Adequacy of Empiric Antibiotics Therapy and Its Impact on Outcomes in Adult Critically Ill Sepsis Patients: A Review

Ahmad Habeeb Hattab Dala Ali Al-Ani1,2, Noordin Othman3,4, Mohamed Azmi Hassali1, Baharudin Ibrahim5

1 Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Pulau Pinang, Malaysia
2 College of Pharmacy, Almaarefa University, Riyadh, Saudi Arabia
3 Department of Clinical and Hospital Pharmacy, College of Pharmacy, Taibah University, Al-Madinah Al-Munawarah, Saudi Arabia
4 Department of Clinical Pharmacy, Management and Science University, Selangor, Malaysia
5 Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur, Malaysia

Submitted: 26 Apr 2021
Accepted: 6 Aug 2021
Online: 28 Oct 2022

To cite this article: Al-Ani AHHDA, Othman N, Hassali MA, Ibrahim B. Adequacy of empiric antibiotics therapy and its impact on outcomes in adult critically ill sepsis patients: a review. Malays J Med Sci. 2022;29(5):17–23. https://doi.org/10.21315/mjms2022.29.5.3

To link to this article: https://doi.org/10.21315/mjms2022.29.5.3

Abstract

Sepsis is a medical emergency that involves a systemic immunological response due to an infection, resulting in the end-stage organs malfunction and death. It is associated with high mortality rate despite a better understanding of the disease pathology and the mechanism involved. This review was designed to summarise the available evidences regarding the adequacy of the empiric antimicrobial therapy (EAMT), its predictors and its impact on the outcomes in intensive care unit (ICU) sepsis patients. Providing an adequate EAMT is considered one of the cornerstones of sepsis management as it has been found to be associated with better survival and is a good predictor for shorter ICU-length-of-stay. In contrast, inadequate EAMT in sepsis patients is associated with poor clinical outcomes including increased mortality and prolonged hospital stay. Evidence from this review suggest that it is important to identify determinants of inadequate EAMT to optimise the antimicrobial therapy provided to sepsis patients. Predictors of inadequate EAMT included co-morbidities (cancer), source and type of infection, higher Acute Physiology and Chronic Health Evaluation (APACHE-II) score and long hospital stay prior to the infection. As EAMT is considered as one of the effective treatment strategies to prevent sepsis associated death, healthcare providers should ensure the adequate antimicrobial therapy is provided for sepsis patients to improve and optimise their management.

Keywords: sepsis, empiric antimicrobial therapy, mortality, predictors, determinants

Introduction

Sepsis is a systemic illness that involves the invasion of normally sterile body parts by the microbes (1). It is a medical emergency involving a systemic immunological response due to an infection, resulting in an end stage organ malfunction and death (2). Although the understanding about the sepsis disease process has been established (2), still it is associated with high mortality rate. It has been estimated that sepsis has led to 11 million deaths in 2017.
globally. Also, it is the leading cause of death in non-coronary intensive care units (ICUs) in the United States (3, 4).

Antibiotic therapy is considered as one of the effective treatment strategy in the management of sepsis patients (5). Early initiation of the adequate antibiotic therapy has been shown to be associated with lower mortality rates and better survival in bacteremia patients (5–7). This suggests that early initiation of the adequate antibiotic therapy in the moderate to severe infections is beneficial (7). Antibiotic therapy is often guided by empirical evidence particularly in the absence of information regarding causative pathogen or its sensitivity to the antibiotics. Evidently, in severe sepsis and septic shock cases, the initiation of an effective antibiotic therapy within the first hour should be the goal of the therapy (7, 8).

Providing empiric antimicrobial therapy (EAMT) is challenging as it may lead to additional complications (9). Furthermore, inadequate EAMT is considered a life-threatening issue that has often been associated with poor clinical outcomes (9). To understand this aspect more, in this article we reviewed the available literature regarding the adequacy and impact of EAMT on sepsis patients’ outcomes and provide an insight about this critical aspect of sepsis management.

**Methods**

To search for studies that described the adequacy of EAMT and its impact on the outcomes of the sepsis patients, we searched PubMed database and google scholar search engine. Terms and their combinations used for searching English-language articles included: adequate, inadequate, appropriate, adequacy, empiric antimicrobial therapy, sepsis, severe sepsis, septic shock, mortality, length of stay, outcomes, survival, ICU and intensive care unit. The inclusion criteria were studies that assessed the adequacy of EAMT and the impact of inadequate EAMT on sepsis ICU patients. We excluded studies which were published in non-English language, assessed impact of EAMT on the outcomes in non-sepsis patients or included non-adult or pediatric sepsis patients.

**Result and Discussion**

**Sepsis Associated Mortality**

Sepsis is considered as a significant public health issue affecting millions of people and represents one of the leading causes of death around the globe (10). Studies that evaluated the mortality rates due to the sepsis in several countries indicated variable results (Figure 1). In Malaysia, sepsis-associated mortality rates were found to be non-consistent. As per the study conducted by Mat Nor and Md Ralib (11), sepsis-associated mortality was 40.0%; on the other hand Al-sunaidar et al. (9) reported sepsis-associated mortality to be almost double (84.6%). Sepsis-associated mortality rates reported from France, Brazil, Spain, Croatia, Tunisia, the United States, Norway and Japan were found to be 59.0%, 56.3%, 48.3%, 43.9%, 41.7%, 41.2%, 25.0% and 21.8%, respectively (12–19). The lowest hospital mortality in sepsis patients was identified in Austria (11.4%) (20). Mortality in sepsis patients can be associated with several causes which are unlikely to be preventable including cancer diseases, heart failure and other co-morbidities (21). Mortality rates in some studies were found to be higher (27.1%–72.1%) in septic shock patients when compared with severe sepsis patients (15.7%–33.7%) and sepsis (17.0%) (12, 18). These findings may partly be explained by the inadequacy of EAMT in the sepsis patients which could be prevented by providing adequate EAMT (21).

![Figure 1. Mortality rates in sepsis patients](image-url)
Definition of Empiric Antimicrobial Therapy Adequacy

EAMT refers to the initial antibiotic regimen that is started within 24 h of the admission of the patient (22). There are several studies that have been conducted worldwide to measure the adequacy of the EAMT in the sepsis patients. However, the definition of the EAMT adequacy was inconsistent in these studies (Table 1). For instance, Fitousis et al. (23) have stratified it into appropriateness and accuracy. In this definition, appropriateness referred to an empiric antimicrobial regimen that would cover all suspected organisms based on the suspected site of infection, regardless of the susceptibility data. Accuracy was defined as an empiric antimicrobial regimen that was susceptible to the isolated microorganisms. Most studies defined adequate EAMT as ‘causative microorganism being sensitive to at least one drug administered within 24 h of the culture collection’ or ‘providing an antimicrobial agent(s) in accordance with published guidelines’ or ‘improvement in symptoms’ (Table 1).

| Study                          | According to culture and sensitivity tests | Other                                      |
|-------------------------------|-------------------------------------------|--------------------------------------------|
| Trifi et al. (19)             | √                                         | Improvement in symptoms                    |
| Oshima et al. (18)            | √                                         | Improvement in symptoms                    |
| Moraes et al. (16)            | √                                         | According to the local guidelines          |
| Yokota et al. (24)            | √                                         | -                                          |
| Ratzinger et al. (20)         | √                                         | -                                          |
| Nygård et al. (17)            | -                                         | According to the local guidelines          |
| Degoricija et al. (12)        | √                                         | According to the local guidelines          |
| Micek et al. (15)             | √                                         | -                                          |
| Kanji and Dumaresque (25)     | √                                         | According to the local guidelines          |
| Al-Sunaidar et al. (9)        | √                                         | According to the local guidelines          |
| Garnacho-Montero et al. (13)  | √                                         | According to the local guidelines          |
| Garnacho-Montero et al. (26)  | √                                         | According to the local guidelines          |
| Garnacho-Montero et al. (5)   | -                                         | Two antipseudomonal agents if Pseudomonas aeruginosa was isolated |

Adequacy of the Empirical Antimicrobial Therapy in Sepsis Patients in the ICU Settings

In the management of the sepsis, therapies are provided to manage the basic elements of the sepsis including infection, organ dysfunction and host response (27). According to the latest surviving sepsis campaign’s international guidelines for the management of sepsis and septic shock, intravenous antimicrobial agents should be started as soon as possible after the recognition of sepsis and it should be within one hour for both sepsis and septic shock (28).

Adequacy of the EAMT has been described by several studies worldwide. Some of these studies have demonstrated that EAMT was provided in an adequate manner in sepsis patients in the ICU settings. These studies showed that adequate EAMT were noted in 90.0%, 82.0%, 81.4% and 89.0% of sepsis patients admitted to the ICU in Canada (25), United States (23), Norway (17) and France (14), respectively. In contrast, lower percentage of adequate EAMT provided to sepsis patients in the ICU setting was seen in many countries. In Tunisia, only 52.0% of the patients were adequately treated with EAMT (19), 27.1% in Malaysia (9) and 58.9% in Austria (20). In addition, we found that there is a lack of studies which described the adequacy of EAMT provided to sepsis patients in the Middle East countries. The percentages of the adequate EAMT provided to sepsis patients reported by the studies around the world have been summarised in Table 2.
Table 2. Percentage of adequate EAMT provided to sepsis patients

| Percentage of adequate EAMT (%) | Country     | Reference |
|--------------------------------|-------------|-----------|
| 52.0                           | Tunisia     | (19)      |
| 77.3                           | Japan       | (18)      |
| 89.0                           | Brazil      | (16)      |
| 58.9                           | Austria     | (20)      |
| 81.0                           | Norway      | (17)      |
| 82.0                           | US          | (23)      |
| 68.7                           | US          | (15)      |
| 60.8 (survivors)               | Croatia     | (12)      |
| 30.4 (non-survivors)           |             |           |
| 91.0                           | Canada      | (25)      |
| 28.1                           | Malaysia    | (9)       |
| 69.6 (prior ICU admission)     | Spain       | (13)      |
| 30.4 (after ICU admission)     |             |           |
| 91.0                           | Spain       | (26)      |
| 83.0                           | Spain       | (5)       |
| 89.0                           | France      | (14)      |

Impact of the Adequacy of Empirical Antimicrobial Therapy in Sepsis Patients on Patient’s Outcomes

Providing an adequate and appropriate EAMT is essential and critical for the treatment of sepsis (29). Providing adequate EAMT to sepsis patients was found to be associated with reduced mortality and increased survival i.e. protective factor (9, 12, 13, 24). However, the impact of the EAMT adequacy on the mortality outcome in sepsis patient seems to be variable in the literature. Several studies have demonstrated a significant association of inadequate EAMT with increased mortality in ICU sepsis patients (9, 19, 20, 26). Moreover, inadequate EAMT was identified as an independent predictor of mortality (15, 17). On the contrary, even though mortality rates were found to be higher in patients who received inadequate EAMT, a significant association between the two was not established in other studies (14, 18, 23).

With regards to the association of EAMT adequacy with the length of hospital stay, most of the studies focused on the mortality outcome. Al-Sunaidar et al. (9) found that providing an appropriate EAMT to critically ill sepsis patients was considered as a good predictor for the decreased ICU-length-of-stay. On the other hand, inadequate EAMT was significantly associated with longer length of stay in both ICU and the hospital (26).

Figure 2. Impact of EAMT adequacy on clinical outcomes of sepsis patients
Determinants of the Adequacy of Empirical Antimicrobial Therapy in Sepsis Patients in the ICU Settings

As discussed in the above sections, several studies have indicated inadequate antimicrobial therapy to be associated with increased mortality in critically ill sepsis patients (9, 19, 20, 26). Therefore, it was important to decipher the risk factors associated with inadequate EAMT. In this context, five studies were found which identified the determinants of the adequacy of the EAMT in sepsis patients (Table 3). Garancho-Montero et al. (5) have found that the presence of fungal infection and previous exposure to the antibiotics as a potential risk factors for inadequate EAMT. This might be due to the fact that the utilization of the antifungal agents is not commonly practiced during admissions to the ICU (5, 30). Also, the previous exposure to the antimicrobials is a risk factor for developing antimicrobial resistance which consequently might lead to the inadequate EAMT (30, 31). According to a matched cohort study, the rate of the nosocomial infection was significantly higher (16.1%) in patients who received inadequate EAMT in comparison to the patients treated adequately with EAMT (3.4%) (26). Besides, cancer patients, poly-microbial infections and higher Acute Physiology and Chronic Health Evaluation (APACHII) score were also identified as risk factors of the inadequate EAMT (5, 19, 24, 26, 32).

Table 3. Factors associated with inadequate EAMT provided to sepsis patients

| Factors associated with inadequate EAMT | Reference |
|----------------------------------------|-----------|
| Cancer patients                        | (32)      |
| Nosocomial infections                  | (26)      |
| Previous exposure to antimicrobials    | (5)       |
| Fungal infection                       | (5)       |
| Poly-microbial infection               | (24)      |
| APACHII score                          | (24)      |
| Length of hospital stay prior to infection | (19)    |

Conclusion

Several studies have demonstrated the negative impact of the inadequate EAMT on the outcomes of sepsis patients. According to the retrospective and prospective studies, inadequate EAMT were significantly associated with the poor clinical outcomes in these patients including increased mortality and longer length of hospital stay. As EAMT is considered as one of the preventable causes of sepsis associated death, healthcare providers should ensure that adequate antimicrobial therapy is provided to the patients to improve and optimise the management of sepsis patients. Moreover, hospitals may implement periodically updated empirical antibiotic regimens for the specific sites of infection based on the local microbiology and resistance patterns and according to established practice guidelines to optimise the empirical antimicrobial prescription in sepsis patients.

Acknowledgements

None.

Conflict of Interests

None.

Funds

None.

Authors’ Contributions

Conception and design: AHHDAAA, NO
Analysis and interpretation of the data: AHHDAAA
Drafting of the article: AHHDAAA, NO
Critical revision of the article for important intellectual content: NO, MAH, BI
Final approval of the article: AHHDAAA, NO, MAH, BI
Administrative, technical or logistic support: MAH, BI

Correspondence

Ahmad Habeeb Hattab Dala Ali Al-Ani
PhD Candidate (Universiti Sains Malaysia), M ClinPharm (Universiti Teknologi MARA), ABPS (Arab Board for Pharmacy Specialties Part 1), B Pharm (The National University Sudan) Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 USM, Pulau Pinang, Malaysia.
Tel: +60 197054010
E-mail: alani.a.dallaali@gmail.com
References

1. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. BMJ. 2007;335(7625):879–883. https://doi.org/10.1136/bmj.39346.495880.AE

2. Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: the evolution in definition, pathophysiology, and management. SAGE Open Med. 2019;7:2050312119835043. https://doi.org/10.1177/2050312119835043

3. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease study. Lancet. 2020;395(10219):200–211. https://doi.org/10.1016/S0140-6736(19)32989-7

4. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5(1):4–11. https://doi.org/10.4161/viru.27372

5. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med. 2003;31(12):2742–2751. https://doi.org/10.1097/01.CCM.0000098031.24329.10

6. Cisneros JM, Reyes MJ, Pachón J, Becerril B, Caballero FJ, García Garmendia JL, et al. Bacteremia due to Acinetobacter baumannii: epidemiology, clinical findings, and prognostic features. Clin Infect Dis. 1996;22(6):1026–1032. https://doi.org/10.1093/clinids/22.6.1026

7. Fraser A, Paul M, Almanasreh N, Tacconelli E, Frank U, Cauda R, et al. Benefit of appropriate empirical antibiotic treatment: thirty-day mortality and duration of hospital stay. Am J Med. 2006;119(11):970–976. https://doi.org/10.1016/j.amjmed.2006.03.034

8. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39(2):165–228. https://doi.org/10.1007/s00134-012-2769-8

9. Al-Sunaidar KA, Abd Aziz NP, Hassan YP. Appropriateness of empirical antibiotics: risk factors of adult patients with sepsis in the ICU. Int J Clin Pharm. 2020;42:527–538. https://doi.org/10.1007/s11096-020-10054-4

10. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–810. https://doi.org/10.1001/jama.2016.0287

11. Mat Nor MB, Md Rabli A. Procalcitonin clearance for early prediction of survival in critically ill patients with severe sepsis. Crit Care Res Pract. 2014;2014:1–7. https://doi.org/10.1155/2014/819034

12. Degoricija V, Sharma M, Legac A, Gradišer M, Šefer S, Vučičević Z. Survival analysis of 314 episodes of sepsis in medical intensive care unit in university hospital: Impact of intensive care unit performance and antimicrobial therapy. Croat Med J. 2006;47(3):385–397.

13. Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoressa-Ortega A, Fernández-Delgado E, López-Sánchez JM. Adequate antibiotic therapy prior to ICU admission in patients with severe sepsis and septic shock reduces hospital mortality. Crit Care. 2015;19(1):302. https://doi.org/10.1186/s13054-015-1000-z

14. Leone M, Bourgoin A, Cambon S, Dubuc M, Albanëse J, Martin C. Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. Crit Care Med. 2003;31(2):462–467. https://doi.org/10.1097/01.CCM.0000050298.39549.4A

15. Micek ST, Welch EC, Khan J, Pervez M, Doherty JA, Reichley RM, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: a retrospective analysis. Antimicrob Agents Chemother. 2010;54(5):1742–1748. https://doi.org/10.1128/AAC.01365-09

16. Moraes RB, Guillén JAV, Zabaleta WJC, Borges FK. De-escalation, adequacy of antibiotic therapy and culture positivity in septic patients: an observational study. Rev Bras Ter Intensiva. 2016;28(3):315–322. https://doi.org/10.5935/0103-507X.20160044
Review Article | EAMT adequacy and its impact on sepsis patients

17. Nygård ST, Langeland N, Flaatten HK, Fanebust R, Haugen O, Skrede S. Aetiology, antimicrobial therapy and outcome of patients with community acquired severe sepsis: a prospective study in a Norwegian university hospital. *BMC Infect Dis*. 2014;14(1):121. https://doi.org/10.1186/1471-2334-14-121

18. Oshima T, Kodama Y, Takahashi W, Hayashi Y, Iwase S, Kurita T, et al. Empiric antibiotic therapy for severe sepsis and septic shock. *Surg Infect*. 2016;17(2):210–216. https://doi.org/10.1089/sur.2014.096

19. Trifi A, Abbessati S, Abdennabi C, Daly F, Nasiri R, Touil Y, et al. Appropriateness of empiric antimicrobial therapy with imipenem/cilistin in severe septic patients: observational cohort study. *Ann Clin Microbiol Antimicrob*. 2018;17(1):39. https://doi.org/10.1086/s12941-018-0292-7

20. Ratzinger F, Eichbichler K, Schwardt M, Tsirkinidou I, Mitteregger D, Haslacher H, et al. Sepsis in standard care: patients’ characteristics, effectiveness of antimicrobial therapy and patient outcome—a cohort study. *Infection*. 2015;43(3):345–352. https://doi.org/10.1007/s15010-015-0771-0

21. Rhee C, Jones TM, Hamad Y, Pande A, Varon J, O’Brien C, et al. Prevalence, underlying causes, and preventability of sepsis-associated mortality in US acute care hospitals. *JAMA Netw Open*. 2019;2(1):e187571. https://doi.org/10.1001/jamanetworkopen.2018.7571

22. Mettler J, Simmock M, Sendi P, Widmer AF, Bingisser R, Battegay M, et al. Empirical use of antibiotics and adjustment of empirical antibiotic therapies in a university hospital: a prospective observational study. *BMC Infect Dis*. 2007;7(1):21. https://doi.org/10.1186/1471-2334-7-21

23. Fitousis K, Moore LJ, Hall J, Moore FA, Pass S. Evaluation of empiric antibiotic use in surgical sepsis. *Am J Surg*. 2010;200(6):776–782. https://doi.org/10.1016/j.amjsurg.2010.09.001

24. Yokota PK, Marra AR, Martino MD, Victor ES, Durão MS, Edmond MB, et al. Impact of appropriate antimicrobial therapy for patients with severe sepsis and septic shock—a quality improvement study. *PloS ONE*. 2014;9(11):e104475. https://doi.org/10.1371/journal.pone.0104475

25. Kanji Z, Dumaresque C. Time to effective antibiotic administration in adult patients with septic shock: a descriptive analysis. *Intensive Crit Care Nurs*. 2012;28(3):288–293. https://doi.org/10.1016/j.iccn.2012.01.009

26. Garnacho-Montero J, Ortiz-Leyba C, Herrera-Melero I, Aldobo-Pallas T, Cayuela-Dominguez A, Marquez-Vacaro JA, et al. Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to the ICU with sepsis: a matched cohort study. *J Antimicrob Chemother*. 2008;61(2):436–441. https://doi.org/10.1093/jac/dkm460

27. Bullock B, Benham MD. *Bacterial sepsis*. Treasure Island, FL: StatPearls Publishing; 2019. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537054

28. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304–377. https://doi.org/10.1007/s00134-017-4683-6

29. Liang SY, Kumar A. Empiric antimicrobial therapy in severe sepsis and septic shock: optimizing pathogen clearance. *Curr Infect Dis Rep*. 2015;17(7):36. https://doi.org/10.1007/s11908-015-0493-6

30. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*. 2000;118(1):146–155. https://doi.org/10.1378/chest.118.1.146

31. Baran G, Erbay A, Bodur H, Öngürü P, Akneci E, Balaban N, et al. Risk factors for nosocomial imipenem-resistant *Acinetobacter baumannii* infections. *Int J Infect Dis*. 2008;12(1):16–21. https://doi.org/10.1016/j.ijid.2007.03.005

32. Rodriguez-Baño J, Millán AB, Domínguez MA, Borraz C, González MP, Almirante B, et al. Impact of inappropriate empirical therapy for sepsis due to health care-associated methicillin-resistant *Staphylococcus aureus*. *J Infect*. 2009;58(2):131–137. https://doi.org/10.1016/j.jinf.2008.11.003