What Should We Focus On Sepsis Fluid Resuscitation? – A Research Based On Scientometrics And Visual Analysis

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Abstract

Background: Sepsis is a life-threatening condition and a global disease burden. Intravenous fluid therapy has been one of the cornerstones of sepsis treatment for decades. Many of the current views and programs are still controversial. With the rapid development of data science and bibliometrics, it is possible to comprehensively review and discover future research trends by analyzing the temporal evolution of topics.

Methods: In this paper, bibliometric method was used to get a comprehensive review and quantitatively analyze the global development trend, regional distribution and discipline layout of fluid resuscitation in sepsis. VOSviewer and SciMAT were used to analyze the research hotspots, strategic layout and theme changes of fluid resuscitation in sepsis, and to explore the future research direction.

Results: With the development of multi-disciplinary research on fluid resuscitation of sepsis, more attention has been paid to the early prediction and treatment in the emergency medicine department, and the number of basic research (effects of different components of resuscitation fluid) has a downward trend, but the role of albumin is still worthy of further study. The key points of fluid resuscitation in sepsis are the timing of fluid resuscitation, early intervention in the emergency medicine department, looking for accurate and timely indexes of microcirculation perfusion, fluid

resuscitation volume in different resuscitation stages and its effect on respiration, kidney and abdominal cavity.

Conclusion: The method can identify hotspots and detect future directions conveniently, quickly and effectively. The clinical research of fluid resuscitation in sepsis, especially “the early intervention” and “the precise resuscitation” , is paid more attention, and even the recommendations of the consensus and guidelines need to be further confirmed by “multi center research”, which may become the development direction in the future.

Trial registration: it was not registered,because it is an bibliometric analysis based on the published articles.

Key words: Sepsis; Fluid resuscitation; Research hotspots; Future research;

Background

Sepsis is a life-threatening condition and a global disease burden[1-2]. The heterogeneous syndrome is defined as severe organ dysfunction caused by a dys-regulated host response to infection, with renewed emphasis on immune pathophysiology. Researchers around the world constantly update the diagnostic criteria of sepsis, and have put forward such concepts as “sepsis-3”, "Surviving Sepsis Campaign(SSC)[1]", "Early Goal-Directed Therapy (EGDT) [2], "the 3-h and 6-h bundles to an hour-1 bundle[3]", and "limited ventilation", "the best PEEP[4]", "Lung Protective -Ventilation[5]". Despite all efforts of experimental and clinical research during the last three decades, the ability to positively influence course and outcome of the syndrome remains limited[1-2].

The hemodynamic coherence between the macro- and microcirculation is often poor in sepsis. Various diseases lead to vascular changes that may not be readily apparent with current monitoring strategies. Therefore, intravenous fluid resuscitation strategies must take into account not only microcirculatory parameters such as systemic arterial blood pressure, but also downstream measures and/or microcirculatory assessments of the patient's response to treatment. Which are the best indicators of the effect of fluid resuscitation in sepsis, blood lactate level[6,7,8]or other monitoring/observation indicators?. The role of hydroxyethyl starch in fluid resuscitation has been denied, but the ability to maintain crystal liquid has not been effectively improved, and the search for an ideal crystal liquid is still in progress[9].

Based on the bibliometric method, this paper summarizes the research progress of fluid resuscitation of sepsis in the past 10 years, and infers the research hotspots of fluid resuscitation of sepsis in the future according to the changes of literature research hotspots, so as to provide research direction and reference for better carrying out the global research cooperation and guidance of fluid resuscitation of sepsis. And future researches will focus on the effects of different fluid therapy regimens on the macro-and microcirculation/endothelial surface layer in various disease states, the goals and timing of its administration, and ultimately outcome of the patients will likely change fluid therapy in the future.

Methods

Data collection

According to the distribution and retrieval characteristics of medical literature, PubMed, as the most authoritative database of biomedical literature, is first included in the data source. At the same time, considering the time lag characteristics of PubMed database indexing Medical Subject Headings, we decided to use Scopus database as a supplement to give full play to its advantages of comprehensive retrieval of topics, abstracts and keyword fields at the same time. In general, the time span needed to trace back the macro development of a field is ten years, so we set the retrieval time period: January 2011 to December 2020. Use of retrieval strategies:“(“Sepsis”[MH] OR Sepsis[TOPIC] OR (Septic Shock)[TOPIC] OR “Shock, Septic”[MH]) AND(((Fluid Resus

citation)[TOPIC] OR (Resuscitation Fluid)[TOPIC] OR ((Resuscitation[MH] OR Resuscitation[TOPIC])AND (((“Fluid therapy”[MH] OR (Fluid therapy)[TOPIC])) OR (intravenous fluid)[TOPIC] OR (Fluid overload)[TOPIC]])))). A total of 2739 articles were retrieved from PubMed and Scopus databases. After individual cases, reviews, and unrelated articles were removed, 1812 articles remained, and these articles were the basis of further analysis.

Methods of Analysis

Firstly, the global development trend, regional distribution and discipline layout of sepsis fluid resuscitation were quantitatively analyzed by document metrology. Secondly, the visualization tools were used to explore research hotspots, strategic layout and theme evolution path. The visualization tools were used including VOSviewer (Science and Technology Research Center of Leiden University in the Netherlands), and SciMAT (University of cervical cancer in Spain), which can carry out data cleaning, data simplification and network simplification on research topics. VOSviewer can define the specific location of the topic through the correlation strength clustering, and the location relationship can reflect the relationship of the topic. SciMAT can draw the layout of hot topics based on the centrality and density of topics, which has more advantages in evolution analysis. Fig. 1 summarized the research framework of this paper.

Fig.1 Inclusion and exclusion process of fluid resuscitation for sepsis

Results

Research output status and development trend

From 2011 to 2020, the global research output of sepsis fluid resuscitation showed a fluctuating upward trend (Additional file 1: **Fig.S1**). From 2012 to 2013, the research in this field was in a period of rapid development, and the annual output of the paper increased from 123 to 169. The study of fluid resuscitation in sepsis has entered a period of steady development from 2013 to 2016. After that, the study entered the second period of rapid development, the highest annual number of papers up to 227. See the chart of the major contributing countries in Additional file 1: **Fig.S2**.

Distribution and Change of subjects

Through the classification analysis of published journals, it is found that the number of emergency/critical care medical articles continues to increase, while the number of other related disciplines is gradually decreasing (Additional file 1: **Fig.S3**). This shows that sepsis is a complex acute and severe disease, involving a wide range of disciplines. With the rapid development of emergency medicine and critical medicine in the past decade, the centralized treatment of patients with sepsis has become the norm. At the same time, we also further analyzed the statistical analysis of the annual publication year on the subject changes. After verification, it should be caused by SCOPUS's adjustment of the subject attributes of these journals, apart from the influence of discipline classification. Early management of sepsis and septic shock is crucial for patients' prognosis. As the Emergency Department (ED) is the place where the first medical contact for septic patients is likely to occur, emergency physicians play an essential role in the early phases of patient management, which consists of accurate initial diagnosis, resuscitation, and early antibiotic treatment.

Three of the articles published in the New England Journal of Medicine were cited more than 1000 times, YEALY, D.M. Et al.[10], A Randomized Trial of Protocol-based Care For Early partial Shock (Cited 1504), PEAKE, S. L. Et al.[11] (Cited 1181) and PERNER,A. Et al.[12] (Number of citations: 1210). In fact, the basic research (effects of different components of resuscitation fluid) has a downward trend, but the effect of hypertonic saline and the role of albumin is still worthy of further

study.

Although there are a lot of guidelines and consensus guidance of the fluid resuscitation in sepsis, multi- center and large sample studies are still needed to verify and optimize the clinical treatment plan. And we are looking for accurate and timely indexes of microcirculation perfusion, exploring the volume of fluid resuscitation at different resuscitation phase, and its effects on respiration, kidney and abdominal cavity. See the thematic evolution path diagram of 2011-2020 (Additional file 1: Fig.S6).

Research hotspots and changes

Lactate and lactate clearance rate

At present, there is no consensus on the effect feedback of fluid resuscitation in sepsis, whether it is blood lactate level[16,17] or other monitoring/observation indicators. The affirmation of lactate index makes lactate clearance rate one of the objective monitoring indicators of fluid resuscitation in patients with sepsis.

Perfusion of microcirculation and hemodynamic index

From a hemodynamic perspective, septic shock is characterized by the presence of simultaneous alterations at both the macrocirculation and microcirculation levels, resulting in the imbalance between oxygen demand and oxygen delivery. The goal of fluid resuscitation is to quickly restore the volume in the early stage, especially the full perfusion of microcirculation. With the rapid decline of the use of pulmonary

catheters, transpulmonary thermodilution (TPTD) has become the new gold standard technique for CO measurement. Echocardiography is, on the other hand, a completely non-invasive and rapidly available tool at the bedside. Capillary refill time (CRT), defined as the time taken for a distal capillary bed to regain its color after pressure has been applied to cause blanching, has emerged over the recent years as a tool for the assessment of peripheral tissue perfusion. But the best hemodynamic index is still in the screening.

Effects of resuscitation fluid

The key to optimize fluid therapy is to reduce capillary leakage. The debate on whether to use crystal or colloid for rehydration has gradually decreased, and the role of hydroxyethyl starch in fluid resuscitation is no longer recognized. Albumin therapy in the form of concentrated albumin or plasma products has sparked interest for its potential ability to protect the glycocalyx due to its ability to carry erythrocyte-derived sphingosine-1-phosphate to the endothelium, but results of glycocalyx evaluation following albumin therapy in septic patients are not yet available. The advantages and disadvantages of isotonic solution, equilibrium solution and hypertonic solution are still debated. Hyperchloremia and moderate increase in serum chloride are associated with acute kidney injury in severe sepsis and septic shock patients. The continuous positive equilibrium resuscitation of sepsis patients often leads to potential renal injury, pulmonary edema, and elevated abdominal pressure. Therefore, the positive and negative equilibrium of resuscitation fluid, and

even fluid responsiveness, are still the research hotspots.

Predictors of resuscitation fluid volume

The best possible predictors are dynamic indicators, such as ultrasound monitoring, PPV, SVV, passive leg raising test, or end expiratory obstruction test. However, the existing indicators present an overview of the structure, function and regulation of the microcirculation and endothelial surface layer in the sepsis have their own shortcomings, so we still need to find more convenient, more intuitive and more effective observation indicators.

Indicators of combination vasoactive drugs add fluid resuscitation

Patients with septic shock usually need vasoactive drugs to correct hypotension at the same time of fluid resuscitation. The hemodynamic coherence between the macro- and microcirculation is often poor in sepsis. In case of vasopressors administration, invasive arterial blood pressure monitoring is recommended, but the placement of arterial catheter and central venous catheter (CVC) should not delay the use of NE(norepinephrine). Under these conditions, vasopressor treatment can be initiated on a peripheral venous line with non-invasive BP monitoring, and it should be shifted to CVC administration accompanied by invasive arterial pressure monitoring as soon as possible. Since basic hemodynamic monitoring is not able to detect the effects of fluid challenge on CO, methods for continuous CO monitoring are recommended to track changes in CO both during tests of preload responsiveness

and fluid challenge. Current guidelines recommend norepinephrine as the first-line pressor drug, but NE(norepinephrine) has the risk of causing myocardial cell and peripheral circulation ischemia. More and more attention has been paid to vasopressin as a possible alternative to norepinephrine. Selepressin is a selective vasopressin V1a receptor agonist. Many clinical trials have shown that selepressin reduces the dosage of norepinephrine. Further study[18] showed that in patients with septic shock receiving norepinephrine treatment, there was no significant difference in the time of no vasoactive drug use and the number of days of ventilator use within 30 days in patients receiving selepressin compared with the placebo group. At what point vasopressors should be started and fluid therapy stopped is still unclear. Thus, prospective studies evaluating the impact of early vasopressor therapy on the development of multiorgan dysfunction and the total volume of resuscitation fluids required during early septic shock are clearly needed. Some drugs, including activator protein C, adrenomedullin, alkaline phosphatase and selepressin, have shown the ability to inhibit the increase of sepsis related vascular permeability to a certain extent.

Multiple organ injuries

We not only focus on early prediction index of the myocardial injury, acute kidney injury, acute lung injury, brain injury induced by fluid resuscitation in patients with sepsis, but also on possible protective factors. With the in-depth study of sepsis, more attention has been paid to the fluid management of special groups (obese and

patients with limited cardiopulmonary reserve): it can cause pulmonary edema, hypoxemia, respiratory failure, edema of other organs, increased intra-abdominal pressure, prolonged ICU stay and mechanical ventilation time, and even increased the risk of death. See the key words co-occurrence clustering network chart and the strategic coordinate chart for 2011-2020 (Additional file 1: **Fig.S4** and **Fig.S5**), we can find that the hotspot and difficulty of sepsis fluid resuscitation lie in the rapid change of complex conditions of sepsis patients and the precise and individualized resuscitation.

Fluid resuscitation process and research hotspot of severe sepsis as shown in Fig.2. The effects of different fluid therapy prescriptions on the macro- and microcirculation/endothelial surface layer in various disease states, the goals and timing of its administration, and ultimately outcome of the patients will likely change fluid therapy in the future.

Fig.2 Fluid resuscitation process and research hotspot of severe sepsis(Red words were hotspot and more rigorous design studies are needed to prove)

NS: Normal Saline; SVV: Stroke Volume Variation; PPV: Pulse Pressure Variability;

Δ IVCd: Inferior Vena Cava Diameter; TVC: Tidal Volume Loading Test; EEO:

End-expiratory Breath Holding Test; ELW: Extravascular Lung Water

4. Discussion

Since 2011, the research on fluid therapy for sepsis has been in a fluctuating growth trend. The basic research contents of fluid composition, biotechnology,

genetics and toxicology of fluid therapy for sepsis are declining. The clinical research on early intervention and precise resuscitation as well as the interaction between resuscitation and organ/function support represented by emergency department is in the ascendant.

For severe sepsis, insufficient blood volume can lead to organ dysfunction, coagulation disorders, shock and other life-threatening pathological processes. So we need to identify and give fluid supplement support as soon as possible to ensure tissue perfusion and prevent blood hypercoagulability and microthrombosis. Early goal-directed (EGDT) fluid support is particularly important in the early stage of sepsis. The surviving sepsis campaign (SSC) recommends that patients with sepsis induced hypoperfusion receive an intravenous infusion of 30 mL/kg crystalloid solution within 3 hours after diagnosis. However, due to disease limitations (such as end-stage renal disease, heart failure, etc.), patients often fail to meet the recovery standard in clinical practice. Moreover, rapid and excessive volume load may lead to vascular wall injury, which cause edema and dysfunction of organs. ProCESS study and ARESE study obtained negative results on the clinical application of traditional EGDT. It was considered that EGDT had no advantage in 60 day in-hospital mortality, long-term mortality and organ support needs[19-20] Although a consensus has been reached on the choice of crystal or colloid for rehydration, there are still many problems in clinical application: the role of hydroxyethyl starch in fluid resuscitation has been denied, the balance solution is superior to normal saline, albumin is good but expensive, and the maintenance capacity of crystal solution has not been effectively

improved, The liquid load caused by rapid and large amount of liquid therapy is still perplexing clinical work, and the search for ideal crystal solution is still in progress [9].

The treatment has not improved the prognosis of patients according to the existing guidelines and consensus standards, whether the current measures are really effective in restoring tissue perfusion (especially the restoration of microcirculation), so it is more intuitive and accurate dynamic hemodynamic monitoring of fluid response in patients with sepsis, ultrasound and other monitoring of the impact of fluid volume on cardiac function in patients with continued research.

However, due to the lag of etiology determination and the rapid change of disease condition, early, rapid and effective liquid therapy to restore tissue perfusion often determines the prognosis of patients. This paper reviews the changes of research hotspots of sepsis recovery in the past 10 years. According to the changes of hotspot path in the past literature, we can infer the future research path. There are still many controversies about fluid resuscitation of sepsis, but more attention is still paid to the individualized precise resuscitation scheme for patients with sepsis (especially for special groups such as children, the elderly and obese people) under complex pathological state, as well as the observation indexes that can more intuitively, accurately and quickly reflect the hemodynamic changes and microcirculation perfusion of patients with sepsis after resuscitation.

The inadequacies of this study: Only English-language publications are included, with the inevitable omission of studies publishing by other languages. The data source

of this study can continue to be expanded, and there is a certain delay in the publication of literature based on the changes of research hotspots and topics discussed in the paper.

Conclusion: The study is an bibliometric analysis based on 2,739 published articles. The method can identify hotspots and detect future directions conveniently, quickly and effectively. The clinical research of fluid resuscitation in sepsis, especially “the early intervention” and “the precise resuscitation” , is paid more attention, and even the recommendations of the consensus and guidelines need to be further confirmed by “multi center research”, which may become the development direction in the future.

List of abbreviations

No

Declarations

Ethics approval and consent to participate

Ethics approval

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

These authors contributed equally to this article.

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