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The impact of timing of antimicrobial therapy on outcome and mortality in severe sepsis and septic shock

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***Abstract*---**Even though new antimicrobial treatments have been available for over 60 years, the fatality rate from septic shock has not decreased. Evolutionary pressure on microbial pathogens has, as expected, led to selection towards resistant species as a consequence of the creation of ever more broad-spectrum and strong antimicrobials. The ineffectiveness of antibiotic treatment of septic shock un the decades that followed may have been a result of this phenomena. The treatment of septic shock has traditionally focused on resuscitative measures. The management of these serious illnesses has not prioritised the prompt provision of effective antibiotic treatment.

***Keywords*---**antimicrobial therapy, septic shock, mortality in severe sepsis.

Introduction

In highly developed nations, septic shock and sepsis-associated multiple organ failure remain the primary causes of death in intensive care units (ICUs). Death rates associated with sepsis and septic shock have historically ranged between 50 and 75 percent. The main breakthrough in the treatment of septic shock occurred 50 years ago with the introduction of antibiotic therapy. This led to a significant decrease in the death rate associated with sepsis, bringing it down to a range of 30% to 50%. Over the course of the last four decades, there has been a steady and incremental rise in the occurrence of sepsis on an annual basis. Consequently, there has been a significant rise in the overall number of fatalities. Current estimates indicate that despite a 33% increase in population, the number of severe sepsis cases in the US will double to 1.6 million by 2050. Approximately 10–15 percent of all intensive care unit (ICU) admissions are currently the result of serious sepsis and septic shock. Approximately 25% of sepsis cases progress to septic shock, while 50% to 75% of severe sepsis cases do so as well. Septic shock

counts for an estimated 5% to 8% of the total number of patients admitted to the intensive care unit (ICU). (1).

Appropriateness of Antimicrobial Therapy

Not starting antibiotic treatment that targets the specific organism is linked to significant increases in fatality rates, particularly in cases of septic shock. Hence, it is essential that empirical antibiotic regimens provide comprehensive coverage, ideally targeting 100% of the potential microorganisms responsible for the suspected cause of illness. The occurrence of inappropriate antibiotic medication initiation in intensive care unit (ICU)-hospitalized patients with nosocomial bacteremia and community-acquired bacteremia is as high as 17.1% and 34.3%, respectively. An additional comprehensive study revealed that patients who were initially diagnosed with septic shock received inadequate antimicrobial treatment at 18.8% and 28.4%, respectively. Mortality increases from 30% to 60% in intensive care unit patients with bacteremia to 70 percent to 100 percent in cases of gram-negative shock when initial empiric treatment is ineffective in targeting the underlying infection. Failure to provide proper empiric antimicrobial medication, which does not effectively target the pathogen, is linked to a significant decrease in survival rates. Specifically, the survival rate drops by around five times, ranging from 2.5 to 10 times in some subgroups, resulting in a decrease from 55% to around 11%. In cases of severe infections caused by Candida spp., gram-negative bacteria, and gram-positive bacteria, the results indicate that the risk of mortality significantly increases when the initial antimicrobial treatment fails. Comparable outcomes were documented in relation to a number of severe infections, including community-acquired pneumonia, pneumonia associated with hospitals and ventilators, and bacterial peritonitis. (2).

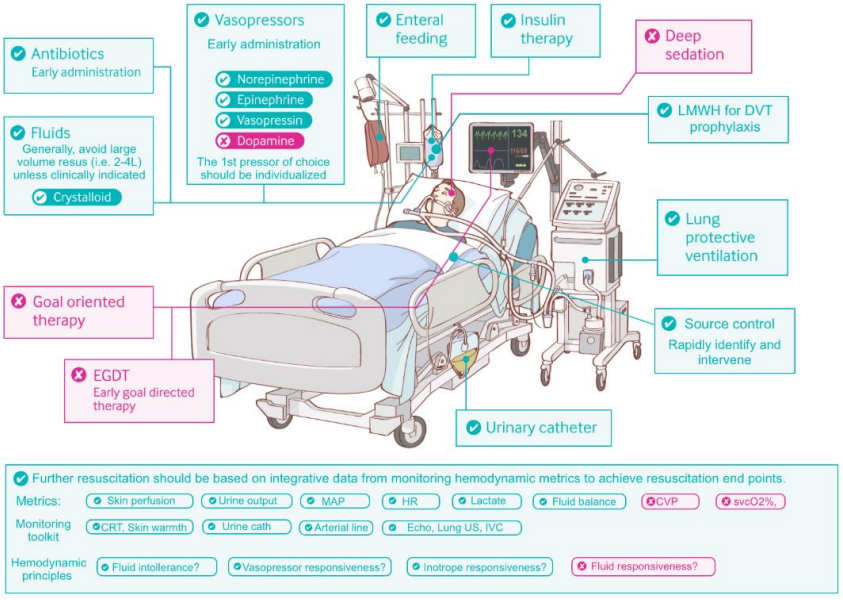

Fig 1: The effect of the timing of antimicrobial therapy on outcomes and death in cases of severe sepsis and septic shock. (3)

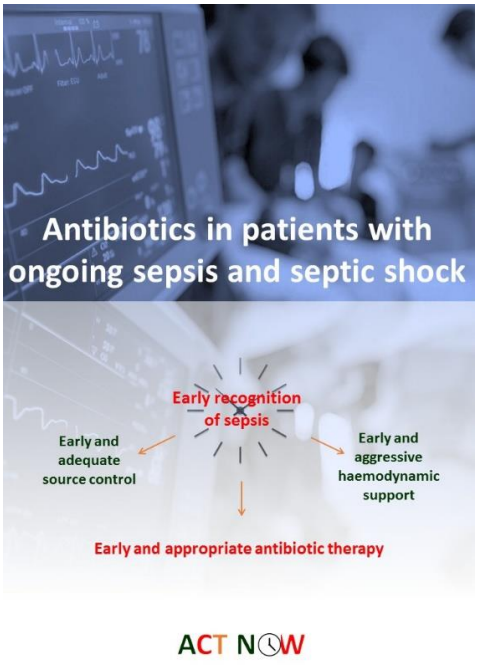

Fig 2: The influence of the timing of antimicrobial therapy on outcomes and death in cases of severe sepsis and septic shock. (4)

Antimicrobial Delay

The mortality of septic shock is significantly influenced by delays in starting proper antimicrobial treatment. The significant impact of these delays becomes evident in the substantial increase in mortality seen in murine septic shock cases treated with antibiotics, which occurs simultaneously with the onset of hypotension and lactic acidosis. A significant increase in mortality occurs rapidly in experimental severe illnesses when effective antibiotic medication is not administered. There was a higher chance of death when the right antimicrobial drugs were not given within 24 hours after confirming the presence of Pseudomonas bacteremia. A study conducted on a large group of Medicare patients found that when antibiotic treatment for community-acquired pneumonia was not administered within 8 hours of admission to the emergency room, there was a higher risk of fatality. (5) Prompt initiation (ideally within 30 minutes) of intravenous administration of a wide range of antimicrobial drugs is necessary upon clinical diagnosis of septic shock. Patients suffering from other severe infections also benefit greatly from promptly starting antibiotic treatment. In the case of prolonged hypotension, which indicates probable septic shock, it is crucial to promptly start appropriate, intravenous, broad-spectrum empiric treatment upon clinical suspicion of infection. Avoid assuming that chronic or recurring low blood pressure is triggered by anything other than sepsis in the presence of confirmed or suspected infection, unless there is compelling clinical evidence suggesting a particular alternative cause. The user's text is "(6)"

The influence of the promptness of administering antibiotics on the prognosis of individuals with sepsis and septic shock

An estimated 49 million individuals worldwide are afflicted with sepsis, which claims the lives of nearly 11 million annually. The mortality rate for patients with sepsis is approximately 10%, whereas the rate for patients with septic shock exceeds 40%. The utilisation of appropriate antimicrobial medications forms the cornerstone of sepsis treatment bundles and recommendations.3–8 However, the target time-to-antibiotic treatment for patients with sepsis is a subject of considerable disagreement demonstrates that early administration of antibiotics reduces sepsis-related mortality.

However, other research has failed to find a correlation between prompt antibiotic treatment and positive patient outcomes (7). The need of differentiating time-to-antibiotic recommendations based on sepsis severity is well acknowledged. Antibiotics should be given to individuals with septic shock without delay because of the exceptionally high fatality rates associated with this condition. Given that sepsis is a continuous illness with no distinct rare zones, it is challenging to provide therapy with strong predictive validity over a wide range of disease probabilities. No discernible temporal threshold was identified in the data pertaining to this particular subgroup, despite the fact that delays were likewise linked to higher mortality among individuals with sepsis. Patients suspected of having sepsis might potentially have their antibiotic dosing schedules adjusted based on the probability of infection (8)

Clinical results and time to antibiotic treatment in individuals with septic shock and sepsis

Sepsis is an infectious disease that causes biochemical, physiological, and pathological problems; it leads to multiorgan failure and a high fatality rate. There is strong evidence that delays in starting the right antibiotic treatment might increase the risk of death; hence, antibiotic administration is seen as an essential part of early sepsis treatment. Regarding this matter, the earlier Surviving Sepsis Campaign guidelines included antibiotic delivery in the hour-1 bundle, and it was highly advised to adopt the hour-1 bundle to prevent mortality and morbidity. The Surviving Sepsis Campaign bundle was connected with a higher risk of death in individuals with sepsis, according to several international studies. (9)

However, there is still a lot of debate over whether people with sepsis or septic shock would have better results if they had antibiotics within an hour of symptoms onset, and if there is a correlation between the timing of antibiotic administration and clinical outcomes. Aggressive antibiotic therapy within 1 hour may not be helpful in sepsis and may lead to accidental exposure to broad-spectrum antibiotics, according to the Infectious Diseases Society of America. Additionally, there is no data to suggest a hard and fast time limit for antibiotic delivery in sepsis patients, according to the American College of Emergency Physicians. Not all patients with sepsis can be treated with antibiotics within 1 hour of presentation, and it takes a lot of time and energy to coordinate their prompt delivery. (10)

Prior recommendations that broad-spectrum antibiotics be administered to all patients with sepsis within one hour were mostly based on retrospective research or investigations on patients with septic shock. The results of our research are corroborated by two other recent multicenter investigations that used large sample numbers. Patients with septic shock had a 7% greater risk of in-hospital death for every hour of delay in antibiotic administration, compared to patients without shock, when examining the impact of time to treatment on mortality of required emergency care for sepsis in 149 hospitals in New York. Our study is the first of its kind to thoroughly assess the correlation between the duration before antibiotics were given and the risk of death in a large prospective multicenter cohort of patients diagnosed with sepsis or septic shock using the Sepsis-3 criteria. (11)

There are several concerns about the use of antibiotics in patients suspected of sepsis. One is the potential for antibiotic-related side effects. Another is the increased risk of antimicrobial resistance, which can worsen the situation. Lastly, there is the added financial burden and other negative outcomes that can result from aggressively treating all patients with rapid-onset broad-spectrum antibiotics. In addition, the majority of healthcare facilities lack the means to promptly treat every patient who shows signs of sepsis with antibiotics. More than half of the sepsis patients in a prior study that looked at the impact of treatment delay on mortality from required emergency care for sepsis in 149 hospitals in New York did not receive antibiotics within three hours of the start of sepsis, even though the severe sepsis and septic shock management bundle was in place. Improving the treatment of sepsis and septic shock might be prioritised by identifying a subset of patients who would gain the most from this intervention. (12)

Early antibiotic therapy may be beneficial for individuals with many differentiating features, including the presence of shock. Patients with clinically severe illness should take antibiotics as soon as feasible, since there was a substantial decrease in in-hospital mortality among patients with higher SOFA scores or who were admitted to the ICU owing to early medication. Age, the absence of a history of antibiotic therapy within the last three months, and a non-pulmonary infection as the origin of sepsis were other characteristics linked to increased survival. To determine if early antibiotic medication could be beneficial for individuals with these features, more research is required. (13)

The identification of sepsis by the treating physician in the emergency department was an intriguing component linked with better outcome. Clinicians may be more likely to diagnose critically sick patients with sepsis rather than only classifying them according to the location of infection, suggesting that this may potentially serve as a proxy measure of patients' illness severity. Finding out if sepsis patients would have better outcomes if emergency doctors were better educated on the diagnosis and management of the condition would be an intriguing experiment. (14)

Antibiotic Timing and Its Effects on Severe Sepsis and Septic Shock Outcomes

There is a strong correlation between severe sepsis and septic shock and high healthcare expenditures, morbidity, and death rates; these conditions also continue to be a leading cause of visits to emergency departments and admissions to intensive care units. Enhanced results were achieved by using a defined resuscitation protocol, which mainly included administering intravenous (IV) fluids, administering timely broad-spectrum antibiotics, and administering vasopressor medication. Previous studies examining the correlation between the time to antibiotic treatment and outcomes have shown conflicting conclusions, despite the fact that some writers have argued that prompt antibiotic therapy is crucial for improved mortality in severe sepsis and septic shock. (15)

Kumar et al. (2006) found that for every hour that passed after shock began, the death rate in sepsis patients increased by 7.6%. Several studies have shown an increase in mortality linked to delays in antibiotic delivery, whether it's from shock detection or time from emergency department triage, while later research have not shown as dramatic findings. Prior research has been inconclusive in its failure to establish a correlation between antibiotic administration beyond the recommended triage time and an increase in mortality. (16) The most recent Surviving Sepsis Campaign (SSC) guidelines state, "The goal of therapy should be the administration of effective via IV antibiotics within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C)." These guidelines also contain specific recommendations regarding the timing of antibiotics. In addition, broad-spectrum antibiotics should be administered within three hours of emergency department triage, per the "sepsis bundle" of the SSC. Prior studies have indicated that adherence to antibiotic administration recommendations is rarely achieved. In light of this, the authors of the SSC guidelines acknowledge that it may not always be feasible to achieve these goals in practical application. Notwithstanding these limitations, the duration required to administer antibiotics to patients afflicted with severe sepsis and septic shock is being contemplated as a potential gauge of treatment efficacy. Furthermore, in accordance with the SSC's global guidelines for managing severe sepsis and septic shock, antibiotics ought to be administered within three hours of emergency department triage and one hour after identification. Antibiotics administered within 3 hours of emergency department triage and/or one hour of shock identification do not substantially reduce mortality in patients with severe sepsis and septic shock, according to our findings and the existing literature. (18)

With a consistently high mortality rate, doctors continue to face the difficult and hard task of diagnosing and treating severe sepsis and septic shock. Over the last fifteen years, studies have shown that sepsis is better treated and detected earlier in the course of the disease. This is probably because of a number of factors, such as increased awareness of the condition, the ability to reverse hypoperfusion, heightened microcirculatory or endothelial dysfunction, and the elimination of infectious nidus. Studies looking at the effects of when antibiotics are given have shown mixed findings. (19)

Although it is acknowledged that ineffective anti-microbial treatment would eventually harm patient outcomes, the precise timing of this change is uncertain. Also, no randomised clinical trials have looked at how antibiotic timing affects outcomes, and it's doubtful that any direct experimental investigation will be planned anytime soon due to ethical concerns about patient safety and the current recommendations from guidelines. (20)

Antibiotics used within three hours of triage or one hour of severe sepsis/septic shock identification may not reduce mortality, although there are a number of possible reasons for this. One, a single dosage of antibiotics probably won't make much of a difference in terms of survival, especially considering the intricacy of the pathophysiologic insult that causes organ failure in sepsis. Actually, after decades of investigation, no other medicinal substance has ever been shown to provide this outcome. According to the latest findings from the ProCESS experiment, it seems that many of the forceful treatments that have been targeted over the last several years may not have had the desired effect. Furthermore, it is reasonable to assume that in certain cases, it is best to start resuscitation before giving antibiotics so the host can have a strong hemodynamic response to the inflammatory cascade and subsequent insult that can be caused by components released during bacterial lysis. (21)

Time to antibiotic treatment and its effect on the prognosis of ED patients with bacterial infections: consequences for antibiotic stewardship

Some infectious clinical syndromes, such septic shock and bacterial meningitis, are so severe that prompt antibiotic treatment is essential. On the other hand, there are costs to the environment due to the selection of resistant microorganisms and the adverse effects of needless empirical broad-spectrum antibiotic treatment. Particularly among patients coming to the ED with prevalent community-acquired diseases, a large number of patients have infections caused by bacteria that are resistant to narrow-spectrum medicines. Furthermore, many illnesses that are falsely thought to be bacterial are really viral or otherwise non-infectious. One important aspect of antibiotic stewardship could be to wait to start antibiotics until diagnostic test results are available. This could allow for targeted, narrow-spectrum therapy and reduce the use of unnecessary antibiotics. Examples of diagnostic tests include biomarkers, radiological examinations, and point-of-care tests twenty-one)

Findings

Even though new antimicrobial treatments have been available for over 60 years, the fatality rate from septic shock has not decreased. Evolutionary pressure on microbial pathogens has, as expected, led to selection towards resistant species as a consequence of the creation of ever more broad-spectrum and strong antimicrobials. The ineffectiveness of antibiotic treatment of septic shock un the decades that followed may have been a result of this phenomena. (13) By making better use of the antibiotics we currently have, we may be able to obtain better results in cases of severe infections and septic shock. The treatment of septic shock has traditionally focused on resuscitative measures. The management of these serious illnesses has not prioritised the prompt provision of effective

antibiotic treatment. A key component of first resuscitation in septic shock, according to the reviewed evidence, should be the empiric use of broad-spectrum antibiotics. The current body of research indicates that this strategy ought to considerably reduce the fatality rate associated with septic shock. (22)

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