.<sup>17</sup> The main components of mirabilite are sodium sulfate, calcium sulfate, and magnesium sulfate. Mirabilite has strong water absorbing power and some effects including against diarrhea and detumescence, as well as diuretic effects. External application of mirabilite on the abdomen can withdraw the ascites, ease the burden of abdominal distension and intestinal tract, promote the detumescence of enterocolia swollen organs, and is beneficial to the control of inflammation and recovery of intestinal functions.<sup>18</sup> Acupuncture at acupoints of Stomach Meridian of Foot-Yangming has some effects including regulating spleen and stomach, invigorating spleen-reinforcing Qi, clearing and activating the channels and collaterals, strengthening body resistance and eliminating evil, dual-direction regulation of nerve-internal secretion-immune systems, inhibition of systemic inflammatory response, and few adverse reactions.<sup>19</sup> A previous study showed that acupuncture at ST36 and EA could improve the intestinal mucosal barrier in sepsis.<sup>13</sup>

DAO is an enzyme with high activity that exists in the intestinal mucosal epithelium. Under pathological states, intestinal mucosal cells suffer from an ischemic injury, and DAO is released into circulation; it is therefore a marker of intestinal damage. D-lac is a metabolite of intestinal bacteria fermentation and endotoxin is a direct marker

of the presence of Gram-negative intestinal bacteria. Normally, D-lac and endotoxins cannot get through the intestinal mucosal barrier; therefore, any increase of their blood levels indicates changes of intestinal permeability or barrier function, and D-lac and DAO are early diagnosis indicators of gastrointestinal mucosal barrier function injury.<sup>20</sup> The present study showed that on the 3rd day after admission, the levels of D-lac, DAO, and endotoxin in the intervention group were lower than in the control group, but without reaching statistical significance ( $P>0.05$ ), but on the 7th day, levels of D-lac, DAO, and endotoxin in the intervention group were significantly lower than in the control group, indicating that gastrointestinal mucosal barrier function injury was alleviated.

MTL and GAS are key gastrointestinal hormones involved in gastrointestinal motility. MTL is an excitant gastrointestinal hormone that can regulate the cyclic activity of interdigestive myoelectric complexes, maintain normal peristalsis of stomach and small intestine, and prevent the over-growth of gastrointestinal bacteria.<sup>21</sup> GAS is secreted by G-cells in the antrum and duodenum, and can promote gastric acid secretion. In patients with severe sepsis who are in a stress state, the gastrointestinal blood supply is reduced suddenly, acid-base balance is impaired, GAS secretion increases constantly and stress ulcer hemorrhage is easily induced. The present study showed that on the 3rd and 7th day after admission, MTL in the intervention group was higher than in the control group, and GAS in the intervention group was lower than in the control group, strongly suggesting that TCM bundle therapy can significantly improve the secretion of gastrointestinal hormones in patient with severe sepsis and should help maintaining the gastrointestinal functions.

In recent years, some studies demonstrated that acupuncture could stimulate the release of peptidergic neurotransmitters including MTL, and activate the peptidergic neural pathway to play a role and promote the recovery of inhibited gastric myoelectric activity.<sup>22</sup> The present study also found that at on the 3rd and 7th days, the intra-abdominal pressure in the intervention group was obviously lower than in the control group and that the incidence of abdominal compartment syndrome was decreased, leading to improved gastrointestinal function of patient with severe sepsis.

The present study showed that after TCM bundle intervention, the AGI incidence over 7days was significantly decreased. GIF and APACHE II scores of patients with AGI II and III in the intervention group were lower than in the control group, but without difference in AGI IV. Therefore, TCM bundle therapy might effectively improve light and moderate gastrointestinal dysfunction. However, with aggravating disease, the factors influencing gastrointestinal function are increased and probably overcome the effects of TCM. Thus, the present study indicated that there was no difference of GIF and APACHE II scores for patients with AGI IV. TCM treatments should be studied further to determine more effective approaches.

Fang et al.,<sup>23</sup> found that the APACHE II, SOFA, and GIF scores of patients with MODS in the rheum officinale intervention group were obviously lower than in the standard group, and that the prognosis was better. In the present study, TCM bundle therapy was used to prevent AGI and good effects were achieved, as reflected by the lower GIF and APACHE II scores. After analysis of patients with various APACHE II scores, the study showed that TCM was more effective for patients with low APACHE II scores at admission. Zhang et al.,<sup>24</sup> considered that AGI levels were significantly associated with 28-day mortality and APACHE II score. In the present study, compared with controls, APACHE II scores in the intervention group were lower, mechanical ventilation time and stay in ICU was shorter, and 28-day mortality

and gastrointestinal-related mortality were lower. These data strongly suggest that TCM bundle intervention could reduce disease severity of patients with severe sepsis. A recent meta-analysis revealed that addition of TCM added benefits in patients with sepsis.<sup>12</sup>

The present study is not without limitations. Indeed, the sample size was small. In addition, the patients were highly selected. Furthermore, even if a number of studies have shown the beneficial effects of TCM, the exact mechanisms of action are still mostly unknown. Additional studies are necessary to characterize TCM and improve its efficacy.

In conclusion, for patients with severe sepsis, early TCM bundle therapy might help avoiding AGI and improve prognosis.

## Methods

### Study design

This was a prospective multicenter study of 551 consecutive patients with severe sepsis treated at the ICUs of the Zhejiang Provincial Hospital of Traditional Chinese Medical, Tongde Hospital of Zhejiang Province, Xinhua Hospital of Zhejiang Province, and Hangzhou Traditional Chinese Medical Hospital between March 2013 and November 2014. The study protocol was approved by the Ethics Committee of each participating hospital. Informed consent forms were signed by the legal representatives of the patients.

### Patients

All patients have been diagnosed with severe sepsis according to the diagnostic criteria of severe sepsis of the International Guidelines for Management of Severe sepsis and Septic Shock 2012.<sup>1</sup> The patients had to meet any of the following criteria<sup>25</sup> and be accompanied with organ dysfunction and/or tissue hypoperfusion caused by sepsis: 1) hypotension caused by sepsis; 2) lactic acid levels are higher than the normal value; 3) although given enough fluid resuscitation, urine volume is <0.5 ml/kg/h for at least 2hours; 4) non-pneumonic acute lung injury and PaO<sub>2</sub>/FiO<sub>2</sub> <200mmHg; 5) pneumonic acute lung injury and PaO<sub>2</sub>/FiO<sub>2</sub> <200mmHg; 6) serum creatinine >176.8μmol/L (2.0mg/dl); 7) bilirubin >34.2μmol/L (2mg/dl); (8) platelets <100,000/μL; and/or 9) blood coagulation disorders (international normalized ratio (INR) >1.5).

Exclusion criteria were: 1) ICU stay <3 days; 2) aged ≤18years; 3) pregnant or lactating women; 4) terminal malignant tumor; 5) Marshall score ≥20; 6) esophagus, stomach, or intestinal medical and surgical histories or primary injury to the gastrointestinal tract when admitted at the ICU; 7) with AGI at admission; or 8) unstable hemodynamics or significantly abnormal coagulation function after 2days at the ICU that cannot be treated with TCM nasal feeding (APTT >2times of upper limit of normal).

### Allocation

Patients with stable hemodynamics (mean arterial pressure (MAP) ≥65mmHg) were immediately assigned to one of two groups, based on the willingness of the patients to receive TCM: 156 patients refused TCM (controls) and 175 accepted TCM (intervention group). The patients in the intervention group received TCM bundle therapy.

### Treatments

In the control group, according to the International Sepsis Treatment Guide 2012, all patients received early EGDT for shock patients, respiratory and circulation support, active anti-infection therapy, and maintenance of electrolyte and acid base balance. Cases with stable

hemodynamic received early EN support<sup>26,27</sup> as soon as possible. A naso-intestinal tube was indwelled in each patient. EN was performed with continuous infusion by nutrition pump. Parenteral nutrition (PN) support within a week was avoided as much as possible.

In the intervention group, patients received TCM bundle therapy in addition to the treatments of the control group. According to the *Diagnosics of Traditional Chinese Medicine*,<sup>28</sup> the patients were divided into four types according to syndrome differentiation of TCM: I) Qi activity stagnation (n=45), which was treated with Simo Yinzi; II) Qi stagnation and blood stasis (n=36), which was treated with taohe chengqitang; III) asthenia of spleen and stomach (n=35), which was mainly treated with the six gentlemen decoction; and VI) dampness and heat from interior (n=30), which was mainly treated with peptic powder. All decoctions were made to 80mL decoction in decoction room. The patients received one dose (80mL) each day, by nasal feeding, in two doses of 40mL. If syndrome type changed during treatment, the treatment was adjusted.

The patients in the intervention group were treated with acupuncture at the acupoints of Stomach Meridian of Foot-Yangming: st 36, Tien chu, Shangjuxu, and Xiajuxu. The location standard of acupoint was made referring to the National Standard Nomenclature and Location of Acupuncture Points 2006 (GB/T12346- 2006). The operating doctors had to be certified in acupuncture specialty. The needle was retained for 30minutes after developing needle sensation, one time a day. Acupuncture was not performed for patients with local skin infection and anabrosis around the acupoints.

For external application of mirabilite to the abdomen, 500g of mirabilite were mashed into granules and put in a sand bag (about 25×20cm). The sand bag was spread to middle and upper abdomen. The bag was replaced when it became hard or crystallized. The bag was applied 3times per day, 2hours each time.

The defecation drug mixture was made by the Zhejiang Provincial Hospital of Traditional Chinese Medical. Each liter of mixture contained 8.2g of Chinese honey locust and 160g of honey. Fifty mL of the mixture was slowly infused in the rectum and retained for 20min, once a day. This was not performed for patients with severe diarrhea.

The details of drug formulations are as follow. Simo Yinzi: 6g of lignum aquilariae sinensis, 6g of root of combined spicebush root, 6g of south common vladimiria root, and 6g of fructus aurantii. Taohe chengqitang: 12g of semem persicae, 12g of rheum officinale, 12g of prepared Licorice root, 6g of cassia twig, and 6 g of mirabilite. Six gentlemen decoction: 6g of ginseng, 12g of bighead atractylodes rhizome, 6g of poria cocos, 4g of liquorice, 5g of orange peel, 6g of roast pinellia ternata, 5g of fructus amomi, and 4g of radix aucklandiae. Peptic powder: 12g of rhizoma atractylodis, 9g of mangnolia officinalis, 6g of orange peel, and 3g of liquorice.

### Data collection and laboratory examinations

Age, gender, source of infection, and reason of ICU admission were collected at admission. Sequential organ failure assessment (SOFA), APACHE II, and MODS occurring within 24hours were recorded. Blood was sampled on the 1st, 3rd, and 7th days after admission to determine the levels of D-lactic acid (D-lac), diamine oxidase (DAO), endotoxin, motilin (MTL), gastrin (GAS), and intra-abdominal pressure. The 28-day survival was collected.

D-lac, DAO, endotoxin, MTL, GAS, prealbumin, and albumin levels were determined at a third class A hospital. DAO was determined

by spectrophotometry, while D-lac was determined with modified enzymatic spectrophotometry (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). The quantitative determination of endotoxin was performed with a limulus kit (Sigma, St Louis, MO, USA). GAS was determined with the GAS radioimmunoassay kit (China Institute of Atomic Energy, Beijing, China). MTL was determined with the motilin radioimmunoassay kit (Shanghai Kerui Biotechnology Center, Shanghai, China). GAS and MTL were determined with ELISA. The amount of EN amount was determined as the fed EN solution volume through minus the gastric residual volume, which was determined by extracting per 6hours.

Foley catheters were connected with urine storage bag and piezometer tube for the patients in supine position. Then, the bladder was emptied, the urine storage bag was closed and filled with 20mL of sodium chloride (0.9%) through the piezometer tube. The piezometer tube and transducer were connected, the distal end was open, and after zero adjustment with the pubic symphysis taken as the zero, the intravesical pressure was determined as the reference of intra-abdominal pressure.

AGI, as proposed by the European Society Intensive Care Medicine (ESICM) in 2012,<sup>29</sup> indicates gastrointestinal dysfunction caused by acute illness of patients with critical illness. Depending on the severity, AGI could be divided into four levels: Level I indicates that there are risks of gastrointestinal dysfunction and temporary gastrointestinal symptoms with definite reasons; Level II indicates gastrointestinal dysfunction (GID)<sup>30</sup> in which gastrointestinal digestion-absorption function cannot satisfy the need for nutrient substance and water, without the influence on the general physical condition of patient. Level III indicates gastrointestinal failure (GIF), in which the gastrointestinal function fails to recover and general physical condition is not improved although some intervention treatments are taken. Level IV indicates that GIF and other organs are severely impacted with MODS and shock. Due to the reversibility and spontaneous recovery of with AGI I, the cases with AGI II, III and IV were grouped as being diseased. Reintam et al.,<sup>31</sup> proposed three typical gastrointestinal syndromes of GIF: feeding intolerance syndrome (FI), gastrointestinal hemorrhage (GIH), and paralytic ileus (PI).

According to the standard for GIF evaluation by Reintam et al.,<sup>32</sup> & Sun et al.,<sup>33</sup> 0 indicates that the gastrointestinal function is normal; 1 indicates that the EN amount is less than 50% of necessary amount or the patients that cannot take food 3days after abdominal operation; 2 indicates gastrointestinal nutrition intolerance or intra-abdominal hypertension; 3 indicates gastrointestinal nutrition intolerance with intra-abdominal hypertension; and 4 indicates abdominal compartment syndrome.

### Adverse events

If an adverse event was suspected of resulting from the Chinese medicine intervention, the investigator had to fill the form of adverse event, and drop the patient out of the study.

### Statistical analysis

Continuous data were presented as mean  $\pm$  standard deviation and was analyzed with the independent-samples t test or ANOVA with the Tukey's post hoc test, as appropriate. Categorical data are presented as frequencies and were analyzed with the Fisher Exact test. Survival was analyzed according to the Kaplan-Meier method and was analyzed with the Log rank test. Statistical analysis was performed with SPSS 21.0 (IBM, Armonk, NY, USA). Two-sided P-values <0.05 were considered statistically significant.

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## Author contributions

YF.W and YH.Z significantly contributed to the study design and RL.J contributed to concept. YF.W and YH.Z drafted the manuscript. All authors reviewed and approved the manuscript.

## Conflicts of interest

Author declares there are no conflicts of interest.

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