HEALTH, ENVIRONMENT, DEVELOPMENT

THE NEED TO ADMINISTER ANTIBIOTIC THERAPY FOR SEPTIC SHOCK DURING TRANSPORTATION TO THE EMERGENCY DEPARTMENT FOR MORE THAN AN HOUR

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Summary

The article compares different views on empirical antibiotic therapy during the first hour from the onset of suspected septic shock to the patient's transportation to the emergency department. The article is based on protocols and clinical guidelines from the Ministry of Health of Ukraine (MoH), Infectious Diseases Society of America (IDSA), and Society of Critical Care Medicine (SCCM).

The aim of the study is to determine the feasibility of antibiotic therapy for septic shock within the first hour of its onset based on studies by foreign authors, comparison of protocols and clinical guidelines from the Ministry of Health of Ukraine (MoH), Infectious Diseases Society of America (IDSA) and Society of Crirtical Care Medicine (SCCM). To determine the optimal antibiotic regimen to prevent patient death based on the recommendations of the Ministry of Health of Ukraine and the Society of Critical Care Medicine (SCCM).

Materials and methods. The following methods were used in the study: content analysis, comparative analysis and systematization of the research material. The study was conducted based on the study of clinical guidelines and protocols of the Ministry of Health of Ukraine (MoH), Infectious Diseases Society of America (IDSA) and Society of Criminal Care Medicine (SCCM), as well as publications of foreign authors. The search was conducted on the basis of PubMed and Google Scholar databases in 2017–2023.

Results. According to the results of many scientists from around the world Ferrer R. (2014), Liu V. (2017), Singer M. (2017), Sherwin R. and co-authors (2017), Bloos F. (2017), Johnston A. (2017), Whiles B. (2017), Kim R. (2018), Sung W. (2020), Rothrock S. (2020), Sankar J. (2021), Asner S. (2021), Al-Kader D. (2022) Bisarya R. (2022) found that each additional hour of delayed antibiotic administration from triage to drug administration leads to an 8% to 34% increase in mortality among patients with septic shock before drug administration. Patients with a suspected septic process should receive antibiotics as soon as possible after diagnosis, otherwise the chances of complications in the form of septic shock increase with each passing hour.

Conclusions. Antibiotic therapy for suspected sepsis or septic shock should be started as early as possible, but the recommendations of the IDSA and other studies should also be taken into account to reduce complications and deaths caused by septic shock.

Key words: sepsis, septic shock, empirical antibiotic therapy, emergency medical care, antibiotic therapy regimens.

1. Introduction

In today's conditions of peace, war and pandemic, septic shock is a fairly common problem. Due to the full-scale war in Ukraine, emergency medical teams are not always able to deliver a patient to an emergency department within 1 hour. According to the order of the Ministry of Health of Ukraine dated 05.06.2019 No. 1269 "On Approval and Implementation of Medical and Technological Documents for the Standardisation of Emergency Medical Care", a new clinical protocol "Emergency Medical Care: Pre-hospital stage" *(Chorna, 2023)*, which provides for an approach to antibiotic therapy in case of suspected septic shock if it is possible to take blood samples for sterility in advance (biomaterial is taken up to 10 ml in adults and 0.1–4.0 ml in children) with an antibiogram, which is mandatory in septic conditions, and a bacteriological blood test by venipuncture. These recommendations coincide with the recommendations of the Society of Critical Care Medicine (SCCM), but the Infectious Diseases Society of America (IDSA) opposes this approach.

Septic shock is an emergency condition that is the most severe manifestation of sepsis, characterised by organ dysfunction, hypotension, changes in systemic haemodynamics and inadequate response to the pathogenic pathogen. This condition requires immediate treatment, hospitalisation, and infusion therapy, otherwise there is a high risk of death.

The main goals and principles of emergency care can be identified, which include the earliest possible start of antibiotic therapy with broad-spectrum drugs; determination of the source of infection and the relevant pathogen, its sensitivity to a particular drug. It is necessary to take into account the patient's anamnesis and take into account previous antibiotic use and their reaction to them, concomitant diseases, allergic reactions. Do not use drugs that may have been in the patient's prescription list for the last 30–60 days. It is necessary to carry out resuscitation measures, use drugs to maintain the body's acid-base state and water-electrolyte metabolism, prevent hypotension, hypoxia, and hypoperfusion. The control of vital signs and prevention of multiple organ dysfunction syndrome is carried out conservatively, and if necessary, promptly.

Treatment of septic shock should be initiated within the first hour of diagnosis of this emergency. Delaying antibiotic therapy increases the risk of complications for the body or death of the patient, so after diagnosis, a broad-spectrum antibiotic is prescribed until the appropriate pathogen is identified using the data of a laboratory test of blood for sterility with an antibiogram.

According to the Order of the Ministry of Health of Ukraine No. 1269 "On Approval and Implementation of Medical and Technological Documents for Standardisation of Emergency Medical Care" dated 05.06.2019, as well as the new clinical protocol "Emergency Medical Care: Pre-hospital Stage", it is recommended to consider empirical antibiotics in case of suspected septic shock if it is possible to obtain a culture of microorganisms in advance, and to perform a bacteriological blood test for sterility with an antibiogram. These recommendations coincide with the Society of Critical Care Medicine (SCCM) guidelines, which focus on identifying the pathogen and its sensitivity to antibiotics, and accordingly recommend that intravenous antimicrobial administration be started as soon as possible (within the first hour) after the pathogen is identified, both for septic shock and sepsis without shock, and that empirical broad-spectrum antimicrobials be discontinued. In addition, studies have shown that delaying antibiotic administration increases the number of deaths for each hourly delay after the onset of shock.

2. Materials and methods

The following methods were used in the study: content analysis, comparative analysis and systematisation of the research material. The study was conducted on the basis of the clinical guidelines and protocols of the Ministry of Health of Ukraine (MoH), Infectious Diseases Society of America (IDSA) and Society of Critical Care Medicine (SCCM), as well as publications by foreign authors. The search was conducted on the basis of PubMed and Google Scholar databases in 2017–2023.

3. Results

A retrospective analysis by of patients with sepsis and septic shock showed that delayed antibiotic administration was associated with an increase in in-hospital mortality with a linear increase in the risk of death for each hour of delayed antibiotic administration by 1.09% *(Liu, 2017)*. Similar results were demonstrated in a cohort of emergency department patients. These recommendations are not supported by the Infectious Diseases Society of America (IDSA) and the following arguments are given *(Masur, 2018)*:

1. About 40% of patients admitted to the intensive care unit with a diagnosis of sepsis do not have an infectious process.

2. Patients with suspected sepsis may have a viral infection. In this case, antibiotic therapy is not only ineffective, but also harmful.

3. The IDSA agrees that broad-spectrum antibiotics should be prescribed as soon as septic shock is suspected, but trying to meet the one-hour time limit may increase the frequency of antibiotic prescriptions for patients without an infectious process.

It should also be noted that the New Clinical Protocol "Emergency Medical Care: Prehospital Stage" states that empirical antibiotic therapy can be started if it is possible to take a bacteriological blood test for sterility with an antibiogram.

In the context of pre-hospital care by an emergency medical team, it is not always possible to choose the right antibiotic for empirical antibiotic therapy. According to the results of, there is a correlation between the start of antibiotic administration and the improvement of the patient's condition *(Singer, 2017)*. Therefore, an hourly delay in taking the drug increased mortality by 7.5% with each subsequent hour. Schmidt G.A. (2023) in a prospective cohort study conducted in an inpatient setting found that empirical antibiotic therapy was incorrectly selected in 32% of patients. Mortality in these patients was significantly higher than in those who received appropriate antibiotics (34% vs. 18%) *(Schmidt, 2023)*.

Sherwin R. and co-authors (2017), based on the analysis of data from studies on septic shock regarding early (up to 1 hour) administration of antibiotic therapy, determined that it is within this timeframe that there is a great need for antibiotic therapy to reduce the number of patient deaths. They recommend conducting laboratory tests for antibiotic susceptibility within the first 45 minutes of diagnosing an emergency, and then administering an etiotropic drug within the first hour of diagnosis. They noted that a delay of more than 3 hours significantly increased the number of patient deaths *(Sherwin, 2017)*.

Evaluated patients Ferrer R. with septic shock who received antibiotics after diagnosis *(Ferrer, 2014)*. The in-hospital mortality rate was 29.7%. According to the author, there was an increase in the number of fatalities due to delayed administration of antibiotics. Thus, if more than 1 hour had passed since the diagnosis, this significantly increased the proportion of mortality in people with septic shock. In addition, a linear dependence was noted, meaning that with each hourly delay, the number of deaths increased.

Described a randomised trial of patients with severe sepsis or septic shock, as well as those who underwent surgery with conventional Continuing Medical Education (62.0%) *(Bloos, 2017)*. The mortality rate within 28 days was 35.1% in the experimental group (which included surgery) and 26.7% in the control group (which did not undergo surgery). Surgical intervention was not a risk factor for mortality, as this difference was present from the start of the study. The average time to start antibiotics was 1.5 hours in the experimental group and 2.0 hours in the control group. The risk of death increased by 2% per hour in the group that underwent surgery due to delayed administration of antibiotics and by 1% per hour in the control group that did not undergo surgery.

At the same time, concluded that it is not necessary to specify a certain time frame of up to 1 hour in case of suspected sepsis, as this can lead to negative consequences in those patients whose shock is not caused by sepsis, and therefore the administration of broad-spectrum antibiotics will cause multiorgan failure *(Kalil, IDSA 2017*). Therefore, many scientists are of the opinion that antibiotic therapy is appropriate in the case of an accurate diagnosis of an emergency and blood sampling for sterility with an antibiogram.

Whiles B. (2017) and co-authors conducted a retrospective analysis of patients with severe sepsis and an overall mortality rate of 12.8% *(Whiles, 2017)*. Some patients (25.0%) developed a complication in the form of septic shock. The average time to administration of broad-spectrum antibiotics was 3.7 hours in those whose condition was deteriorating and 2.7 hours in those who were stable. It was determined that the time before administration of the drug was important in relation to the further recovery of patients. Each hour from the start of the diagnosis and delay in drug administration contributed to an 8% increase in rapid mortality.

In a systematic review by Al-Kader D and colleagues (2022), they determined the feasibility of administering antibiotics as soon as possible when diagnosing septic shock based on an analysis of articles for the period 2010–2021. They found that 66% of studies showed a correlation between the rapid use of broad-spectrum drugs and reduced mortality, but that accurate diagnosis of the emergency condition played a significant role. Delayed administration of drugs more than 6–12 hours after diagnosis increased mortality by 80%. At the same time, those who received drugs within 1 hour had a 33% lower risk of mortality. It was concluded that in two-thirds of the clinical trials, there was an association between the start of drug administration and mortality, but there was no clear line on the start of antibiotic therapy in relation to the time interval *(Al-Kader, 2022)*.

Asner S. (2021) analyzed the studies and found that in 54% of cases, antibiotic therapy was appropriate, of which 83% of patients received etiotropic drugs, which increased treatment success and reduced mortality. In 68.6% of cases, a linear relationship was found between the start of antibiotic therapy and mortality reduction. Delayed administration of the drug within 1, 2, 3 or 6 hours increased mortality with each subsequent hour. There are no clear time limits for drug administration *(Asner, 2021)*.

A study by Sankar and co-authors, (2021) among children with septic shock showed that 55% had a delayed start of antibiotic treatment and 45% had early treatment. The proportion of children in the first group is significantly higher in terms of the number of deaths (29%) compared to the second group (20%). The study concluded that delayed administration of the drug for more than 1 hour increases the number of deaths in children with septic shock *(Sankar, 2021)*.

Interesting are the data from the study by on patients with septic shock and the time of antibiotic administration. Patients were divided into four groups depending on the time of the antibiotic administration (up to 1 hour (group 1), 1–2 hours (group 2), 2–3 hours (group 3), more than 3 hours (group 4)). The average time of drug administration was 2 hours and 29 minutes. It was determined that mortality in the second and fourth groups was significantly higher than in the first and third groups. It was concluded that rapid administration of antibiotics reduced mortality, but there was no hourly dependence *(Sung, 2020)*.

Since the decision on when to start a broad-spectrum antibiotic is a relevant one and a group of researchers conducted a meta-analysis of two groups of patients: those who were administered the drug up to 1 hour after diagnosis of the condition, and 1 to 3 hours in the second group. They found that there was no association between the start of drug administration and mortality in these two groups, but the authors emphasize that it is better to prescribe drugs as early as possible and start using them to avoid fatalities *(Rothrock, 2020)*.

In the study by *(Johnston, 2017),* using a meta-analysis on the importance of immediate (within 1 hour) or delayed (more than 1 hour) administration of an antibiotic, it was found that mortality in the first group was reduced by 33%, respectively. Therefore, the authors are in favour of immediate initiation of antibiotic therapy to reduce patient deaths.

A retrospective analysis of patients with septic shock in the period from 2007–2020 by Bisarya, (2022) shows that 88% of patients received antibiotic therapy within 5 hours of diagnosis. Each hour delayed before the drug was administered increased the severity of the patient's condition by 4% for each subsequent hour. Therefore, it was concluded that patients with suspected septicaemia should receive antibiotics as soon as possible after diagnosis, otherwise the chances of complications in the form of septic shock increase with each passing hour *(Bisarya, 2022)*.

Data from Kim, (2018) showed that patients with sepsis and septic shock, in whom the time from the beginning of diagnosis to the administration of broad-spectrum drugs was minimal, had a decrease in mortality. It was found that mortality increased by 22% for each subsequent hour of delayed antibiotic administration from triage to drug administration and by 15% from triage to drug administration. Therefore, it was concluded that in both cases, the number of deaths increased, and therefore there is a need to start prescribing and administering drugs as soon as possible *(Kim, 2018)*.

4. Conclusions

Based on the data obtained from the literature review, it can be concluded that empirical antibiotic therapy for suspected sepsis or septic shock should be started as early as possible, but recommendations from the IDSA and other studies should also be taken into account to reduce complications and deaths caused by septic shock. And also to specify the relevant points of the New Clinical Protocol "Emergency medical care: pre-hospital stage".

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