Introduction

Recently, quite rapid advances have been recognized in sepsis treatment. As a result, the international guidelines was proposed in 2004, Surviving Sepsis Campaign (SSC) guidelines. This guideline recommended several novel treatment strategies including intensive insulin therapy, low-dose corticosteroid therapy for shock, and recombinant activated protein C. The efficacy of these therapies, however, has been questioned in subsequent replication studies, resulting in modification of the guidelines in 2008. Thus, the trend of sepsis treatment is rapidly changing, with much of supporting evidence being collected. However, the international guidelines have until now adopted a very small number of studies from Japan as evidence. On the other hand, there are several unique therapies which have been developed and are widely used in Japan, such as polymyxin B-immobilized fiber column-direct hemoperfusion (PMX-DHP), anticoagulant therapy for disseminated intravascular coagulation (DIC), and sivelestat sodium for acute respiratory distress syndrome (ARDS), these are not referred to in the aforementioned guidelines. Among these therapies, no reliable clinical research on PMX-DHP, developed in the 1980s had been conducted in Japan, and this therapeutic modality began to attract international attention only after its efficacy was examined in a randomized controlled trial (RCT) accomplished in Italy in 2009. Therefore, not only the overdue in preclinical research and development, but also the lack of subsequent clinical studies may contribute to the current situation of several therapies developed in Japan not yet being adopted internationally. Since sepsis remains a serious disease with a high morbidity and mortality rate, we investigated the current status of sepsis researches. This work must stimulate the active and high-quality research work regarding sepsis conducted in Japan.
To confirm the exact numbers of papers published in individual countries is difficult. Therefore, we instead searched for papers in MEDLINE using the key words "sepsis" and the name of each country (e.g., (“2007” [Publication Date] : “2009” [Publication Date]) AND (“sepsis” AND “Japan”) ). The results are shown in Figure 1. These numbers do not necessarily reflect the exact numbers of reports from each country, but can be used as a guidepost. The results show that the number of articles from the United States of America (USA) was the highest by far, being 6 to 7 times that from other countries. This is thought to reflect the outstanding research activity in USA. Among other developed countries, Germany had published the next highest number of articles, followed by France, with the number being comparable to that from Japan. Among the developing countries, the number of reports from China is rapidly increasing, nearly reaching the number from Japan. Of greater concern, however, is the trend in the last three years of the number of papers from Japan decreasing, while the number from other countries has been steadily increasing. Actually, this issue is not only the problem of sepsis research but also same in other scientific subjects\(^ {11} \). The reason is unclear, however, in addition to the shortage of the doctors and the limited official financial support due to the declined economy may contribute to this phenomenon. But, what we really concern is about the decrease of dignity for science in Japan. Anyway, it is necessary to lead government, public as well as medical staffs to a better understanding of this matter.

**Comparison of research content**

The left column in Figure 2 shows the total number of papers published from 1998 to 2009. Japan ranks third after the USA (20737 in total number, not included in the figure) and Germany in terms of the total number, but only fourth, after France also, in the number of human studies performed. The proportion of papers on human studies was 66% for Japan, 72% for US, 75% for Germany, and 84% for France, indicating that it was the lowest for Japan.

In case of the number of clinical trials (the right column of Figure 2), Japan ranks low again, with the number of trials performed in Japan being much less than that in the USA (1492 in total), and also lower than half of those in Germany and France. Actually, this trend is not the story of this
In order to evaluate the quality of papers in the intensive or critical care fields, the number of papers published in the following seven high-ranked journals was compared: American Journal of Respiratory and Critical Care Medicine (Impact Factor [IF]: 9.09), Critical Care Medicine (IF: 6.59), Intensive Care Medicine (IF: 5.06), Critical Care (IF: 4.55), Shock (IF: 3.39), Journal of Neurotrauma (IF: 3.53), and Resuscitation (IF: 2.51) (right column of Figure-3). As a result, the number published in these journals shows a tendency towards increasing over time, even though the total number of papers from Japan is decreasing, which indicates improvement of the quality. However, the number is still half of that published from Germany and France, and the number of papers from developing countries is rapidly increasing and becoming comparable to that from Japan.

Issues and measures in sepsis research

Recently, sepsis treatments are increasingly being standardized worldwide\textsuperscript{13}--\textsuperscript{15}. Nevertheless, large differences are seen between the international standardized treatments and the clinical practice in Japan\textsuperscript{16}. This difference may have arisen because many of the standardized treatment options being based on not enough evidences\textsuperscript{8}, as well as Japan having a different situation in terms of the authorized drugs and the health insurance system\textsuperscript{17}. Furthermore, the treatment options unique to Japan are also provided with some degree of evidence, such as single institute and small-sized RCTs, and health care professionals empirically believe in their efficacy. Under these circumstances, it is needed to evaluate and determine whether we should use the standardized treatment options in accordance with the international trend, or we should develop our own treatment guidelines\textsuperscript{17}. At the same time, the important issue immediately be solved is promoting research on sepsis in Japan, and introduce the results in an appropriate manner, so that these results are incorporated in the standardized treatment guidelines. In other words, we should not be
satisfied only with having our own treatment options, but must make active measures to obtain international recognition for them. In order to realize this, an inter-institutional network that will enable multicenter studies should be built immediately. Finally, we strongly insist that financial and organizational support system is mandatory for keeping up the research activity.

Conclusions

Evidence Based Medicine (EBM) has gained much popularity in sepsis treatment. However, most of the evidences have been made depending on articles from other countries. Then, many problems have arisen if evidence obtained or guidelines developed in foreign countries are applied to clinical practice in Japan. Therefore, despite the current sluggish economic situation, we must advocate the importance of official financial support and build a framework for sepsis research that remains undeveloped, and establish a clinical treatment system unique to Japan.

References

抄録

国際標準化がすすめられるつつあるセプシス治療において、本邦から発信されているエビデンスは比較的少ない。また諸外国におけるセプシス研究が活性化している中で、本邦からの論文報告数は頭打ちとなっている。本邦からの報告の特徴としては臨床系研究の割合が少ないことが挙げられ、特に無作為比較試験の数が少ないことが課題である。しかし掲載される雑誌から評価する研究の質には向上の兆しがみられおり、今後は多施設間検討などの良質な臨床研究を実施できる基盤整備を行うことによって、一層の国際貢献が可能になるものと考える。

キーワード
セプシス、無作為比較試験、臨床試験、メッドライン、エビデンスベースドメディシン