ORIGINAL ARTICLE

Appropriateness of Antibiotics in Sepsis Patients at a Tertiary Referral ICU

Raghavendra Deshpande[1], Pradeep Rangappa[2], Ipe Jacob[3], Karthik Rao[4]

Received on: 02 March 2023; *Accepted on:* 25 April 2023; *Published on:* 03 May 2023

Abstract

Background: Sepsis is a life-threatening condition that requires the early use of appropriate empirical antibiotics. However, sepsis outcomes are often complicated by the increased incidence of antibiotic resistance, which is attributed to the use of inappropriate antibiotics. Antibiotics are termed inappropriate when the suspected pathogen is resistant to the drug administered or when there is a delay in administration.

Materials and methods: This is a prospective observational study that aims to compare the impact of appropriate antimicrobial therapy (AAT) and inappropriate antimicrobial therapy (IAAT) on the outcome of sepsis or septic shock cases in the intensive care unit (ICU). Primary outcome measures included ICU mortality and 28-day mortality, and secondary outcome measures, vasopressor free days (VFD), hemodialysis free days (HFD), ventilator free days, ICU length of stay (LOS), and oxygen requirement days.

Results: Out of 100 patients included in the study, 49 patients received AAT and had a lower ICU mortality compared to the 51 patients who received IAAT (10 vs 31%, $p = 0.009$) and also 28-day mortality (14 vs 37%, $p = 0.009$). ICU LOS was also shorter in those receiving AAT.

Conclusion: The use of appropriate and timely antibiotics can lead to decreased mortality and morbidity in patients with sepsis. This requires an understanding of the prevailing local microbiological flora and the local antibiograms and the use of standardized protocols.

Keywords: Empirical antibiotic, ICU mortality, 28-day mortality, ICU length of stay, Antibiotic resistance.

Journal of Acute Care (2022): 10.5005/jp-journals-10089-0057

Introduction

Sepsis is a medical emergency that affects millions of people worldwide, representing one of the leading causes of death. It is a life-threatening condition causing organ failure owing to a dysregulated host response to infection.[1] Septic shock is a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase mortality. The 2021 Surviving Sepsis Campaign guidelines strongly recommend that the administration of intravenous (IV) broad-spectrum antibiotics should be initiated as soon as possible, preferably within an hour of sepsis recognition.[1]

Acquired nosocomial infections in ICUs have increased tremendously in recent years. The EPIC II study in 2007 reported a prevalence of 51%, which is much higher than the previous EPIC I study of 20% in 1995.[2] One of the main causes is the misuse of antibiotics and an increased incidence of antibiotic resistance. IAAT, in general, refers to the use of an antimicrobial agent to which the pathogen is resistant at the time of administration, given after a delay, or used to treat noninfectious conditions, contaminants, etc.[3,4] This accounts for approximately 30% of antibiotic administered in the ICU. IAAT is directly associated with increased mortality in patients with sepsis or in septic shock. Another dreaded side-effect is that of antibiotic resistance, which is no longer a topic discussed only among the medical fraternity but is part of public awareness.

Materials and Methods

Study Design and Aim

This is a prospective, observational study conducted at a tertiary care ICU which aims to compare the impact of AAT and IAAT on the outcome of patients admitted with a diagnosis of sepsis or septic shock. Appropriate antibiotics were defined as an agent to which the pathogen was sensitive within the stipulated point of time, with the correct dosage and timing of administration <3 hours in suspected sepsis and <1 hour in septic shock. It was approved by the Institutional Ethics Committee (Reg No ECR/105/Inst/KA/2013/RR19 - dated 04/07/2019).

[1–4]Department of Critical Care, Manipal Hospital Yeshwantpur, Bangalore, Karnataka, India

Corresponding Author: Ipe Jacob, Department of Critical Care, Manipal Hospital Yeshwantpur, Bangalore, Karnataka, India, Phone: +91 809844208268, e-mail: ipe.jacob@gmail.com

How to cite this article: Deshpande R, Rangappa P, Jacob I, *et al.* Appropriateness of Antibiotics in Sepsis Patients at a Tertiary Referral ICU. J Acute Care 2022;1(3):124–127.

Source of support: Nil

Conflict of interest: None

Outcome Measures

The primary outcome measures were ICU mortality and 28-day mortality. Secondary outcome measures included VFD, HFD, mechanical ventilator free days, ICU-LOS, and oxygen requirement days.

Study Population

The study included all adult ICU patients admitted with a provisional diagnosis of sepsis or septic shock over a period of 12 months between January 2019 to December 2019 and with an ICU LOS of at least 2 days. Criteria for exclusion were pregnancy, immunocompromised state, and patients on end-of-life care. Patients were started on empirical antibiotics as per the local antibiogram within 1 hour of admission and after obtaining culture samples. All patients received other standard care of treatment, including fluid administration (20–30 mL/kg) for septic shock, subcutaneous enoxaparin 40 mg once daily or unfractionated heparin 5000 u twice daily for deep vein thromboprophylaxis, IV ranitidine 50 mg thrice daily and paracetamol 1 gm IV for fever.

Statistical Analysis

Keeping the power of the study at 80%, with a 5% level of significance, the sample size required was calculated at 73 patients. A binary logistic regression technique was used to measure the risk in terms of odds ratio (OR). The Chi-squared test was used to measure the association between the study variables and outcome mortality. Student *t*-test was used to test the significance between the mean score in two independent variables.

Data Collection

Data were collected from patient charts and electronic medical records, including demographics, vital signs, laboratory investigations, culture reports, the number of days on mechanical ventilation, vasopressor support, supplemental oxygen, and hemodialysis. The antibiotic given and its timing was noted and correlated with the culture and sensitivity reports. Data were analyzed using Predictive Analytics SoftWare Statistics for Windows, Version 18.0, IBM, Chicago, Illinois, United States of America, released in 2009.

Results

Out of 149 patients admitted with sepsis over the study period, 100 patients satisfied the inclusion and exclusion criteria. Of these, 49 patients were given appropriate antibiotics and formed the AAT group. The remaining 51 patients formed the IAAT group. Demographic details, including age, sex ratio, and acute physiology and chronic health evaluation (APACHE II) score, are summarized in Table 1. Mean age (65.81 vs 64.75 years, $p = 0.727$) and APACHE II scores (21 vs 20, $p = 0.319$) were equivalent between AAT and IAAT groups. Males accounted for 57% of the patients in both AAT and IAAT groups. Of the 51 IAAT patients, 30% had multi-drug resistant organisms, 40% had viral sepsis, 20% showed sterile culture, and in 10%, there was a delay in starting the antibiotic. Urosepsis (41%) was the most common cause of sepsis or septic shock, followed by bloodstream infections (38%). The most common isolate was *Escherichia coli* in both urine and blood cultures.

Both primary outcome measures were improved in the AAT group, as shown in Table 2. ICU mortality rate was 10.2% in the AAT and 31.4% in the IAAT group ($p = 0.009$). The 28-day mortality rate was 14.3% in the AAT group and 37.3% in the IAAT group ($p = 0.009$). Logistic regression analysis, as shown in Table 3, shows improved ICU mortality [OR = 4.023; 95% confidence interval (CI) of 1.34–12.06] and 28-day mortality (OR = 3.562; 95% CI of 1.336–9.502).

The secondary outcomes are listed in Table 4. There was a difference in ICU LOS between AAT and IAAT groups [6.57 days, standard deviation (SD) 4.58 vs 9.72 days, SD 7.56, $p = 0.014$] and in oxygen requirement days (6.38 days, SD 4.78 vs 10.09 days, SD 7.94; $p = 0.006$). There was no difference in VFD, HFD, and ventilator free days.

Discussion

The present study examines the impact of the appropriateness of antibiotics on adult patients admitted with sepsis. It showed that about half the patients admitted to the ICU with suspected sepsis received inappropriate empirical antibiotics. This was associated with a higher ICU mortality as compared to those who received appropriate antibiotics (37 vs 10%) and also 28-day mortality (37 vs 14%). Inappropriate antibiotics were independently associated with significant patients' odds for ICU mortality (OR = 4.023) and 28-day mortality (OR = 3.23). The two groups had equivalent APACHE II scores.

A meta-analysis by Marquet et al., which included 27 trials and a total of 13,014 patients, showed that the percentage of inappropriate empiric antibiotic use ranged from 14.1 to 78.9% (median of 49%).[5] This wide range can be explained by heterogeneity in definitions, settings, illnesses, and infectious organisms. Quoting an average value for this incidence can be misleading since there is considerable heterogeneity. However, 13 of 27 studies in the meta-analysis reported an incidence of inappropriate antibiotics of >50%. Both 28-day and 60-day mortality were higher in patients receiving inappropriate antibiotics ($p < 0.02$). In a prospective study, Kang et al. noted a 30-day mortality rate of 33.2% in patients with sepsis caused by gram-negative bacilli who received inappropriate antibiotics.[6]

In the present study, 81% of the patients received a single antibiotic as the initial empirical therapy, while the remaining received combination of antibiotics. The most common single antibiotic used was IV piperacillin-tazobactam 4 gm every 6 hours, followed by IV ertapenem 1 gm once daily. Urosepsis was the commonest infection, accounting for 41% of the cases of sepsis or septic shock, followed by bloodstream infections (38%). *Escherichia coli* was the most commonly isolated organism in both blood and urine cultures. Among the reasons for an antibiotic being classified as inappropriate, the most common was viral sepsis, seen in 19 patients (around 37%). Multi-drug resistance was seen in 15 out of 51 patients (29%). Another 20% of patients had sterile cultures, and in 10% of the patients, antibiotics were started after a delay.

While it is difficult to accurately determine the cause of sepsis based on history, clinical findings, and initial investigations such as leukocyte count, compounded by the long waiting time for culture results, clinicians may be compelled to start empirical antibiotics given the high mortality associated with untreated or delayed treatment of sepsis. The results of this study bring out the need to depend on markers such as procalcitonin and advanced tests such as molecular diagnostics. Such tests with a rapid turn-around time of 20 minutes–2 hours may help to avoid the initiation of antibiotics when unnecessary.[7]

Table 1: Demographic data and APACHE II scores in AAT vs IAAT groups

Age	*AAT*	*IAAT*	*p-value*
Mean Age in years	65.81	64.75	0.727
Sex	Males 57%	Males 57%	
APACHE II score	21	20	0.319

APACHE, acute physiology and chronic health evaluation

Table 2: Outcomes in appropriate and inappropriate antibiotic therapy groups

	AAT (in %)	*IAAT (in %)*	*p-value*
ICU mortality	10.20%	31.40%	0.009*
28-day mortality	14.3	37.3	0.009

AAT, appropriate antimicrobial therapy; IAAT, inappropriate antimicrobial therapy

Table 3: Logistic regression analysis of primary outcome measures

Logistic regression	*OR*	*95% CI of the difference*	*p-value*
ICU Mortality	4.023	1.342, 12.06	0.013
28-d Mortality	3.562	1.336, 9.502	0.011

Table 4: Secondary outcome measures in AAT vs IAAT groups

	AAT	*IAAT*	*p-value*
VFD (mean, SD)	6.02, 4.30	6.88, 5.91	0.408
HD free days (mean, SD)	7.14, 5.32	8.11, 4.83	0.340
Ventilator free days (mean, SD)	8.42, 6.81	8.23, 4.63	0.868
ICU LOS (mean, SD)	6.57, 4.58	9.72, 7.56	0.014
Oxygen requirement days (mean, SD)	6.38, 4.78	10.09, 7.94	0.006

LOS, length of stay; SD, standard deviation

Appropriate antibiotics are associated with a quicker recovery, as shown by the shorter duration of stay in the ICU (about 7 days vs 10 days in the IAAT group. This, in turn, reduces the possibility of an inflammatory cascade, release of toxins by the pathogen, reducing the possibility of organ failure. A similar outcome was noted in a retrospective cohort trial of 760 subjects with sepsis caused by gram-negative pathogens by Shorr et al.[8] The median ICU LOS in patients receiving IAAT was 11 vs 9 days in those on AAT. Again, in a prospective study that included 192 patients admitted to ICU with pneumonia, patients on IAAT had longer ICU LOS vs those on AAT (7 vs 4 days, $p = 0.017$).[9]

In this study, patients who received appropriate antibiotics also required fewer days on supplemental oxygen (6 days) as compared to those who received inappropriate antibiotics (10 days). Oxygen supplementation was titrated to maintain oxygen saturation between 92 and 96% in all patients. [10–13] Apart from early initiation of fluid resuscitation, vasopressor supports maintaining mean arterial pressure >65 mm Hg, optimizing cardiac preload, afterload, and myocardial contractility; the use of early and appropriate empirical antibiotics is also recommended as a measure to reduce the oxygen requirement.[14]

The mean VFD did not differ between AAT and IAAT groups (7 vs 6 days) in this study. This could be attributed to many confounding factors like persistent inflammatory cascades, immunosuppression, catabolism, and postsepsis syndrome.[15–17] Similarly, there was no difference between AAT patients and IAAT patients on ventilator free days (about 8 days in both groups) or HFD (7 vs 8 days). A prospective trial[17] studying the use of antibiotics in patients receiving hemodialysis concluded that the use of inappropriate antibiotics increased the need for renal replacement therapy.

Administering inappropriate antibiotics not only increases the mortality rate but also increases the economic burden in terms of prolonged hospital stay, laboratory costs, and infection control measures.[18] There is also a need to develop newer antibiotics due to antimicrobial resistance that arises from increased inappropriate antibiotic usage. Whereas mortality at 6 months remains high for septic shock (60%) and severe sepsis (36%), the sepsis-related hospital has increased from 811,644 to 1,136,889 from 2012 to 2018, with an increased economic burden from $27.7 to $41.5 billion.[19]

Conclusion

Inappropriate antibiotic therapy increases both morbidity and mortality. Appropriate antibiotic therapy decreases ICU stay and thereby decreases complications associated with prolonged stay, reducing the financial burden and stress on patients. Relying on sepsis markers and molecular diagnostics may help to ensure the appropriateness of empirical antibiotic therapy and timely administration.

References

1. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47(11):1181–1247. DOI: 10.1007/s00134-021-06506-y
2. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) study. EPIC International Advisory Committee. JAMA 1995;274(8):639–644.
3. Davey PG, Marwick C. Appropriate vs. inappropriate antimicrobial therapy. Clin Microbiol Infect 2008;14(Suppl 3):15–21. DOI: 10.1111/j.1469-0691.2008.01959.x
4. Brusselaers N, Labeau S, Vogelaers D, et al. Value of lower respiratory tract surveillance cultures to predict bacterial pathogens in ventilator-associated pneumonia: systematic review and diagnostic test accuracy meta-analysis. Intensive Care Med 2013;39(3):365–375. DOI: 10.1007/s00134-012-2759-x
5. Marquet K, Liesenborgs A, Bergs J, et al. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. Crit Care 2015;19(1):63. DOI: 10.1186/s13054-015-0795-y
6. Kang CI, Kim SH, Park WB, et al. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Antimicrob Agents Chemother 2005;49(2):760–766. DOI: 10.1128/AAC.49.2.760-766.2005

7. Sinha M, Jupe J, Mack H, et al. Emerging technologies for molecular diagnosis of sepsis. Clin Microbiol Rev 2018;31(2):e00089-17. DOI: 10.1128/CMR.00089-17
8. Shorr AF, Micek ST, Welch EC, et al. Inappropriate antibiotic therapy in Gram-negative sepsis increases hospital length of stay. Crit Care Med 2011;39(1):46–51. DOI: 10.1097/CCM.0b013e3181fa41a7
9. Kioka MJ, DiGiovine B, Rezik M, et al. Anaerobic antibiotic usage for pneumonia in the medical intensive care unit. Respirology 2017;22(8):1656–1661. DOI: 10.1111/resp.13111
10. Lellouche F, Simon M, L'Her E. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med 2018;378(2):201. DOI: 10.1056/NEJMc1714937
11. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and metaanalysis. Lancet 2018;391(10131): 1693–1705. DOI: 10.1016/S0140-6736(18)30479-3
12. Mackle D, Bellomo R, Bailey M, et al. Conservative oxygen therapy during mechanical ventilation in the ICU. N Engl J Med 2020;382(11):989–998. DOI: 10.1056/NEJMoa1903297
13. O'Driscoll BR, Howard LS, Earis J, et al. British thoracic society guideline for oxygen use in adults in healthcare and emergency settings. BMJ Open Respir Res 2017;4(1):e000170. DOI: 10.1136/bmjresp-2016-000170
14. Otero RM, Nguyen HB, Huang DT, et al. Early goal-directed therapy in severe sepsis and septic shock revisited: concepts, controversies, and contemporary findings. Chest 2006;130(5):1579–1595. DOI: 10.1378/chest.130.5.1579
15. Mira JC, Gentile LF, Mathias BJ, et al. Sepsis pathophysiology, chronic critical illness and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med 2017;45(2):253–262. DOI: 10.1097/CCM.0000000000002074
16. Mostel Z, Perl A, Marck M, et al. Post-sepsis syndrome–an evolving entity that afflicts survivors of sepsis. Mol Med 2020;26(1):6. DOI: 10.1186/s10020-019-0132-z
17. Hui K, Nalder M, Buising K, et al. Patterns of use and appropriateness of antibiotics prescribed to patients receiving haemodialysis: an observational study. BMC Nephrol 2017;18(1):156. DOI: 10.1186/s12882-017-0575-9
18. McGowan JE Jr. Economic impact of antimicrobial resistance. Emerg Infect Dis 2001;7(2):286–292. DOI: 10.3201/eid0702.010228
19. Buchman TG, Simpson SQ, Sciarretta KL, et al. Sepsis among medicare beneficiaries: 1. The burdens of sepsis, 2012–2018. Crit Care Med 2020;48(3):276–288. DOI: 10.1097/CCM.0000000000004224