Review Article

Current epidemiology of sepsis in mainland China

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Abstract: The disease burden of sepsis is a global issue. Most of the large-scale epidemiological investigations on sepsis have been carried out in developed countries. The population of 1.3 billion in mainland China accounts for approximately 1/5th of the whole world population. Thus, the knowledge of the incidence and mortality of sepsis in mainland China is vital before employing measures for its improvement. However, most of the epidemiological data of sepsis in mainland China was obtained from ICU settings, and thus lacks the population-based incidence and mortality of sepsis. In the present review, we summarized the limited literature encompassing the incidence, mortality, long-term outcome, and pathogens of sepsis in mainland China. Therefore, it might provide some valuable information regarding the sepsis disease burden and current issues in the management of sepsis in mainland China.

Keywords: Sepsis; epidemiology; incidence; mortality

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Introduction

Although the rate of mortality related to sepsis has been significantly declined in the developed countries, the issue is yet of concern (1,2). Due to the increased incidences, the absolute number of sepsis-related mortality cases is considerably high. In addition, the long-term mortality is not optimistic, and increasing number sepsis survivors are confronting poor quality of life (3,4). On the other hand, the mortality of sepsis in developing countries, which occupy most of the world's population, remains high or may be rendered such due to the lack of epidemiological data. China is a distinct country, which has more than 1.3 billion people, occupies a huge land mass, experiences an extremely rapid economic development while relatively slow medical health care system evolvement (5).

Thus, the knowledge of the modern epidemiology of sepsis in our country is critical before preventive measures can be employed for improvement. To the best of our knowledge, there is no large-scale epidemiological investigation of sepsis throughout the country. In the present review, we summarized the limited epidemiological sepsis data available in mainland China and assessed the possible population-based incidence and mortality according to high-income-country data. Thus, we anticipate that this would provide some useful information regarding the sepsis disease burden and its management issues in the mainland.

Incidence of sepsis

Incidence of ICU-treated sepsis

Only a few studies of the incidence of sepsis from ICU settings were available from mainland China. The first survey was conducted in ten university surgical ICUs from December 2004 to November 2005 (6). Among the 3,665 patients admitted to ICU, 318 developed severe

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sepsis, i.e., 8.68% of the total population. Another prospective, observational cohort study conducted in 22 ICUs from July 2009 to August 2009 reported that among 1,297 patients enrolled, 484 (37.3%) developed severe sepsis and septic shock (7). Both of the studies used the American College of Chest Physicians/Society of Critical Care Medicine consensus criteria to define severe sepsis. The higher incidence of sepsis in the latter study may be attributed to the increased incidence of sepsis and different population, as it encompassed both medical and surgical patients. Moreover, all the participating ICUs in the two studies were from tertiary teaching hospitals in metropolitan cities. Therefore, the data could not represent the total sepsis incidence in ICUs throughout the mainland. One sepsis epidemiology investigation enrolled 44 ICUs throughout mainland China using sampling method according to population has been completed (ClinicalTrials.gov identifier: NCT02448472). Results from the study may give us more representative data of sepsis in Chinese ICUs.

Incidence of hospital-treated sepsis

Based on the previous data from the USA, it is known that about 50% of severe sepsis patients were treated outside ICU (8). As is well known the ICU beds in the USA accounted for 9.0% while that in China is 3% of hospital beds (9). Thus, we could speculate that more severe sepsis patients might be treated in the general ward in China. However, we could not collect the data about the incidence of hospital-treated sepsis. A recent well-designed meta-analysis showed that the aggregate global estimate of population incidence for sepsis and severe sepsis in the past few years was 288 (95% CI, 215–386) (τ=0.55) and 148 (95% CI, 98–226) (τ=0.99) cases per 100,000 person-years, respectively (10). Du *et al.* aimed to investigate the epidemiology of sepsis in a sub-district in Beijing (1/7 administrative regions of Xicheng District is ongoing). It is the first study that will demonstrate the incidence of hospital-treated sepsis and severe sepsis in a region (ClinicalTrials.gov identifier: NCT02285257).

Incidence of population-based sepsis

With more than 1.3 billion and 0.25 billion [2014] floating population, it is logistically and economically impractical to obtain the data of incidence of population-based sepsis. The nationwide disease surveillance points (DSPs) is now comprised of 145 reporting sites selected by stratified cluster random sampling and encompasses 1% representative sample of China's population. The surveillance system plays a major role in explaining the natural history of infectious diseases, describing the distribution of case occurrence, monitoring epidemic of infectious diseases during natural disasters, predicting and controlling epidemics, and providing the basis for policy adjustment (11). However, sepsis was not constituted in this system. With the deep insight of the heavy burden of sepsis, the scenario might alter in the future. For speculation, if sepsis and severe sepsis was estimated from recent investigations [2003–2015], which is 437 and 270 cases per 100,000 person-years respectively, we have at least 5.68 million sepsis and 3.51 million severe sepsis cases that need to be treated in 1 year (10,12).

Mortality of sepsis

Similar to the situation of incidence, the mortality data of sepsis originated from ICU settings. One study reported the population-based mortality rates [2003–2007] of sepsis according to *China Health Statistical Yearbook* issued by the Ministry of Health of China (MOH) (13). The crude mortality was 0.24–0.83 per 100,000 persons varied among different ages, districts, and years. However, the sepsis was defined according to the ICD-9-CM code for septicemia, which is defined as, "*A systemic disease associated with the presence of pathological microorganisms or toxins in the blood, which can include bacteria, viruses, fungi, or other organisms*." This definition greatly narrowed the relevant spectrum of sepsis population.

From the above two multicenter investigations in ICUs of mainland China, the reported that the overall hospital mortality for patients with severe sepsis was 48.7% and 33.5%, respectively. Another single center retrospective study from a teaching hospital that reviewed 419 severe sepsis patient data from 2009–2012, also reports a high ICU mortality rate of 43.9% (14). This death rate is greater than that in the developed countries. In Australia and New Zealand, the hospital mortality of severe sepsis has been decreased from 35% in the year 2000 to 18.4% in 2012 (1) while in the US, the mortality of sepsis (defined by ICD-9-CM) has decreased from 27.8% to 17.9% from 1979 through 2000 (2). In the previously described meta-analysis (10), the estimated hospital treated fatality rate in the last decade [2003–2015] was 26% (95% CI, 20–33%) (τ=0.62) for severe sepsis. Although the reported

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epidemiology data emanated from different diagnostic criteria of sepsis and many factors may influence the comparability of the data, the significant disparity in the mortality rate could not be explained completely by the heterogeneity of the sepsis population (15).

The following reasons may contribute to the high mortality rate of severe sepsis in mainland China: (I) treatment delay. For treatment of sepsis, time is pivotal. The most efficient way to improve prognosis was to complete the initial resuscitation bundles in the first few hours after the onset of sepsis. However, due to the lack of early triage of sepsis system, limited ICU resources, and low-to-high level hospital medical visiting system, many septic patients might lose the precious period when they could receive the intensive care management (5,16). The efficacy of thymosin alpha 1 for severe sepsis (ETASS) study conducted in Guangdong province, an economically developed region in mainland China, reported that the median time when the patient developed first organ failure and enrollment was 28 and 42 h, respectively in the control and treatment groups (17). While the data from our sepsis database represents the economically less developed area, more than 60% of the severe sepsis patients developed organ failure after more than 48 h upon ICU admission. Most of them revealed a history of treatment in other hospitals before sepsis aggravation; (II) poor compliance of sepsis bundles. A 7.5-year study conducted in 218 centers in USA, South America, and Europe demonstrated that increased compliance with sepsis performance bundles was associated with a reduction in the mortality rate (18). Another investigation conducted in 62 countries also showed that patients with severe sepsis whose care included compliance with all the metrics of the 3 h bundle, and 6 h bundle had 40% and 36% reduction in hospital mortality, respectively (19). A multicenter observational study conducted from September 2007 to October 2008 in 11 ICUs of Chinese teaching hospitals showed that the overall compliance during 6 h resuscitation and 24 h management bundles were 5.5% and 17.4%, respectively (20). Another study conducted in 150 ICUs in 16 Asian countries in July 2009 showed similar results (21). Currently, we can access all the advanced information from literature and scientific proceedings; however, the basic knowledge and skill training courses are inadequate. How to implement these basic but most efficient treatment bundles requires further exploration (22); (III) high prevalence of nosocomial infection in the ICU. International Nosocomial Infection Control Consortium (INICC) reported the device-associated infection rates of 398 ICUs in Shanghai [2004–2009], which is the largest and the most developed city in China. Compared with the data from US National Healthcare Safety Network (US NHSN) from 2006–2008, the CLBSI, UTI, and VAP rates were much higher in Shanghai ICUs. The difference was particularly evident in the VAP rate, which was 21.2 (19.5–23.1) and 20.8 (20.2–21.6) in medical and surgical ICUs, respectively, per 1,000 device-days in Shanghai, whereas it was 2.2 (2.0–2.4) and 4.9 (4.6–5.1) correspondingly in the US (23). A recent meta-analysis and systematic review of 334 publications published between January 2007 and May 2012 revealed that the incidences of ICU-acquired pneumonia and VAP were 16.2% (95% CI, 12.8–20.4%) and 33.7% (95% CI, 31.4–36.1%), respectively; mortality rates were 37.4% (95% CI, 24.6–52.2%) and 34.5% (95% CI, 29.2–40.1%), respectively (24). Based on the limited data, we observed that the nosocomial infection in ICUs poses a significant threat to the patient safety. An Asian ICU survey revealed that in China, only 22% ICUs have single room and 7% ICUs have negative pressure room; 51% ICUs' nurse-patient ratio was 1:1 (9). Concerning the nosocomial infection control, facility and human input serves as the foundation. It is undeniable that deficiency in the facilities and personnel contributes to the high prevalence of nosocomial infection. However, studies concerning the compliance of hand wash or other isolation measures in the ward or ICU were exceedingly rare. Although difficult, it is critical to strengthening the infection control training, monitoring, and improving the situation gradually.

Long-term consequences of sepsis

Recently, long-term consequences of septic patients is a topic of focus in developed countries, as the number of sepsis survivors increased due to the increased incidence and decreased short-term mortality. However, the long-term mortality of sepsis is not optimistic. Furthermore, neuropsychological, physical, and immune impairment caused by sepsis resulted in an extreme impact on long-term quality of patient life and health care resource consumption, which turns it into a "hidden public health disaster" (3,4). Therefore, it is imperative to investigate the long-term quality of life of sepsis patients in China. Through literature review, we found only one multicenter study that used a real personal interview to inquire into the long-term quality life of sepsis patients, and compared it with non-sepsis critically ill patients and community residents using a 36-item brief

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health-related quality of life (HRQOL) questionnaire (25). Among the eight domains of SF-36, no statistically significant differences were noted between the sepsis group and the critically ill control group. However, compared to the community control group, the sepsis group showed clinically relevant and statistically significant decreases in the physical function (P=0.016), vitality (P=0.037), emotional role (P=0.043), and mental health (P=0.038) domains of SF-36. Notably, the present study was the first attempt to investigate the long-term quality of life in Chinese sepsis population. However, out of the 225 sepsis patients followed-up, only 42 completed the interview, which indicates a poor patient follow-up system. With the development of electronic medical record system, several centers have initiated their sepsis database in mainland China, which may reveal increased amount of data from our patient population.

Pathogen

The Extended Prevalence of Infection in Intensive Care (EPIC II) study (26), which was conducted in 1,265 participating ICUs from 75 countries showed that 62% patients were infected with Gram-negative organisms, 47% were Gram-positive, and 19% were fungi. Similar to these results, Zhou *et al.* (7) showed that among patient with severe sepsis and septic shock, Gram-negative organisms ranked the highest (62.5%), followed by Gram-positive organisms (14.5%) and fungi (2.2%), respectively. Since mainland China lacks the national investigation of the pathogen of sepsis, it may vary in different districts and ICU wards. However, much attention is required to the multidrug-resistance (MDR) issue. It is known that the antibiotic drug consumption is a major driver of antibiotic resistance. A global antibiotic consumption analysis of national pharmaceutical sales data from 2000–2010, showed that China ranked as the 2nd largest antibiotic consumer in 2010 with 10.0×10^9 units (7.5 units per person) (27). The MOH has attempted several efforts to improve the antibiotic usage and launched a 3-year national level regulatory campaign in 2011 to control the total antibiotic use. The preventive measures undertaken included designation of antibiotics as prescription-only drugs, the introduction of national guidelines, and formation of surveillance networks for both antibiotic use and antibiotic resistance. Consequently, a significant decrease was observed in antibiotic consumption in recent years (28,29). The latest data from CHNET surveillance of bacterial resistance reported the change of antibiotic resistance pattern from 2005 to 2014 (30). The resistance rates of extended spectrum β-lactamase production among *Escherichia coli* isolates were stable, between 51.7% and 55.8%. The resistance of *E. coli* and *Klebsiella pneumoniae* to amikacin, ciprofloxacin, piperacillin/tazobactam, and cefoperazone/sulbactam decreased gradually. Moreover, the resistance of *Pseudomonas aeruginosa* strains against all of the antimicrobial agents tested including imipenem and meropenem decreased eventually. A marked reduction of methicillin resistance from 69% in 2005 to 44.6% in 2014 was observed for *Staphylococcus aureus*. On the contrary, carbapenem resistance among *K. pneumoniae* isolates increased from 2.4% to 13.4% and *Acinetobacter baumannii* isolates rose from 31% to 66.7%. We could speculate that the decrease of resistance in most bacteria may be correlated with the reduction of antibiotic overuse. However, carbapenem-resistant *K. pneumonia* and *Acinetobacter baumannii* continue to remain a significant challenge. In order to resolve this complicated issue, preventing the nosocomial infection, early diagnosis, and controlling the source of infection are indispensable.

Role of the new definition of sepsis in Chinese population

The new definition of sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis could be diagnosed with suspected infection plus increase SOFA score of more than two points. For patients outside ICU settings, adult patients with suspected infection plus qSOFA score of more than two points (at least two of the following: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less) can identify septic patients efficiently (26). As the diagnostic criteria came from database of developed countries, some scholars doubt its role in developing or low-income countries (16). For example, they argued that use 22/min as the threshold might not be the best, as it was influenced by age and comorbidity. As presented in an interesting study from Uganda, they use respiratory rates ≥30/min as one of the index of the prognostic score for predicting hospital mortality of sepsis also showing good performance (31).

In fact, role of the new diagnostic criteria hasn't been tested in our Chinese population, which accounted for approximately 1/5th population of the whole world. We believe that this new definition and diagnostic criteria was built on deeper understanding of sepsis pathogenesis and

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could help us identify high-risk patients and then give appropriate intervention as early as possible. However, there are two problems need to be resolved before we could use it widely. First, as intensive care resources are still relatively inadequate in mainland China, the sensitive diagnostic criteria seem impractical currently. Second, as the most readers or learners of the new definition are ICU doctors, how can it be applied to doctors outside ICU settings is also of great concern. We have the responsibility to collect and analyze more data from our population. We know that many centers have initiated related investigations recently.

Summary

In summary, we lack population-based incidence, mortality, and long-term consequences data on sepsis in mainland China. Most of the epidemiological investigations originated from the ICU settings, which indicates limited knowledge or insufficient recognition of sepsis outside the ICU settings. Based on the currently limited data, we estimated a significantly large population with disease burden of sepsis in mainland China that requires treatment. The high mortality indicated an urgent need to improve the early sepsis triage system, strengthen the core knowledge and skills of our clinicians, and control nosocomial infections.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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