

Challenging the “golden hour” of sepsis treatment – is it contributing to the over-administration of antibiotics?

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Abstract

The first hour after recognising symptoms of sepsis in a patient is known as the “golden hour”. Clinicians hold increased importance to this hour and believe that many therapeutic interventions will be most effective if administered within this time. One example is administering broad-spectrum antibiotics to septic patients to help eliminate the pathological cause of sepsis. However, antibiotic resistance still needs to be considered as part of antibiotic stewardship. It is important to balance the usefulness of the “golden hour” principle whilst considering the negative implications that overuse of antibiotics has on antibiotic resistance.

A literature search was conducted to explore this issue further. The key findings were that although antibiotics are paramount in sepsis treatment, administering them within one hour of sepsis diagnosis is not associated with an improvement in mortality. One could argue that giving broad-spectrum antibiotics is futile and will worsen antibiotic resistance. Other clinical interventions should be considered when trying to reduce the occurrence of antibiotic resistance, such as improved diagnosis of sepsis and de-escalation of antibiotic therapy.

Abbreviations

NEWS2 – National Early Warning Score 2
qSOFA – Quick Sequential Organ Failure Assessment
SOFA – Sequential Organ Failure Assessment

Introduction

Medical students, doctors and the general public hear the word sepsis and a sense of panic begins to set in. This increased vigilance is reflected in the hounding of emergency teams to administer antibiotics within the first hour of sepsis recognition, hailed as the

“golden hour”. However, the practicality of this protocol has been questioned in a landmark study conducted by Kumar et al¹ Is it worth administering antibiotics that could potentially save a septic patient’s life, whilst running the risk of unnecessarily contributing to antibiotic resistance?

What is sepsis?

Sepsis is a life-threatening disorder that is characterised by a dysregulated immune response to infection and can lead to organ failure and eventually death.² Septic shock is a more advanced version of sepsis, whereby there are circulatory, cellular, or metabolic abnormalities.³

The diagnosis of sepsis is made based on symptoms that overlap with other non-infective pathologies. In addition, it takes a long time to determine the causative pathogen from blood cultures; this makes it harder to ascertain that the condition is sepsis in the acute stages of disease.⁴ Some common symptoms are mottled or bluish skin; tachypnoea or hypotension.⁵

The exact incidence of sepsis is unknown – this is because there is a lack of an agreed definition for it. However, according to NHS England in 2015, sepsis was a contributory cause to 23,135 deaths. The exact contribution that sepsis plays in these deaths is currently unknown, as some of these patients had multiple comorbidities and frailty.⁶ The UK Sepsis Trust shares that in 2017 there were 200,000 admissions to hospitals in England with one of the “definitely septic” diagnostic codes.⁷

Methods

Literature search

To investigate the issue of the “golden hour” further, a literature search was conducted primarily using PubMed, an online database.

Additionally, Google Scholar was used to search for further literature. The terms searched for included a combination of keywords from: "sepsis", "septic shock", "sepsis management", "antibiotic resistance", "antibiotic use", "sepsis six" and "golden hour of sepsis", using Boolean operators where appropriate to refine the search. Citation chaining was also used to find relevant articles.

Results

The initial search yielded 20 journal articles. After manually screening the abstracts for relevance to this literature review, eight were excluded as they were not specific to antibiotic administration or sepsis treatment in adults.

Discussion

How is sepsis managed clinically?

The Surviving Sepsis Campaign (SSC) is a collaborative initiative launched to reduce the risk of death from sepsis and septic shock worldwide, through developing and implementing protocols. These guidelines are evidence-based, which provides credibility for the widespread promulgation of said guidelines and is why the Campaign is commonly mentioned in the discourse surrounding sepsis. Participating in the Surviving Sepsis Campaign was associated with a 5.4% absolute survival rate for septic patients.⁸

One of the guidelines the Surviving Sepsis Campaign recommends is the Sepsis Six care bundle, commonly remembered by the 'BUFALO' acronym: bloods, urine, fluids, antibiotics, lactate, oxygen. In further detail, this involves taking two blood samples (to undergo microbiological culturing), monitoring urine output, starting the patient on fluids, administering intravenous antibiotics, measuring serum lactate and delivering high-flow oxygen.⁹

How are antibiotics used?

The general medical community acknowledge that one of the most important tenets of sepsis treatment is antibiotic administration. The common goal of antibiotic therapy is to have a drug concentration high enough to sufficiently kill as many bacteria as possible.¹⁰ In an ideal world, this could be done by administering as many antibiotics as possible without any repercussions. However, one major threat to the value of these drugs is antibiotic resistance. Bacteria replication over time will naturally give rise to genetic mutations that cause it to become resistant to the antibiotics used to treat bacterial infections, and therefore making the antibiotic futile. This is becoming an increasingly worrying issue within healthcare as antibiotics are an essential part of treating serious infections. With the stagnation in antibiotic discovery someday antibiotics could be rendered useless if bacteria continue to develop resistance. This makes the debate surrounding the "golden hour" is so important.¹¹

Deciding which antibiotics to start patients on in the acute setting may be difficult, as there is often a lack of more definitive blood culture data on the species and sensitivities of the infective micro-organisms. Sometimes clinicians get it wrong – studies have shown that 10-40% of the antibiotic regimens that are administered initially are inadequate or inappropriate.¹² The Surviving Sepsis Campaign recommends that the patient is started with broad-spectrum antibiotics intravenously, and then after the causative agent is determined, the therapy is to be de-escalated to be more targeted to the pathogen.¹³

During the initial stages of treatment, an antibiotic that targets a wide range of pathogens is needed. Piperacillin and Tazobactam are antibiotics that can be combined and used to treat gram-negative or *Pseudomonas* spp. bacterial infections, whereas Vancomycin can be used for gram-positive or Methicillin-resistant *Staphylococcus aureus* bacteria. Broad-spectrum carbapenems are also commonly used in sepsis treatment.¹⁴ It may seem counter-intuitive to start a patient

on antibiotics when you do not know what the bacteria causing the infection is. However, sepsis is a condition that is too unpredictable to wait for microbiological blood culture results as this can sometimes take several days.¹⁵ During this time, the patient's health can potentially deteriorate and this could lead to death.

After considering both sides of the scale, it seems understandable that clinicians would rather take the risk of increased antibiotic resistance from administering broad-spectrum antibiotics, rather than the patient's deterioration and death.

Why is the timing of antibiotic administration important?

The timing of antibiotic administration is thought to be a major tenet of sepsis management since patients can rapidly deteriorate. There is common agreement that once sepsis is recognised, timely antibiotic administration will benefit the patient more and lead to better outcomes. However, the 60-minute time constraint of the "golden hour" is increasingly being called into question.⁶

Professor Mervyn Singer is very vocal about his discontent with 'timely' being misinterpreted as 'early'. In his letter to the *Lancet*, he highlights that a reason for inappropriate antibiotic administration is that clinicians will often administer antibiotics straight away, just for the sake of taking action against suspected sepsis. He argues that they do not realise that 'timely' means avoiding unnecessary delays, and not just administering them straight away.¹⁶ Spiegel et al also address the one-hour time constraint in an editorial for the *Annals of Emergency Medicine*. They explain that although treatment with no delay is paramount in sepsis management, condensing the six treatment directives into a one-hour time limit may cause operational problems for emergency departments that are already struggling with three- and six-hour time limits previously used for sepsis treatment.¹⁷ This may cause clinicians to be more rushed and could cause harm to patients.

The problem with misdiagnosing sepsis

A big issue with adhering to the golden hour protocol is that to meet the one-hour goal, clinicians in a rush may misdiagnose a patient with sepsis, and then start them on this treatment bundle. Essentially, the patient is being given high doses of broad-spectrum antibiotics for no clinical reason, which goes against a major dogma in antibiotic stewardship – broad-spectrum antibiotics should only be used when necessary due to the potential they have to increase antibiotic resistance.

A way to prevent this is by increasing the accuracy of sepsis diagnosis. SOFA (Sequential Organ Failure Assessment score) and qSOFA (quick SOFA) are two tools commonly used in determining prognosis in critical illness however, they are not recommended for sepsis identification. Instead, NEWS (National Early Warning Score) is more commonly used as it has better sensitivity and specificity compared to qSOFA, which only includes three of the seven NEWS2 criteria. In clinical practice it is recommended that if the patient has a qSOFA score above two, then the full SOFA score is obtained. However, this includes taking arterial blood gases, which is not routinely done in septic patients, and could jeopardise the small time window in sepsis management.¹⁸ This further stresses the need for other measurements taken urgently such as serum lactate, in addition to NEWS2 to detect sepsis and diagnose it accurately.

Accurate diagnosis is important because many cases are diagnosed as sepsis but are not in reality. A retrospective cohort study looked at patients with acutely decompensated heart failure between 2015 and 2018 and found that sepsis was misdiagnosed in 25% of the patients.¹⁹ This possibly taints the results yielded from the study, which puts the usefulness of the "golden hour" protocol into jeopardy. However, as 75% of the patients were accurately diagnosed, there needs to be a way to reduce misdiagnosis without eliminating the "golden hour" approach.

The evidence behind the “golden hour” protocol

A retrospective cohort study done by Kumar et al between 1989 and 2004 is the main piece of long-standing evidence used to back the “golden hour”. This was the first landmark study done to examine the relationship between antibiotic administration and sepsis survival. The main finding was that patients who received antibiotics within the first hour of sepsis recognition had a 79.9% chance of survival. It was also found that with every additional hour, the chance of survival decreased by 7.6%.¹ Through critically appraising this study, a strength of it is that it is a large cohort study that used data from 14 ICUs and 10 hospitals in Canada and the USA. However, a weakness of this study is because of its retrospective design and the time span of 15 years, there is the potential for an absence of data on the confounding factors of this study, leading to confounding bias and diminish the quality of the study.

On the other hand, another study published in 2016 opposes the recommendations of the Surviving Sepsis Campaign. This is a systematic review and meta-analysis of 11 publications and sought to find evidence for the SSC guidelines.²⁰ In total, 11,017 patients' data was used. The results of this conflicted with those of the previous study and provided evidence against the Surviving Sepsis Campaign's recommendations. It was found that antibiotic administration within one hour of sepsis recognition in septic patients was not associated with an improvement in mortality.

A strength of this meta-analysis is that the selection process of the papers was very refined and ensured that only high-quality papers, all of which were multi-centre and had a large sample size, and closely related to the aim of the meta-analysis. Each study was scored, with eight being the highest, based on how sepsis was recognised, the study design, population sampling and data on the timing of antibiotics. The studies that yielded a score above four were included. However, a downside to this study is the potential for information bias. Some studies were not included in this meta-analysis due to a lack of response after contacting the author, therefore it is possible that not all potential data had been collected, which could alter the results.

No other studies have been done to directly compare the timing of antibiotic administration and sepsis survival. A randomised clinical trial comparing immediate and delayed antibiotic administration would be a very useful study to refer to, however this is difficult to organise and conduct due to ethical and patient safety concerns.²⁰ There is not enough data available to make a clear and direct claim.

De-escalation of antibiotic therapy

After the results of the blood cultures have been received, the emergency team will know the pathogen that is causing the patient's sepsis. Naturally, the antibiotic regimen could be adapted at this point to follow a more individualised approach. The antibiotic therapy can be changed from broad-spectrum antibiotics to a more narrow-spectrum antibiotic. This is called the de-escalation of antibiotic therapy. The main purpose of this is to prevent the unnecessary development of antibiotic resistance, which would happen if broad-spectrum antibiotics were used for the whole treatment plan.²¹

A meta-analysis of published studies sought to determine if de-escalation was a useful programme in septic patients – and the results support it to be. It was found that there is no difference in the length of hospital stay, and also there was significantly lower mortality in the de-escalation group when compared to the non-de-escalation group.²² This forms the evidence that is backing the implementation of de-escalation protocols in hospitals. In the NHS, the “Start Smart then Focus” strategy is being implemented to back de-escalation of therapy after reviewing the regimen at 48–72 hours.²³

Aside from data from academic studies, de-escalation as a programme ingrained into sepsis treatment is logical. We are in the

age where antibiotics cannot be used freely – resistance plagues their massive potential, and we need to implement programmes to reduce it wherever possible. Antibiotic stewardship needs to underpin every single avenue of antibiotic therapy, including sepsis treatment. Switching to a narrow spectrum antibiotic as soon as the opportunity presents itself will help to reduce the unnecessary use of broad-spectrum antibiotics, which contribute to antibiotic resistance.

Conclusion

We can see that the current evidence for the “golden hour” of sepsis treatment is underwhelming. Setting a stringent time limit of one hour may be practically unfeasible and could inadvertently lead to the overtreatment of patients who are not septic. Antibiotic resistance will only continue to increase unless reasonable, logic-based programmes are implemented to combat it, for example de-escalation programmes and accurate sepsis diagnosis which is very important.

However, this does not mean that antibiotic administration is unimportant, in fact it is the cornerstone of sepsis treatment. Instead, this highlights the importance of evidence-based and operationally feasible guidelines. Nonetheless, the principle that the “golden hour” seeks to uphold is important. Timely antibiotic administration is paramount in such a time-dependent condition like sepsis. However, to back the stringent time limit of one hour, more studies need to be conducted.

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References

1. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589-96.
2. Sepsis Alliance. What is Sepsis. <https://www.sepsis.org/sepsis-basics/what-is-sepsis/>. Accessed: 1 March 2022
3. Esposito S, De Simone G, Boccia G, De Caro F, Pagliano P. Sepsis and septic shock: New definitions, new diagnostic and therapeutic approaches. *J Glob Antimicrob Resist*. 2017;10:204-12.
4. Case-based learning: recognising sepsis. <https://pharmaceutical-journal.com/article/ld/case-based-learning-recognising-sepsis>. Accessed: 28 February 2022
5. NHS Inform. Sepsis. <https://www.nhsinform.scot/illnesses-and-conditions/blood-and-lymph/sepsis>. Accessed: 1 March 2022
6. BMJ Best Practice. Sepsis in adults. <https://bestpractice-bmj-com.plymouth.idm.oclc.org/topics/en-gb/3000098/epidemiology> Accessed: 28 February 2022
7. UK Sepsis Trust. References and Sources. <https://sepsistrust.org/about/about-sepsis/references-and-sources/>. Accessed: 25 October 2022
8. Marshall JC, Dellinger RP, Levy M. The Surviving Sepsis Campaign: a history and a perspective. *Surg Infect (Larchmt)*. 2010;11:275-81.
9. Daniels R, Nutbeam T, McNamara G, Galvin C. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. *Emerg Med J*. 2011;28:507-12.
10. van Zanten AR. The golden hour of antibiotic administration in severe sepsis: avoid a false start striving for gold*. *Crit Care Med*. 2014;42:1931-2.
11. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T*. 2015;40:277-83.
12. Garnacho-Montero J, Gutierrez-Pizarra A, Escobedo-Ortega A, Fernandez-Delgado E, Lopez-Sanchez JM. Adequate antibiotic therapy prior to ICU admission in patients with severe sepsis and septic shock reduces hospital mortality. *Crit Care*. 2015;19:302.
13. Battula V, Krupanandan RK, Nambi PS, Ramachandran B. Safety and Feasibility of Antibiotic De-escalation in Critically Ill Children With Sepsis - A Prospective Analytical Study From a Pediatric ICU. *Front Pediatr*. 2021;9:640857.

14. Allison MG, Heil EL, Hayes BD. Appropriate Antibiotic Therapy. *Emerg Med Clin North Am.* 2017;35:25-42.
15. Sepsis Alliance. Testing for Sepsis. <https://www.sepsis.org/sepsis-basics/testing-for-sepsis/>. Accessed: 28 February 2022
16. Singer M, Inada-Kim M, Shankar-Hari M. Sepsis hysteria: excess hype and unrealistic expectations. *Lancet.* 2019;394:1513-4.
17. Spiegel R, Farkas JD, Rola P, Kenny JE, Olusanya S, Marik PE, et al. The 2018 Surviving Sepsis Campaign's Treatment Bundle: When Guidelines Outpace the Evidence Supporting Their Use. *Ann Emerg Med.* 2019;73:356-8.
18. Norse AB, Guirgis F, Black LP, DeVos EL. Updates and controversies in the early management of sepsis and septic shock. *Emerg Med Pract.* 2021;23:1-24.
19. Pino E, Ramos Tuarez F, Saona J, Chen K, Ceka E, Gradeja Chavex J, et al. Misdiagnosis of Sepsis in Patients with Acutely Decompensated Heart Failure. Real World Outcomes. *Journal of Cardiac Failure.* 2019;25.
20. Sterling SA, Miller WR, Pryor J, Puskarich MA, Jones AE. The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. *Crit Care Med.* 2015;43:1907-15.
21. Martinez ML, Plata-Menchaca EP, Ruiz-Rodriguez JC, Ferrer R. An approach to antibiotic treatment in patients with sepsis. *J Thorac Dis.* 2020;12:1007-21.
22. Gutierrez-Pizarra A, Leone M, Garnacho-Montero J, Martin C, Martin-Loeches I. Collaborative approach of individual participant data of prospective studies of de-escalation in non-immunosuppressed critically ill patients with sepsis. *Expert Rev Clin Pharmacol.* 2017;10:457-65.
23. Hamilton WL, Pires SM, Lippett S, Gudka V, Cross ELA, Llewelyn MJ. The impact of diagnostic microbiology on de-escalation of antimicrobial therapy in hospitalised adults. *BMC Infect Dis.* 2020;20:102.



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Hi! I am Mehnaz and I'm a second-year medical student studying at Peninsula Medical School, Plymouth University. My interest in medicine stems from my love of interacting with people of all different backgrounds. Writing has always been a way for me to delve deeper into topics that fascinate me, such as the protocols that surround sepsis management, and I really enjoy it! My passions outside medicine are reading, art and playing the piano. I am excited to be more involved in research and academic medicine as I continue my studies!