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## The efficacy and safety of different anticoagulants on severe septic patients: a protocol for network meta-analysis of randomized controlled trials

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**The efficacy and safety of different anticoagulants on severe septic patients: a protocol for network meta-analysis of randomized controlled trials**

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22  
23 Medicine Group (CECCEBMG). Libing Jiang and Shouyin Jiang make equal contribution to this  
24  
25 work. And Mao Zhang and Yuefeng Ma are co- corresponding author authors.  
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### 31 ABSTRACT

32  
33 **Introduction:** Sepsis is the leading cause of mortality in non-cardiologic critically ill patients.  
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35 There are as many as 20 million cases of sepsis annually worldwide, with a mortality rate of  
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37 around 35%. It has been reported that the dysregulation of hemostatic system due to the  
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39 interaction between coagulation system and inflammatory response is a strong predictor of  
40  
41 mortality in patients with severe sepsis. In this context, several anticoagulants have been evaluated  
42  
43 in recent year. However, the results of these studies were inconsistent, and even were contradictory.  
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45 In addition, there is insufficient evidence comparing the efficacy and safety of different  
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47 anticoagulants. The purpose of our study is to carry out a systematic review and network  
48  
49 meta-analysis comparing the efficacy and safety of different anticoagulants for severe sepsis based  
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51 on existing randomized controlled trials (RCTs) and ranking these anticoagulants for practical  
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53 consideration.  
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55 **Methods and analysis:** PubMed, EMASE, Cochrane Library databases will be systematically  
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57 searched for eligible studies. Randomized controlled trials (RCT) on anticoagulant therapy of  
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4 severe sepsis with multiple outcome measures will be included. The Cochrane Risk of Bias Tool  
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6 will be used to assess the quality of included studies. The primary outcomes are mortality and  
7  
8 bleeding events. The secondary outcomes including the length of intensive care stay, the length of  
9  
10 hospital stay, and duration of mechanical ventilation. Direct pair-wise meta analysis (DMA),  
11  
12 indirect treatment comparison meta analysis (ITC) and network meta-analysis (NMA) will be  
13  
14 conducted to compare different anticoagulants.  
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17  
18 **Ethics and dissemination:** Ethical approval is not required given this is a protocol for a  
19  
20 systematic review. The protocol of this systematic review will be disseminated in a peer-reviewed  
21  
22 journal and presented at a relevant conference.  
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25 **Registration details:** This protocol has been registered in PROSPERO ([http:// www. crd. york. ac.](http://www.crd.york.ac.uk/PROSPERO/)  
26  
27 [uk / PROSPERO/](http://www.crd.york.ac.uk/PROSPERO/)) under registration number CRD42014013886.  
28

#### 29 **Strengths and limitations of this study**

- 30  
31 ● This is the first comprehensive review comparing the efficacy and safety of five different  
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33 anticoagulants through network meta-analysis.
- 34  
35 ● The results of this systematic review will help clinicians in making decisions in clinical  
36  
37 practice.
- 38  
39 ● The methods of this review are state of the art, including extensive literature search, explicit  
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41 inclusion and exclusion criteria, independent study selection, data extraction, quality  
42  
43 assessment and advanced statistical methods. In addition, we will use the Grading of  
44  
45 Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate  
46  
47 the quality of evidence.
- 48  
49 ● This study is inherently retrospective and based on the published randomised controlled trials  
50  
51 only.  
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#### 53 **INTRODUCTION**

54  
55 Sepsis has been reported as the leading cause of mortality in non-cardiologic critically ill patients.<sup>1</sup>  
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57 In the US , nearly 200,000 deaths are attributed to sepsis per year.<sup>2</sup> And it is likely that there are as  
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3 many as 20 million cases of sepsis annually worldwide, with a mortality rate of around 35%.<sup>3</sup>  
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5 Sepsis, defined as infection-induced systemic inflammatory response syndrome (SIRS) involves  
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7 multiple mechanisms, including the release of cytokines, the activation of complement systems,  
8  
9 coagulation systems, and fibrinolytic systems.<sup>4</sup> Of these, the dysregulation of hemostatic system  
10  
11 from insignificant coagulopathy to severe disseminated intravascular coagulation (DIC) has been  
12  
13 shown to be related with the development of multiple organ dysfunction syndrome (MODS).<sup>5-7</sup> In  
14  
15 a prospective epidemiologic study, the authors found that the prevalence of DIC, MODS and the  
16  
17 risk of death were associated the severity of disease, the more severe the infection (from SIRS to  
18  
19 septic shock), the higher the risk for the DIC, MODS and death.<sup>1</sup> And it has been reported that  
20  
21 DIC can be found in 25% to 50% of patients with sepsis.<sup>8,9</sup> Therefore, it is reasonable to speculate  
22  
23 that use of anticoagulants to inhibit the over-activated coagulation cascade may be useful in the  
24  
25 resolution of DIC and reducing the mortality of sepsis. Following this hypothesis, the efficacy and  
26  
27 safety of several anticoagulants were evaluated in many randomised controlled trials (RCTs) and  
28  
29 meta-analysis. However, the results of these studies were inconsistent, even were contradictory.<sup>10</sup>  
30  
31 As a result, considerable differences exist between guidelines, in the areas of treatment of DIC.  
32  
33 The guideline published by UK recommended the use of recombination activated protein C (rAPC)  
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35 for serious cases, however, the guideline published by Japan recommended the use of  
36  
37 supplement-dose of antithrombin.<sup>10</sup> Moreover, in major of these studies, the target drugs were  
38  
39 often compared with placebo, therefore, up to now, there is no evidence that which one is better.  
40  
41 The purpose of our study is to carry out a systematic review and network meta-analysis comparing  
42  
43 the efficacy and safety of different anticoagulants for severe sepsis based on existing randomized  
44  
45 controlled trials (RCTs) and ranking these anticoagulants for practical consideration.

## 46 **METHODS AND ANALYSIS**

### 47 **Design**

48 Systematic review and Bayesian network meta-analysis. The present systematic review and  
49  
50 meta-analysis will be reported according to the recommendations from the preferred reporting  
51  
52 items for systematic reviews and meta-analyses (PRISMA, [www.prisma-statement.org/](http://www.prisma-statement.org/))

### 53 **Data sources and searches**

54  
55 We will systematically perform an electronic search of PubMed, EMBASE and Cochrane Library.  
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58 In addition, we will also search conference abstracts from Society of Critical Care Medicine, the  
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European Society for Intensive Care Medicine, the American Thoracic Society, and the American College of Chest Physicians, as well as the Clinicaltrials.gov and Controlled-trials.com, along with the bibliographies of eligible studies and relevant review articles or meta-analysis. The following medical subject headings terms and text words will be used alone or in combination: SIRS, systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock, pyemia\*, pyohemia\*, pyaemia\*, septicemia\*, bacteremia, anticoagulant\*, anticoagulation therapy, heparin, antithrombin, drotrecogin alfa (activated), activated protein C, xigris, rAPC, rhAPC, recombinant thrombomodulin, recombinant human soluble thrombomodulin, rTM, rhTM, ART, tissue factor pathway inhibitor, TFPI, Tifacogin, and random, controlled trial, and RCT. No limitation will be placed on publication status or language.

### Eligibility criteria

- ◆ *Participants* Inclusion—Adult patients (>18 yr) with sepsis of any severity, defined according to the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine consensus (SCCM) definition or ACCP/SCCM/European Society of Intensive Care Medicine/American Thoracic Society/Surgical Infection Society definition.<sup>11, 12</sup> And patients with sepsis-induced DIC should fulfill the International Society on Thrombosis and Hemostasis (ISTH) DIC score or the Japanese Association for Acute Medicine (JAAM) DIC scoring system.<sup>13</sup>
- ◆ *Interventions* Inclusion—any RCT that evaluates the efficacy and safety of five anticoagulants including heparin, antithrombin, rAPC, rhTM, and TFPI (of any dose).
- ◆ *Controls* Inclusion—any RCT that evaluates the efficacy and safety of five anticoagulants including heparin, antithrombin, rAPC, rhTM, and TFPI (of any dose) and placebo or other standard therapy according to the Surviving Sepsis Campaign (<http://www.survivingsepsis.org/Resources/Pages/default.aspx>).
- ◆ *Outcome* Inclusion—the primary outcome of this study is mortality with the longest follow-up period, and bleeding events during therapy process (including minor and major bleeding events, the definitions of minor and major bleeding events are developed by individual studies). The secondary outcomes including the length of intensive care stay, the length of hospital stay, and duration of mechanical ventilation. In addition, we will also evaluate the difference of acute physiology and chronic health evaluation (APACHE) II

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3 scores, sequential organ failure assessment (SOFA) scores, and DIC scores between two  
4 groups.

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7 ◆ *Types of study* Inclusion—only RCTs will be included.  
8  
9 ◆ Exclusion criteria—age less than 18 years old, patients with non-infection SIRS, studies that  
10 evaluates other drugs or combined treatments of multiple drugs, there are no original data  
11 (e.g., case reports, reviews, and commentary), experimental studies and observational studies.  
12

### 13 14 15 **Study selection**

16 The titles and abstracts of literature search will be screened by two reviewers independently for  
17 potentially relevant studies according to the above mentioned inclusion and exclusion criteria.  
18 After excluding the duplicated and apparently irrelevant studies, the remaining studies will be read  
19 in full text. Any disagreement will be resolved by consensus. The primary selection process is  
20 presented in Figure 1.  
21

### 22 23 24 25 **Data extraction and quality assessment**

26 The following data will be extracted independently and in duplicate by two reviewers into a  
27 predefined spreadsheet: the name of the first author, publication year, country of origin, patients  
28 characteristics (gender, age, number, inclusion and exclusion criteria, APACHE II score, SOFA  
29 scores, and DIC scores ), characteristics of interventions (type and dose of target drug),  
30 characteristics of control treatment, outcomes (mortality at different time points, bleeding events,  
31 the length of intensive care stay, the length of hospital stay and duration of mechanical ventilation).  
32 Any discrepancy will be resolved by consensus. If necessary, we will try to contact the  
33 corresponding authors for more information.  
34

35 The Cochrane Risk of Bias Tool will be adopted to assess the risk of bias for each RCT by two  
36 reviewers.<sup>14</sup> This tool includes six domains: sequence generation, allocation concealment, blinding,  
37 incomplete data assessment, selective outcome reporting, other sources of bias. And based on the  
38 above domains, the included RCTs will be classified into three categories: low risk, high risk and  
39 unclear. Any discrepancy will be resolved by consensus and discussion.  
40

### 41 42 43 44 **Assessment of reporting biases**

45 A funnel scatter plot of sample and effect size will be constructed to determine the presence of  
46 publication bias, and the contour enhanced funnel plot will be applied to aid in interpreting the  
47 funnel plot. If studies are missing in areas of low statistical significance, the asymmetry may be  
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3 due to publication bias. If studies are missing in areas of high statistical significance, the  
4 asymmetry may be due to other factors. Begg-Mazumdar rank correlation and Egger's regression  
5 will be used to assess small trial bias statistically.<sup>15-17</sup>  
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### 8 9 **Data synthesis**

10 Direct pair-wise meta-analysis (DMA) will be conducted by Review Manager Version 5.3  
11 (<http://tech.cochrane.org/revman>). We will calculate risk ratio (RR) with its 95% confidence  
12 intervals (CIs) for dichotomous data and mean differences (MD) with its 95% CIs for continuous  
13 data. Weighted mean differences will be used for data measured on the same scales and for which  
14 the same units are used; otherwise, standardized mean differences will be used  
15 (<http://www.cochrane.org/handbook>). Heterogeneity will be quantified with the Q-statistic and I<sup>2</sup>  
16 index,  $P < 0.1$  or  $I^2 > 50\%$  indicates the presence of at least moderate heterogeneity, in this case, the  
17 random-effect model will be used, otherwise, the fixed-effect model will be used. I<sup>2</sup> will be  
18 calculated according to the equation  $I^2 = 100\% \times (Q - df) / Q$ , where Q is the Cochran heterogeneity  
19 statistic.<sup>18, 19</sup>  
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22 When lacking head-to head evidence, indirect treatment comparison meta-analysis (ITC) will be  
23 retrieved from available evidence. ITC software ([http://www.cadth.ca/en/resources/about-this-](http://www.cadth.ca/en/resources/about-this-guide/chapter-2-using-the-itc-application)  
24 [guide/chapter-2-using-the-itc-application](http://www.cadth.ca/en/resources/about-this-guide/chapter-2-using-the-itc-application)) will be used to obtain indirect data. In this  
25 meta-analysis, only indirect results between two comparisons such as A vs. B and B vs. C, an  
26 indirect result (A vs. C) will be calculated.  
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29 Network Meta-Analysis (NMA) is a technique to meta analyze more than two drugs at the same  
30 time. In our study we will use a full Bayesian evidence network. NMA will be performed using  
31 ADDIS software (<http://www.medfloss.org/node/812>). We will estimate the ranking probability  
32 for each anticoagulant, i.e., the most efficacious, the second-best, the highest bleeding incidence,  
33 the second-highest bleeding incidence, and so on, and presented the results graphically. The data  
34 will also be expressed as RR or MD with 95% CI.  
35  
36

37 Consistency between direct and indirect evidence will be checked by a node-splitting model  
38 through ADDIS software. When 95% CIs of inconsistency factors included zero or  $P > 0.05$   
39 indicates there is non-significant inconsistency between direct and indirect evidences.<sup>20</sup>  
40  
41 Meanwhile, Z test described by Song will used to evaluate the difference between DMA or ITC  
42 and NMA effects.  $P < 0.05$  indicates there is significant difference between DMA or ITC and NMA  
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3 effects.<sup>21</sup>  
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### 5 **Subgroup analysis**

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7 Several subgroup analyses will be performed according to the number of studies available based  
8 on the length of the follow-up period (ICU mortality, hospital mortality, 28/30 days mortality and  
9 90 days mortality), the severity of disease (APACHE II $\geq$ 25 or  $<$ 25), the incidence of DIC (yes or  
10 no).  
11

### 12 **Sensitivity analysis**

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14 We will assess the robustness of our results through a series of sensitivity analysis, i.e., excluding  
15 trials at high risk of bias, removing 1 study at a time iteratively, using odds ratios and risk  
16 differences as a measure of treatment effect, and using both fixed and random effects models.  
17

### 18 **Quality of evidence**

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20 The quality of evidence will be assessed by GRADE four-step approach for rating the quality of  
21 treatment effect estimates from network meta-analysis (NMA), and the process is shown in Figure  
22 2.<sup>22</sup>The quality of evidence is classified by the GRADE group into 4 levels: high quality, moderate  
23 quality, low quality and very low quality. The quality rating of RCT may be rated down by -1  
24 (serious concern) or -2 (very serious concern) for the following reasons: risk of bias,  
25 inconsistency, indirectness, imprecision, and publication bias. This process will be performed using  
26 GRADE pro 3.6 software (<http://www.gradeworkinggroup.org/>).  
27

## 28 **DISCUSSION**

29  
30 To our best knowledge, our study will be the first network meta-analysis to compare the efficacy  
31 and safety of different anticoagulants including heparin, antithrombin, rAPC, rhTM, and TFPI. It  
32 is important for clinicians to utilize best evidence to guide the clinical practice. The dysregulation  
33 of hemostatic system, especially the incidence of DIC, is a strong predictor of mortality.<sup>23</sup> Thus it  
34 should be diagnosed and treated early.<sup>24,25</sup> In the past few decades, several anticoagulants have  
35 been extensively evaluated, however, the results of these studies are inconsistent. In 2001, a  
36 randomized, double blind, placebo-controlled multicenter phase 3 study (Recombinant Human  
37 Activated Protein C Worldwide Evaluation in Severe Sepsis [PROWESS]) found that  
38 administration of rAPC (24 $\mu$ g/kg/h over 96 h) to sepsis patients was associated with a significant  
39 decrease of death.<sup>26</sup> However, this mortality benefit was not observed in a subsequent larger study  
40 (Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis  
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3 and Septic Shock [PROWESS-SHOCK] study).<sup>27</sup> At the end, the decision to withdraw rAPC was  
4 made voluntarily by the manufacturer. Whereas, in a subsequent observational study containing  
5 15022 participants, of these, 1009 (8%) received rAPC treatment, Casserly B et al. demonstrated  
6 that treatment with rAPC could significantly improve the survival rate of patients with severe  
7 sepsis.<sup>28</sup> Moreover, the mortality benefit was confirmed in a large meta-analysis, and such effects  
8 could still be observed when the PROWESS-SHOCK data were added to the analysis.<sup>29</sup> Regarding  
9 antithrombin, a large RCT named KeyberSept fund there was no significant effect of antithrombin  
10 on survival of patients with severe sepsis.<sup>30</sup> However, a subsequent RCT and two observational  
11 studies all reported antithrombin supplement therapy at the dose of 3000 IU/day could improve  
12 survival rate and increase the recovery rate from DIC without any risk of bleeding in DIC patients  
13 with sepsis.<sup>31-33</sup> Regarding TFPI, in two RCTs, the authors fund a trend toward reduction of the  
14 28-day mortality with the administration of TFPI.<sup>34,35</sup> However, this effect was not observed in a  
15 subsequent larger RCTs.<sup>36</sup> rTM is a novel anticoagulant. In a phase 2b study, the authors fund a  
16 trend toward reduction of the 28-day mortality with the administration of rTM, and the 28-day  
17 mortality was 17.8% in the rTM group and 21.6% in the placebo group (P=0.273).<sup>37</sup> Based the  
18 above analysis, a randomized, double-blind, placebo-controlled, phase 3 study to assess the safety  
19 and efficacy of rTM in subjects with severe sepsis and coagulopathy is currently recruiting  
20 participants (<http://clinicaltrials.gov/ct2/show/NCT01598831?term=ART-123&rank=2>). Finally, in  
21 a large meta-analysis including 17 studies, the authors demonstrated that heparin significantly  
22 decreased 28-day mortality in patients with sepsis without increasing the risk of bleeding.  
23 However, the methodological quality of studies included in this meta-analysis was poor.<sup>38</sup>

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26 As outlined above, based on these inconsistent results, guidelines published by UN, Japan and  
27 Italy recommended different drugs for the treatment of severe sepsis induced coagulopathy.  
28 Another concern is that, in most of current studies, the target drugs are often compared with  
29 placebo. Therefore, we don't know which one is better in terms of efficacy and safety. The  
30 purpose of our study is to carry out a systematic review and network meta-analysis comparing the  
31 efficacy and safety of different anticoagulants for severe sepsis based on existing randomized  
32 controlled trials (RCTs) and ranking these anticoagulants for practical consideration.  
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4 **Contributors:** LBJ, YFM contributed to the conception of the study. The manuscript protocol was  
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6 drafted by LBJ, SYJ and XF was revised by YFM and MZ. The search strategy was developed by  
7  
8 all the authors and will be performed by LBJ, XF, and SYJ, who will also independently screen  
9  
10 the potential studies, extract data from the included studies, assess the risk of bias and complete  
11  
12 the data synthesis. MZ and YFM will arbitrate in cases of disagreement and ensure the absence of  
13  
14 errors. All authors approved the publication of the protocol. The above authors all are members of  
15  
16 China Emergency and Critical Care Evidence-based Medicine Group (CECCEBMG). And Libing  
17  
18 Jiang and Shouyin Jiang make equal contribution to this work.  
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23  
24 **Competing interests:** None  
25

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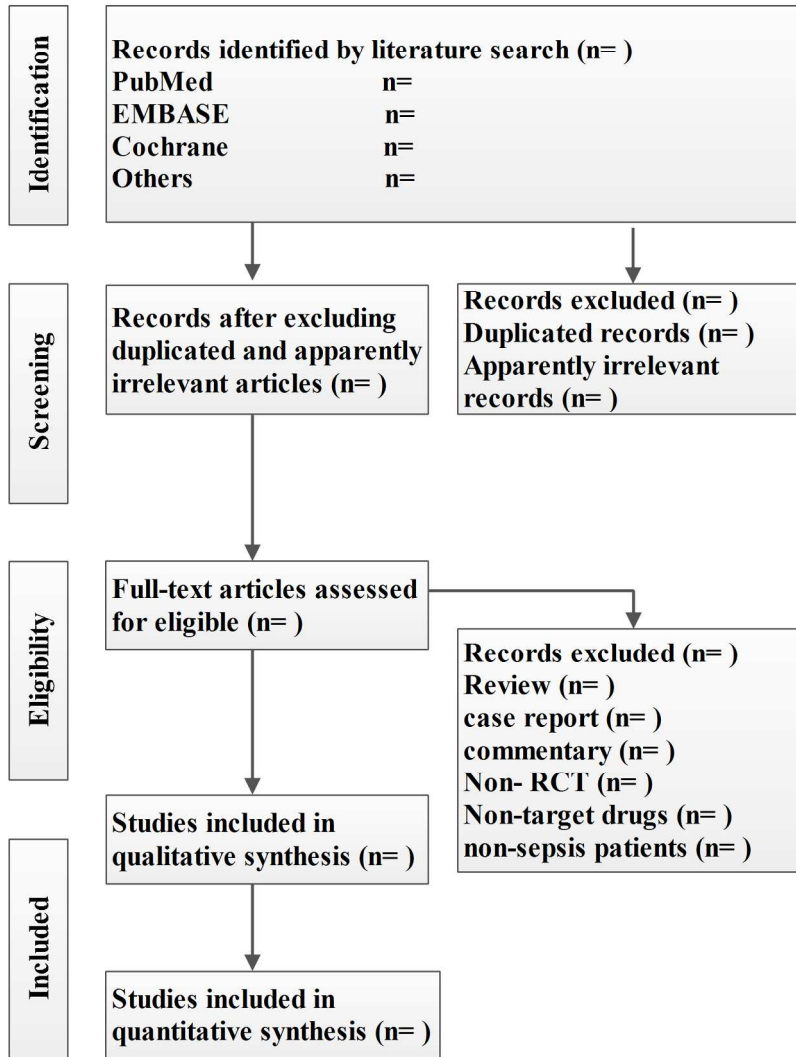
#### 24 **FIGURE LEGEND**

25 **Figure 1** The primary selection process.

26 **Figure 2** Approach for rating the quality of network meta-analysis (NMA) estimates.

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graph TD; A[Step 1  
Present direct and indirect estimate  
for each comparison of the evidence network] --> B[Step 2  
Rate quality of direct and indirect estimate]; B --> C[Step 3  
Present network meta-analysis estimate]; C --> D[Step 4  
Rate quality of network meta-analysis estimate];
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**Step 1**  
**Present direct and indirect estimate  
for each comparison of the evidence network**

**Step 2**  
**Rate quality of direct and indirect estimate**

**Step 3**  
**Present network meta-analysis estimate**

**Step 4**  
**Rate quality of network meta-analysis estimate**

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# BMJ Open

## The efficacy and safety of different anticoagulants on patients with severe sepsis and derangement of coagulation: a protocol for network meta-analysis of randomized controlled trials

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<b>Primary Subject Heading</b>:	Emergency medicine
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Keywords:	Adult intensive & critical care < ANAESTHETICS, Bleeding disorders & coagulopathies < HAEMATOLOGY, Infection control < INFECTIOUS DISEASES

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3 **The efficacy and safety of different anticoagulants on patients with severe sepsis and**  
4 **derangement of coagulation: a protocol for network meta-analysis of randomized controlled**  
5 **trials**  
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Medicine Group (CECCEBMG). Libing Jiang and Shouyin Jiang made equal contribution to this  
work. And Mao Zhang and Yuefeng Ma are co- corresponding author authors.

## ABSTRACT

**Introduction:** Sepsis is the leading cause of mortality in non-cardiologic critically ill patients. There are as many as 20 million cases of sepsis annually worldwide, with a mortality rate of around 35%. It has been reported that the dysregulation of hemostatic system due to the interaction between coagulation system and inflammatory response is a strong predictor of mortality in patients with severe sepsis. In this context, several anticoagulants have been evaluated in recent year. However, the results of these studies were inconsistent, and even were contradictory. In addition, there is insufficient evidence comparing the efficacy and safety of different anticoagulants. The purpose of our study is to carry out a systematic review and network meta-analysis comparing the efficacy and safety of different anticoagulants for severe sepsis based on existing randomized controlled trials (RCTs) and ranking these anticoagulants for practical consideration.

**Methods and analysis:** PubMed, EMASE, Cochrane Library databases will be systematically

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3 searched for eligible studies. Randomized controlled trials (RCT) on anticoagulant therapy of  
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5 severe sepsis with multiple outcome measures will be included. The Cochrane Risk of Bias Tool  
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7 will be used to assess the quality of included studies. The primary outcomes are mortality and  
8  
9 bleeding events. The secondary outcomes including the length of intensive care stay, the length of  
10  
11 hospital stay, and duration of mechanical ventilation. Direct pair-wise meta analysis (DMA),  
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13 indirect treatment comparison meta analysis (ITC) and network meta-analysis (NMA) will be  
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15 conducted to compare different anticoagulants.  
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21 **Ethics and dissemination:** Ethical approval is not required given this is a protocol for a  
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23 systematic review. The protocol of this systematic review will be disseminated in a peer-reviewed  
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25 journal and presented at a relevant conference.  
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27 **Registration details:** This protocol has been registered in PROSPERO ([http:// www. crd. york. ac.](http://www.crd.york.ac.uk/PROSPERO/)  
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29 [uk / PROSPERO/](http://www.crd.york.ac.uk/PROSPERO/)) under registration number CRD42014013886.  
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### 31 **Strengths and limitations of this study**

- 32 ● This is the first comprehensive review comparing the efficacy and safety of five different  
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34 anticoagulants through network meta-analysis.  
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- 37 ● The results of this systematic review will help clinicians in making decisions in clinical  
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39 practice.  
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- 41 ● The methods of this review are state of the art, including extensive literature search, explicit  
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43 inclusion and exclusion criteria, independent study selection, data extraction, quality  
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45 assessment and advanced statistical methods. In addition, we will use the Grading of  
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47 Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate  
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49 the quality of evidence.  
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- 51 ● This study is inherently retrospective and based on the published randomised controlled trials  
52  
53 only.  
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### 55 **INTRODUCTION**

56  
57 Sepsis has been reported as the leading cause of mortality in non-cardiologic critically ill patients.<sup>1</sup>  
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3 In the US , nearly 200,000 deaths are attributed to sepsis per year.<sup>2</sup> And it is likely that there are as  
4 many as 20 million cases of sepsis annually worldwide, with a mortality rate of around 35%.<sup>3</sup>  
5  
6 Sepsis, defined as infection-induced systemic inflammatory response syndrome (SIRS) involves  
7 multiple mechanisms, including the release of cytokines, the activation of complement systems,  
8 coagulation systems, and fibrinolytic systems.<sup>4</sup> Of these, the dysregulation of hemostatic system  
9 from insignificant coagulopathy to severe disseminated intravascular coagulation (DIC) has been  
10 shown to be related with the development of multiple organ dysfunction syndrome (MODS).<sup>5-7</sup> In  
11 a prospective epidemiologic study, the authors found that the prevalence of DIC, MODS and the  
12 risk of death were associated the severity of disease, the more severe the infection (from SIRS to  
13 septic shock), the higher the risk for the DIC, MODS and death.<sup>1</sup> And it has been reported that  
14 DIC can be found in 25% to 50% of patients with sepsis.<sup>8,9</sup> Therefore, it is reasonable to speculate  
15 that use of anticoagulants to inhibit the over-activated coagulation cascade may be useful in the  
16 resolution of DIC and reducing the mortality of sepsis. Following this hypothesis, the efficacy and  
17 safety of several anticoagulants were evaluated in many randomised controlled trials (RCTs) and  
18 meta-analysis. However, the results of these studies were inconsistent, even were contradictory.<sup>10</sup>  
19 As a result, considerable differences exist between guidelines, in the areas of treatment of DIC.  
20 The guideline published by UK recommended the use of recombinant activated protein C (rAPC)  
21 for serious cases, however, the guideline published by Japan recommended the use of  
22 supplement-dose of antithrombin.<sup>10</sup> Moreover, in major of these studies, the target drugs were  
23 often compared with placebo, therefore, up to now, there is no evidence that which one is better.  
24  
25 The purpose of our study is to carry out a systematic review and network meta-analysis comparing  
26 the efficacy and safety of different anticoagulants for severe sepsis based on existing randomized  
27 controlled trials (RCTs) and ranking these anticoagulants for practical consideration. And this  
28 study is expected to begin in August 2014 and conclude in November 2015.

## 29 **METHODS AND ANALYSIS**

### 30 **Design**

31 Systematic review and Bayesian network meta-analysis. The present systematic review and  
32 meta-analysis will be reported according to the recommendations from the preferred reporting  
33 items for systematic reviews and meta-analyses (PRISMA, [www.prisma-statement.org/](http://www.prisma-statement.org/))

### 34 **Data sources and searches**

We will systematically perform an electronic search of PubMed, EMBASE and Cochrane Library. In addition, we will also search conference abstracts from Society of Critical Care Medicine, the European Society for Intensive Care Medicine, the American Thoracic Society, and the American College of Chest Physicians, as well as the Clinicaltrials.gov and Controlled-trials.com, along with the bibliographies of eligible studies and relevant review articles or meta-analysis. The following medical subject headings terms and text words will be used alone or in combination: SIRS, systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock, pyemia\*, pyohemia\*, pyaemia\*, septicemia\*, bacteremia, anticoagulant\*, anticoagulation therapy, heparin, antithrombin, drotrecogin alfa (activated), activated protein C, xigris, rAPC, rhAPC, recombinant thrombomodulin, recombinant human soluble thrombomodulin, rTM, rhTM, ART, tissue factor pathway inhibitor, TFPI, Tifacogin, and random, controlled trial, and RCT. No limitation will be placed on publication status or language.

#### **Eligibility criteria**

- ◆ *Participants* Inclusion—Adult patients (>18 yr) with sepsis of any severity, defined according to the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine consensus (SCCM) definition or ACCP/SCCM/European Society of Intensive Care Medicine/American Thoracic Society/Surgical Infection Society definition.<sup>11, 12</sup> And patients with sepsis-induced DIC should fulfill the International Society on Thrombosis and Hemostasis (ISTH) DIC score or the Japanese Association for Acute Medicine (JAAM) DIC scoring system.<sup>13</sup>
- ◆ *Interventions* Inclusion—any RCT that evaluates the efficacy and safety of five anticoagulants including heparin, antithrombin, rAPC, rhTM, and TFPI (of any dose).
- ◆ *Controls* Inclusion—any RCT that evaluates the efficacy and safety of five anticoagulants including heparin, antithrombin, rAPC, rhTM, and TFPI (of any dose) and placebo or other standard therapy according to the Surviving Sepsis Campaign (<http://www.survivingsepsis.org/Resources/Pages/default.aspx>).
- ◆ *Outcome* Inclusion—the primary outcome of this study is mortality with the longest follow-up period, and bleeding events during therapy process (including minor and major bleeding events, the definitions of minor and major bleeding events are developed by individual studies). The secondary outcomes including the length of intensive care stay, the

length of hospital stay, and duration of mechanical ventilation. In addition, we will also evaluate the difference of acute physiology and chronic health evaluation (APACHE) II scores, sequential organ failure assessment (SOFA) scores, and DIC scores between two groups.

- ◆ *Types of study* Inclusion—only RCTs will be included.
- ◆ Exclusion criteria—age less than 18 years old, patients with non-infection SIRS, studies that evaluates other drugs or combined treatments of multiple drugs, there are no original data (e.g., case reports, reviews, and commentary), experimental studies and observational studies.

### **Study selection**

The titles and abstracts of literature search will be screened by two reviewers independently for potentially relevant studies according to the above mentioned inclusion and exclusion criteria. After excluding the duplicated and apparently irrelevant studies, the remaining studies will be read in full text. Any disagreement will be resolved by consensus. The primary selection process is presented in Figure 1.

### **Data extraction and quality assessment**

The following data will be extracted independently and in duplicate by two reviewers into a predefined spreadsheet: the name of the first author, publication year, country of origin, patients characteristics (gender, age, number, inclusion and exclusion criteria, APACHE II score, SOFA scores, and DIC scores ), characteristics of interventions (type and dose of target drug), characteristics of control treatment, outcomes (mortality at different time points, bleeding events, the length of intensive care stay, the length of hospital stay and duration of mechanical ventilation). Any discrepancy will be resolved by consensus. If necessary, we will try to contact the corresponding authors for more information.

The Cochrane Risk of Bias Tool will be adopted to assess the risk of bias for each RCT by two reviewers.<sup>14</sup> This tool includes six domains: sequence generation, allocation concealment, blinding, incomplete data assessment, selective outcome reporting, other sources of bias. And based on the above domains, the included RCTs will be classified into three categories: low risk, high risk and unclear. Any discrepancy will be resolved by consensus and discussion.

### **Assessment of reporting biases**

A funnel scatter plot of sample and effect size will be constructed to determine the presence of

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3 publication bias, and the contour enhanced funnel plot will be applied to aid in interpreting the  
4 funnel plot. If studies are missing in areas of low statistical significance, the asymmetry may be  
5 due to publication bias. If studies are missing in areas of high statistical significance, the  
6 asymmetry may be due to other factors. Begg-Mazumdar rank correlation and Egger's regression  
7 will be used to assess small trial bias statistically.<sup>15-17</sup>

### 12 **Data synthesis**

13  
14 Direct pair-wise meta-analysis (DMA) will be conducted by Review Manager Version 5.3  
15 (<http://tech.cochrane.org/revman>). We will calculate risk ratio (RR) with its 95% confidence  
16 intervals (CIs) for dichotomous data and mean differences (MD) with its 95% CIs for continuous  
17 data. Weighted mean differences will be used for data measured on the same scales and for which  
18 the same units are used; otherwise, standardized mean differences will be used  
19 (<http://www.cochrane.org/handbook>). Heterogeneity will be quantified with the Q-statistic and I<sup>2</sup>  
20 index,  $P < 0.1$  or  $I^2 > 50\%$  indicates the presence of at least moderate heterogeneity, in this case, the  
21 random-effect model will be used, otherwise, the fixed-effect model will be used. I<sup>2</sup> will be  
22 calculated according to the equation  $I^2 = 100\% \times (Q - df) / Q$ , where Q is the Cochran heterogeneity  
23 statistic.<sup>18, 19</sup>

24  
25 When lacking head-to head evidence, indirect treatment comparison meta-analysis (ITC) will be  
26 retrieved from available evidence. ITC software ([http://www.cadth.ca/en/resources/about-this-](http://www.cadth.ca/en/resources/about-this-guide/chapter-2-using-the-itc-application)  
27 [guide/chapter-2-using-the-itc-application](http://www.cadth.ca/en/resources/about-this-guide/chapter-2-using-the-itc-application)) will be used to obtain indirect data. In this  
28 meta-analysis, only indirect results between two comparisons such as A vs. B and B vs. C, an  
29 indirect result (A vs. C) will be calculated.

30  
31 Network Meta-Analysis (NMA) is a technique to meta analyze more than two drugs at the same  
32 time. In our study we will use a full Bayesian evidence network. NMA will be performed using  
33 ADDIS software (<http://www.medfloss.org/node/812>). We will estimate the ranking probability  
34 for each anticoagulant, i.e., the most efficacious, the second-best, the highest bleeding incidence,  
35 the second-highest bleeding incidence, and so on, and presented the results graphically. The data  
36 will also be expressed as RR or MD with 95% CI.

37  
38 Consistency between direct and indirect evidence will be checked by a node-splitting model  
39 through ADDIS software. When 95% CIs of inconsistency factors included zero or  $P > 0.05$   
40 indicates there is non-significant inconsistency between direct and indirect evidences.<sup>20</sup>

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Meanwhile, Z test described by Song will used to evaluate the difference between DMA or ITC and NMA effects.  $P < 0.05$  indicates there is significant difference between DMA or ITC and NMA effects.<sup>21</sup>

### Subgroup analysis

Several subgroup analyses will be performed based on the length of the follow-up period (ICU mortality, hospital mortality, 28/30 days mortality and 90 days mortality), the severity of disease (APACHE II  $\geq 25$  or  $< 25$ ), and the incidence of DIC (yes or no).

### Sensitivity analysis

We will assess the robustness of our results through a series of sensitivity analysis, i.e., excluding trials at high risk of bias, removing 1 study at a time iteratively, using odds ratios and risk differences as a measure of treatment effect, and using both fixed and random effects models.

### Quality of evidence

The quality of evidence will be assessed by GRADE four-step approach for rating the quality of treatment effect estimates from network meta-analysis (NMA), and the process is shown in Figure 2.<sup>22</sup> The quality of evidence is classified by the GRADE group into 4 levels: high quality, moderate quality, low quality and very low quality. The quality rating of RCT may be rated down by -1 (serious concern) or -2 (very serious concern) for the following reasons: risk of bias, inconsistency, indirectness, imprecision, and publication bias. This process will performed using GRADE pro 3.6 software (<http://www.gradeworkinggroup.org/>).

### DISCUSSION

To our best knowledge, our study will be the first network meta-analysis to compare the efficacy and safety of different anticoagulants including heparin, antithrombin, rAPC, rhTM, and TFPI. It is important for clinicians to utilize best evidence to guide the clinical practice. The dysregulation of hemostatic system, especially the incidence of DIC, is a strong predictor of mortality.<sup>23</sup> Thus it should be diagnosed and treated early.<sup>24, 25</sup> In the past few decades, several anticoagulants have been extensively evaluated, however, the results of these studies are inconsistent. In 2001, a randomized, double blind, placebo-controlled multicenter phase 3 study (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis [PROWESS]) found that administration of rAPC (24  $\mu\text{g}/\text{kg}/\text{h}$  over 96 h) to sepsis patients was associated with a significant decrease of death.<sup>26</sup> However, this mortality benefit was not observed in a subsequent larger study



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(Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock [PROWESS-SHOCK] study).<sup>27</sup> At the end, the decision to withdraw rAPC was made voluntarily by the manufacturer. Whereas, in a subsequent observational study containing 15022 participants, of these, 1009 (8%) received rAPC treatment, Casserly B et al. demonstrated that treatment with rAPC could significantly improve the survival rate of patients with severe sepsis.<sup>28</sup> Moreover, the mortality benefit was confirmed in a large meta-analysis, and such effects could still be observed when the PROWESS-SHOCK data were added to the analysis.<sup>29</sup> Regarding antithrombin, a large RCT named KeyberSept fund there was no significant effect of antithrombin on survival of patients with severe sepsis.<sup>30</sup> However, a subsequent RCT and two observational studies all reported antithrombin supplement therapy at the dose of 3000 IU/day could improve survival rate and increase the recovery rate from DIC without any risk of bleeding in DIC patients with sepsis.<sup>31-33</sup> Regarding TFPI, in two RCTs, the authors found a trend toward reduction of the 28-day mortality with the administration of TFPI.<sup>34,35</sup> However, this effect was not observed in a subsequent larger RCTs.<sup>36</sup> rTM is a novel anticoagulant. In a phase 2b study, the authors fund a trend toward reduction of the 28-day mortality with the administration of rTM, and the 28-day mortality was 17.8% in the rTM group and 21.6% in the placebo group (P=0.273).<sup>37</sup> Based the above analysis, a randomized, double-blind, placebo-controlled, phase 3 study to assess the safety and efficacy of rTM in subjects with severe sepsis and coagulopathy is currently recruiting participants (<http://clinicaltrials.gov/ct2/show/NCT01598831?term=ART-123&rank=2>). Finally, in a large meta-analysis including 17 studies, the authors demonstrated that heparin significantly decreased 28-day mortality in patients with sepsis without increasing the risk of bleeding. However, the methodological quality of studies included in this meta-analysis was poor.<sup>38</sup>

As outlined above, based on these inconsistent results, guidelines published by UN, Japan and Italy recommended different drugs for the treatment of severe sepsis induced coagulopathy. Another concern is that, in most of current studies, the target drugs are often compared with placebo. Therefore, we don't know which one is better in terms of efficacy and safety. The purpose of our study is to carry out a systematic review and network meta-analysis comparing the efficacy and safety of different anticoagulants for severe sepsis based on existing randomized controlled trials (RCTs) and ranking these anticoagulants for practical consideration.

**Contributors:** LBJ, YFM contributed to the conception of the study. The manuscript protocol was drafted by LBJ, SYJ and XF was revised by YFM and MZ. The search strategy was developed by all the authors and will be performed by LBJ, XF, and SYJ, who will also independently screen the potential studies, extract data from the included studies, assess the risk of bias and complete the data synthesis. MZ and YFM will arbitrate in cases of disagreement and ensure the absence of errors. All authors approved the publication of the protocol. The above authors all are members of China Emergency and Critical Care Evidence-based Medicine Group (CECCEBMG). And Libing Jiang and Shouyin Jiang made equal contribution to this work.

**Competing interests:** None

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**Data sharing statement:** No additional data available

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## FIGURE LEGEND

**Figure 1** The primary selection process.

**Figure 2** Approach for rating the quality of network meta-analysis (NMA) estimates.

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3 **The efficacy and safety of different anticoagulants on patients with severe sepsis and**  
4 **derangement of coagulation: a protocol for network meta-analysis of randomized controlled**  
5 **trials**  
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work. And Mao Zhang and Yuefeng Ma are co- corresponding author authors.

## ABSTRACT

**Introduction:** Sepsis is the leading cause of mortality in non-cardiologic critically ill patients. There are as many as 20 million cases of sepsis annually worldwide, with a mortality rate of around 35%. It has been reported that the dysregulation of hemostatic system due to the interaction between coagulation system and inflammatory response is a strong predictor of mortality in patients with severe sepsis. In this context, several anticoagulants have been evaluated in recent year. However, the results of these studies were inconsistent, and even were contradictory. In addition, there is insufficient evidence comparing the efficacy and safety of different anticoagulants. The purpose of our study is to carry out a systematic review and network meta-analysis comparing the efficacy and safety of different anticoagulants for severe sepsis based on existing randomized controlled trials (RCTs) and ranking these anticoagulants for practical consideration.

**Methods and analysis:** PubMed, EMASE, Cochrane Library databases will be systematically

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3 searched for eligible studies. Randomized controlled trials (RCT) on anticoagulant therapy of  
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5 severe sepsis with multiple outcome measures will be included. The Cochrane Risk of Bias Tool  
6  
7 will be used to assess the quality of included studies. The primary outcomes are mortality and  
8  
9 bleeding events. The secondary outcomes including the length of intensive care stay, the length of  
10  
11 hospital stay, and duration of mechanical ventilation. Direct pair-wise meta analysis (DMA),  
12  
13 indirect treatment comparison meta analysis (ITC) and network meta-analysis (NMA) will be  
14  
15 conducted to compare different anticoagulants.  
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21 **Ethics and dissemination:** Ethical approval is not required given this is a protocol for a  
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23 systematic review. The protocol of this systematic review will be disseminated in a peer-reviewed  
24  
25 journal and presented at a relevant conference.  
26

27 **Registration details:** This protocol has been registered in PROSPERO ([http:// www. crd. york. ac.](http://www.crd.york.ac.uk/PROSPERO/)  
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29 [uk / PROSPERO/](http://www.crd.york.ac.uk/PROSPERO/)) under registration number CRD42014013886.  
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### 31 **Strengths and limitations of this study**

- 32 ● This is the first comprehensive review comparing the efficacy and safety of five different  
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34 anticoagulants through network meta-analysis.  
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- 37 ● The results of this systematic review will help clinicians in making decisions in clinical  
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39 practice.  
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- 41 ● The methods of this review are state of the art, including extensive literature search, explicit  
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43 inclusion and exclusion criteria, independent study selection, data extraction, quality  
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45 assessment and advanced statistical methods. In addition, we will use the Grading of  
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47 Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate  
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49 the quality of evidence.  
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- 51 ● This study is inherently retrospective and based on the published randomised controlled trials  
52  
53 only.  
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### 55 **INTRODUCTION**

56 Sepsis has been reported as the leading cause of mortality in non-cardiologic critically ill patients.<sup>1</sup>  
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3 In the US , nearly 200,000 deaths are attributed to sepsis per year.<sup>2</sup> And it is likely that there are as  
4 many as 20 million cases of sepsis annually worldwide, with a mortality rate of around 35%.<sup>3</sup>  
5  
6 Sepsis, defined as infection-induced systemic inflammatory response syndrome (SIRS) involves  
7 multiple mechanisms, including the release of cytokines, the activation of complement systems,  
8 coagulation systems, and fibrinolytic systems.<sup>4</sup> Of these, the dysregulation of hemostatic system  
9 from insignificant coagulopathy to severe disseminated intravascular coagulation (DIC) has been  
10 shown to be related with the development of multiple organ dysfunction syndrome (MODS).<sup>5-7</sup> In  
11 a prospective epidemiologic study, the authors found that the prevalence of DIC, MODS and the  
12 risk of death were associated the severity of disease, the more severe the infection (from SIRS to  
13 septic shock), the higher the risk for the DIC, MODS and death.<sup>1</sup> And it has been reported that  
14 DIC can be found in 25% to 50% of patients with sepsis.<sup>8,9</sup> Therefore, it is reasonable to speculate  
15 that use of anticoagulants to inhibit the over-activated coagulation cascade may be useful in the  
16 resolution of DIC and reducing the mortality of sepsis. Following this hypothesis, the efficacy and  
17 safety of several anticoagulants were evaluated in many randomised controlled trials (RCTs) and  
18 meta-analysis. However, the results of these studies were inconsistent, even were contradictory.<sup>10</sup>  
19 As a result, considerable differences exist between guidelines, in the areas of treatment of DIC.  
20 The guideline published by UK recommended the use of recombinant activated protein C (rAPC)  
21 for serious cases, however, the guideline published by Japan recommended the use of  
22 supplement-dose of antithrombin.<sup>10</sup> Moreover, in major of these studies, the target drugs were  
23 often compared with placebo, therefore, up to now, there is no evidence that which one is better.  
24  
25 The purpose of our study is to carry out a systematic review and network meta-analysis comparing  
26 the efficacy and safety of different anticoagulants for severe sepsis based on existing randomized  
27 controlled trials (RCTs) and ranking these anticoagulants for practical consideration. **And this  
28 study is expected to begin in August 2014 and conclude in November 2015.**

## 29 **METHODS AND ANALYSIS**

### 30 **Design**

31 Systematic review and Bayesian network meta-analysis. The present systematic review and  
32 meta-analysis will be reported according to the recommendations from the preferred reporting  
33 items for systematic reviews and meta-analyses (PRISMA, [www.prisma-statement.org/](http://www.prisma-statement.org/))

### 34 **Data sources and searches**



We will systematically perform an electronic search of PubMed, EMBASE and Cochrane Library. In addition, we will also search conference abstracts from Society of Critical Care Medicine, the European Society for Intensive Care Medicine, the American Thoracic Society, and the American College of Chest Physicians, as well as the Clinicaltrials.gov and Controlled-trials.com, along with the bibliographies of eligible studies and relevant review articles or meta-analysis. The following medical subject headings terms and text words will be used alone or in combination: SIRS, systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock, pyemia\*, pyohemia\*, pyaemia\*, septicemia\*, bacteremia, anticoagulant\*, anticoagulation therapy, heparin, antithrombin, drotrecogin alfa (activated), activated protein C, xigris, rAPC, rhAPC, recombinant thrombomodulin, recombinant human soluble thrombomodulin, rTM, rhTM, ART, tissue factor pathway inhibitor, TFPI, Tifacogin, and random, controlled trial, and RCT. No limitation will be placed on publication status or language.

#### **Eligibility criteria**

- ◆ *Participants* Inclusion—Adult patients (>18 yr) with sepsis of any severity, defined according to the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine consensus (SCCM) definition or ACCP/SCCM/European Society of Intensive Care Medicine/American Thoracic Society/Surgical Infection Society definition.<sup>11, 12</sup> And patients with sepsis-induced DIC should fulfill the International Society on Thrombosis and Hemostasis (ISTH) DIC score or the Japanese Association for Acute Medicine (JAAM) DIC scoring system.<sup>13</sup>
- ◆ *Interventions* Inclusion—any RCT that evaluates the efficacy and safety of five anticoagulants including heparin, antithrombin, rAPC, rhTM, and TFPI (of any dose).
- ◆ *Controls* Inclusion—any RCT that evaluates the efficacy and safety of five anticoagulants including heparin, antithrombin, rAPC, rhTM, and TFPI (of any dose) and placebo or other standard therapy according to the Surviving Sepsis Campaign (<http://www.survivingsepsis.org/Resources/Pages/default.aspx>).
- ◆ *Outcome* Inclusion—the primary outcome of this study is mortality with the longest follow-up period, and bleeding events during therapy process (including minor and major bleeding events, the definitions of minor and major bleeding events are developed by individual studies). The secondary outcomes including the length of intensive care stay, the

length of hospital stay, and duration of mechanical ventilation. In addition, we will also evaluate the difference of acute physiology and chronic health evaluation (APACHE) II scores, sequential organ failure assessment (SOFA) scores, and DIC scores between two groups.

- ◆ *Types of study* Inclusion—only RCTs will be included.
- ◆ Exclusion criteria—age less than 18 years old, patients with non-infection SIRS, studies that evaluates other drugs or combined treatments of multiple drugs, there are no original data (e.g., case reports, reviews, and commentary), experimental studies and observational studies.

### **Study selection**

The titles and abstracts of literature search will be screened by two reviewers independently for potentially relevant studies according to the above mentioned inclusion and exclusion criteria. After excluding the duplicated and apparently irrelevant studies, the remaining studies will be read in full text. Any disagreement will be resolved by consensus. The primary selection process is presented in Figure 1.

### **Data extraction and quality assessment**

The following data will be extracted independently and in duplicate by two reviewers into a predefined spreadsheet: the name of the first author, publication year, country of origin, patients characteristics (gender, age, number, inclusion and exclusion criteria, APACHE II score, SOFA scores, and DIC scores ), characteristics of interventions (type and dose of target drug), characteristics of control treatment, outcomes (mortality at different time points, bleeding events, the length of intensive care stay, the length of hospital stay and duration of mechanical ventilation). Any discrepancy will be resolved by consensus. If necessary, we will try to contact the corresponding authors for more information.

The Cochrane Risk of Bias Tool will be adopted to assess the risk of bias for each RCT by two reviewers.<sup>14</sup> This tool includes six domains: sequence generation, allocation concealment, blinding, incomplete data assessment, selective outcome reporting, other sources of bias. And based on the above domains, the included RCTs will be classified into three categories: low risk, high risk and unclear. Any discrepancy will be resolved by consensus and discussion.

### **Assessment of reporting biases**

A funnel scatter plot of sample and effect size will be constructed to determine the presence of

1  
2  
3 publication bias, and the contour enhanced funnel plot will be applied to aid in interpreting the  
4 funnel plot. If studies are missing in areas of low statistical significance, the asymmetry may be  
5 due to publication bias. If studies are missing in areas of high statistical significance, the  
6 asymmetry may be due to other factors. Begg-Mazumdar rank correlation and Egger's regression  
7 will be used to assess small trial bias statistically.<sup>15-17</sup>

### 12 **Data synthesis**

13  
14 Direct pair-wise meta-analysis (DMA) will be conducted by Review Manager Version 5.3  
15 (<http://tech.cochrane.org/revman>). We will calculate risk ratio (RR) with its 95% confidence  
16 intervals (CIs) for dichotomous data and mean differences (MD) with its 95% CIs for continuous  
17 data. Weighted mean differences will be used for data measured on the same scales and for which  
18 the same units are used; otherwise, standardized mean differences will be used  
19 (<http://www.cochrane.org/handbook>). Heterogeneity will be quantified with the Q-statistic and I<sup>2</sup>  
20 index,  $P < 0.1$  or  $I^2 > 50\%$  indicates the presence of at least moderate heterogeneity, in this case, the  
21 random-effect model will be used, otherwise, the fixed-effect model will be used. I<sup>2</sup> will be  
22 calculated according to the equation  $I^2 = 100\% \times (Q - df) / Q$ , where Q is the Cochran heterogeneity  
23 statistic.<sup>18, 19</sup>

24  
25 When lacking head-to head evidence, indirect treatment comparison meta-analysis (ITC) will be  
26 retrieved from available evidence. ITC software ([http://www.cadth.ca/en/resources/about-this-](http://www.cadth.ca/en/resources/about-this-guide/chapter-2-using-the-itc-application)  
27 [guide/chapter-2-using-the-itc-application](http://www.cadth.ca/en/resources/about-this-guide/chapter-2-using-the-itc-application)) will be used to obtain indirect data. In this  
28 meta-analysis, only indirect results between two comparisons such as A vs. B and B vs. C, an  
29 indirect result (A vs. C) will be calculated.

30  
31 Network Meta-Analysis (NMA) is a technique to meta analyze more than two drugs at the same  
32 time. In our study we will use a full Bayesian evidence network. NMA will be performed using  
33 ADDIS software (<http://www.medfloss.org/node/812>). We will estimate the ranking probability  
34 for each anticoagulant, i.e., the most efficacious, the second-best, the highest bleeding incidence,  
35 the second-highest bleeding incidence, and so on, and presented the results graphically. The data  
36 will also be expressed as RR or MD with 95% CI.

37  
38 Consistency between direct and indirect evidence will be checked by a node-splitting model  
39 through ADDIS software. When 95% CIs of inconsistency factors included zero or  $P > 0.05$   
40 indicates there is non-significant inconsistency between direct and indirect evidences.<sup>20</sup>

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Meanwhile, Z test described by Song will used to evaluate the difference between DMA or ITC and NMA effects.  $P < 0.05$  indicates there is significant difference between DMA or ITC and NMA effects.<sup>21</sup>

### Subgroup analysis

Several subgroup analyses will be performed based on the length of the follow-up period (ICU mortality, hospital mortality, 28/30 days mortality and 90 days mortality), the severity of disease (APACHE II  $\geq 25$  or  $< 25$ ), and the incidence of DIC (yes or no).

### Sensitivity analysis

We will assess the robustness of our results through a series of sensitivity analysis, i.e., excluding trials at high risk of bias, removing 1 study at a time iteratively, using odds ratios and risk differences as a measure of treatment effect, and using both fixed and random effects models.

### Quality of evidence

The quality of evidence will be assessed by GRADE four-step approach for rating the quality of treatment effect estimates from network meta-analysis (NMA), and the process is shown in Figure 2.<sup>22</sup> The quality of evidence is classified by the GRADE group into 4 levels: high quality, moderate quality, low quality and very low quality. The quality rating of RCT may be rated down by -1 (serious concern) or -2 (very serious concern) for the following reasons: risk of bias, inconsistency, indirectness, imprecision, and publication bias. This process will performed using GRADE pro 3.6 software (<http://www.gradeworkinggroup.org/>).

### DISCUSSION

To our best knowledge, our study will be the first network meta-analysis to compare the efficacy and safety of different anticoagulants including heparin, antithrombin, rAPC, rhTM, and TFPI. It is important for clinicians to utilize best evidence to guide the clinical practice. The dysregulation of hemostatic system, especially the incidence of DIC, is a strong predictor of mortality.<sup>23</sup> Thus it should be diagnosed and treated early.<sup>24, 25</sup> In the past few decades, several anticoagulants have been extensively evaluated, however, the results of these studies are inconsistent. In 2001, a randomized, double blind, placebo-controlled multicenter phase 3 study (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis [PROWESS]) found that administration of rAPC (24  $\mu\text{g}/\text{kg}/\text{h}$  over 96 h) to sepsis patients was associated with a significant decrease of death.<sup>26</sup> However, this mortality benefit was not observed in a subsequent larger study

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(Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock [PROWESS-SHOCK] study).<sup>27</sup> At the end, the decision to withdraw rAPC was made voluntarily by the manufacturer. Whereas, in a subsequent observational study containing 15022 participants, of these, 1009 (8%) received rAPC treatment, Casserly B et al. demonstrated that treatment with rAPC could significantly improve the survival rate of patients with severe sepsis.<sup>28</sup> Moreover, the mortality benefit was confirmed in a large meta-analysis, and such effects could still be observed when the PROWESS-SHOCK data were added to the analysis.<sup>29</sup> Regarding antithrombin, a large RCT named KeyberSept fund there was no significant effect of antithrombin on survival of patients with severe sepsis.<sup>30</sup> However, a subsequent RCT and two observational studies all reported antithrombin supplement therapy at the dose of 3000 IU/day could improve survival rate and increase the recovery rate from DIC without any risk of bleeding in DIC patients with sepsis.<sup>31-33</sup> Regarding TFPI, in two RCTs, the authors found a trend toward reduction of the 28-day mortality with the administration of TFPI.<sup>34,35</sup> However, this effect was not observed in a subsequent larger RCTs.<sup>36</sup> rTM is a novel anticoagulant. In a phase 2b study, the authors fund a trend toward reduction of the 28-day mortality with the administration of rTM, and the 28-day mortality was 17.8% in the rTM group and 21.6% in the placebo group (P=0.273).<sup>37</sup> Based the above analysis, a randomized, double-blind, placebo-controlled, phase 3 study to assess the safety and efficacy of rTM in subjects with severe sepsis and coagulopathy is currently recruiting participants (<http://clinicaltrials.gov/ct2/show/NCT01598831?term=ART-123&rank=2>). Finally, in a large meta-analysis including 17 studies, the authors demonstrated that heparin significantly decreased 28-day mortality in patients with sepsis without increasing the risk of bleeding. However, the methodological quality of studies included in this meta-analysis was poor.<sup>38</sup>

As outlined above, based on these inconsistent results, guidelines published by UN, Japan and Italy recommended different drugs for the treatment of severe sepsis induced coagulopathy. Another concern is that, in most of current studies, the target drugs are often compared with placebo. Therefore, we don't know which one is better in terms of efficacy and safety. The purpose of our study is to carry out a systematic review and network meta-analysis comparing the efficacy and safety of different anticoagulants for severe sepsis based on existing randomized controlled trials (RCTs) and ranking these anticoagulants for practical consideration.

**Contributors:** LBJ, YFM contributed to the conception of the study. The manuscript protocol was drafted by LBJ, SYJ and XF was revised by YFM and MZ. The search strategy was developed by all the authors and will be performed by LBJ, XF, and SYJ, who will also independently screen the potential studies, extract data from the included studies, assess the risk of bias and complete the data synthesis. MZ and YFM will arbitrate in cases of disagreement and ensure the absence of errors. All authors approved the publication of the protocol. The above authors all are members of China Emergency and Critical Care Evidence-based Medicine Group (CECCEBMG). And Libing Jiang and Shouyin Jiang made equal contribution to this work.

**Competing interests:** None

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**Data sharing statement:** No additional data available

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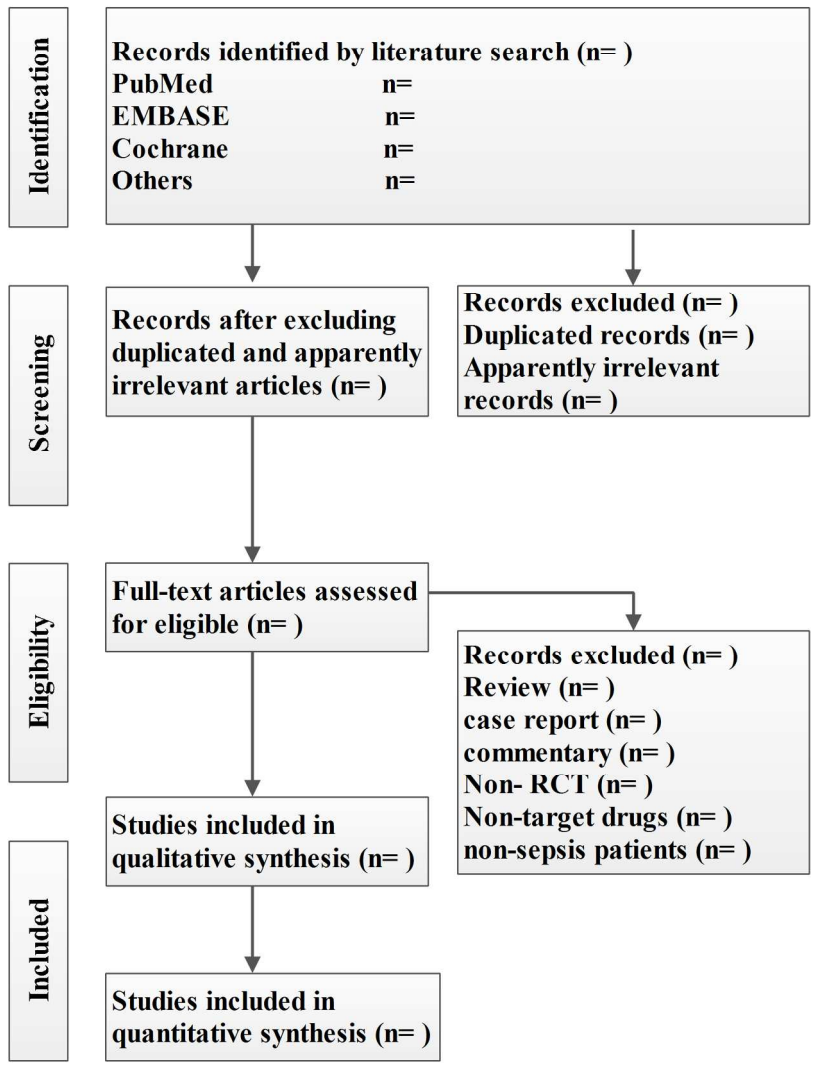
## FIGURE LEGEND

**Figure 1** The primary selection process.

**Figure 2** Approach for rating the quality of network meta-analysis (NMA) estimates.



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graph TD; A[Step 1  
Present direct and indirect estimate  
for each comparison of the evidence network] --> B[Step 2  
Rate quality of direct and indirect estimate]; B --> C[Step 3  
Present network meta-analysis estimate]; C --> D[Step 4  
Rate quality of network meta-analysis estimate];
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**Step 1**  
**Present direct and indirect estimate  
for each comparison of the evidence network**

**Step 2**  
**Rate quality of direct and indirect estimate**

**Step 3**  
**Present network meta-analysis estimate**

**Step 4**  
**Rate quality of network meta-analysis estimate**

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