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Original Research Article

Antibacterial drug utilization study in patient of sepsis due to *Staphylococcus aureus*

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ABSTRACT

Background: Sepsis is the most common and highly fatal clinical syndrome due to infection. Gram-positive organisms as a cause of sepsis have increased in frequency over time more common than gram-negative infections. *S. aureus* bacteremia (SAB) is one of the most prevalent and difficult to treat infections associated with significant morbidity and mortality. Aim was to study antibacterial drug utility, sensitivity and resistance pattern of antibacterial drugs in *S. aureus* infective septic patient in medicine department.
Methods: A prospective observational study was done in medicine department of SSG hospital, Vadodara over a period of 9 months.
Results: Total 50 *S. aureus* were tested for their sensitivity and resistance pattern towards ten antibacterial agents in microbiology department by disc diffusion method. The antibiogram of *S. aureus* indicated widespread resistance antibacterial agent ranging from a minimum resistant to vancomycin (4%) to a maximum of 90% against penicillin G. Total 142 antibacterial agents were prescribed in 50 patients. Metronidazole, ceftriaxone and piptaz were the most frequently prescribed antibacterial agents with DDD/1000 patient days 2.44, 3.55 and 2.62 respectively. 30 out of 50 patients needed a change in antibacterial agents during their course of treatment either due to antibacterial agent failure or after culture sensitivity report. 60% of the patients were prescribed ≥3 antibacterial agents at any point of time during treatment. Mean DOT/LOT was 2.22±0.84.
Conclusions: There is a need of antibacterial agent usage guidelines and restriction policies for the rational prescribing of antibacterial agent in critically ill patients.

Keywords: Sepsis, *S. aureus*, Antibacterial sensitivity

INTRODUCTION

Sepsis is defined as systemic illness caused by microbial invasion of normally sterile parts of the body.[1] Sepsis is the most common and highly fatal clinical syndrome due to infection.[2]

Sepsis with its associated complications remains a major public health problem and economic burden in industrialized world. The incidence of the sepsis has been growing over the past few years.[3] Worldwide 31.5 million cases of sepsis occurs annually and 5.3 million people have died annually.[2]

Approximately two-third of the cases occurs in patient with significant underlying illness.[4] The rising incidence of sever sepsis has been attributable to the increasing longevity of patients with chronic diseases, and co morbid conditions like HIV-AIDs. The widespread use of

immunosuppressive drugs, indwelling catheters, and mechanical device has also played a role.[4]

Gram positive bacteria are the most frequently isolated causative agent in patients with sepsis. The most common gram-positive organisms isolated is *S. aureus*. Others are *Enterococcus species* and *S. pnomoniae*. Most common gram-negative species isolated are *E. coli, K. pnemoniae, Acinetobacter baumannii and pseudomonas species.*[2]

S. aureus, the most virulent of the many *Staphylococcus* species has demonstrated its versatility by remaining a major cause of morbidity and mortality worldwide despite the availability of numerous effective anti-*Staphylococcus* antibiotics. *S. aureus* is both commensal and opportunistic pathogen. After colonization staphylococcus replicate at the initial site of infection, elaborating enzymes that include serine protease, hyaluronidases, thermonucleases and lipases. These enzymes facilitate survival and local spread across tissue surfaces.[4]

The choice of antimicrobial agents to treat *Staphylococcal* infection has become increasingly problematic because of the prevalence of multi drug resistant strain. *Staphylococcal* resistance to most antibiotic families, including β-lactams, aminoglycosides, fluroquinolones and glycopeptides has increased. 40-50% of *Staphylococcal aureus* isolates are now resistant to methicillin.

Resistant to methicillin indicates resistant to all semisynthetic penicillinase resistant penicillin as well as to all cephalosporins.[4]

Aim

Aim of the study was to determine antibacterial drug utilization, sensitivity and resistance pattern in *S. aureus* infective septic patients admitted in the medicine department.

Objectives

Objectives were to study antibacterial drug utilization pattern in *S. aureus* positive septic patients, to study sensitivity and resistance pattern of antibacterial drugs in and *S. aureus* positive septic patients admitted in medicine department, to study the outcome of treatment in patient with sepsis due to *S. aureus.*

METHODS

An observational-prospective study was conducted among the indoor patients of medicine wards, medical college Baroda and SSG hospital, Vadodara. The study was carried out over a period of 9 months from 1st July 2017-31st March2018. An initial pilot study was carried out for a period of 15 days.

Study setting

The study has been carried out at inpatient department (IPD) of medicine at SSG hospital, Baroda.

Study population

The patients admitted in medicine ward satisfying diagnostic criteria for sepsis whose blood culture was positive for *S. aureus* and gave written informed consent.

Study duration

The study duration was from 9 months (From July 2017 to March 2018).

Study design

It was a prospective-observational study.

Sampling and sample size

It was a time-bound study carried out over a period of 9 months, wherein data of 50 patients were collected. (Approximately 1-2 patients were admitted per week in medicine department which came to approximately 4-5 sepsis patients per month. So, in all we managed to enrol 50 patients for data collection over a period of 9 months).

Inclusion criteria

Patients satisfying two or more of the following conditions for the diagnosis of the sepsis.[4] Fever (oral temperature >38ºC) or hypothermia, tachypnea (>24 breaths/ min), tachycardia (heart rate >90 beats/min), leukocytosis (>12,000/µL), Leukopenia (4,000/µL) and presence of *S. aureus* in blood, as evidenced by positive blood cultures.

Exclusion criteria

Patients of sepsis with multiple causative organisms. And patient who refused to give written informed consent.

Study permission

Approval of institutional ethics committee for human research (IECHR) was taken before initiation of the study.

Informed consent

Written Informed Consent of the patients was taken before obtaining required information from his/her case.

Confidentiality issues and data safety

Confidentiality and data safety has been maintained.

Data collection procedure

Reports of positive blood culture for *S. aureus* was screened in the department of microbiology on daily basis

and their detailed blood culture reports were collected. Such cases were followed up in the medicine department. Demographic and clinical details of such patients were obtained from the case record of the patients as well as by consultation with the treating physician.

The primary cause for sepsis, pharmacotherapy given for the same, relevant past and present history were noted.

The patients were followed up daily and relevant clinical observations, if any change in treatment protocol, if any adverse drug reaction developed had been noted down in pre-structured case record form.

Patients were followed up till they got discharged and outcome like cured, death, DAMA, absconded, other was noted.

Data analysis

The recorded data was entered in excel sheet and analyzed using suitable statistical tests (such as mean±SD and percentage) with the help of appropriate statistical software.

The drug utilization data was analyzed by the WHO core drug use prescribing indicators.

ADRs developed by the patients during treatment were evaluated for causality by WHO-UCM system, for severity by modified Hartwig and Siegel scale and for preventability by Schumock and Thornton scale.

RESULTS

Total 50 patients of sepsis due to *Staphylococci spp*, diagnosed in microbiology department and treated in medicine ward, SSG Hospital during period of 9 months (July 2017 to March 2018) were recruited in the study.

Mean (SD) age of patient in our study found to be 39.2±17 years and median was 35.5 years 37 (74%) patients had fever, 18 (36%) patients complained of generalized weakness, 11 (22%) patients had cough, 10 (20%) patients had vomiting, 9 (18%) patients had abdominal pain, 9 (18%) patients had altered sensorium and 7 (14%) patients had breathlessness at the time of admission in the hospital.

Among the patients of sepsis due to staphylococci, 10 (20%) had to stay in the hospital for >2 weeks. For 22 (44%) patients, duration of hospital stay was 1-2 weeks and 18 (36%) patients stayed in hospital for <1 week

Mean (SD) duration of hospital stay in our study found to be 10.78±6 days. Median duration of hospital stay for 50 patients was 11 days.

The 39 (78%) patients were cured (Recovered), while 11 (18%) were lost to follow up in which, 8 (16%) took DAMA (Discharge against medical advice) and 1 (2%) absconded (left without informing), 2 (4%) patients died during treatment.

Sensitivity and resistant pattern of antimicrobial agent

As per Figure 1, ten different antimicrobial agents were tested in the microbiology laboratory for their sensitivity and resistance towards *Staphylococcal* species (by disk diffusion method). 48 (96%) *Staphylococci* were sensitive to vancomycin, whereas 2 (4 %) were resistant to vancomycine, 47 (94%) *Staphylococci* were sensitive to linezolide and 3 (6 %) were resistant, 42 (84%) *Staphylococci* were sensitive to gentamycin and 8 (16%) were resistant, 32 (64%) *Staphylococci* were sensitive to cefoxitin and methicillin and 18 (36%) were resistant, out of 18 (36%) patients who were resistant to methicillin 7 (14%) were MRSA. 28 (56%) *Staphylococci* were sensitive to amoxi + clavulanic acid and 22 (44%) were resistant, 25 (50%) *Staphylococci* were sensitive to clindamycin and 25 (50%) were resistant, 26 (52%) *Staphylococci* were resistant to co-trimoxazole and 24 (48%) were sensitive, 36 (72%) *Staphylococci* were resistant to erythromycin and 14 (28%) were sensitive, 45 (90 %) patients were resistant to penicillin-G and 5 (10%) were sensitive.

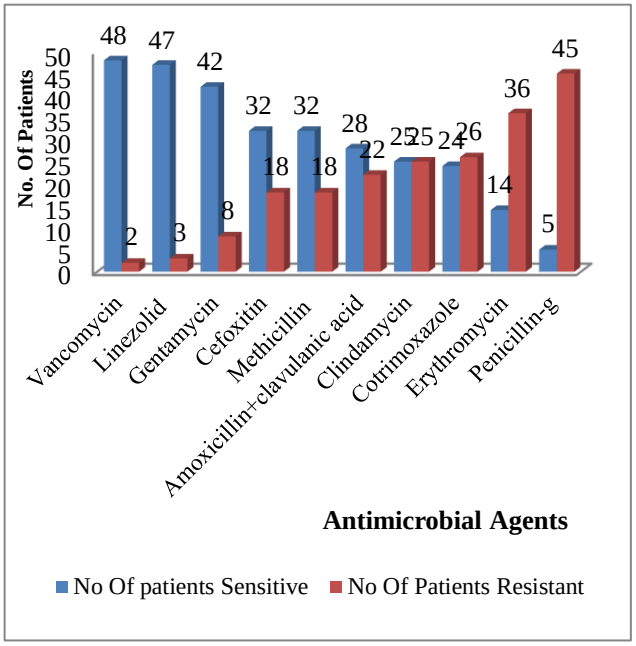

Figure 1: Sensitivity and resistant pattern of antimicrobial agent.

Different antimicrobial agents used

As per Table 1, total 14 different types of antimicrobial agents were used in patients suffering from staphylococcal sepsis. Among which, metronidazole was the most commonly used AMA in 30 (21%) patients, followed by ceftriaxone in 24 (17%) and piptaz in 19 (13%) patients, cefotaxime, Vancomycin and Azithromycin were used in 18 (13%), 15 (11%) and 14 (10%) patients respectively.

While Augmentin, linezolide, meropenum and levofloxacin were used in 5 (4%), 5 (4%), 4 (3%) and 3 (2%) patients respectively.

Table 1: Different antimicrobial agents used.

Name of the drug	Total
Metronidazole	30
Ceftriaxone	24
Piptaz	19
Cefotaxime	18
Vancomycin	15
Azithromycin	14
Augmentin	5
Linezolide	5
Meropenem	4
Levofloxacin	3
Clindamycin	2
Amikacin	1
Cefo+sulbactum	1
Ciprofloxacin	1
Total	142

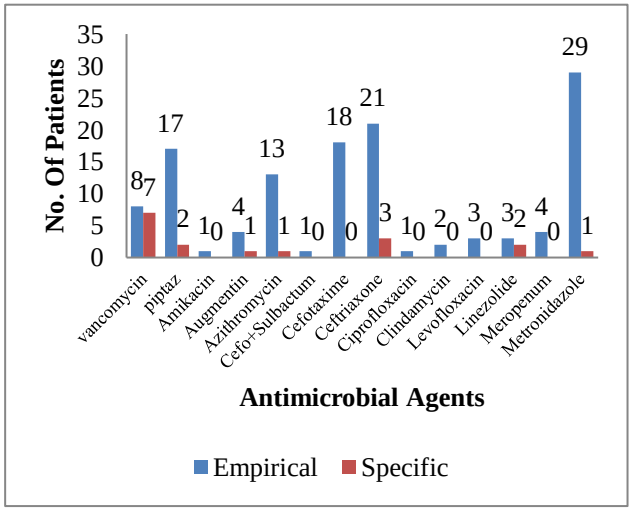

Figure 2: Antimicrobial agents started empirically.

Antimicrobial agents started empirically

As per Figures 2, out of total 142 antimicrobial agents total 125 antimicrobial agents were started empirically, in 8 (16%) patients vancomycin was started empirically, while in 7 (14%) of patients it was started as a target specific therapy, in 17 (34%) patients Piptaz was started empirically, while in 2 (4%) patients target specific piptaz was started. Ceftriaxone was started empirically in 21 (42%) patients, while target specific treatment was started in 3 (6%) patients. Linezolide was started empirically in 3 (6%) patients and in 2 (4%) patients started as target specific treatment. Augmentine, azithromycin and metonidazole were started as empirical therapy in 4 (8%), 13 (26%) and 29 (58%) patients respectively and all 3 were started as a specific therapy in 1 (2%), 1 (2%) and 1 (2%) respectively. Rest of the all drugs started only empirically. Amikacin started empirically in1 (2%), cefo+sulbactum in 1 (2%) and ciprofloxacin in 1 (2%) patient. Cefotaxime, levofloxacin and meropenum started empirically in 18 (36%), 3 (6%) and 4 (8%) patients respectively.

There were 2 routes of antimicrobial agent administration oral and parenteral (intravascular injection). The 90% of the antimicrobial agents were given parenterally and 10% of the antimicrobial agents were given orally.

Azithromycin was the only antibacterial which was given by oral route WHO prescribing Indicators were as follow, average No. of medicines prescribed per patients encounter was 13±3.9, percentage of medicine prescribed by generic name for antimicrobial agents was 18%. All the prescription contained antimicrobial agents and all the prescription contained injection. All the antimicrobial agents prescribed were from the essential medicine list.

Table 2: WHO prescribing indicators.

Prescribing indicators	No. of drugs
Average number of medicines prescribed per patient encounter	13±3.9
Percentage medicines prescribed by generic name [AMA]	18%
Percentage encounters with an antimicrobial prescribed	100%
Percentage encounters with an injection prescribed	100%
Percentage medicines prescribed from essential medicines list or formulary [AMA]	100%

Defined daily dose

DDD (Defined daily dose) and DDD/1000 patient days were calculated and they were as per the Table 3.

Table 3: Defined daily dose.

Name of drug	Mean PDD	DDD	DDD/1000 patient days
Metronidazole	1.5	1	2.44
Ceftriaxone	2.9	1.45	3.55
Piptaz	15	1.07	2.62
Cefotaxime	3	0.75	1.83
Vancomycin	1.5	0.75	1.83
Azithromycin	0.5	1.66	4.07
Augmentin	3.6	1.2	2.93
Linezolide	1.1	0.92	2.26
Meropenum	2	1	2.44
Levofloxacin	0.5	1	2.44
Clindamycin	1.2	0.66	1.63
Amikacin	0.5	0.5	1.22
Cefo-Sulbactum	6	1.5	3.67
Ciprofloxacin	0.4	0.4	0.98

The DDD of the ceftriaxone, piptaz, azithromcin and cefosulbactum was greater than 1, which shows doses prescribed were higher than the WHO DDD which were 1.45, 1.07, 1.66 and 1.5 respectively.

The DDD/1000 patient days was lowest in ciprofloxacin which was 0.98 and higher among azithromycin, cefosulbactum, and ceftriaxone which was 4.07, 3.67 and 3.55 respectively.

Days of therapy and length of therapy

As per Table 4, DOT (Days of therapy) for antibacterial agents in 50 patients ranged from 2 to 62 days with mean DOT of 19.54±14.22 days and median of 17 days.

LOT (length of therapy) ranged from 2 to 21 days with mean LOT of 8.18±4.05 days and median of 7 days. DOT/LOT ranged from 1 to 4 days with mean DOT/LOT of 2.22±0.84.

Table 4: Days of therapy and Length of therapy.

Variables	DOT	LOT	DOT/LOT
Mean	19.54	8.18	2.22
±SD	±14.22	±4.05	±0.84
Median	17	7	

DISCUSSION

Sepsis is a serious and often fatal clinical syndrome, resulting from infection.[18] It is a major cause of morbidity and mortality and the second leading cause of death worldwide. Epidemiologic data on sepsis varies depending on the origin of database-community-based or hospital-based, nature of data collection-retrospective chart review, discharge diagnoses, diagnosis in death certificates, or prospective observational studies.[19]

Many different infections can lead to sepsis.[18] The type of organism causing sepsis is an important determinant of outcome.

Gram-positive organisms as a cause of sepsis have increased in frequency over time and are now more common than gram-negative infections.[20] Among gram-positive sepsis, SAB is one of the most prevalent and difficult to treat infections and is associated with significant morbidity and mortality.[21]

On Indian subcontinent, diversity in health care system and a lack of resources are major hurdles in obtaining relevant clinical and demographic data to establish the burden of disease due to *S. aureus* accurately.[21]

Approximately 20% of healthy persons are persistent carriers of *S. aureus*, and 60% are intermittent carriers. Colonization rates are increased in hemodialysis patients, illicit injection drug users, surgical patients, and patients with insulin-dependent or poorly controlled diabetes.[22]

Because of high incidence, morbidity, and antimicrobial resistance, *S. aureus* infections are a growing concern for family physicians. Strains of *S. aureus* that are resistant to vancomycin are now recognized. Increasing incidence of unrecognized community-acquired methicillin-resistant *S. aureus* infections pose a high risk for morbidity and mortality. Although the incidence of complex *S. aureus* infections is rising, new antimicrobial agents, including daptomycin and linezolid, are available as treatment.[22]

Why need for surveillance to track antimicrobial use and resistance

As per the national treatment guidelines for antimicrobial use in infectious diseases, increasing levels of antimicrobial resistance correlate with inappropriate antibiotic use as shown at the population and individual level.[23] Therefore, our goal should be to use antimicrobials rationally and for that we need to know how antimicrobials are being used. Monitoring of antimicrobial use is a crucial component to identify targets for improving antimicrobial use and to further correlate with antimicrobial resistance surveillance programmes. world health organization (WHO) highlights the establishment of effective, epidemiologically sound surveillance of antimicrobial use and AMR among common pathogens in the community, hospitals and other health-care facilities as one of the key public health priorities. Surveillance systems are required to understand trends in antibiotic use and AMR, as well as the long-term temporal associations between these two in different areas. Tracking antimicrobial use, and the emergence and spread of resistant strains of bacteria provides information, insights, and tools needed to guide policy and to evaluate measures taken to promote appropriate antimicrobial use at all levels, from local to global. Data could also stimulate a sense of urgency to act. Improving antibiotic use is the key feature in efforts to contain AMR. Strategies for interventions to reduce antibiotic use have to be prioritized and customized based on local realties. Data from surveillance could help in identifying priorities and processes and in documenting a baseline for monitoring effects of interventions.[23]

In the present study of antimicrobial drug utilization in patients of sepsis due to *S. aureus*, 50 clinical isolates of *S. aureus* obtained from blood culture of patients from medicine departments, SSG hospital and medical college Baroda during period of 9 months (July 2017 to March 2018) were studied.

Majority of our patient population belonged to young individuals with the median age of 35.5 years. Which is different than that reported by Kalwaje et al and Noskin et al where median age was 44 and 68 years respectively.[21,24]

In our study, out of 50 clinical isolates of S Aureus, two (4%) were resistant to vancomycin. While the rest isolates were VSSA. There is wide variation in the resistance pattern of staph aureus towards vancomycin in different regions of India with 14.28% in Banglore, 3.33% in

Chennai, 7.22% in Delhi, 20.51% in Palakkad (Kerala), 7.69% in Gulbarga (Karnataka). Overall vancomycin Sensitivity pattern of staph aureus isolates at our set up is quite better than that reported by other studies.[25]

Similarly, 64% of the *S. aureus* isolates were MRSA. Which is greater than that reported by 54% by Eshwara et al and 45% by Kumarmeden et at.[21,25]

Resistance to linezolid in the staph aureus isolated in our set up was 6% which is 33% in study by Kumarmeden et al and 0% in study by Shariq et al.[25,26]

The 50% of the isolates were resistant to clindamycin in our study which is greater than study by Saikiaet al which is 43.50%.[27]

In our study of 50 patients, 14 different types of antimicrobial agents were used to treat *Staphylococcal* infection. Most commonly used antimicrobial agent was metronidazole used in 30 (21%) patients, followed by ceftriaxone in 24 (17%) patients, and piptaz in 19 (13%) patients. Total 141 antimicrobial agents were used out of which 125 antimicrobial agents were started empirically and 17 were started as target specific therapy.

In our study, vancomycin was used in a total of 15 patients. Out of which in 08 patients it was started as empirical therapy while in rest of 07 patients as a target specific therapy. Piptaz was used in 19 patients, 17 were started empirically and only 2 patients were stated as a target specific treatment. Linezolide was used in 5 patients, empirically started in 3 patients and in 2 patients started as a target specific treatment. Meropenum was used in 4 patients empirically.

However, according to *S. aureus* bacteraemia management guideline v1.1 (Govt. of South Australia), when staphylococcal species are sensitive to methicillin, appropriate ß-lactam such as flucloxacillin should be prescribed and vancomycin should be prescribed if the *Staphylococcal* spices are resistant to methicillin.[28]

Similarly, according to national treatment guidelines for antimicrobial use in infectious diseases, in case of methicillin sensitive organism/if staph aureus is known to be MRSA negative, cloxacillin should prescribed.[23]

However, in our study, vancomycin, linezolid, piptaz and meropenum were started as empirical therapy in 8, 3, 17 and 4 patients respectively. As these are reserve antimicrobials, should be used only when there is compelling indication for the use.

In our study, we have calculated the DDD and DDD/1000 patient days of the drugs used in the treatment for *Staphylococcal* blood culture positive patients. The DDD of ceftriaxone, piptaz, azithromcin and cefosulbactum was higher than 1, showing that the prescribed doses were higher than the WHO defined daily doses.

DDD/1000 patient days show a rough estimate of the proportion of the study population treated daily with a particular drug or group of drugs.

In our study, the DDD/1000 patient days was lowest for ciprofloxacin which was 0.98 and higher for azithromycin, cefosulbactum, and ceftriaxone which was 4.07, 3.67 and 3.55 respectively.

We did not find any similar study reporting DDD/1000 patients days for the patients of *S. aureus* septicemia.

However, in a study by Bansal et al reported DDD/1000 patient days of ceftriaxone was 143.22, for Metronidazole was 5.92, for azithromycin was 66.37, augmentin was 32.33, cefo-sulbactum was 33.39 and piptaz was 25.02.[29]

Study by Candeloro et al reported DDD/1000 patient days were 296.25, 187.20, 65.43 and 69.06 for piptaz, vancomycin, metronidazole and meropenum respectively.[30]

In the present study, DOT (Days of therapy) for antibacterial agents in 50 patients ranged from 2 to 62 days with mean DOT of 19.54±14.22 days and median of 17 days. LOT (length of therapy) ranged from 2 to 21 days with mean LOT of 8.18±4.05 days and median of 7 days. With DOT/LOT ranged from 1 to 4 days with mean DOT/LOT of 2.22±0.84. This suggest that in every patient, two to three antibacterial agents were used at any given point of time during the course of treatment.

In our study, out of 50 patients, maximum number of patients {22 (44%)} stayed in hospital for the period of 1-2 weeks, followed by 36% patients stayed for less than 1 week and 20% patients had greater than 2 weeks of hospital stay.

We could not find the similar study for the comparison of the duration of the hospital stay for the patient of *Staphylococci* sepsis.

In our study out of all 50 patients' treated, 39 (78%) patients got cured (recovered from the diseases). The 9 (18%) patients were lost to follow up. Out of these 9 patients, 8 patients took DAMA (Discharge against medical advice) except one, who was absconded (left without asking). So, the outcome status of the patient (weather the disease was cured or not) remained unknown to us. Two (4%) patients died during the treatment.

We could not find any similar study of *Staphylococci aureus* sepsis for the comparison of outcome of treatment.

Most of the patients were prescribed injectable antimicrobials, probably because all the patients were from indoor setting. Majority of antimicrobials were prescribed from national list of essential medicine, India and in WHO model list of essential medicines.

Limitations

Although all efforts have been made to explain the study, there are still limits to a relatively smaller sample size due to time constraints, as the results will be more significant with the larger sample population.

Since the reporting of blood culture is the time-consuming diagnostic test of the laboratory, many patients were discharged before the report was dispatched.

Similar studies done on large scale can substantially reflect changing pattern of drug prescribing thus contributing toward improvisation in health care decision making. Moreover, as our study was limited to a multispecialty tertiary care institute, it would not necessarily reflect the nationwide trends.

CONCLUSION

Antibacterial drug utilization study in the patients of sepsis due to *S. aureus* was conducted in medicine ward, SSG hospital and medical college, Vadodara for the duration period of 9 months (From July 2017 to March 2018). Increasing resistance to the available antimicrobial agents is a global concern with limited availability of antimicrobial agent for such patients. Such scenario results into poor treatment outcome and increasing duration of hospital stay and with overall increase in economic burden. Effective Antimicrobial stewardship practices especially formulary restriction and aggressive infectious control measures is the need of the hour.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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