Review Article

Timeliness of antibiotics for patients with sepsis and septic shock

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Abstract: For many years, sepsis guidelines have focused on early administration of antibiotics. While this practice may benefit some patients, for others it might have detrimental consequences. The increasingly shortened timeframes in which administration of antibiotics is recommended, have forced physicians to sacrifice diagnostic accuracy for speed, encouraging the overuse of antibiotics. The evidence supporting this practice is based on retrospective data, with all the limitations attached, while the only randomized trial on this subject does not show a mortality benefit from early administration of antibiotics in a population of patients with sepsis as often seen in the emergency department (ED). Physicians are challenged to treat patients suspected of having sepsis within a short period of time, while the real challenge should be to identify patients who would not be harmed by withholding treatment with antibiotics until the diagnosis of infection with a bacterial origin is confirmed and the appropriateness of a course of antibiotics can be evaluated more adequately. Therefore, in the general population of patients with sepsis, taking the time to gather additional data to confirm the diagnosis should be encouraged without a specific timeframe, although physicians should be encouraged to perform an adequate work-up as soon as possible. Patients with suspected sepsis and signs of shock should immediately be treated with antibiotics, as there is no margin for error.

Keywords: Antibiotics; sepsis; shock; Surviving Sepsis Campaign (SSC); prehospital antibiotics against sepsis (PHANTASi)

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Introduction

Sepsis is one of the major health problems of the 21st century. It is currently defined as a dysregulated host response to an infection, which causes life-threatening organ dysfunction and a mortality risk of about 10% (1). The risk of mortality increases to over 40% for patients with septic shock (1). Although there still is no specific treatment for sepsis, general treatment with fluids and antibiotics has been the gold standard for many years. A frequently cited paper by Kumar *et al.* in 2006 showed that every hour of delay in the administration of antibiotics decreased the chances of survival by 7.6% (2). Although the study by Kumar and colleagues was based on retrospective data and only counted the delay in antibiotics from the onset of persistent hypotension, the term 'golden hour of sepsis' was introduced, suggesting that there is only a small window of opportunity to optimize the treatment strategy for these patients. Since then, most treatment protocols for sepsis have focused on administering antibiotics as soon as possible. While this practice may benefit some patients, for others it might have detrimental consequences.

Surviving Sepsis Campaign (SSC) guidelines

Currently, the SSC guidelines are widely used to guide

treatment for patients with sepsis (3). The main focus of these guidelines is early identification of sepsis, treatment with broad spectrum antibiotics and administration of intravenous fluids when needed. Since the initiation of the SSC in 2002, the guidelines have proposed several bundles that included elements of treatment which have to be started within a specific time period. With newer iterations of the guidelines, the timeframe in which antibiotic treatment had to be initiated was shortened, without a high level of evidence for these updated recommendations (4-6). Following the 3- and 6-hour timeframes of the previous bundles, the latest update of the SSC guidelines proposed an "hour-1" bundle to initiate treatment as early as possible for all patients suspected of having sepsis (7). This bundle was immediately challenged by many physicians. After extensive debates (8-10), the Society of Critical Care Medicine (SCCM) and the American College of Emergency Physicians (ACEP) finally issued a statement recommending against the use of the SSC 1-hour bundle, leaving many physicians and hospitals in doubt about which guidelines to use for patients with suspected sepsis in the emergency care setting.

Overuse of antibiotics

The increasingly shortened timeframes in which guidelines recommend administration of antibiotics for sepsis have forced emergency care personnel to sacrifice diagnostic accuracy for speed (8). Limiting the time to perform a proper diagnostic work up has inevitably encouraged overuse of antibiotics (6). A study in the Netherlands showed that up to 43% of patients admitted to the intensive care unit (ICU) because of sepsis were unlikely to even have an infection (11). Another study showed that 29% of patients who were diagnosed with sepsis and received antibiotics in the emergency department (ED) were unlikely to have an underlying bacterial infection (12). This unnecessary use of antibiotics can have many negative effects such as an increased rate of *Clostridium difficile* infections, organ injury and a disruption of the gut microbiome (5,13). On a population level, overuse of antibiotics can increase antibiotic resistance, leading to a further acceleration of this global crisis (14). On the other hand, it is questionable whether this practice actually benefits all patients with sepsis.

Evidence for early administration of antibiotics

Following the paper by Kumar and colleagues (2), numerous studies on the effects of early administration of antibiotics for patients with sepsis have been conducted. A systematic review and meta-analysis by Sterling *et al.* in 2015 included 11 retrospective observational studies on this subject (15). Although there was significant heterogeneity between the included studies, the authors concluded that there was no significant increase in risk of mortality for each hour of delay in treatment, when looking at the pooled effect of these studies. Another two key retrospective studies have been published since. Both Liu *et al.* and Seymour *et al.* found significant increases in mortality for each hour of delay in antibiotics administration (16,17). This was most prominent for patients with septic shock. However, it should be acknowledged that multiple studies that found significant and often linear effects on mortality, favoring early administration of antibiotics, have limitations associated with their study design. Firstly, all these studies have been conducted retrospectively on databases that were not created for this purpose (5). Then, the outcomes have been adjusted for many variables, raising the risk of overadjustment (18), while often neglecting factors such as concomitant treatments, appropriateness of antibiotic therapy or confounding by indication (5,6). Lastly, the premise of a linear increase in mortality when antibiotic treatment is delayed is questionable (5). Time zero, or the time when the infection or organ dysfunction started, is hard to define. This could have been hours to even days before the presentation in the ED. It thus seems highly unlikely that the first few hours in the ED will see such an increase in mortality (5).

Besides retrospective analyses, there have also been some prospective studies on this subject. In 2012, Hranjec *et al.* evaluated the effects of conservative initiation of antimicrobial treatment, rather than aggressive and early administration of antibiotics for critically ill surgical ICU patients with suspected infection (19). The authors concluded that an aggressive approach significantly increased the risk of mortality when compared with a conservative approach. Also, the conservative approach led to more appropriate antimicrobial therapy and a shorter treatment period. de Groot and colleagues published another study that prospectively evaluated early administration of antibiotics, which did not show any benefits of this practice (20). Finally, in 2018, the first and thus far only randomized trial on the subject of early antibiotics for sepsis was conducted by our group: the prehospital antibiotics against sepsis (PHANTASi) trial (21). This large trial evaluated the effects of administration of

antibiotics to patients with sepsis in the ambulance, rather than in the ED. Emergency medical personnel was trained to recognize patients with sepsis. Afterwards patients were randomized to receive either usual supportive care or a dose of 2,000 mg ceftriaxone in addition to the supportive care in the ambulance. The usual care group received their first dose of antibiotics in the ED. The early intervention resulted in a difference in time to antibiotics of 96 minutes between the intervention and usual care group. However, the 28- and 90-day mortality rates did not differ between the groups. The only difference that was found between these groups, was the 28-day readmission rate, which was significantly higher in the control group (7% *vs.* 10%). The population of patients with septic shock was just 3% of the complete study population, which made it hard to detect potential effects of early antibiotics on mortality in this subgroup.

The PHANTASi trial provided a couple of interesting findings. The design of the trial gave it the unique opportunity to randomize between early and late antibiotic treatment, which would otherwise have been unethical given the standard practice at that point in time. Some important limitations of this study should be addressed. Firstly, this was a select population of patients that had a suspected infection and a minimum of two of a selection of three of the systemic inflammatory response syndrome (SIRS) criteria (temperature >38 or <36 ℃, heart rate >90 beats per minute, respiratory rate >20 per minute) which was the gold standard for diagnosing sepsis at the time the study was conducted. As just 3% of the study population had septic shock, we cannot compare these results to other studies given that these included only critically ill sepsis patients. However, the patient-mix in the PHANTASi trial was probably very similar to the general ED population of sepsis patients (22). Secondly, the reduction in time to antibiotics was just 96 minutes. Over 40% of patients in the usual care group received antibiotics within one hour of presentation to the ED and about 85% of patients within 3 hours (21). Even in the retrospective studies that report significant increases in mortality when antibiotics are not administered early, the risk of mortality does not increase immensely in these first hours. It is thus questionable whether we can expect any significant differences in this short time frame. Lastly, we have to consider the fact that, although there was no difference in mortality rates, there was a difference in readmission rates. It has been proposed that the early administration of antibiotics may have inhibited the development of organ dysfunction in some patients (23). There may thus well be a beneficial effect of early administration of antibiotics in selected groups (23).

Summarizing the evidence on the early administration of antibiotics for patients with sepsis, we can conclude that evidence for supporting this practice mainly comes from retrospective observational studies, with all the limitations attached. One prospective study even found favorable effects from a conservative approach regarding initiation of antimicrobial therapy (19). Furthermore, when significant effects favoring early administration of antibiotics are found, this is usually in the most critically ill patients with septic shock. The most compelling evidence, from the only randomized trial (the PHANTASi trial) on this subject (21), does not show a mortality benefit from early administration of antibiotics in a population as often seen in the ED.

Identifying patients with sepsis

When considering the appropriateness of existing sepsis protocols which focus on early administration of antibiotics, we also have to examine the specific groups of patients who are labelled as having sepsis. Currently, according to the sepsis-3 guidelines, sepsis should be suspected in patients who have a positive quick Sequential Organ Failure Assessment (qSOFA) score and have an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 or more points, due to suspected infection (1). To break it down, the definition consists of two components: organ dysfunction quantified by the qSOFA and SOFA score and suspicion of infection. Both these components cause problems when used to select patients to treat with antibiotics in an early stage. Firstly, some parts of the SOFA score are based on the results of laboratory test, which are not immediately available in every setting. The SOFA score is therefore rarely used outside the ICU and the use of SOFA in conjunction with qSOFA to define sepsis is thus rather confusing and impractical. In clinical practice, scores such as the qSOFA, National Early Warning Score (NEWS) or SIRS are often used as independent tools to detect patients with a high risk of mortality due to suspected infection (24). They are easy to use, but far from accurate (24). The qSOFA is not sensitive enough to be used as a screening tool (25,26), while the SIRS criteria lack specificity and cause many false positive results (24). With current protocols, physicians could be forced to either underdiagnose a substantial amount of patients with sepsis,

or treat a significant proportion of these patients with antibiotics, while many may not need them.

The other part of the definition of sepsis states that the organ dysfunction has to be caused by a suspected infection. This is purely based on clinical judgement, as there are no objective criteria for this component of the definition. More experienced clinicians will likely be more accurate when suspecting an infection. Increasing the accuracy with which physicians can assess the likelihood of an infection will increase the validity of the sepsis criteria and may also improve the accuracy of scores like qSOFA and SIRS. Assessment of patients with sepsis by a senior attending would greatly help in this regard. Furthermore, it is of importance that only patients who are suspected of having a bacterial infection, and not viral infection, are treated with antibiotics. The study by Minderhoud *et al.* showed that out of a total of 78 patients (29%) who received antibiotics without evidence of a bacterial infection, 21 patients (8%) actually suffered from proven or suspected viral infections (12).

Considerations

We have discussed the intricacies of the assessment and treatment of patients suspected of having sepsis in a non-ICU setting. It remains challenging to accurately suspect infection and identify patients with sepsis, especially in the elderly with atypical presentations (27). Even more difficult perhaps is the distinction between bacterial and non-bacterial disease, for which there are no reliable diagnostic tests yet. Treating a general group of patients who are suspected of having sepsis, causes many patients to be treated with antibiotics unnecessarily. Protocols that have challenged physicians to sacrifice diagnostic accuracy in order to initiate treatment within a certain timeframe, have only amplified this effect. Furthermore, these protocols could also be misused as a performance measurement for hospitals, with unwanted consequences. As there is little evidence to support the early administration of antibiotics, especially for the general ED population of patients with sepsis, an updated international guideline is needed. A striking fact about the current situation is that we have had the same problem with the management of community-acquired pneumonia and do not seem to have learned from that experience. A quality measure was instituted in 2002 in the United States, forcing physicians to treat patients with suspected pneumonia with antibiotics within four hours (28). This practice, not based on high quality evidence, led to the same problem of overdiagnosis and unnecessary use of antibiotics. Eventually, the negative effects were recognized and the quality metric was removed.

Considering all the available evidence on this subject, it seems reasonable to suggest that rapid administration of empiric antibiotics will benefit critically ill sepsis patients with signs of shock benefit (16,17) and that there is certainly no margin for error in this group (29). However, for patients who are suspected of having a systemic infection, but who are not in shock, physicians could take additional time to gather information to further confirm the diagnosis of sepsis and the suspicion of a bacterial cause. This is even more relevant given the technological advances regarding molecular diagnostic tests such as polymerase chain reaction (PCR) to rapidly detect causative agents with high sensitivity (30). Instead of being challenged to treat patients within a set period of time, physicians should be challenged to identify the patients with suspected sepsis who will not be hurt by taking time to gather additional patient data and only administer antibiotics when it really could benefit the patient. New guidelines for the treatment of patients with sepsis should thus not only stipulate goals separately for patients with sepsis and patients with septic shock, they should also avoid pursuing specific time periods in which treatment should be initiated for the general sepsis population. However, physicians should be encouraged to perform an adequate work-up as soon as possible (*Box 1*).

The clinical dilemma between early administration of antibiotics according to the guidelines and an approach more similar to what we have just described was presented in the *New England Journal of Medicine* by Mi and colleagues (31). In this case vignette of two patients with suspected infection, arguments were made for both immediate administration of antibiotics and a more careful approach where additional information could be gathered before deciding to administer antibiotics (31). Interestingly, a poll at the end of the article showed that the total of 3,118 responders were split fifty-fifty between these two options. Readers of this article seem to value the existing literature differently. Another possibility would be that many readers chose their answer based on the existing guidelines, not having had the time to evaluate the literature themselves. Consensus about the evidence and updated international protocols are much needed, to make sure that sepsis care is based on the best available evidence and is comparable between different hospitals.

Box 1 Key recommendations

In the general population of patients with sepsis, taking the time to gather additional data to confirm the diagnosis should be encouraged without a specific timeframe, although physicians should be encouraged to perform an adequate work-up as soon as possible

Critically ill patients with suspected sepsis and signs of shock should be treated with antibiotics as soon as possible, as there is no margin for error with these patients

Conclusions

Studies regarding the use of early antibiotics for patients with sepsis are often limited by problems inherent to this heterogeneous and enigmatic syndrome. With the existing guidelines, physicians are challenged to treat patients suspected of having sepsis within a very short period of time, while the real challenge should be to identify patients who would not be harmed by withholding treatment with antibiotics until the diagnosis of infection with a bacterial origin is confirmed and the appropriateness of a course of antibiotics can be evaluated more adequately. Therefore, in the general population of patients with sepsis, taking the time to gather additional data to confirm the diagnosis should be encouraged without a specific timeframe, although physicians should be encouraged to perform an adequate work-up as soon as possible. Patients with suspected sepsis and signs of shock should immediately be treated with antibiotics, as there is no margin for error.

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Footnote

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