Original research article

Effectiveness of Empirical Antimicrobial Therapy on Clinical Outcome in Adult Critical Care Patients with Sepsis

Amita Dabhi[1], Chirag Modi[2], Rachit Patel[3]

[1]Post graduate student, Department of Microbiology, Pramukhswami Medical College, Bhaikaka University, Karamsad- 388325 Dist-Anand, Gujarat, India

E-mail: amitadabhi113@gmail.com

[2]Professor, Department of Microbiology, Pramukhswami Medical College, Bhaikaka University, Karamsad- 388325 Dist-Anand, Gujarat, India

E-mail: drchiragmodi812901@gmail.com

[3]Consultant intensivist, Department of Critical care, Pramukhswami Medical College, Bhaikaka University, Karamsad- 388325 Dist-Anand, Gujarat, India

E-mail: rachitjpatel@yahoo.in

Corresponding Author: Dr. Amita Dabhi

ABSTRACT

Context: Sepsis is one of the leading causes of death in hospital settings. Timely administration of rational and effective antimicrobial therapy, as per hospital's antibiotic policy, is one of the components of antimicrobial stewardship program. In absence of definitive pathogen identification and susceptibility pattern, initial antibiotic regimen is selected which is defined as empirical antibiotic therapy. Although an empirical antimicrobial policy is in place at our institute, it has not been evaluated since its inception for its effectiveness.

Aims: To assess the adherence to the empirical antimicrobial policy for sepsis and to evaluate its effectiveness on clinical outcome of sepsis in adult critical care patients.

Setting and study design: A prospective, cross-sectional study was conducted in adult non covid critical care units of Shree Krishna Hospital.

Methodology: Following approval from Institutional Ethics Committee, prospective cross-sectional study was conducted from 1st August-2021 to 31st July-2022 at non-covid intensive care units. The adherence to the empirical antibiotic policy was calculated as percentage of patients with sepsis in whom antimicrobial agent was started as per the policy. The effectiveness of the antimicrobial policy was assessed on the basis of the improvement in the clinical and laboratory parameters as well as Sequential organ failure assessment (SOFA) score of the patient over a period of five days.

Statistical analysis: Microsoft Excel 2019, Version 2209 was used for data entry and data analysis. Proportions were calculated using descriptive analysis. Data was analysed using Chi-square calculation. Significance was considered at P-value <0.05.

Results: The adherence to the antimicrobial policy in sepsis was 59.80%, (n = 61 out of 102) whereas adherence to initiation of antimicrobial agent within one hour of diagnosis of clinical sepsis was 96.07% (n =98 out of 102). The antimicrobial agent started as per antibiotic policy was susceptible in culture report in 55.31% (n = 26 out of 47) of patients. Effectiveness of empirical antimicrobial policy in patients with sepsis in adult critical care units based on improvement of SOFA score after five days of diagnosis of clinical sepsis was 51.06%, (n=24 out of 47). There was no significant correlation (P ≥0.05) found between age groups,

gender, risk stratification categories, type of blood stream infections and type of organisms isolated, i.e., Gram negative and Gram positive with regards to effectiveness of empirical antimicrobial policy. There was no significant difference noted between improvement in SOFA score of the patients in whom antimicrobial agent was started as per policy and in whom the antimicrobial agent was not started as per policy (P = 0.72).
Conclusion: The adherence to antimicrobial policy for sepsis was low and further studies to evaluate the reasons for low compliance need to be conducted. Although the effectiveness was not significantly different when the antimicrobial agent was started as per policy compared to when it was not started as per policy, we still recommend using antimicrobial agent as per policy in order to avoid non uniformity in prescriptions and development of antimicrobial resistance.
Key-words: Antimicrobial policy, Antimicrobial stewardship, Antimicrobial resistance, SOFA Score, Sepsis, Blood stream infection, Blood culture

Introduction

Sepsis is one of the leading causes of death in hospital settings and a major healthcare problem which is affecting millions of people around the world every year and killing as many as one in four.[1] Timely administration of rational and effective antibiotic therapy is must in management of sepsis.[2] At the time of hospital admission of patients with suspected sepsis in critical care units, the etiological agent of sepsis is not known. As a result, empirical antimicrobial therapy targeting wide range of etiological agents, is started before sending blood cultures.[1]

Over prescribing broad-spectrum antimicrobials as part of empirical therapy not only increase antimicrobial resistance, but also fail to treat infections and increase mortality; therefore, optimizing the use of antimicrobials is critical.[1,3] Critical care unit is an area of healthcare facility where maximum antibiotics are used and therefore chances of antibiotic resistance are more in these areas.[4] Antimicrobial resistance is directly proportional to the use of antibiotics and antibiotic stewardship program can help reducing the spread of antimicrobial resistance.[5,6,7] Several studies have been performed to evaluate the impact of antimicrobial stewardship program on antimicrobial resistance.[5,6,7]
In our hospital, an antimicrobial policy for various infections is in place. However, the policy has not been evaluated since its inception. The present study was conducted to assess the adherence to the antibiotic policy as well as its effectiveness in treating the patients with sepsis.

Methods:

A prospective, cross-sectional study was conducted in the non-COVID Adult Critical Care Units for a period of 1 year (1st August-2021 to 31st July-2022) following approval from Institutional Ethics Committee at Shree Krishna Hospital, Karamsad. The source of data includes inpatient records of patients admitted in non-COVID adult critical are units as well as laboratory information system (LIS).All adult participants admitted in non-COVID adult critical care units with suspected sepsis or who develop sepsis during their stay in these units AND having a laboratory confirmed bloodstream infection (LCBI) were included in the study. The identification of pathogen and its susceptibility pattern was done using Vitek-2 automated system. Antimicrobial agents were chosen and reported as per CLSI guidelines. Participants in whom blood culture grew an isolate that had been previously isolated from blood culture of the same participant and was suggestive of persistent infection with the same

isolate, were excluded from the study. Blood culture samples that grew skin contaminants were excluded after clinical correlation.

Empirical antimicrobial therapy was initiated by the clinician after collection of blood culture sample. The empirical therapy was expected to be started as per the hospital's antibiotic policy. After receiving blood culture report from Microbiology lab, the antimicrobial therapy was continued or escalated or deescalated as per the isolated organism and its antibiogram. A structured proforma was used for collection of the data.

Once the participant was confirmed of having an LCBI, the investigator visited the critical care unit to look into the risk stratification, details of the empirical antimicrobial agent started in the participant, clinical details and laboratory workup of the participant.

Risk stratification of patients: The participants were stratified into one of the four risk categories which is part of antibiotic policy described as per Table 1. The risk stratification would help the clinician to assume the probable pathogens of sepsis and thereby select an antimicrobial agent defined for the risk category in which the participant falls.

Table 1: Risk stratification categories of the patients

Patient Type 1 (CAI)
No contact with health care system in last 90 days
No prior antibiotic treatment in last 90 days
Patient young with no or few co-morbid conditions
Patient Type 2 (HCAI)
Recent contact with health care system (hospital / nursing home admission, CAPD) without major invasive procedure
Antibiotic treatment in last 90 days
Patient old (> 65 years) with few co-morbidities.
Patient Type 3 (NI)
Hospitalization >5 days ± infections following major invasive procedures
Recent & multiple antibiotic therapies
Patient old (> 65 years) + multiple co-morbidities (e.g. structural lung disease, immunodeficiency)
Patient Type 4 (NI)
Type 3 patient with fever despite antibiotic therapy (>5days) with no obvious source / after appropriate source control
± severe sepsis/septic shock
Plus ≥1 of the following (but not limited to) risk factors for invasive fungal infections:
Total Parenteral Nutrition (TPN)
Haemodialysis
Immunodeficiency of variable origin
Major abdominal surgery
multi-focal candida colonization
Diabetes

Details of the empirical antimicrobial agent: The investigator looked whether the empirical antimicrobial agent/s was started as per the antimicrobial agents defined for each risk stratification. The antibiogram of the blood culture isolate was looked upon to see whether the empirical antimicrobial agent initiated in the participant falls into the 'susceptible' category.

Clinical and laboratory details: The clinical details were recorded from the inpatient record/direct observation and the laboratory workup was recorded from the laboratory

information system. The clinical details and the laboratory parameters were collected for five days with day one being the day of onset of clinical sepsis.

Effectiveness of the antibiotic policy: The effectiveness of the empirical antimicrobial policy was evaluated on the basis of the improvement in the clinical and laboratory parameters as well as SOFA score of the participant over a period of five days. Day one and two being the two days prior to the day on which the isolate and its antibiogram was reported by laboratory. Day three was the day on which the isolate was reported by laboratory. Day four and day five being the two days after the day on which the isolate was reported.

Statistical Analysis: Microsoft Excel 2019, Version 2209 was used for data entry and data analysis. Proportions were calculated using descriptive analysis. Data was analysed using Chi-square calculation. Significance was considered at P-value <0.05.

Results:
A total of 3001 blood culture samples were received during the period from 1st August 2021 to 31st July 2022, of which 1922 (64.04%) were negative. From 1079 (35.95%) positive cultures, 418 (38.73%) were true pathogens and 661 (61.26%) were contaminants. Out of 418 positive blood cultures, 102 blood cultures belonged to ICU patients and were included in the study. Of the 102 patients who became eligible for the further study, 19 patients took discharge against medical advice before completion of five days of evaluation period and therefore SOFA score on the 5th day of diagnosis of sepsis could not be evaluated in them. Hence these patients were excluded during further analysis pertaining to effectiveness of antimicrobial policy. Compliance and effectiveness rates are as described in table 2A and 2B.

Table 2: Compliance and effectiveness rates for empirical antimicrobial policy in patient with suspected sepsis (n=83)

Table 2A: Patients who completed five days evaluation period.

Parameter assessed	**Percentage of total compliance (n = 83)**
Primary bloodstream infections Secondary bloodstream infections Unknown source bloodstream infections	4.81%, (n=4) 81.92%, (n=68) 13.25%, (n=11)
Participants in whom antimicrobial agent was started as per policy	48.19%, (n=47)
Participants in whom antimicrobial agent was started as per policy and within 1 hour of diagnosis of sepsis	96.07%, (n=83)
Effectiveness of empirical antimicrobial therapy irrespective of whether antimicrobial agent was started as per policy or not	49.39%, (n=41)

Table 2B: Patients in whom anti-microbial agent was started as per policy.

Parameter assessed	**Percentage of total compliance (n = 47)**
Participants in whom antimicrobial agent was started as per policy and within 1 hour of diagnosis of sepsis	100%, (n=47)
Effectiveness of empirical antimicrobial therapy in whom	51.06%, (n=24)

antimicrobial agent was started as per policy	
Effectiveness of empirical antimicrobial therapy for patients in whom antimicrobial agent was started as per policy in various risk stratification categories: Category1 Category 2 Category 3 Category 4	 60%, (n=3) 64.28%, (n=9) 41.66%, (n=5) 0%, (n=0)
Percentage of participants in whom antimicrobial agent was started as per policy and the antimicrobial agent was susceptible in the antibiogram report	55.31%, (n=26)

Escherichia coli (43%, n = 44) was most commonly isolated followed by *Klebsiella pneumoniae subspp. pneumoniae* (17%, n = 18), *Staphylococcus aureus* (8.82%, n = 9), *Pseudomonas aeruginosa* (4.9%, n = 5), *Acinetobacter baumannii* (4.9%, n = 5), *Burkholderia cepacia* and *Enterococcus faecalis* (2.94%, n = 3), *Enterococcus faecium* (3.92%, n = 4), *Staphylococcus hominis, Salmonella typhi, Stenotrophomonas maltophilia,* and *Streptococcus pneumoniae* (1.93%, n = 2); *Proteus mirabilis, Staphylococcus hemolyticus* and *Achromobacter xylosoxidans* (0.98%, n = 1).

The highest number of patients with sepsis belonged to risk stratification 2 (50.6%, n = 42) followed by risk stratification 3 (33.73%, n = 28), risk stratification 1 (12.04%, n = 10) and risk stratification 4 (3.61%, n = 3).

There was no significant association found between age group of the patients and effectiveness of empirical antimicrobial policy (n=83, P= 0.31).

There was a significant association between effectiveness of antimicrobial policy and number of comorbidities present in the patient as decribed in table 3(n=83, P=0.026).
There was no significant association found between risk stratification of the patients and effectiveness of empirical antimicrobial policy as seen in figure 1.(P=0.32)

Table 3:Effectiveness of policy based on co-morbidities

Number of comorbidities	Effectiveness	Ineffectiveness	P-value
0	7(8.43%)	15(18.07%)	0.026
1	11(13.25%)	13(15.66%)	
2	20(24.09%)	8(9.63%)	
3	3(3.61%)	6(7.22%)	
Total	41(49.39%)	42(50.60%)	

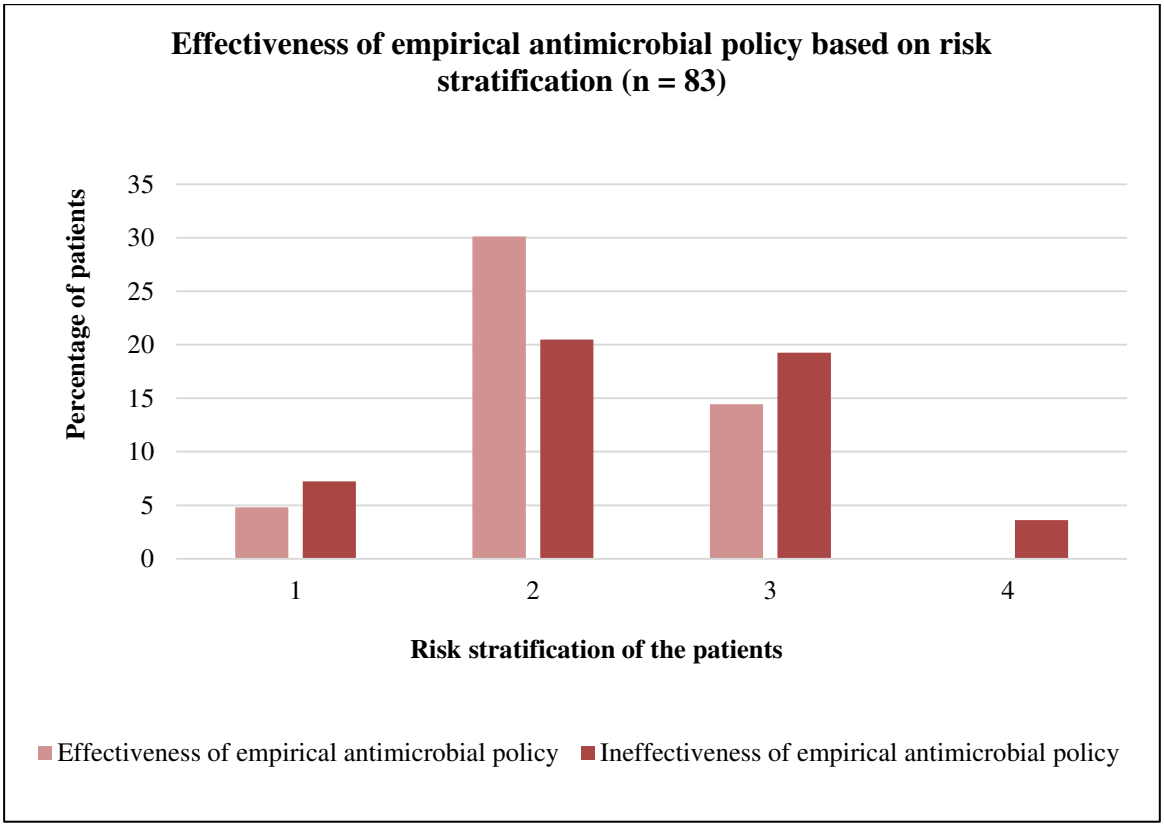

Figure 1: Effectiveness of empirical antimicrobial policy based on risk stratification (n = 83, P=0.32)

When compared effectiveness of the policy in gram negative and gram-positive organisms, effectiveness was less in gram positive 46.66% (n=7) compared to gram negative organisms 50%(n=34). There was no significant correlation between effectiveness and type of organism (n=83, P=0.81).

There was no significant difference (n=83, P=0.72) in effectiveness whether antimicrobial agent was started as per policy or not, based on the improvement in SOFA score on the 5th day of initiation of antimicrobial agent. The effectiveness of antimicrobial therapy was only 0.86 times more if the antimicrobial therapy was started as per the policy when compared to antimicrobial agent started was not as per policy (Relative risk: 0.93, Odds ratio: 0.86).

Discussion:

The antibiotic policy is the set of strategies and activities undertaken to organize the antimicrobial treatment in the hospital and to achieve health outcomes for patients. The basic principles are to be direct evidence-based medicine, local epidemiology and freedom for prescribing physicians.

To decrease the morbidity and mortality is the main aim of hospital antimicrobial policy due to infection by antimicrobial-resistant bacteria; and to preserve the effectiveness of AMA in the treatment and prevention of communicable diseases. Our study aims to evaluate the adherence and effectiveness of hospital antibiotic policy in our institute.

During the entire study period from 1st August-2021 to 31st July-2022, a total of 3001 blood culture samples were received of which includes 1079 (35.95%) positive cultures. Out of

them, 418 (38.73%) were true pathogens which included 102 blood cultures which belonged to ICU patients and were included in our study. Of the 102 patients who became eligible for the further study, 19 patients took discharge against medical advice before completion of five days of empirical antimicrobial therapy and therefore SOFA score on the 5th day of diagnosis of sepsis could not be evaluated in them. Hence these patients were excluded during further analysis pertaining to effectiveness of antimicrobial policy.

Clinical isolates in sepsis in adults in critical care:
Organisms commonly isolated are of utmost important as antibiotic policy has to be framed depending upon the nature of the pathogen and its resistance pattern in geographical area and also for timely administration of appropriate antimicrobials. Based on the primary site of infection and severity of infection, there are diverse pathogens isolated in blood culture. Most commonly isolated pathogen in present study was *Escherichia coli* (43%, n = 44) followed by *Klebsiella pneumoniae sub spp pneumoniae* (17%, n = 18)*, Staphylococcus aureus* (8.82%, n = 9) and *Pseudomonas aeruginosa* (4.9%, n = 5).

When compared with other studies, we found that most Indian studies identified gram negative organisms as predominant pathogens in causing blood stream infections with most common being *Escherichia coli*.[8,9,10,11]

However, several studies from western countries showed contradictory results as gram positive organisms particularly *Staphylococcus aureus* and CoNS (Coagulase negative *Staphylococcus*) being the most common pathogens.[12,13,14,15]

Early initiation of empirical antimicrobial therapy for sepsis:
Percentage of participants in whom antimicrobial agent was started within one hour of diagnosis of sepsis was 95.18% for 83 patients in whom effectiveness of empirical antimicrobial policy was evaluated. The overall patients (n = 102) in whom antimicrobial agent was administered within one hour of diagnosis of sepsis was 96.07%.

Adherence to empirical antimicrobial policy:
In our hospital, the hospital antibiotic policy was developed based on a locally developed hospital-specific antibiogram built using data obtained from microbiological sampling of patients. The policy specifies that the empiric therapy of infections should be based on the possible clinical syndrome, primary site of infection and the possible pathogens, taking into account the risk of drug-resistant pathogens based on host characteristics and disease severity.
The overall compliance for all 102 patients was 59.61% to the adherence of empirical antimicrobial policy in sepsis in adult patients admitted in our intensive care units. When 19 patients who did not complete five days evaluation period for effectiveness of antimicrobial policy were excluded, the compliance was found to be 48.19% in the remaining 83 patients. Various studies have been conducted in the past which have evaluated compliance to their local antimicrobial policy.

As seen in Table 4 below, adherence to empirical antimicrobial policy in various studies has been inadequate. Few studies did identify reasons for the poor adherence to the empirical antimicrobial therapy.[16,17] As the objective in the present study was to assess the adherence rate to the antimicrobial policy, we did not assess the reasons behind the lack of compliance

to the policy. As there is a lot of scope to improve the compliance rate in our institute, we would recommend conducting further study to assess the reasons for poor compliance.

Table 4: Comparison of present study with others with regards to compliance of hospital antibiotic policy

Studies	Compliance to respective hospital antibiotic policy	Specific criteria
Pillay et al[18]	15% (n=67)	All acute admissions in hospital
Banerjee et al[19]	21.18% (n=170)	Only ICU patients irrespective of culture reports
Aldeyab et al[20]	31% (n=183)	Surgery ward patients
Eticha et al[21]	36.4% (n=217)	Only patients with community acquired pneumonia
Chowdhury et al[22]	41.8% (n=280)	Only patients from SICU and CCU
Aly et al[23]	52.7% (n=1,112)	All indoor patients
Present study	59.80% (n=102)	Only adult patients with culture confirmed BSI in ICU
Wathne et al[24]	62% (n=1,756)	Medical wards of three different hospitals
Metz et al[25]	63% (n=101)	Only patients from general paediatric wards
Dixit et al[26]	72% (n=304)	Only patients from general wards of internal medicine
Thomas et al[27]	77.7% (n=4,871)	All patients of Surgery, Orthopaedics and Gynaecology department

Effectiveness of empirical antimicrobial policy:

In the present study, the effectiveness of the empirical antimicrobial policy was evaluated by following SOFA score of the patient from two days prior to the positive blood culture results and two days after the blood culture results. Empirical antimicrobial therapy is started at this point in the patient while the results of blood culture are awaited. An inappropriate selection of empirical antimicrobial agent may affect the patient's outcome in the initial 48 hours till the culture results are available. Once the causative pathogen and its antimicrobial susceptibility pattern is available within next 48 – 72 hours, the definitive therapy replaces the empirical therapy based on the culture results. If one needs to assess the effectiveness of the empirical antimicrobial agent, one should be looking into the improvement of clinical and laboratory parameters. The overall effectiveness of the empirical antimicrobial agent based on SOFA score in the present study was found to be 51.06%(n=24 out of 47).

We have found very few studies who have evaluated the effectiveness of empirical antimicrobial policy.[24,28] In the present study, the effectiveness of our antimicrobial policy was found to be 51.06 % with end point being improvement in the SOFA score of the patient after 5 days of initiation of empirical therapy. Present study did not evaluate route of administration, rate of infusions and dosage of antimicrobial agent used in the patient, which have been found to be important factors in a successful outcome in the patient and could have influenced the rate of effectiveness in the present study.[23,26]

There was no significant difference noted in the effectiveness of the policy with regards to various risk stratification categories (P = 0.32). Effectiveness of the policy as per risk

stratification categories was necessary as changes in the current policy need to be targeted only to the categories where ineffectiveness was significantly higher compared to the other categories. Similarly, there was no difference noted in effectiveness of antimicrobial policy on gender of the patient (P = 0.44).

When the effectiveness of the empirical antimicrobial policy was evaluated as per various age groups of patients in the present study, there was no significant correlation noted between age group and effectiveness of the empirical antimicrobial policy (P=0.31).

A primary bloodstream infection is the one where source of infection is located in the intravascular system e.g., infective endocarditis or presence of an intravascular catheter. Focus of bloodstream infection when located outside the cardiovascular system, e.g., urinary tract, respiratory tract, etc. leads to secondary bloodstream infection. When neither of the two are identified, we label the bloodstream infection as having an unknown source. We evaluated the effectiveness of antimicrobial policy for various types of bloodstream infection. Although the difference was not found to be statistically significant (P = 0.39), the results would have a bias as most of (81.92%) our bloodstream infections were secondary bloodstream infections.

The effectiveness of empirical antimicrobial policy did not depend on the causative pathogen being gram positive or gram-negative organism (P = 0.81). The possible reason would be the inclusion of antimicrobial agent in the policy that has a wider spectrum of activity, i.e., against both gram positive and gram-negative organisms.

The effectiveness of antimicrobial therapy was only 0.86 times more if the antimicrobial therapy was started as per the policy when compared to antimicrobial agent started was not as per policy (Relative risk: 0.93, Odds ratio: 0.86). Although there was not much difference in the effectiveness in both the groups, we would still recommend adhering to the empirical antimicrobial policy for selection of antimicrobial agent in order to prevent non uniform use of antimicrobials as this could further increase antimicrobial resistance.

Conclusion:

There was no significant difference noted between improvement in SOFA score of the patients in whom antimicrobial agent was started as per policy and in whom the antimicrobial agent was not started as per policy (P = 0.72). We still recommend using antimicrobial agent as per policy in order to avoid non uniformity in prescriptions and development of antimicrobial resistance.

References:

1. 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 Mar;43(3):304–77.
2. Strich JR, Heil EL, Masur H. Considerations for Empiric Antimicrobial Therapy in Sepsis and Septic Shock in an Era of Antimicrobial Resistance. J Infect Dis. 2020 Jul;222(Suppl 2):S119– 31.
3. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane database Syst Rev. 2017 Feb;2(2):CD003543.

4. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother. 2011 Jun;66(6):1223–30.
5. Struelens MJ, Byl B, Vincent JL. Antibiotic policy: a tool for controlling resistance of hospital pathogens. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 1999 Mar;5 Suppl 1:S19–24.
6. Gould IM. A review of the role of antibiotic policies in the control of antibiotic resistance. J Antimicrob Chemother. 1999 Apr;43(4):459– 65.
7. Badawi H, Diab MS, Said M El. Impact of Antibiotic Policy in a Tertiary Care Research Institute Hospital in Egypt: Three Years' Experience. Int J Infect Control [Internet]. 2007 Dec 14;3(2 SE Original Articles). Available from: https://ijic.info/article/view/2384
8. orbes BA, Sahm DF WA. Bailey and Scott‟s Diagnostic Microbiology;2017. Chapter 67, Bloodstream Infections; 924-941. chapter 67. 2017;14th:924–41.
9. Umemura Y, Ogura H, Takuma K, Fujishima S, Abe T, Kushimoto S, et al. Current spectrum of causative pathogens in sepsis: A prospective nationwide cohort study in Japan. Int J Infect Dis [Internet]. 2021;103:343–51
10. Rhee C, Kadri SS, Dekker JP, Danner RL, Chen HC, Fram D, et al. Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use. JAMA Netw open. 2020 Apr;3(4):e202899
11. Laupland KB, Pasquill K, Steele L, Parfitt EC. Burden of bloodstream infection in older persons: a population-based study. BMC Geriatr [Internet]. 2021;21(1):31. Available from: https://doi.org/10.1186/s12877-020-01984-z
12. Birru M, Woldemariam M, Manilal A, Aklilu A, Tsalla T, Mitiku A, et al. Bacterial profile, antimicrobial susceptibility patterns, and associated factors among bloodstream infection suspected patients attending Arba Minch General Hospital, Ethiopia. Sci Rep. 2021 Aug;11(1):15882.
13. Abdollahi A, Tabriz HM, Mahfoozi S. Frequency of Pathogens and Antimicrobial Susceptibility of Bacteria Isolated from Bloodstream Infections. Iran J Pathol. 2010;5:143–9.
14. Rehman ZU, Hassan Shah M, Afridi MNS, Sardar H, Shiraz A. Bacterial Sepsis Pathogens and Resistance Patterns in a South Asian Tertiary Care Hospital. Cureus. 2021 May;13(5):e15082.
15. Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and Mortality Associated with Bloodstream Organisms: a Population-Wide Retrospective Cohort Study. J Clin Microbiol. 2022 Apr;60(4):e0242921.
16. Banerjee T, Anupurba S, Singh DK. Poor compliance with the antibiotic policy in the intensive care unit (ICU) of a tertiary care hospital in India. J Infect Dev Ctries. 2013 Dec;7(12):994–8.
17. Chowdhury SS, Sastry AS, Sureshkumar S, Cherian A, Sistla S, Rajashekar D. The Impact of Antimicrobial Stewardship Programme on Regulating the Policy Adherence and Antimicrobial Usage in Selected Intensive Care Units in a Tertiary Care Center - A Prospective Interventional Study. Indian J Med Microbiol [Internet]. 2020;38(3):362–70. Available from: https://www.sciencedirect.com/science/article/pii/S0255085720315450
18. Pillay R, Rathish B, Wilson A, Warrier A, Philips GM. A quality improvement project on adherence to antibiotic policy in acute admissions from a tertiary care hospital in south India. Clin Med. 2021 Jan;21(1):e88–91.

19. Banerjee T, Anupurba S, Singh DK. Poor compliance with the antibiotic policy in the intensive care unit (ICU) of a tertiary care hospital in India. J Infect Dev Ctries. 2013 Dec;7(12):994–8.
20. Aldeyab MA, Elshibly SM, McElnay JC, Davies E, Scott MG, Magee FA et al. An evaluation of compliance with an antibiotic policy in surgical wards at a general teaching hospital in Northern Ireland. Infection Control and Hospital Epidemiology. :921–2. Available from: https://doi.org/10.1086/599308
21. Eticha EM, Gemechu WD. Adherence to Guidelines for Assessment and Empiric Antibiotics Recommendations for Community-Acquired Pneumonia at Ambo University Referral Hospital: Prospective Observational Study. Patient Prefer Adherence. 2021;15:467–73.
22. Chowdhury SS, Sastry AS, Sureshkumar S, Cherian A, Sistla S, Rajashekar D. The Impact of Antimicrobial Stewardship Programme on Regulating the Policy Adherence and Antimicrobial Usage in Selected Intensive Care Units in a Tertiary Care Center - A Prospective Interventional Study. Indian J Med Microbiol [Internet]. 2020;38(3):362–70. Available from: https://www.sciencedirect.com/science/article/pii/S0255085720315450
23. Aly NY, Omar AA, Badawy DA, Al-Mousa HH, Sadek AA. Audit of physicians‟ adherence to the antibiotic policy guidelines in Kuwait. Med Princ Pract Int J Kuwait Univ Heal Sci Cent. 2012;21(4):310–7.
24. Wathne JS, Harthug S, Kleppe LKS, Blix HS, Nilsen RM, Charani E, et al. The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study. Antimicrob Resist Infect Control. 2019;8:63.
25. Metz J, Oehler P, Burggraf M, Burdach S, Behrends U, Rieber N. Improvement of Guideline Adherence After the Implementation of an Antibiotic Stewardship Program in a Secondary Care Pediatric Hospital. Front Pediatr. 2019;7:478.
26. Dixit D, Ranka R, Panda PK. Compliance with the 4Ds of antimicrobial stewardship practice in a tertiary care centre. JAC-antimicrobial Resist. 2021 Sep;3(3):dlab135.
27. Thomas AP, Kumar M, Johnson R, More SP, Panda BK. Evaluation of antibiotic consumption and compliance to hospital antibiotic policy in the surgery, orthopedics and gynecology wards of a tertiary care hospital. Clin Epidemiol Glob Heal [Internet]. 2022;13:100944. Available from: https://www.sciencedirect.com/science/article/pii/S2213398421002529
28. Wiener-Well Y, Hadeedi M, Schwartz Y, Yinnon AM, Munter G. Prospective Audit of Empirical Antibiotic Therapy for Septic Patients. Isr Med Assoc J. 2020 Jun;22(6):378–83.