Hotspot Analysis of Sepsis Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AB 1 **Changhai Xu**
CD 2 **Zhe Wang**
E 3 **Kaining Lu**
ABG 4 **Hongxu Jin**

1 Department of Emergency Medicine, General Hospital of Shenyang Military Command, Shenyang, Liaoning, P.R. China
2 Medical Oncology Department of Gastrointestinal Cancer, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, Liaoning, P.R. China
3 Department of Urology, China Medical University, Hospital 1, Shenyang, Liaoning, P.R. China
4 Department of Emergency Medicine, General Hospital of Shenyang Military Command, Shenyang, Liaoning, P.R. China

Corresponding Author: Hongxu Jin, e-mail: Hongxuj@126.com
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Background: Sepsis is a common life-threatening pathological process. However, the transformation efficiency of studies on the treatment of sepsis is relatively low. Therefore, a hotspot and trend development study was attempted on the treatment area of sepsis in accordance with the literature.

Material/Methods: We selected 2511 studies most related to the treatment of sepsis within the past 5 years as research samples. Text and co-word matrix were established by analyzing and selecting high-frequency words using BICOMB software. Classifications in hotspot areas were obtained through biclustering and visual analysis of high-frequency words using Ggluto software. Strategy coordinates for hotspot research were conducted using a co-word matrix.

Results: A total of 41 high-frequency words, text, and co-word matrix were conducted within the 2511 studies. A peak map was drawn based on biclustering analysis. The density and concentricity of each hotspot were calculated using the result of the co-word matrix and biclustering analysis.

Conclusions: The research concluded 4 categories and 9 aspects for the treatment of sepsis. Additionally, calculation results showed that the relationship between the prognosis of sepsis and the hematological prognosis was in the fourth quadrant of the strategic diagram, that means it was the potential hotspot area for the treatment of sepsis. This conclusion provides potential value for future exploratory stages of study.

MeSH Keywords: **Bibliometrics • Sepsis • Therapeutics**

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Background

Both sepsis and septic shock are common pathological processes associated with high fatality rates and significant medical costs. Sepsis is caused by the maladjustment of host responses, which is shown to lead to organ tissue damage and even death [1]. The incidence rate of sepsis in low- and medium-economically developed countries (L/MEDCs) has reached 288 persons/100 000 person/year, and the incidence rate of serious sepsis is 148 persons/100 000 person/year [2]. The management of sepsis mainly relies on the identification of accurate treatment strategies at the early stage [3, 4]. Because of the pathogenesis of sepsis, epidemiology and other factors are inextricably linked to the treatment and prognosis of the disease. In this paper, all research directions for sepsis are considered as part of the treatment of sepsis. All the research directions are related to the fundamental purpose of treatment. To date, research into sepsis and its treatment has mainly focused on the following aspects: the pathology and physiology mechanisms of sepsis [5,6], studies involving animal models of sepsis [7,8], antibiotics treatments [9–11], fluid resuscitation therapies [12,13], shock treatments of sepsis [14,15], vasoactive medicine [16,17], prognosis of sepsis [18–20], prevention of sepsis, and epidemiologic studies [21–23]. However, disappointingly, the underlying pathogenesis of sepsis is not yet clear, but it involves complex systemic inflammatory network effects, genetic polymorphisms, immune dysfunction, coagulation disorders, tissue damage, and abnormal host responses to pathogenic microorganisms and their toxins from different infections. It is closely related to the pathophysiological changes of multiple organs and systems. The pathogenesis of sepsis still needs further study; therefore, no treatment based on the pathogenesis of sepsis has been found yet [24]. Accordingly, further research should be based on the current results of sepsis research to study the development of hotspots and trends in the treatment of sepsis. With growing methods and tools based on bibliometrics, it is becoming increasingly possible to study the development tendency of sepsis accurately in a single area, which relies on a large-scale literature as a starting point of the analysis. Calculations of statistical indicators of a given topic's contribution within document clustering may represent hotspots and tendency of such research [25]. Co-word analysis is a common method applied in the analysis of bibliometrics, which was first invented by French bibliometricians [26], by which the hotspot could be distinguished and necessary information from the literature may be found. The principles are as follows: if 2 terminologies are used in the same article, a potential relationship between them may exist. Hence, the higher the frequency of co-words presenting in the same article, the more likely it is that a relationship exists between them. Accordingly, if the relationship of this co-presence were to be combined with statistical techniques such as clustering and factors analysis, the hotspot for subsequent research areas may

be concluded by presupposing threshold values of key words. It is well known that clustering analysis can be applied to extract a semantic relationship of a given research topic. Compared with traditional clustering methods [27], biclustering analysis has the following advantages: it can cluster lines and columns at the same time [28], it can cluster whole information, and it can perform a partial analysis with a large amount of data [29].

Therefore, the present study is first to conduct a literature bibliometrics and visual analysis for the treatment of sepsis. The situation of research on the treatment of sepsis within the past 5 years is revealed in a completely new light (for example, hotspot strategy coordinates are established). Additionally, related analyses and predictions are made for future trends of sepsis treatment, offering hotspot references for researchers to study.

Material and Methods

Data collection

We searched PubMed for relevant articles without any language restrictions. PubMed is a retrieval serving system widely used across the medical literature. Its data resources mainly contain MEDLINE, OLDMEDLINE, records in process, and those supplied by publishers. Its data categories mainly contain journal articles, reviews, and other database links. To ensure that data search results were as accurate and trustworthy as possible, we collected a research article on sepsis on August 10th, 2017. The search strategy was detailed as follows: #1 "sepsis" [MeSH Major Topic] AND "therapeutics" [MeSH Major Topic] and ("2012/0101" [PDAT]: "3000" [PDAT]).

Based on the above search strategy, 2529 publications were found in PubMed. Screening of titles and summaries of publications was based on inter-article relevance and screening criteria, incorporating the following criteria: (1) the contents of papers primarily focused on sepsis and its treatment and (2) all research design. Exclusion criteria were media coverage and science briefings. Two researchers independently assessed and studied each of these data and reached a consensus on the results of the inclusion analysis. The agreement between the 2 researchers was 96%, indicating a strong correlation. Finally, based on the analysis results, a total of 2511 related articles were included in this study. PubMed contains the following key qualifications: title, author, institution, country, source, year of publication, and MeSH terms. These data are saved as 2 files in XML and MEDLINE formats.

Data extraction and analysis

The Bibliographic Item Co-Occurrence Matrix Builder (BICOMB) is mainly used for data extraction and analysis. It was designed

by China Medical University Professor Cui, who made many further improvements [30]. To explore research hotspots for sepsis and its treatment, all highly frequent major MeSH terms were visualized after data extraction. By referring to bilinguals, it is possible to show the relationship between major MeSH terms and source articles at high frequencies.

Subsequently, using the "gCLUTO" version 1.0 software, a binary matrix was constructed from BICOMB that used the term MeSH frequently as a row and source article as columns. This is a graphical cluster toolkit and is the graphical front-end of the CLUTO data clustering library developed by the University of Minnesota's Rasmussen, Newman, and Karypis [31]. According to the literature [32], the biclustering parameters in gCLUTO are set according to those parameters suitable for the biclustering analysis. The clustering method chooses the duplicate bisect, the similarity function is the cosine, and the clustering criterion function is I2. In order to distinguish the best number of clusters, 2 clusters are performed again using a different number of clusters. We performed visualization of high-frequency and high-frequency dual-focus results with MeSH articles via Alpine and Matrix. With the help of the semantic relationship between MeSH terms and the content of the representative papers in each group, the basic framework of sepsis research hotspots and their treatment are abstracted and analyzed.

Strategic diagram

A strategic diagram was used for further analysis on the research hotspots of sepsis and its treatment by utilizing a co-word matrix of highly frequent words. The diagram uses 2D coordinates using centrality and density as parameters to describe internal relationships within certain categories and the interacted influence among them [33]. In the strategic diagram, the x-axis was set as centrality, which expressed the intensity of interacted influence. It was found that the larger the amount of one category related with others and the greater the intensity is, the role of the category tended to more central in the research process [34]. The centrality of a category was calculated through the intensity of links between the major MeSH terms of the category with those of other categories. The y-axis was set as density, which expresses the intensity of the internal relationships within one particular category. It also expresses the capacity of maintaining and developing itself in a category [35]. The density of a category was calculated through the average links within a category.

Results

Research hotspots of sepsis

For publications from January 1st 2012 to date, 3738 major MeSH terms were found. After discussion, the main MeSH terms that occurred more than 37 times were defined as high-frequency terms, with a cumulative total of 4172. In addition, 41 high-frequency major MeSH terms were extracted from the listed publications, with a cumulative percentage of 32.03% (Table 1). According to the co-occurrence of high-frequency MeSH terms in the same article, a high-frequency main MeSH term was established as a matrix of row names and source articles as column names. This matrix (localized view in Table 2) shows the availability of the main MeSH terms in the source article. A "1" in a cell indicates that there are major MeSH terms in the article, and a "0" means no.

We used different numbers of clusters for double cluster analysis. The biclustering results for the high-frequency main MeSH term source matrix are shown in the mountain and matrix visualizations. Figure 1 shows each cluster represented as a peak labeled by cluster numbers 0–3. The volume, height, and color of the peaks are used to depict information about the related clusters. The peak is the position on the plane relative to the other peaks. The distance between a pair of peaks in a plane indicates the relative similarity of their clusters. The height of each peak is directly proportional to the internal similarity of the cluster. The volume of the peak is proportional to the number of MeSH terms contained in the cluster. Finally, the color of the peak represents the internal standard deviation of a clustered object. Red indicates low deviation and blue indicates high deviation. Figure 2 shows a matrix visualization where the row labels represent the major MeSH terms that are highly frequent and the column labels at the right and bottom of the matrix are the PubMed unique identifiers (PMIDs) of the source items. The color of each grid represents the relative frequency of occurrence of MeSH terms in a given article. Darker shades of red represent larger values and white represent values near zero. Matrix visualization shows that 41 major MeSH terms that are highly frequent are clustered into 4 clusters. The hierarchical tree on the left describes the relationship between the major MeSH terms that are highly frequent, and the top hierarchical tree shows the relationship between the articles. In addition, it shows the corresponding articles for each high-frequency MeSH entry in each cluster. A careful reading of each group's representative articles helps identify and summarize the topics for each group. The descriptive and discriminating features of articles in each cluster are shown in Table 3.
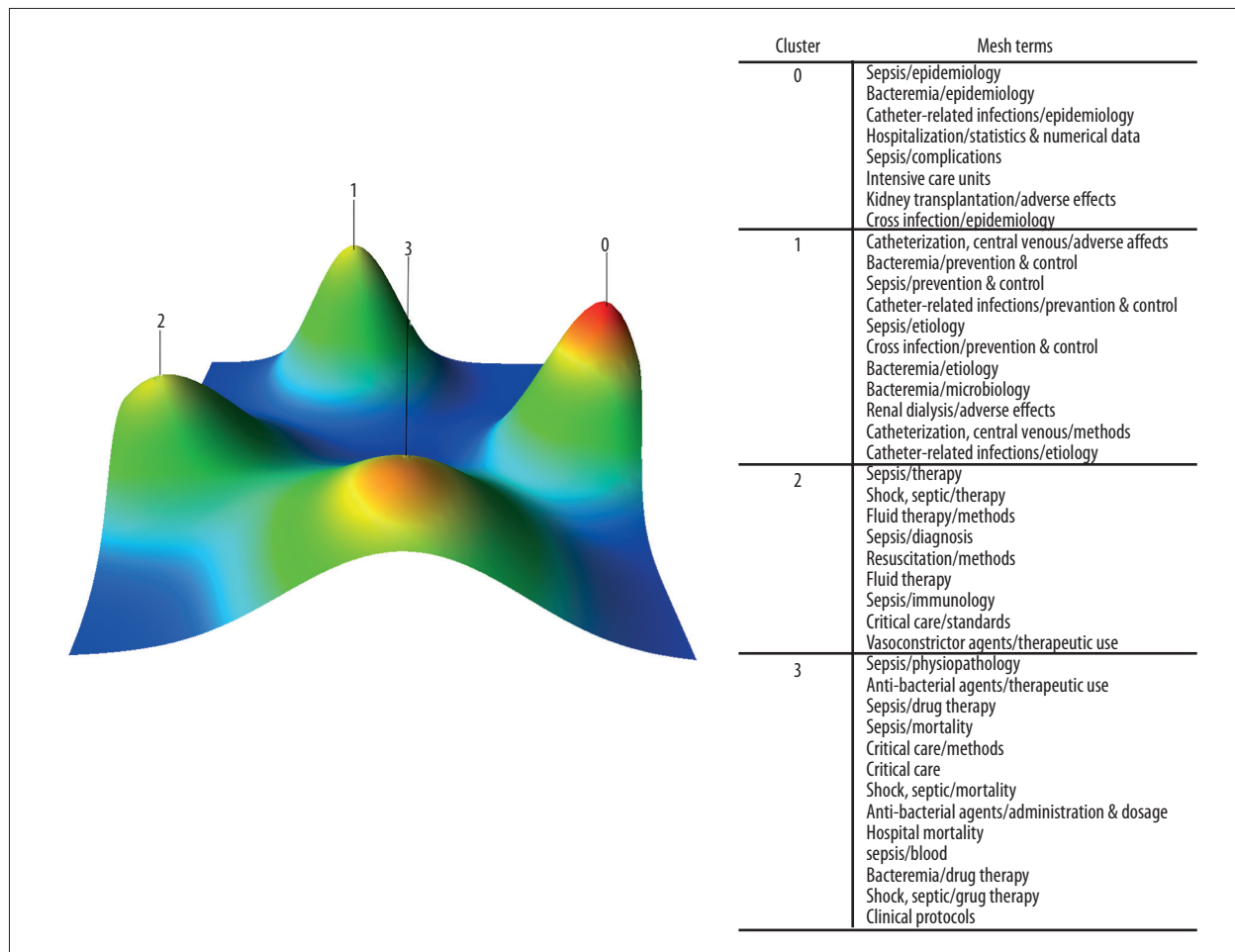
In addition, some clusters may be subdivided into smaller topics based on the following criteria discussed by the study

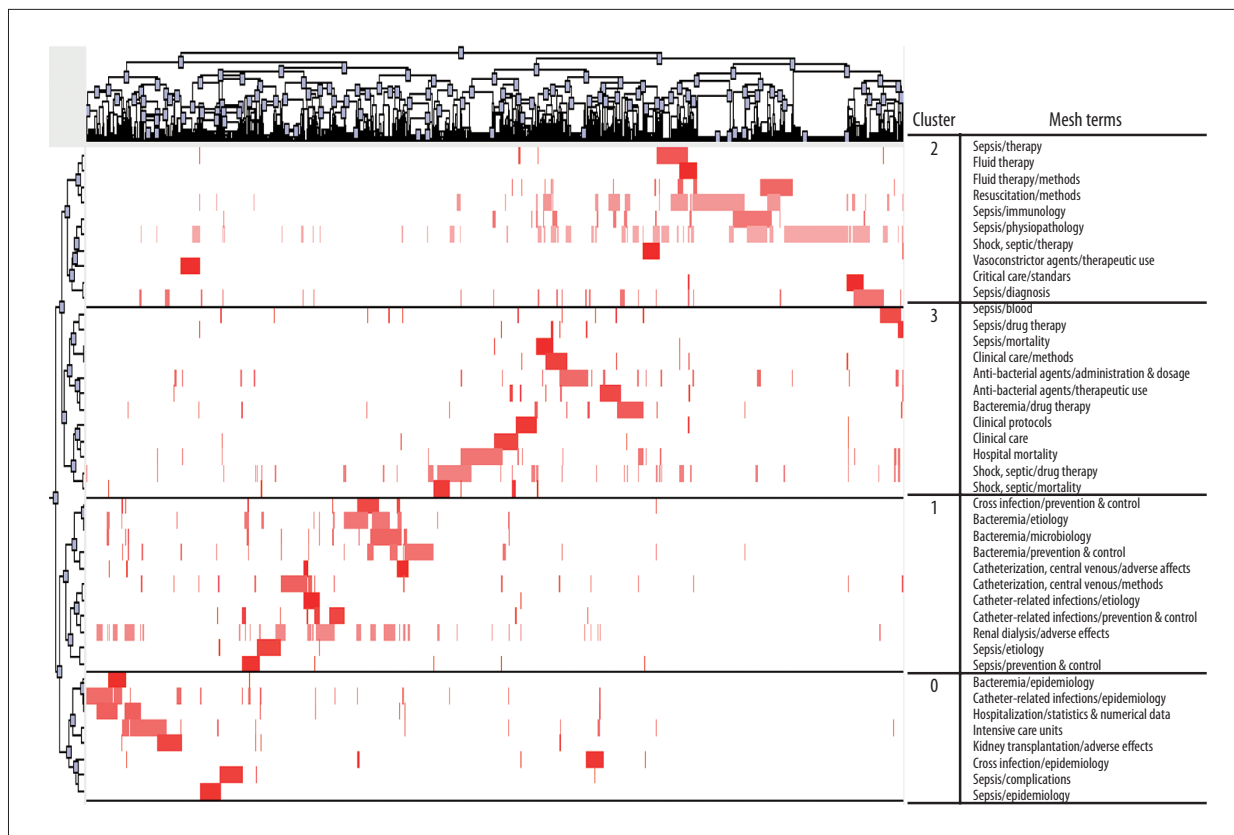Table 1. Highly frequent major MeSH terms from the included publications on sepsis and therapeutics (n=3738).

No.	MeSH terms	Frequency n (%)		Cumulative percentage, %
1	Sepsis/therapy	474	(3.60)	3.6024
2	Shock, septic/therapy	308	(2.34)	5.9432
3	Catheterization, central venous/adverse effects	222	(1.69)	7.6303
4	Anti-bacterial agents/therapeutic use	182	(1.38)	9.0135
5	Fluid therapy/methods	150	(1.14)	10.1535
6	Bacteremia/prevention & control	147	(1.12)	11.2707
7	Sepsis/drug therapy	145	(1.10)	12.3727
8	Sepsis/diagnosis	139	(1.06)	13.4291
9	Sepsis/prevention & control	137	(1.04)	14.4703
10	Sepsis/epidemiology	123	(0.93)	15.4051
11	Bacteremia/epidemiology	123	(0.93)	16.3399
12	Sepsis/mortality	122	(0.93)	17.2671
13	Resuscitation/methods	116	(0.88)	18.1487
14	Catheter-Related Infections/prevention & control	108	(0.82)	18.9694
15	Sepsis/etiology	103	(0.78)	19.7522
16	Catheter-related infections/epidemiology	99	(0.75)	20.5046
17	Critical care/methods	93	(0.71)	21.2114
18	Fluid therapy	87	(0.66)	21.8726
19	Critical care	74	(0.56)	22.435
20	Shock, septic/mortality	71	(0.54)	22.9746
21	Cross infection/prevention & control	71	(0.54)	23.5142
22	Hospitalization/statistics & numerical data	67	(0.51)	24.0234
23	Bacteremia/etiology	67	(0.51)	24.5326
24	Anti-bacterial agents/administration & dosage	66	(0.50)	25.0342
25	Bacteremia/microbiology	65	(0.49)	25.5282
26	Hospital mortality	63	(0.48)	26.007
27	Sepsis/complications	62	(0.47)	26.4782
28	Sepsis/blood	57	(0.43)	26.9114
29	Bacteremia/drug therapy	57	(0.43)	27.3446
30	Shock, septic/drug therapy	56	(0.43)	27.7702
31	Intensive Care Units	54	(0.41)	28.1806
32	Kidney transplantation/adverse effects	53	(0.40)	28.5834
33	Renal dialysis/adverse effects	52	(0.40)	28.9786
34	Sepsis/immunology	49	(0.37)	29.351
35	Cross infection/epidemiology	46	(0.35)	29.7006
36	Catheterization, central venous/methods	45	(0.34)	30.0426
37	Critical care/standards	45	(0.34)	30.3846
38	Clinical protocols	44	(0.33)	30.719
39	Vasoconstrictor agents/therapeutic use	44	(0.33)	31.0534
40	Catheter-related infections/etiology	43	(0.33)	31.3801
41	Sepsis/physiopathology	43	(0.33)	31.7069

Table 2. Highly frequent major MeSH terms-source articles matrix (localized).

No.	Major MeSH terms	PubMed Unique Identifiers of source article				
		19800754	20807391	21195419	...	28591533
1	Sepsis/therapy	0	0	0	...	0
2	Shock, septic/therapy	0	0	0	...	1
3	Catheterization, central venous/adverse effects	0	0	0	...	0
4	Anti-bacterial agents/therapeutic use	0	0	0	...	0
...	...				...	
40	Catheter-related infections/etiology	0	0	0	...	0
41	Sepsis/physiopathology	0	0	0	...	0

Cluster	Mesh terms
0	Sepsis/epidemiology Bacteremia/epidemiology Catheter-related infections/epidemiology Hospitalization/statistics & numerical data Sepsis/complications Intensive care units Kidney transplantation/adverse effects Cross infection/epidemiology
1	Catheterization, central venous/adverse affects Bacteremia/prevention & control Sepsis/prevention & control Catheter-related infections/prevantion & control Sepsis/etiology Cross infection/prevention & control Bacteremia/etiology Bacteremia/microbiology Renal dialysis/adverse effects Catheterization, central venous/methods Catheter-related infections/etiology
2	Sepsis/therapy Shock, septic/therapy Fluid therapy/methods Sepsis/diagnosis Resuscitation/methods Fluid therapy Sepsis/immunology Critical care/standards Vasoconstrictor agents/therapeutic use
3	Sepsis/physiopathology Anti-bacterial agents/therapeutic use Sepsis/drug therapy Sepsis/mortality Critical care/methods Critical care Shock, septic/mortality Anti-bacterial agents/administration & dosage Hospital mortality sepsis/blood Bacteremia/drug therapy Shock, septic/grug therapy Clinical protocols

Figure 1. A mountain visualization biclustering of highly frequent major MeSH terms and articles on sepsis and therapeutics.

Figure 2. A visualized matrix biclustering of highly frequent major MeSH terms and PubMed Unique Identifiers (PMIDs) of articles on sepsis and therapeutics.

Table 3. Descriptive and discriminating features.

Descriptive and discriminating features					
Cluster 0	size 8				
Descriptive:	23577195		23651883	23651884	23375574
Discriminating	23577195		24237085	24329640	24329641
Cluster 1	size 11	Isim: 0.0198	Esim: 0.013		
Descriptive:	22645119		25986020	27104606	24177238
Discriminating	22645119		25986020	27104606	24177238
Cluster 2	size 10	Isim: 0.0190	Esim: 0.016		
Descriptive:	24275413		24275412	26280432	26244317
Discriminating	28320242		25180196	26280432	26244317
Cluster 3	size 11	Isim: 0.0198	Esim: 0.013		
Descriptive	25344412		27133236	25479113	25700057
Discriminating	25344412		25830524	25398103	25830525

Table 4. The centrality and density of the 4 clusters.

Cluster	Intra-class link averages	Density-Y	Inter-class link average	Centrality-X
0	19.125	−2.14084596	1.534090909	−0.235601215
1	21.4	0.13415404	1.372727273	−0.396964852
2	31.47777778	10.21193182	2.048387097	0.278694973
3	13.06060606	−8.205239899	2.123563218	0.353871094
Average	21.26584596		1.769692124	
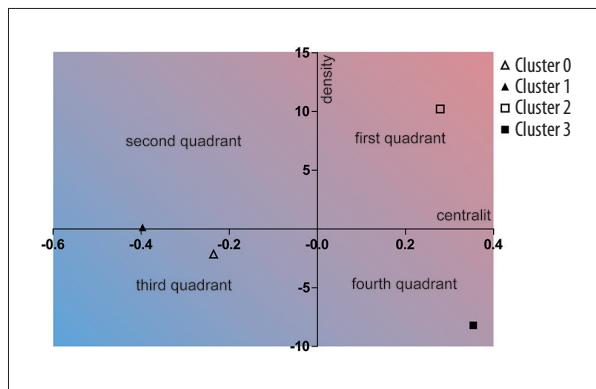
Figure 3. A strategic diagram of the clusters.

group: (1) the semantic relationship between the MeSH vocabulary and a larger cluster; (2) the year in which MeSH terms are introduced into the MeSH term; and (3) the category of the MeSH terms. Each smaller topic was summarized to a separate hotspot. Therefore, the following 9 hot topics were found in the field of sepsis and its treatment: (1) Epidemiological studies on sepsis (cluster 0); (2) The effects of age and sex on a prevention strategy of sepsis (cluster 1); (3) Active treatment of primary disease and prevention of infection (cluster 1); (4) The effects of iatrogenic factors on a prevention strategy of sepsis (cluster 1); (5) Pathophysiology mechanisms of sepsis (cluster 2); (6) Fluid resuscitation therapies (cluster 2); (7) The use of vasoconstrictor drugs (cluster 2); (8) Antimicrobial treatment with antibiotics (cluster 2); and (9) Sepsis-related hematological indicators such as the level of lactic and its correlation with a prognosis (cluster 3) (Table 4).

Density was set as the y-axis on the strategic diagram. From the upper right quarter in a clockwise direction, they are the first, second, third, and fourth quadrants. Gradually deepening red represents a higher centrality and density, and the an increasingly darker shade of blue represents lower centrality and density. Categories 2, 1, 0, and 3 are located in the first, second, third, and fourth quadrants, respectively (Figure 3).

Discussion

Hotspot classification

Sepsis is a syndrome characterized by difficult-to-cure overt clinical symptoms. The rate at which the incidence of sepsis has been increasing is widely agreed to be 1.5–1.8% every year in LEDCs. However, medical technology leading to a potential cure has not been improving in recent years [36].

Epidemiological studies on sepsis

To ensure proper prevention and treatment through research, epidemiological investigations mainly study the distribution of stage, area, and race of certain diseases and the factors which impact incidence rate. For major clinical syndromes like sepsis, epidemiological investigations have been widely focused. For example, the first authoritative epidemiological investigation of sepsis was developed by Martin, developed based on incidence situation and prognosis from 1979 to 2000 in the USA [37]. The incidence rate of sepsis has risen from around 1/1000 in 1979 to 3/1000 in 2000 in the USA alone. Medicines to combat this spread grew rapidly from 1979 to 1991, during which incidence rates were found to increase. However, with the invention of cutting-edge medical technology, some critically ill patients whose organs were exhausted after surgery were successfully saved; however, this prolonged ICU stays. Additionally, ICU patients were found to be older overall, which may be due to an aging society. During this period, the development of invasive monitoring and the use of ventilators were found to be significant causes of this increase in incidence rate, both of which were found to be attributed to an increase in infection of ICU patients.

Prevention strategy for sepsis

Age and sex

As both age and sex are anthropic factors, and they could not be manipulated in this study. The adopted prevention strategies on race difference were decided as lowering the transmission

of AIDS and incidence rate of the complications associated with diabetes [38].

Active treatment on primary diseases and preventing infection

It was important to actively predict the incidence of acute organ dysfunction. For example, monitoring urine volume and taking necessary treatment actions, which may improve the long-term patient prognosis [4,39].

Iatrogenic factors

According to the operating situation and literature, antipyretic therapy of sepsis has no obvious beneficial effect on reducing mortality risk, but it is worth further investigation in the treatment of sepsis in the future [40]. Antibiotics in catheters was allowed under sterile working conditions. For example, rifampicin-minocycline tubes, silver platinum carbon tubes, and silver sulfadiazine-coated venous catheters were used to reduce catheter-related infection [41].

Immune mechanisms and treatment

Septic shock can be defined as a subset of septicemia, during which serious circulation problems and cell and metabolism abnormalities occur. Compared with sepsis, septic shock is found to significantly increase mortality rates. For example, septic shock patients may be evaluated clinically by the use of a vascular compression device to maintain 65 mmHg or more average arterial pressure, and more than 2 mmol/L (>18 mg/dL) serum level of lactic acid in the condition of blood volume depletion. This combination is related to mortality and the degree of correlation was found to be greater than 40 [42].

Fluid resuscitation therapies

Fluid resuscitation during therapy was found to play an important role in sepsis. In fluid resuscitation therapy, fluid types mainly include crystalline and colloidal solutions. The crystal solution can be further divided into unbalanced and balanced solutions, while the colloidal solution mainly includes albumin, dextran, and hydroxyethyl starch solutions. [43]. Because many of the components of EGDT have been incorporated into commonly used care protocols, the effect of early goal-oriented therapies on overall mortality in sepsis has not been much different from conventional care in recent years, and more stringent randomized controlled trials are needed to adjust factors that reduce the effect of treatment between groups [44].

Use of vasoconstrictor drugs

The use of vasopressor and blood pressure drugs has been mentioned in the literature [45,46]. In 2016, 6 instructions on the use of vasoconstrictive drugs were brought up to date in an international guideline [47]. For example, the use of norepinephrine was found to lead to a lower mortality and lower risk of arrhythmia compared to the use of dopamine [48]. If hemodynamic stability was not restored by proper fluid resuscitations, oral corticosteroids were found to lower ICU mortality and in-hospital mortality rates [49].

Antimicrobial treatment

Proper anti-fungal treatment is considered an efficient treatment for septicemia. Sepsis patients should start antibiotic treatment as soon as possible. For example, according to epidemic situations in this study, it was found that rapid injections of experimental antimicrobial treatment were effective. A non-dependent method that rapidly identifies infected microorganisms was found to contribute to the choice of antibiotic in the future. Interestingly, when culture results were found to be effective, the choice of antibiotic was reassessed and adjusted to a narrower spectrum [50,51].

Minimize the use of spectrum antibiotics

It was important to select the appropriate antibiotics to use against pathogens. For example, the application of mechanical ventilation patients. In the case of taboo, a semi-recumbent state was preferred by adjusting the top of the bed to a 30–45-degree angle. This was found to reduce the incidence of ventilator-pneumonia. Keeping hands clean was found to be the most effective method for preventing and controlling the incidence of infection because it was found to effectively inhibit the spread of pathogens from both person-to-person and person-to-animal. Finally, implementing oral care was found to reduce accumulation and colonization of mouth flora, thereby reducing the risk of iatrogenic infection. Additionally, it has been reported that a more than 4 mmol/l concentration of lactic acid could reduce the short-term patient mortality of serious sepsis or septic shock patients through early goal-directed therapy. However, it was not found to effect long-term mortality [52]. Interestingly, avitaminosis D was found to increase risk of death in seriously infected and critical patients [53].

The strategic diagram was divided into 4 quadrants, each of which was used to describe the development situation of each category.

1. The first quadrant is density and centrality. Density indicates closer internal links, which means that the research tended to be mature. Centrality indicates the correlation between

certain categories and others, which is central to internet research. Category 2 can be found in the first quadrant, and describes pathophysiology mechanisms of sepsis and its fluid, pharmacy, and antimicrobial treatments (Figure 3). It was defined as the research center and research hotspot of sepsis and its treatment.

2. In the second quadrant, density is high, but centrality is low, indicating that internal links were close together with a clear topic. Additionally, research institutions performed formal research on the topic, but the research was not a main priority. Category 1 can be found in the first quadrant and is closer to the x-axis and describes a prevention strategy for sepsis (Figure 3). The research on this topic was shown to be relatively mature, with little correlation with other research.

3. In the third quadrant, density and centrality are both low and indicate that internal links were loose, with no close relations found. Category 0 can be found in this quadrant and describes the epidemiological study of sepsis. The research on this topic was shown to be mature, with little correlation with other research.

4. In the fourth quadrant, density was low and centrality high, indicating close relations with other research. However, the research was not found to be mature. Category 3 can be found in this quadrant and describes the level of lactic acid and its correlation with a prognosis. The research on this

topic was shown to have potential value, and is now in the exploratory stage; however, more research is required.

Conclusions

We analyzed the literature on sepsis and its treatment in the past 5 years using a visualized biclustering method. Nine research hotspots were identified. The pathophysiology mechanisms of sepsis, fluid resuscitation therapies, use of vasoconstrictor drugs, and antimicrobial treatment in these 4 quadrants is now the most important research center and hotspot in the study of sepsis and its treatment. Additionally, we found that the relationship between the prognosis of sepsis and the hematological prognosis was a potential hotspot area for the treatment of sepsis. Therefore, it can be used as the main research hotspot in the future treatment of sepsis to either develop effective therapeutics or to achieve prevention strategy for sepsis.

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