



Clinical practice guideline on traditional Chinese medicine therapy alone or combined with antibiotics for sepsis

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Background: To develop the clinical practice guidelines for the treatment of sepsis with traditional Chinese medicine (TCM) therapy alone or TCM combined with antibiotics.

Methods: The methods and process for developing the international clinical practice guidelines were fully consulted between a group of doctors. A total of 25 experts from 14 units were involved in the development of this guideline. The major clinical questions that needed to be solved were raised first, and the best available evidence to solve them was researched. Finally, according to the principle set by the GRADE system, the available evidence was graded with levels ranging from high to low. This formed the recommendation strengths, which included strong recommendation and weak recommendation, or an expert consensus recommendation.

Results: The guideline identified the terms and definition for sepsis. For example, it identified its epidemiological characters, the advantages of TCM treatment on sepsis, the diagnosis and its features, the complications, and its rehabilitation and health maintenance. The guideline has put forward 14 recommendations, among which 4 were strong recommendations and 6 were weak recommendations, in addition to 4 expert consensus recommendations.

Conclusions: The methods and processes for developing international clinical practice guidelines were fully consulted under the guide of relevant laws and regulations, and relevant technical documents. Based on the best existing evidence, and combined with the characteristics of TCM and the clinical realities, we developed Clinical practice guidelines for the treatment of sepsis with TCM therapy alone or TCM combined with antibiotics, with full reference to the experts' experience and patients' preferences.

Keywords: Clinical practice guideline; traditional Chinese medicine (TCM); infection; sepsis

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Introduction

Sepsis is a life-threatening organ dysfunction resulting from a dysregulated host response to an infection (1). According to an epidemiological study, the total yearly incidence rate of sepsis is 288 in every 100,000 people. The incidence rate of sepsis in the past 10 years is 437 in every 100,000 people

every year with a mortality rate of 17%. The incidence rate of severe sepsis was 270 in every 100,000 people every year, with a mortality rate of 26%. On this basis alone, according to the statistics from the included developed countries, there are about 31.5 million cases of sepsis and 19.4 million cases of severe sepsis in the world each year, which may result in

5.3 million cases of deaths (2). There are 750,000 cases of sepsis in America each year, and the number increases by 1.5–8% each year. According to foreign epidemiological investigations, the mortality rate of sepsis has exceeded myocardial infarctions, and now has become the major cause of death in non-cardiac patients in the ICU. Although great progress has been made in anti-infective therapy and organ support technology, the death rate of sepsis patients is still up to 30–70%. The treatment of sepsis is costly, and takes up a large amount of medical resources. The disease seriously affects life quality and has become a great threat to human health.

Results from relevant reports (3) have suggested that sepsis patients who are old and weak, severely ill, on long-term use of antibacterial agents, or have been given invasive examinations and treatments, are at a high risk for infection. The pathogenic bacteria derived from those patients have a high drug-resistance rate for the frequently-used antibacterial drugs, and are also characterized as having a multi-drug resistance. The illness is likely to aggravate upon its onset for sepsis patients and may affect many organs and systems. If the disease is treated in time at the early stage, it can be improved quickly with the recovery of organ function to the former condition. In addition, pathogenic bacteria have a high drug-resistance rate to clinically frequently-used antibacterial drugs. According to the 2015 CHINET monitoring report on multiple resistant bacteria (4), the mean detection rates of methicillin-resistant strains in staphylococcus aureus and coagulase negative staphylococcus are 42.2% and 82.6% respectively. The average ESBL-producing rates in escherichia coli, klebsiella and proteus mirabilis are 51.5%, 27.4% and 22.2% respectively. The drug resistance rates of acinetobacter (*A. baumannii* representing 93.4%) on imipenem and meropenem are 62.0% and 70.5% respectively. The occurrence of these drug-resistance bacteria renders clinical treatments even more difficult.

In traditional Chinese medicine (TCM), the treatment of sepsis is divided into three stages based on pattern differentiation (5): the initial stage, the advanced stage, and the recovery stage. The initial stage of sepsis is mostly an excess pattern which is classified into internal exuberance of toxins and heat patterns, internal obstruction of the stasis, and toxin patterns. The pathogenesis is mainly a bacterial infection, so the TCM treatment should focus on preventing the bacterial infection in concordance with antibiotics. The advanced stage of sepsis is classified into qi and yin exhaustion patterns and yang qi depletion patterns,

characterized by the coexistence of deficiency and excess. The recovery stage of sepsis is characterized by a deficiency of healthy qi and the elimination of pathogenic factors, and mostly belongs to the spleen and stomach weakness patterns.

Advantages of TCM treatment on sepsis

TCM believes that these pathogenic toxins can be divided into an externally-contracted pathogenic toxin and an internally-generated pathogenic toxin. These toxins can account for the necessary pathological basis for the development of sepsis. For sepsis, the externally-contracted pathogenic toxin can be the pathogenic microorganism or pathogen. When patients are invaded by external pathogenic factors, they will catch the externally-contracted pathogenic toxins due to a deficiency of healthy qi caused by a lasting illness and body weakness. The consequent body dysfunctions allow for the pathogenic toxins to enter further, and transform into a heat toxin, which may damage the collaterals. Heat-toxin-boiled blood, coupled with powerlessness of qi to move blood and blood stagnation in collaterals, leads to generation of static blood. As a TCM saying goes, “blood stasis leads to edema.” Body fluids will transform into phlegm turbidity if they do not circulate in the body. Therefore, heat toxin, static blood, and phlegm turbidity are bound and then blocked by the collaterals, which are internally-generated pathogenic toxins. The binding of internally-generated and externally-contracted pathogenic toxin can inhibit qi movement, causing further damage to qi, yin and collaterals, and *zang* organs. Coupled with the accumulation of internally-generated pathogenic toxins, it will cause failure of the organs, and even systemic multi-system dysfunction (6). Hence, the fundamental therapeutic principle for sepsis entails paying equal attention to eliminating the pathogenic factors and tonifying the original qi.

It can give full play to the advantages of TCM, especially for the problem of bacterial resistance, in the course of treatment of sepsis with western medicine. According to the research findings (7), by testing the antibacterial effect of TCM decoction on the sensitive strains and multiple resistant mutant strains of escherichia coli and staphylococcus haemolyticus with agar dilution method, it has been found that most medicines do not show any significantly different antibacterial effect on the drug-resistant bacteria and sensitive bacteria of antibiotics. Furthermore, most antibiotic-resistant bacteria are more

sensitive to TCM decoction than the sensitive strains. TCM can bring to bear different advantages in different stages in the treatment of sepsis. In the initial stage of sepsis, the use of TCM combined with antibiotic therapies can reduce the occurrence of drug resistant bacteria and change the existing drug resistance of resistant bacteria or pan-resistant bacteria to reduce the likelihood of multiple infections, especially for patients with drug-resistant infections. During the development of sepsis, the spleen and stomach can be strengthened through the method of ascending lucidity and descending turbidity to reduce the occurrence of multiple organ dysfunction syndrome (MODS). If MODS occurs, TCM therapies can also be used to combat shock and organ dysfunction. Therefore, TCM plays a significant role in the treatment of sepsis, but further research is needed.

Methods

Scope

This guide specifies that patients diagnosed with sepsis can be treated using a TCM therapy combined with antibiotics in the early stage of sepsis, septic shock stage and MODS stage.

This guide is applicable to registered TCM and integrated TCM and Western medicine doctors.

Diagnosis criteria

According to the latest definition of sepsis in version 3.0 (1) from *The Third International Consensus Definitions for Sepsis and Septic Shock* co-issued by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM), the diagnosis criteria for sepsis are the following: organ dysfunction caused by infection, with the dysfunction judged by SOFA score ≥ 2 . For the SOFA marking system, see *Table 1*. Septic shock is defined as sepsis with clear diagnosis, accompanied by persistent low blood pressure. On the basis of full volume replacement, vasopressor is still needed to maintain mean arterial pressure, otherwise hypotension (≤ 65 mmHg) or high serum lactate (>2 mmol/L) will occur. For diagnostic criteria of MODS, see *Table 2*.

Differential diagnosis

Manifestations of inflammatory response body temperature >38.0 °C, or <36.0 °C; heart rate >90 /min; respiratory rate

>20 /min or PaCO₂ <32 mmHg; peripheral blood leucocyte $>12 \times 10^9$ /L, or $<4 \times 10^9$ /L, or immature cells >10 . Infection features: CRP ≥ 10 mg/L; PCT ≥ 0.05 ng/mL; existence of obvious focus of infection.

If it develops into septic shock, then it should be distinguished from the following types of shock: (I) cardiogenic shock caused by insufficient blood perfusion of tissues and organs due to an acute cardiac ejection dysfunction. The common pathological basis for cardiogenic shock includes heart disease, myocarditis, cardiac tamponade, severe arrhythmia, and heart failure. Medical indications such as increased central venous pressure, fall of cardiac index, rise of pulmonary artery wedge pressure and central venous pressure, abnormalities of electrocardiogram and hemodynamics, are all beneficial to differential diagnosis. (II) Hypovolemic shock refers to the circulatory failure caused by a rapid decrease of blood volume due to massive loss of blood and bodily fluids, as well as a burning injury. Symptoms such as a reduced venous pressure, decreased quantity of blood returning to the heart, lower cardiac output and contraction of surrounding blood vessels, may occur. These symptoms can be improved quickly after volume expansion. (III) Obstructive shock refers to poor circulatory perfusion, issue ischemia and histanoxia which is caused by a decreased quantity of blood returning to the heart and lower cardiac output due to the mechanical obstruction of major blood circulation channels like the heart and large vessels.

International registration

After the completion of the proposal formulation, this guideline obtained the project establishment notice from the China Association of Chinese Medicine group standard on related diseases and was registered in the International Practice Guideline Registry Platform bilingually with the registration number: IPGRP-2017CN011.

Selection of project team members

The project team members included chief physicians who were both in TCM and western medicine with an average of 10 years of medical work experience, TCM physicians and sepsis-related clinical experts, epidemiology and evidence-based medicine methodology experts, and all current team members who have participated in the preparation of this guidance, including the guidance group, writing group, document retrieval and analysis teams.

Table 1 Sequential organ failure assessment

Assessment	0	1	2	3	4
Respiration, PaO ₂ /FiO ₂ , mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40.0)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation, Platelet ×10 ⁹ /μL	≥150	<150	<100	<50	<20
Liver, bilirubin, mg/dL (μmol/L)	<1.2 (20.0)	1.2–1.9 (20.0–32.0)	2.0–5.9 (33.0–101.0)	6.0–11.9 (102.0–204.0)	>12.0 (204.0)
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose) ^a	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^a	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^a
Central nervous system, GCS	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110.0)	1.2–1.9 (110.0–170.0)	2.0–3.4 (171.0–299.0)	3.5–4.9 (300.0–440.0)	>5.0 (440.0)
Urine volume, mL/d				<500	<200

^a, catecholamine doses are given as μg/kg/min for at least 1 hour.

Table 2 Diagnostic criteria for MODS

System or organ	Diagnostic criteria
Circulatory system	The systolic blood pressure is less than 90 mmHg, and lasts for more than 1 hour or needs drug support to make the cycle stable
Respiratory system	Acute onset, arterial partial pressure of oxygen/fraction of inspired oxygen (PaO ₂ /FiO ₂) ≤200 mmHg (whether or not the PEEP is applied, bilateral pulmonary infiltration in the chest X-ray, pulmonary artery wedge pressure ≤18 mmHg or without the evidence of left atrial pressure increase
Kidney	Serum creatinine >177.3 μmol/L, accompanied by oliguria or polyuria or need of blood purification treatment
Liver	Hemobilirubin >35 mmol/L, accompanied by elevated transaminases, more than 2 times the normal value or with hepatic encephalopathy
Gastrointestinal	Upper gastrointestinal hemorrhage, the amount of bleeding is more than 400 mL in 24 hours, or food intolerance caused by the disappearance of gastrointestinal peristalsis, or with the necrosis or perforation of the alimentary tract
Blood	Blood platelet <50×10 ⁹ /L or reduced by 25%, or appearance of DIC
Metabolism	Failure to provide the energy for the body, glucose tolerance decreased, insulin needed; or with the symptoms of atrophy and weakness of the skeletal muscle
Central nervous system	GSC <7

MODS, multiple organ dysfunction syndrome.

Retrieval of evidence

The retrieval strategy includes both electronic retrieval and manual retrieval. The retrieval content was then divided into the following categories: domestic and overseas original research database, and clinical test registration bank and

guideline library. The full-text electronic database retrieval mainly included the following original research databases: (I) (English) Medline, Embase and Cochrane Library; (II) (Chinese) CNKI, CQVIP, SinoMed, Traditional Chinese Medical Database, Wanfang Full-Text Database, and the domestic and overseas clinical test registration bank and

Table 3 Grade ratings and their interpretation

Quality	Interpretation
High (A)	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate (B)	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low (C)	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low (D)	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

guideline library including the Clinical Trials Registry Platform (such as Clinical Trial), the National Guideline Clearinghouse, the International Practice Guideline Registry Platform (<http://www.guideline-registry.cn>), and the China Guideline Clearinghouse (<http://cgc-chinaebm.org>), etc. Manually retrieval resources included textbooks, important back issues, important academic conference papers, significant standardized documents and related published books. All relevant articles in these databases were published during the period from the databases' establishment to the 28th of February, 2017. The retrieval words in Chinese were the following: “Nong Du Zheng” (sepsis), “Nong Du Xue Zheng” (septicopyemia), “Zhong Zheng Nong Du Zheng” (severe sepsis), “Nong Du Xing Xiu Ke” (septic shock), “Duo Qi Guan Gong Neng Zhang Ai Zong He Zheng” (MODS), “Hu Xi Shuai Jie” (respiratory failure), “Ji Xing Shen Sun Shang” (acute kidney injury). English retrieval words included the following: “Sepsis”, “Severe Sepsis”, “Pyemia”, “Pyemias”, “Septic Shock”, “MODS”, “Respiratory Failure”, “Acute Kidney Injury” and other keywords.

Screening of evidence

The inclusion criteria were as follows: (I) the diagnostic criteria of the literature, the standard of syndrome differentiation for Chinese medicine, and the evaluation of the curative effect were in conformity with the accepted standards. Diagnostic criteria for western medicine included severe sepsis or septic shock in sepsis 3.0, sepsis 1.0 or sepsis 2.0. (II) Intervention measures included Chinese patent medicine, decoction, acupuncture, and TCM treatment alone or combined with conventional treatment of western medicine (anti-infection treatment). (III) No limitations were made on the control measures. (IV) No limitations were made on research design type.

The exclusion criteria were as follows: (I) both the control group and the intervention group were treated with western medicine combined with TCM; (II) the research was ongoing; (III) the study had incomplete information.

Evaluation of evidence

This guideline is mainly based on the evaluation of the RCT and the conduct evaluation according to the bias risk assessment tool (8) in Cochrane evaluation Handbook 5.1.0. The evaluation considered the following items: (I) random assignment method; (II) allocation concealment; (III) blind method applied to research objects and the treatment implementer; (IV) blind method applied to research result measurer; (V) the completeness of result data; (VI) the research result of selected report. Finally, the documents were judged as being low bias risk, high bias risk or uncertain bias risk. In addition, the system evaluation that was adopted was evaluated by AMSTAR.

Grading of evidence

This guideline adopts the grading of recommendations assessment, development and evaluation system, also known as the GRADE system (8). The GRADE system is a standard used to assess the level of evidence to determine the recommended strength required. GRADE's evaluation of the level of evidence is based on the following aspects: (I) risk of bias; (II) inconsistency; (III) indirectness; (IV) imprecision; (V) publication bias; and (VI) other criteria. Of course, the patient's values and preferences, costs and resources, as well as the feasibility and acceptability of the intervention are included in the assessment of the quality of the evidence based on these factors (*Table 3*). The recommended strength of the evidence reflects the opinion of the entire working group that the trade-off between

Table 4 Four factors that affect the strength of recommendation

Factor	Interpretation
Balance between desirable and undesirable effects	The larger the balance between the desirable effects and undesirable effects is, the stronger the recommendations will likely be, and vice versa
Quality of evidence	The higher the quality of evidence is, the more likely the values and preferences with strong recommendation will be made
Values and preferences	The larger the difference or uncertainty is, the more likely a weak recommendation will be made
Cost (resource allocation)	The higher the cost of treatment measure is (more consumption of resources), the less likely a strong recommendation will be made

expected and adverse effects of evidence effects, and the recommended strength measures are influenced by certain factors, which are outlined in *Table 4*.

Formulation principle of expert consensus

This guideline belongs to the field of “treatment”, which focuses on the TCM treatments that can be used alone or in combination with antibiotics to treat sepsis. The general principle of the consensus is that if the total number of people who strongly recommend one treatment measurement exceeds 75%, then this treatment measurement is strongly recommended. If the number of people who recommend it is below or equal to 50%, then it is not recommended; other situations were sorted into the weakly recommended category. As for classic prescriptions with written recordings in ancient books (before 1911), if the modern research evidence was relatively low, and there was more than 75% of the experts who had reached a consensus to strongly recommend them, then they were strongly recommended.

This guideline is the consensus result of three rounds of the Delphi method combined with a face-to-face consensus conference. The conference consisted of the following members: (I) for frontline clinical experts of sepsis, both TCM and western doctors were included, but mainly TCM doctors; (II) for methodology expertise, experts of evidence-based medicine were included; (III) one patient was included; (IV) one medical management staff was included; (V) and one nurse was included. The first round mainly evaluated the contents of the guideline’s seven aspects. The second round evaluated all the evidence-based treatment measurements. The third round evaluated Chinese patent medicine. After three rounds of the Delphi method and a wide solicitation of opinions, a basic consensus was reached

on all of the contents of this guideline.

Evaluation and consultation process of guideline

The guideline’s draft, after the discussion and revision of the guideline development group, was put on the website of the China Association of Chinese Medicine for two weeks to seek public opinions starting from May 4, 2017. Additionally, two face-to-face expert reviews and interviews were held for the questionnaire and opinions were collected from respondents in a wide range of areas: TCM, clinical and basic research of the combination of Chinese and Western medicine, clinical epidemiology, evidence-based medicine, statistics, health economics, nurse, management staff and patients. Peer review was conducted before the release of the guideline project. Based on the feedback opinions, the questionnaire was modified into the guideline’s standard draft for approval. Then, it was submitted to the China Association of Chinese Medicine to go through the approval process. The notice was released in June 2017.

Conflicts of interest statement

All the members of this guideline have signed a conflict of interest statement, stating that there is not any commercial, professional or other interest related to this guideline’s topic, nor is there any interest related to the possible impact of the outcomes of this guideline. After the signing of the conflicts of interest statement, it will be collected by a secretariat and then submitted to the guideline steering committee. The guideline steering committee will supervise and evaluate the interest statement in order to confirm if there is any existing conflict of interest. If there is a conflict of interest, the guideline steering committee will determine its seriousness and then decide the final outcome.

Results

Treatment

Basic therapeutic principles

- (I) It is recommended that TCM therapy combined with antibiotics should be applied in the treatment of sepsis (expert consensus recommendation)—remarks: TCM therapy combined with antibiotics could reduce the use of antibiotics and its consequent side effects, decreasing antibiotic resistance prevalence, and improving clinical curative effect.
- (II) Combined with antibiotics, TCM treatment is recommended at the early stage to control disease progression and reduce the mortality rate (expert consensus recommendation).

Sepsis

We recommend Qingwen Baidu Decoction (9-17) for sepsis with internal exuberance of toxin and heat pattern (strong recommendation, quality of evidence: D)

Clinical manifestations: persistent high fever, vexation and restlessness, loss of consciousness, nausea and vomiting, jaundice, abdominal distention, constipation or diarrhea, dark red tongue body with yellow and greasy or dry fur, rapid pulse.

Etiology and pathogenesis: at the early stage of the disease, the healthy qi fights fiercely against the pathogenic qi after its invasion; if excess heat pathogenic qi manages to invade into the body at this stage, then the disease will occur.

Treatment method: to clear heat and remove toxin.

- (I) Source: *Achievements in the Treatment of Epidemic Rash* by Yu Shiyu of Qing Dynasty.
- (II) Combination of medicinals: *Gypsum Fibrosum*, *Radix Rehmanniae*, *Rhizoma Coptidis*, *Cornu Bubali*, *Fructus Gardeniae*, *Radix Scutellariae*, *Rhizoma Anemarrhenae*, *Radix Paeoniae Rubra*, *Radix Platycodonis*, *Radix Scrophulariae*, *Cortex Moutan*, *Fructus Forsythiae*, *Herba Lophatheri*, *Radix et Rhizoma Glycyrrhizae*.
- (III) Modification: for convulsion of the limbs, add in *Cornu Saigae Tataricae* and *Bombyx Batryticatus* to clear the liver, extinguish wind, and settle convulsion; for constipation, add in *Radix et Rhizoma Rhei* to drain heat and unblock the bowels; for loss of consciousness with delirious speech, add in Angong Niu Huang Pill.

- (IV) Decoction method: decoct *Gypsum Fibrosum* for 10 minutes at first, and then add in other medicinals to get 600 mL of decoction. Take it in 3 doses by oral administration or nasal feeding.

We recommend Qingying Decoction (18) for sepsis with internal obstruction of stasis and toxin pattern (weak recommendation, quality of evidence: D)

Clinical manifestations: high fever, or stabbing pain, wandering pain aggravated at night, lumps, subcutaneous ecchymosis or bleeding, or small quantity of urination, anuria, edema, dark purple tongue body with/without purple spots on the tongue, obvious purpura in the tongue base, deep and slow pulse, or deep, wiry and unsmooth pulse.

Etiology and pathogenesis: externally-contracted heat toxin or pathogenic qi invades internally and transforms into heat and toxins after an accumulation. Body fluid is boiled into phlegm due to the stagnation of heat toxins. A stasis is formed due to the obstruction of blood after the collaterals are blocked by pathogenic qi. The combination of pathogenic qi and toxic pathogens, leads to internal obstruction.

Treatment method: to activate blood, transform stasis, and remove toxin.

- (I) Source: *Systematic Differentiation of Warm Diseases* by Wu Jutong of Qing Dynasty.
- (II) Combination of medicinals: *Cornu Bubali*, *Radix Rehmanniae*, *Radix Scrophulariae*, *Folium Pleioblasti*, *Radix Ophiopogonis*, *Radix et Rhizoma Salviae Miltiorrhizae*, *Rhizoma Coptidis*, *Flos Loniceriae Japonicae*, *Fructus Forsythiae*. (III) Modification: for loss of consciousness, add in Angong Niu Huang Pill to clear the heart and open the orifices; for convulsive syncope and convulsion, add in Zixue Pill, *Cornu Saigae Tataricae* and *Pheretima* to extinguish wind and arrest convulsions.
- (IV) Decoction method: decoct all the medicinal products to get 600 mL of decoction. Take it in 3 doses by oral administration or nasal feeding.

Recommended Chinese patent medicine: Xuebijing Injection (19) (strong recommendation; evidence quality: C)

- (I) Source: *Catalog of Drugs for National Basic Medical Insurance, Industrial Injury Insurance and Birth Insurance 2017* (or *2017 Catalog of Medical Insurance* for short).
- (II) Combination of medicinals: *Flos Carthami*, *Radix*

Paeoniae Rubra, Rhizoma Chuanxiong, Radix et Rhizoma Salviae Miltiorrhizae, Radix Angelicae Sinensis.

- (III) Actions and indications: to transform stasis and remove a toxin. It applies to warm and febrile diseases for binding of stasis and toxin patterns, manifested by fever, wheezing and panting, palpitation, and dysesthesia. It also applies to systemic inflammatory response syndrome due to infection. It can assist in the treatment of multiple organ disorder syndrome at the stage of impairment of organ function.
- (IV) Usage and dosage: intravenous injection. Systemic inflammatory response syndrome: dilute 50 mL of the drug into 100 mL of normal saline, then perform an IVGTT within 30–40 minutes, twice a day. For severe patients, do this 3 times a day. Multiple organ disorder syndrome: dilute 100 mL of the drug into 100 mL of normal saline, then perform an IVGTT within 30–40 minutes, twice a day. For severe patients, do this 3–4 times a day.

Septic shock

We recommend Shengmai Powder (20,21) for sepsis with qi and yin exhaustion pattern (strong recommendation, quality of evidence: D)

Clinical manifestations: a sudden drop of body temperature; vexation and restlessness; reddish cheeks; spirit lassitude and shortness of breath; sweating; dry mouth with no desire for drink; red tongue with scanty fur; thready, rapid and powerless pulse; or knotted and intermittent pulse.

Etiology and pathogenesis: qi collapse following bleeding, and yang collapse following yin collapse, caused by spitting blood, bloody stool, or damage to the collaterals, and massive blood loss or unclean food, or excessive purgation, damage to spleen and stomach, abnormal ascending and descending, fulminant vomiting and diarrhea, serious damage to yin fluid, qi collapse following fluid exhaustion, and yang collapse following yin collapse.

Treatment method: to reinforce the healthy qi and secure collapse.

- (I) Source: *Origins of Medicine* by Zhang Yuansu of Jin Dynasty.
- (II) Combination of medicinals: *Radix et Rhizoma Ginseng Rubra, Radix Ophiopogonis and Fructus Schisandrae Chinensis.*
- (III) Decoction method: decoct all the medicinals to get 600 mL of decoction. Take it in 3 doses by oral

administration or nasal feeding.

We recommend Modified Sini Decoction (22) for sepsis with yang qi depletion pattern (weak recommendation, quality of evidence: D)

Clinical manifestations: wheezing and distress, loss of consciousness, great dripping sweat, reversal cold of the hands and feet, faint pulse verging on expiry, pale tongue with white fur.

Etiology and pathogenesis: acute loss of blood and water, or trauma, or intense pathogenic toxin, or abnormal qi movement of *zang-fu* organs, stagnation of qi and blood, which leads to deficiency of heat yang, internal cold due to yang deficiency, increasing failure of yang qi, deficiency, exhaustion and collapse of heart yang.

Treatment method: to restore yang and secure the collapse.

- (I) Source: *Treatise on Cold Damage* by Zhang Zhongjing of the Eastern Han Dynasty.
- (II) Combination of medicinals: *Radix Aconiti Lateralis Praeparata, Rhizoma Zingiberis, Radix et Rhizoma Glycyrrhizae Praeparata cum Melle, Radix et Rhizoma Ginseng.*
- (III) Decoction method: decoct all the medicinals to get 600 mL of decoction. Take it in 3 doses by oral administration or nasal feeding.

Recommended Chinese patent medicine: Shenfu Injection (23) (Recommendation strength: strong; Evidence quality: C)

- (I) Source: *2017 Catalog of Medical Insurance.*
- (II) Combination of medicinals: *Radix et Rhizoma Ginseng Rubra, Radix Aconiti Lateralis Praeparata.*
- (III) Actions and indications: to restore yang to save from a collapse. It applies to syncope and collapse pattern due to collapse of yang qi, such as infectious, hemorrhagic or dehydrated shock; it also applies to fright palpitations, fearful throbbing, wheezing, stomachache, diarrhea, or *bi* syndrome, caused by yang deficiency (qi deficiency).
- (IV) Usage and dosage: IVGTT, 20–100 mL per time (dilute it with 250–500 mL of 5% glucose injection before administration).

MODS: gastrointestinal dysfunction

We recommend Houpo Sanwu Decoction for sepsis with gastrointestinal dysfunction (expert consensus recommendation)

Clinical manifestations: abdominal pain with discomfort upon palpitation, abdominal distention, no desire for food

and drink or vomiting upon eating, thirst with/without desire to drink, constipation, palpable strip or globular induration in left lower quadrant, or diarrhea, foul smelling stool, or spitting blood, bloody stool, or dark stools, or high fever, loss of consciousness, delirious speech, or shortage of qi, lack of strength, spirit lassitude, fatigue, red tongue, body with tooth marks or cracks, yellow slimy fur or dirt fur, or with dry fur or without fur, fine, slippery and rapid pulse, or surging and rapid pulse, or rapid and powerless pulse.

Etiology and pathogenesis: internal accumulation of excess heat, qi stagnation, abdominal distention and pain, constipation.

Treatment method: to move qi and eliminate fullness, remove accumulation and relax the bowels.

- (I) Source: *Essentials from the Golden Cabinet* by Zhang Zhongjing of the Eastern Han Dynasty.
- (II) Combination of medicinals: *Cortex Magnoliae Officinalis, Radix et Rhizoma Rhei, Fructus Aurantii Immaturus*.
- (III) Decoction method: Decoct all the medicinals to get 600 mL of decoction. Take it in 3 doses by oral administration or nasal feeding.

Recommended external treatment: acupoint application therapy (24) (weak recommendation, evidence quality: D)

- (I) Indications: abdominal flatulence, decreased bowel sounds; or severe abdominal flatulence, bowel sounds verging on disappearing; adjuvant therapy for paralytic intestinal obstruction, stress ulcer bleeding.
- (II) Manipulation: patients should assume a face-up position with an exposed umbilical region. Mix 2 g of *Fructus Evodiae* powder and 2 g of *Flos Caryophylli* powder in the area with alcohol and put the paste on a two-layer gauze with 4 sides folded. Then, put the bag on Shenque (RN8), and fix and seal it with tap, every 6 hours, every day.

Recommended external treatment: acupuncture therapy (25-27) (weak recommendation, evidence quality: D)

- (I) Actions and indications: to harmonize the middle, fortify the spleen, and regulate qi. It applies to the gastrointestinal dysfunction due to sepsis or serves as an adjuvant therapy for regulating the function of the *zang-fu* organs in the whole body.
- (II) Manipulation: patients should receive treatment in a face-up position with conventional acupoint sterilization. Apply perpendicular insertion of 0.3–0.5

cun to abdominal acupoints up to the extent that no pain is felt.

MODS: acute respiratory distress syndrome

We recommend Xuanbai Chengqi Decoction for sepsis with acute respiratory distress syndrome (expert consensus recommendation)

Clinical manifestations: fever with sweating, sudden panting, respiratory distress, or with vexation and restlessness, anxiety, or constipation, or abdominal distention, or loss of consciousness with delirious speech, red, dark red or dark purple tongue; thick greasy tongue fur, deep rapid pulse or deep excess pulse; or spirit lassitude and fatigue, loss of consciousness and eye heaviness for the worst-case scenario, coldness of the four limbs, pale tongue body with slimy fur, deficient pulse.

Etiology and pathogenesis: obstruction of lung qi, failure of the lung to govern purification and descent, disorder of qi movement, counter flow of qi.

Treatment method: to clear lung fire and calm panting, drain heat and relax the bowels.

- (I) Source: *Systematic Differentiation of Warm Diseases* by Wu Jutong of Qing Dynasty.
- (II) Combination of medicinals: *Gypsum Fibrosum, Radix et Rhizoma Rhei, Semen Armeniacae Amarum, Pericarpium Trichosanthis*.
- (III) Decoction method: decoct all the medicinals to get 600 mL of decoction. Take it in 3 doses by oral administration or nasal feeding.

MODS: acute renal injury

We recommend Wenpi Decoction (28) for sepsis with acute renal injury (weak recommendation, quality of evidence: D)

Clinical manifestations: concentrated (deep colored?) urine or dysuria, or anuria, or clear and copious urine; oppression in the chest and stomach; nausea with desire to vomiting, or vomiting of phlegm-drool; thirst with no desire for drink, or dry throat with desire for drink; bitter and sticky mouth; constipation; no fever or low fever; red or pale red tongue body, pale, or yellow and greasy fur, or thick or scanty fur; slippery and rapid pulse; or deep, thready and powerless pulse.

Etiology and pathogenesis: deficiency cold of middle yang, internal obstruction of cold accumulation.

Treatment method: to treat coagulated cold by purgation, warm and supplement spleen yang.

- (I) Source: *Important Formulas Worth a Thousand Gold*

- Pieces for Emergency* by Sun Simiao of Tang Dynasty.
- (II) Combination of medicinals: *Radix Aconiti Lateralis Praeparata*, *Radix et Rhizoma Rhei*, *Natrii Sulfas*, *Radix Angelicae Sinensis*, *Rhizoma Zingiberis*, *Radix et Rhizoma Ginseng*, *Radix et Rhizoma Glycyrrhizae*.
- (III) Decoction method: decoct all the medicinals to get 600 mL of decoction. Take it in 3 doses by oral administration or nasal feeding.

Recommended external treatment: TCM enema therapy (29) (weak recommendation, evidence quality: D)

- (I) Combination of medicinals: *Radix et Rhizoma Rhei*, *Herba Taraxaci*, *Concha Ostreae*, *Radix et Rhizoma Salviae Miltiorrhizae*, *Radix Astragali*.
- (II) Indications: rapid decrease of urinary volume, and urethra being blocked, persistent fever, thirst and dry mouth, vexation and restlessness, dark red tongue body with yellow and dry fur, thread and rapid pulse.
- (III) Manipulation: soak all the medicinals in cold water for 30 minutes. Then, decoct them with 1,000 mL water and get 200 mL of decoction. Perform retention enema with 100 mL decoction in patients of strong constitution, and with 80 mL decoction in old and weak patients. One time, a day for seven days is counted as a treatment course.

Prevention of complications

Common complications of sepsis including septic shock, acute lung injury, acute respiratory distress syndrome, deep vein thrombosis, stress ulcer, metabolic acidosis, disseminated intravascular coagulation, multiple organ dysfunction or failure, are essentially the clinical manifestations of each pathological and physiological stage of the disease. It is of great importance to prevent the causes of the disease in a clinical environment and do our utmost to reduce the risk factors that induce the infection. The early intervention of TCM treatment in this guideline is beneficial for the treatment and prevention of sepsis.

Rehabilitation and health maintenance

In the recovery stage of sepsis, the treatment should focus on reinforcing the healthy qi and treating the root cause, accompanied by eliminating the pathogenic factors. The combination of both internal use, external application, and functional exercise is commonly used to address this problem. Early rehabilitation exercises can reduce the time of mechanical ventilation and hospitalization for severe

sepsis patients, and improve their muscle force and activity in their daily life.

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Footnote

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