Postintervention, there was increased susceptibility of all GNBs to aminoglycosides; spp. to colistin, which caused BSI.

**Materials and methods:** We compared the susceptibility patterns of gram-negative bacteria (GNB) and gram-positive cocci (GPC) causing BSI and changes in the volume of antibiotics prescribed for the same before and after 2017 by a retrospective analysis.

**Results:** Postintervention, there was increased susceptibility of all GNBs to aminoglycosides; Escherichia coli and Klebsiella spp. to beta-lactam-beta-lactamase inhibitors (BLBLI) combinations; and Klebsiella spp. and Pseudomonas spp. to carbapenem. Acinetobacter spp., Klebsiella spp., and Pseudomonas spp. showed improved susceptibility to doxycycline, whereas E. coli and Klebsiella spp. showed significantly improved susceptibility to fluoroquinolones. Among GPCs, there was increased susceptibility of Staphylococcus aureus (levofloxacin, clindamycin, and aminoglycoside), coagulase-negative S. aureus (CoNS) (chloramphenicol, levofloxacin, clindamycin, and aminoglycoside), and enterococci (chloramphenicol, levofloxacin, and clindamycin). There was a significant reduction in usage of antimicrobials for the treatment of GPCs (linezolid, doxycycline, chloramphenicol, levofloxacin, BLBLI, macrolide, and cephalosporin) and GNBs (levofloxacin, cephalosporin, carbapenem, and colistin), which caused BSI.

**Conclusion:** The present study illustrated that combined ASP and DSP interventions successfully reversed the resistance pattern of organisms causing BSI and resulted in a reduction in antibiotic utilization.

**Keywords:** Antibiotic stewardship, Antimicrobial consumption, Antimicrobial resistance, Carbapenem, Colistin, Gram-negative bacteria, Gram-positive organisms.

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**INTRODUCTION**

Increasing antimicrobial resistance (AMR) among common bacterial pathogens has become an enormous global concern. The World Health Organization in its October 2020 bulletin reemphasized that AMR is one of the top 10 global public health threats facing humanity.1 The cost of AMR to the economy is huge and affects it in multiple ways—protracted illness leading to prolonged intensive care unit (ICU) and hospital stays, need for expensive antimicrobial agents and those with enhanced toxicities, financial challenges for the family, and finally, leading to disability and death. The crisis created by AMR became all the more worrisome as the development of new antibiotics has slowed down considerably over the past decades with the emergence of resistance to newer as well as older generations of antibiotics due to injudicious use and increasing hetero resistance among microorganisms.2

Antimicrobial stewardship (ASP) has been defined as ‘coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.’3 The results of implementing ASP had been mixed. On one hand, ASP had been associated with improved antibiotic prescribing behavior, significant reductions in total antibiotic use, reduced drug costs, and shorter hospitalizations;4,6 there were also reports of increasing resistance.7 In Ireland, it was reported that in spite of 20 years of ASP, there had been a steady increase in antibiotic prescribing and consumption over the past 10 years, with rising AMR, including the advent of carbapenemase-producing Enterobacteriaceae (CRE).8 In a review article published recently, the authors pointed out that there were scant data on ASPs in low- and medium-income countries and deserve urgent attention.9

Among the different areas in a hospital, like outpatient departments, wards, and ICUs, the latter poses the gravest AMR...
challenge to the clinicians. Many ICUs became sinks for multidrug-resistant (MDR) pathogens, as they are the final destination of patients with treatment failure due to AMR. Moreover, empiric regimens are continued too long or too broadly, inadvertently ending up selecting the resistant pathogen they were intended to treat. In addition to the high incidence of AMR among patients admitted to ICUs, they also provide a defined population of “patients and bacterial isolates” in a confined setting, with high rates of infection (thus higher numbers of clinical isolates to evaluate) and high rates of antibiotic use. ICU demands consideration of various factors unique from those in other areas of the hospital. Two important barriers to a successful ASP in ICUs are diagnostic uncertainty and fear among intensivists of not adequately covering the causative pathogen(s), particularly, in septic shock. These lead to empirical therapy, often prolonged. Both these barriers may be surmounted by accurate and earlier diagnosis.

Implementing diagnostic stewardship (DSP) has a definite role as it envisages the right test for the right patient, generating accurate, clinically relevant results at the right time to optimally influence clinical care and to conserve health-care resources.

We hypothesized that implementation of practices incorporating the principles of ASP and DSP would lead to the reversal of the pattern of AMR among common bacteria isolated from those suffering from bloodstream infection (BSI), which in turn will entail the reduction in the volume of antibiotics used.

The aim of the study was to carry out a retrospective analysis to demonstrate whether ASP- and DSP-related interventions improve antibiotic susceptibility among common organisms causing BSI in patients admitted to ICU. Also, we looked into changes in the volume of antimicrobial consumption following ASP- and DSP-related interventions.

**MATERIALS AND METHODS**

The present study is a hospital-based retrospective, cohort study of patients admitted to ICU with bacterial BSI between January 1, 2015, and December 31, 2019. Waiver of consent was approved by the Institute Ethical Committee (IEC 48/20 dated April 20, 2020). Our health-care center is a 500-bedded tertiary referral center. As a result, the hospital receives patients, both directly from the community and transferred from other hospitals in the region. All positive blood cultures with recognized bacterial pathogens among patients who were hospitalized in our 14-bedded ICU during the study period were included in the analysis. BSI was defined by positive blood cultures in a patient with systemic signs of infection and may be either secondary to a documented source or primary—that is, without an identified origin.

The present study was divided into two phases; before and during November 2017 when very few or no intervention was implemented, and after November 2017 when we implemented several ASP- and DSP-related interventions.

ASP measures adopted include nominating full-time intensivist for ICU patients, installing electronic medical records (EMR), regular audit and feedback, optimization of dose and duration of antibiotics, educational and reinforcement programs for judicious use of antibiotics, developing protocol for empirical therapy based on local antibiograms, and combined ICU rounds by intensivists and microbiologists. Bundle approach to minimize central line-associated BSI was strictly enforced. Other measures included hands-on training of resident doctors and nurses regarding hand hygiene, sample collection, and biomedical waste disposal.

DSP was implemented in a phased manner. From 2017 onward, blood culture samples were processed using VersaTREK (TREK Diagnostics System, California, USA), and from June 2019 onward in BacTALERT (BioMérieux, France) automated system; before that manual, only blood culture processing was done. Bacterial identification and disk diffusion testing for antimicrobial susceptibility were being done using conventional biochemical tests or disk diffusion method and were performed using VITEK II (BioMérieux, France) from 2017 onward, and antibiotic susceptibility reports with minimum inhibitory concentration (MIC) and breakpoints were initiated. From May 2019 onward, MALDI-TOF (BioMérieux, France) was used for the identification of organisms.

Antibiotic susceptibilities were performed using Clinical and Laboratory Standards Institute (CLSI) guidelines with breakpoints as mentioned for respective years. The MIC was promptly communicated to the ICU faculty in charge. Subsequently, annual antibiograms constructed were analyzed for any change in the pattern of antibiotic resistance.

The antimicrobials prescribed by intensivists were purchased from the hospital pharmacy, the record of which is maintained by an inbuilt pharmacy hospital information system (HIS). Data were collected from pharmacy stock regarding prescription, purchase, or consumption of antibiotics in the two phases; using pharmacy prescription uploaded in HIS, units of particular antimicrobials prescribed by an intensivist and its dosage were extracted from the pharmacy portal and evaluated for any changes in antibiotic prescribing habits in ICU.

**Data Entry and Statistical Analysis**

The data generated in this retrospective study were subjected for analysis with the help of appropriate statistical tools and the interpretation of significant outcome using IBM SPSS (Statistical Package for the Social Sciences) version 21.0. In cases where there were multiple blood cultures positive with the same pathogen, only the first positive blood culture was included in this study. Standard descriptive statistics were calculated for categorical (in percentage) and continuous variables (median and interquartile, interquartile range). p value was calculated using the chi-square test for a row-by-column contingency table with appropriate degrees of freedom. p <0.05 was considered statistically significant.

**Results**

Table 1 shows the characteristics of the study that include the total number of blood samples received in the microbiology laboratory from patients with suspected BSI from ICU, the number of samples that tested positive for BSI, age, and gender of the patients, annually from 2015 to 2019. There has been a gradual increase in the number of cases enrolled every year, due to an increase in the patient population attending this tertiary care hospital.

Table 2 shows the microbiological etiology of BSI. We found that *Acinetobacter* spp. were the commonest bacteria in 2015 and 2016, whereas *Staphylococcus aureus* was the commonest organism in 2017. In 2018 and 2019, *Klebsiella pneumoniae* was the commonest organism detected in the blood. The important thing to note here is that initially (i.e., in years 2015–16) to counteract extended-spectrum beta-lactamase–producing (ESBL) organisms and *Acinetobacter* spp., there was more use of carbapenem group of drugs, as a result, due to selection pressure, there came a surge in cases of CRE, which explains the rise of *K. pneumoniae* in later years.
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Table 1: Characteristics of the clinical study

| Year | 2015 | 2016 | 2017 | 2018 | 2019 |
|------|------|------|------|------|------|
| Total number of blood culture received | 188 | 365 | 871 | 957 | 1492 |
| Total number of cultures positive for BSI | 85 | 51 | 94 | 98 | 158 |
| Age (years), median (IQR) | 56 (50–62) | 58 (54–62) | 60 (53–67) | 59 (52–66) | 62 (50–74) |
| Female sex, n (%) | 44 (51%) | 26 (51%) | 49 (52%) | 43 (44%) | 67 (42%) |

Table 2: Etiology of bacterial BSIs

| Pathogen | 2015 | 2016 | 2017 | 2018 | 2019 |
|----------|------|------|------|------|------|
| Gram-negative bacilli | | | | | |
| Enterobacteriaceae | | | | | |
| Enterobacter species | 11% | 5% | 5% | 9% | 3% |
| Escherichia coli | 18% | 11% | 12% | 13% | 14% |
| Klebsiella species | 10% | 8% | 17% | 18% | 25% |
| Proteus species | 9% | 10% | 7% | 7% | 6% |
| Providencia species | 6% | 9% | 4% | 6% | 4% |
| Salmonella species | 0% | 0% | 0% | 0% | 0% |
| Serratia species | 0.5% | 1% | 0% | 0% | 1% |
| Non-Enterobacteriaceae | | | | | |
| Acinetobacter species | 23% | 22% | 15% | 17% | 17% |
| Aeromonas species | 0.5% | 0% | 0% | 0% | 0% |
| Burkholderia species | 0% | 0% | 0% | 0% | 0% |
| Stenotrophomonas species | 0% | 1% | 0% | 1% | 2% |
| Pseudomonas aeruginosa | 10% | 10% | 11% | 12% | 13% |
| Gram-positive cocci | | | | | |
| Enterococcus species | 1% | 2% | 3% | 2% | 2% |
| Staphylococcus species | 11% | 21% | 25% | 15% | 12% |
| Streptococcus species | 0% | 0% | 1% | 0% | 0% |

Table 3 shows the change in susceptibility of gram-negative bacteria (GNB) to the antimicrobials between pre- and postintervention. There was increased susceptibility for most antibiotics in all the common GNBs (Acinetobacter spp., Escherichia coli, K. pneumoniae, and Pseudomonas aeruginosa) postintervention compared to preintervention. The increase was significant for aminoglycosides for all GNBs, for beta-lactam-beta-lactamase inhibitors (BLBLI) (like piperacillin-tazobactam and cefoperazone sulbactam) in E. coli, Klebsiella, and Pseudomonas. Klebsiella spp. and Pseudomonas spp. also showed a significant increase in susceptibility to carbapenems. Acinetobacter, Klebsiella, and Pseudomonas showed improved susceptibility to doxycycline, whereas E. coli and Klebsiella showed significantly improved susceptibility to fluoroquinolones.

Table 4 shows the change in susceptibility of common gram-positive cocci (GPC) to antimicrobials. There was increased susceptibility to all the common antimicrobials among GPCs like S. aureus, coagulase-negative Staphylococcus (CoNS), and Enterococci. The increase was significant in the case of S. aureus for levofloxacin, clindamycin, and aminoglycoside. For CoNS, there was a significant increase in susceptibility for chloramphenicol, levofloxacin, clindamycin, and aminoglycoside. Enterococci (E. faecalis and E. faecium) showed increased susceptibility for chloramphenicol, levofloxacin, and clindamycin.

Table 5A shows there was a significant reduction in usage of linezolid, doxycycline, chloramphenicol, levofloxacin, BLBLI, macrolide, and cephalosporin, whereas there was an increase in usage of aminoglycoside for treating BSI caused by GPCs. Table 5B showed that there was a significant reduction in usage of levofloxacin, cephalosporin, carbapenem, and colistin.

Flowchart 1 shows schematically the decrease in turnaround time (TAT) of blood culture samples after the introduction of DSP. Earlier using conventional biochemical identifications and AST methods, laboratory TAT was 72 to 96 hours, which was significantly decreased to 24–48 hours once automated methods for identification and AST were being used.

**Discussion**
This is the first study, to our knowledge, which explored the combined role of implementation of ASP and DSP on changes in susceptibility patterns of common microorganisms and also the changes in volume of antibiotics prescribed or consumed.

India carries one of the largest burdens of drug-resistant pathogens worldwide and alarmingly high resistance among GNB and GPCs. India is also one of the largest consumers of antibiotics worldwide, and antibiotic sale continues to increase rapidly.

Table 3: Change in susceptibility of microorganisms to antimicrobials between pre- and postintervention periods for GNB

| Organisms | Acinetobacter spp. | Escherichia coli | Klebsiella spp. | Pseudomonas aeruginosa |
|-----------|------------------|-----------------|----------------|----------------------|
| Gentamicin | 20% | 35% | 0.01* | 28% | 42% | 0.03* | 26% | 41% | 0.025* | 24% | 37% | 0.04* |
| Piperacillin-tazobactam | 10% | 18% | 0.1 | 15% | 36% | 0.009* | 14% | 29% | 0.011* | 9% | 25% | 0.003* |
| Imipenem | 22% | 34% | 0.06 | 35% | 47% | 0.08 | 37% | 58% | 0.003* | 27% | 41% | 0.03* |
| Ceftriaxone | 5% | 15% | 0.02* | 11% | 33% | 0.003* | 9% | 37% | 0.001* | 12% | 34% | 0.003* |
| Doxycycline | 30% | 45% | 0.02* | 56% | 65% | 0.19 | 53% | 68% | 0.03* | 42% | 58% | 0.02* |
| Levofloxacin | 33% | 38% | 0.46 | 30% | 46% | 0.02* | 32% | 51% | 0.006* | 36% | 49% | 0.06 |
| Colistin | 76% | 83% | 0.22 | 78% | 92% | 0.008* | 75% | 89% | 0.01* | 68% | 75% | 0.27 |

*Significance observed in antimicrobial susceptibility, in post-intervention period; p value was calculated using a paired t-test for a row-by-column contingency table with appropriate degrees of freedom. p <0.05 was considered statistically significant.
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**Table 4:** Change in susceptibility of microorganisms to antimicrobials between pre- and postintervention periods for GPC

| Organism | Antimicrobial | Pre | Post | p value | Pre | Post | p value | Pre | Post | p value |
|----------|---------------|-----|------|---------|-----|------|---------|-----|------|---------|
| S. aureus | Gentamicin | 98% | 99% | 0.6 | 98% | 98% | 0.1 | 98% | 99% | 0.6 |
| CoNS | Doxycycline | 80% | 78% | 0.7 | 83% | 77% | 0.3 | 85% | 82% | 0.6 |

**Table 5A:** Change in antimicrobial consumption for BSI between pre- and postintervention in GPC causing BSI

| Antimicrobial | Number of pre-scribed units | Pre-ASP | Post-ASP | p value |
|---------------|-----------------------------|---------|----------|---------|
| Linezolid     | 2 mg/mL                     | 198     | 195      | 0.001* |
| Doxycycline   | 100 mg                      | 810     | 748      | 0.0001* |
| Gentamicin    | 40 mg/2 mL                  | 151     | 164      | 0.001* |
| Levofloxacin  | 25 mg/mL                    | 706     | 415      | 0.03* |
| Piperacillin  | 4.5 g                       | 761     | 462      | 0.01* |
| Azithromycin  | 500 mg                      | 1150    | 660      | 0.007* |

**Table 5B:** Change in antimicrobial consumption for BSI between pre- and postintervention in GNB causing BSI

| Antimicrobial | Number of pre-scribed units | Pre-ASP | Post-ASP | p value |
|---------------|-----------------------------|---------|----------|---------|
| Doxycycline   | 100 mg                      | 802     | 542      | 0.07   |
| Gentamicin    | 40 mg/2 mL                  | 564     | 421      | 0.05   |
| Levofoxacin   | 25 mg/mL                    | 547     | 443      | 0.008* |
| Piperacillin  | 4.5 g                       | 761     | 457      | 0.07   |
| Ceftiraxone   | 3 MIU                       | 382     | 210      | 0.02*  |

Despite a decline in the incidence of communicable diseases, In spite of this, there are very few published studies from India that evaluate the role of ASP on AMR of common microbes and on the consumption of antibiotics. In a retrospective study published in 2012 from India, the impact of ASP activities on the prevalence of CRE in the hospital was investigated. Authors reported that the incidence of CRE E. coli dropped from 3.7 to 1.6%, whereas CRE Klebsiella spp. reduced from 6 to 3.6%. ESBL-producing E. coli rate increased from 70 to 82%, while for ESBL Klebsiella spp., the rate reduced from 80 to 75%. The average usage of carbapenem group of antibiotics reduced from 955 vials to 745 vials. In a recent prospective cohort study carried out over 18 months involving two ICUs of a tertiary care hospital, infectious diseases (ID) physicians reviewed all prescriptions and gave alternate recommendations if the antibiotic use was inappropriate. Antimicrobial use decreased from 831.5 to 717 days of therapy per 1,000 (<0.000) patient days. De-escalation according to culture sensitivity improved significantly. They found that 73.3% of antibiotic prescriptions were inappropriate indicating that an effective inpatient ASP would make a substantial impact. They used a consultative-based stewardship, which would be difficult to implement in most Indian hospitals because of the lack of ID specialists. Moreover, the authors did not investigate changes in resistance patterns as a result of the ASP program. In another recent study, the authors reported a decrease in the mean monthly cost of consumption of restricted antibiotics and a decreasing trend of defined daily dose of colistin. Adoption of an EMR can improve ASP by providing a centralized location for microbiology results and other relevant clinical data. Absence of EMR had been recognized as one of the barriers to an effective ASP. Multidisciplinary rounds with guideline-based antibiotic recommendations for specific infections have been found to decrease the use and duration of both broad-spectrum and high-end, reserve antibiotics. Since there is a paucity of ID specialists, medical microbiologists play an important role in promoting DSP and supporting common tracking and reporting practices, and making hospital antibiograms. Thus, we believe the combined rounds of intensivists and microbiologists and collective decision taken (on basis of MIC obtained) to start appropriate treatment as well as de-escalation made a huge impact on the rational use of antibiotics in our study.
The presence of a prompt microbiology laboratory, high level of understanding of ASP among staff, an easily accessible antibiogram, and established guidelines for empiric prescribing were identified as important facilitators of an effective ASP in a hospital. We chose BSI because it was associated with a 40–60% increase in the risk of mortality and is considered one of the most devastating entity in ICU with far-reaching consequences, like a prolonged length of hospital stay, high cost to the family and exchequer, and in many instances, death. They represent 15% of all nosocomial infections. It is important to initiate prompt and adequate antimicrobial therapy as it impacted mortality. We found that Acinetobacter spp. were the commonest bacteria in 2015 and 2016, whereas S. aureus was the commonest organism in 2017. In 2018 and 2019, Klebsiella species were the commonest organism detected in blood. The authors reported that the predominant pathogen in BSI was GNBs (Acinetobacter spp. being the commonest followed by Klebsiella) in 82% of cases with S. aureus being the most common pathogen among GPCs.

Carbapenem resistance affects both nonfermenters and fermenters in all regions; however, the rates of carbapenem resistance were higher in nonfermenters than in fermenters. It has posed a huge challenge in the management of several types of life-threatening infections caused by nonfermenters because of the low permeability of the outer bacterial membrane to several antibiotics, including carbapenems. In a recent report, it was found that K. pneumonia and E. coli were the most common CRE among Enterobacteriaceae. These CREs pose the greatest risk to public health because of their high prevalence, high potential for causing a wide range of clinical infections, co-resistance to BL as well as other antimicrobial agents (such as aminoglycosides and fluoroquinolones). The present study showed that there was significantly improved sensitivity of Klebsiella spp. and Pseudomonas aeruginosa (a nonfermenter) to not only carbapenems but also cephalosporins, BLBLI combinations, aminoglycosides, and doxycycline, thus, reversing the trend prevalent worldwide. The presence of a prompt microbiology laboratory, high level of understanding of ASP among staff, an easily accessible antibiogram, and established guidelines for empiric prescribing were identified as important facilitators of an effective ASP in a hospital. We chose BSI because it was associated with a 40–60% increase in the risk of mortality and is considered one of the most devastating entity in ICU with far-reaching consequences, like a prolonged length of hospital stay, high cost to the family and exchequer, and in many instances, death. They represent 15% of all nosocomial infections. It is important to initiate prompt and adequate antimicrobial therapy as it impacted mortality. We found that Acinetobacter spp. were the commonest bacteria in 2015 and 2016, whereas S. aureus was the commonest organism in 2017. In 2018 and 2019, Klebsiella species were the commonest organism detected in blood. The authors reported that the predominant pathogen in BSI was GNBs (Acinetobacter spp. being the commonest followed by Klebsiella) in 82% of cases with S. aureus being the most common pathogen among GPCs.

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Polymyxin E or colistin was withdrawn from clinical use in mid-1970s, on account of its adverse effects, particularly, nephrotoxicity and neurotoxicity. It reemerged in mid-1990s, as a last resort treatment against MDR and extended drug-resistant GNBs. With

The presence of a prompt microbiology laboratory, high level of understanding of ASP among staff, an easily accessible antibiogram, and established guidelines for empiric prescribing were identified as important facilitators of an effective ASP in a hospital.
time, the overuse and misuse of these last resort drugs have also led to the emergence of colistin-resistant bacteria. The results of our study showed that there was significantly increased sensitivity of E. coli and Klebsiella spp. and nonsignificant increase in sensitivity of Acinetobacter spp. and P. aeruginosa to colistin (Table 3).

The high prevalence of resistance of GPC to several commonly used antimicrobials (Table 2) may be ascribed to increasing incidence of community-associated methicillin-resistant S. aureus (CA-MRSA) in causing infections in the hospitals, thus, fading the distinction between CA-MRSA and healthcare-associated MRSA. There had been reports of outbreaks of infections caused by CA-MRSA and also reports of CA-MRSA-associated BSI in significant numbers.

There was a significant reduction in consumption of linezolid, doxycycline, aminoglycoside, levofloxacin, macrolide, and cephalosporin for management of BSI caused by GPCs (Table 5A). We found that there was a significant reduction in usage of levofloxacin, cephalosporin, carbapenem, and colistin, whereas there was an increase in usage of aminoglycoside for treating BSI caused by GNBS. (Table 5B). Several previous studies had reported that ASP had positively impacted the antibiotic utilization and susceptibilities, in the present study, it is not only the ASP intervention that played a vital role, but DSP too. DSP was the first step toward the effective implementation of ASP. With the advent of automated machines, the culture and antibiotic sensitivity result can be available 24–48 hours earlier than the usual conventional and manual techniques. Diminished TAT gave an advantage to intensivist for prompt and appropriate action including de-escalation and removal or change of central line where possible. It was proved that rapid diagnostics only improve clinical outcomes if they are accompanied by stewardship teams that properly interpret results and apply them to treatment decisions.

Limitations of the Study
We understand that the present study suffers from several limitations. This is the experience of the ICU of a single center. We did not differentiate primary from secondary BSI. Two years postintervention is a short time, and it needs to be seen whether the benefit accrued will sustain over a longer time. We have reported only the total number of organisms and not the BSI episodes. Study of BSI episodes classified into community- and hospital-acquired BSIs would have led to a more comprehensive analysis. In spite of these limitations, the present study definitely adds to the scanty data on the implementation of ASP and DSP in India.

Conclusion
The present study illustrates that effectively implemented ASP and DSP interventions can help in successfully controlling and reversing the AMR in gram-negative and gram-positive organisms associated with BSI in an ICU setup and also result in a reduction in antibiotic prescription or consumption. The study further emphasizes building and strengthening of other components, such as information technology in monitoring and surveillance, use of automated methods and sensitizing staff, and broadening the role of different staff members to develop an effective team.

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Reference
1. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.
2. Pickens CI, Wunderink RG. Principles and practice of antibiotic stewardship in the ICU. Chest 2019;156(1):163–171. DOI: 10.1016/j.chest.2019.01.013.
3. Infectious Diseases Society of America. Antimicrobial stewardship: promoting antimicrobial stewardship in health care. Available from: https://www.idsociety.org/policy-advocacy/antimicrobial-resistance/antimicrobial-stewardship/.
4. Evans RS, Pestonnik SL, Classen DC, Clemmer TP, Weaver LK, Orme JF Jr, et al. A computer-assisted management program for antibiotics and other antiinfective agents. N Engl J Med 1998;338(4):232–238. DOI: 10.1056/NEJM199802123380406.
5. Timbrook TT, Hurst JM, Bosso JA. Impact of an antimicrobial stewardship program on antibiotic utilization, bacterial susceptibilities, and financial expenditures at an academic medical center. Hosp Pharm 2016;51(9):703–711. DOI: 10.1310/hpj5109-703.
6. Young MK, Buisin KL, Cheng AC, Thursky KA. Improved susceptibility of Gram-negative bacteria in an intensive care unit following implementation of a computerized antibiotic decision support system. J Antimicrob Chemother 2010;65(5):1062–1069. DOI: 10.1093/jac/dqk058.
7. Gregory JR, Suleyman S. A review of the opportunities and shortcomings of Antibiotic stewardship. U.S. Pharmacist 2018;43(4):HS-7–HS-12.
8. O’Sullivan CE. Antimicrobial stewardship failure: time for a new model. J Antimicrob Chemother 2020;75(5):1087–1090. DOI: 10.1093/jac/dkaa006.
9. Nathwani D, Varghese D, Stephens J, Ansari W. Value of hospital antimicrobial stewardship programs (ASPs): a systematic review. Antimicrob Resist Infect Control 2019;8(1). DOI: 10.1186/s13756-019-0471-0.
10. Messacar K, Parker SK, Todd JK, Dominguez SR. Implementation of rapid molecular infectious disease diagnostics: the role of diagnostic and antimicrobial stewardship. J Clin Microbiol 2017;55(3):715–723. DOI: 10.1128/JCM.02264-16.
11. Timsit JF, Ruppé E, Barbier F, Tabah A, Bassetti M. Bloodstream infections in critically ill patients: an expert statement. Intensive Care Med 2020;46(2):266–284. DOI: 10.1007/s00134-020-05950-6.
12. Marshall J, Mermel L, Fakhri M, Hadaway L, Kallen A, O’Grady N, et al. Strategies to prevent central line–associated bloodstream infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35(7):753–771. DOI: 10.1086/676533.
13. Collee FG, Miles RS, Amyes SGB. Laboratory control of antimicrobial therapy. In: Collee JG, Fraser AG, Marmion BP, Simmons A, editors. Mackie & McCartney practical medical microbiology, 14th ed. London: Churchill Livingstone; 1996. p. 131–150.
14. Miles RS, Amyes SGB. Laboratory control of antimicrobial therapy. In: Collee JG, Fraser AG, Marmion BP, Simmons A, editors. Mackie & McCartney practical medical microbiology, 14th ed. London: Churchill Livingstone; 1996. p. 131–150.
Antimicrobial and Diagnostic Stewardship Reverses Antimicrobial Resistance

& McCartney practical medical microbiology, 14th ed. London: Churchill Livingstone; 1996. p. 151–178. Clinical and Laboratory Standards Institute.

15. Performance standards for antimicrobial susceptibility testing, 30th ed. CLSI document M100; 2020.

16. Dixit A, Kumar N, Kumar S, Trigun V. Antimicrobial resistance: progress in the decade since emergence of New Delhi metallo-β-lactamase in India. Indian J Community Med 2019;44(1):4–8. DOI: 10.4103/jcm. JCM_217_18.

17. Ghafor A, Nagyekar V, Thilakavathy S, Chandra K, Gopalakrishnan R, Vidyalakshmi P, et al. “Save Antibiotics, Save lives”: an Indian success story of infection control through persuasive diplomacy. Antimicrob Resist Infect Control 2012;1(1):29. DOI: 10.1186/2047-2994-1-29.

18. Rupali P, Palanikumar P, Shanthamurthy D, Peter JV, Kandasamy S, Zachaeus NGP, et al. Impact of an antimicrobial stewardship intervention in India: evaluation of post-prescription review and feedback as a method of promoting optimal antimicrobial use in the intensive care units of a tertiary-care hospital. Infect Control Hosp Epidemiol 2019;40(5):512–519. DOI: 10.1017/ice.2019.29.

19. Patel, P. Minding the gap: rethinking implementation of antimicrobial stewardship in India. Infect Control Hosp Epidemiol 2019;40(5):520. DOI: 10.1017/ice.2019.62.

20. Singh S, Menon VP, Mohamed ZU, Kumar VA, Nampoothiri V, Sudhir S, et al. Implementation and impact of an antimicrobial stewardship program at a tertiary care center in South India. Open Forum Infect Dis 2019;6(4):ofy290. DOI: 10.1093/ofid/ofy290.

21. Jawhari B, Keenan L, Zakus D, Ludwick D, Isaac A, Saleh A, et al. Barriers and facilitators to Electronic Medical Record (EMR) use in an urban slum. Int J Med Inform 2016;94:246–254. DOI: 10.1016/j.ijmedinf.2016.07.015.

22. Baubie K, Shaughnessy C, Kostiuk L, Varsha Joseph M, Safdar N, Singh SK, et al. Evaluating antibiotic stewardship in a tertiary care hospital in Kerala, India: a qualitative interview study. BMJ Open 2019;9(5):e026193. DOI: 10.1136/bmjopen-2018-026193.

23. Rimawi RH, Mazer MA, Siraj DS, et al. Impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial utilization and patient outcome. Crit Care Med 2013;41(9):2099–2107. DOI: 10.1097/CCM.0b013e31828e9863.

24. Adrie C, Garrouste-Orgeas M, Ibn Essaied W, Schwebel C, Darmon M, Mourvillier B, et al. Attributable mortality of ICU-acquired bloodstream infections: impact of the source, causative micro-organism, resistance profile and antimicrobial therapy. J Infect 2017;74(2):131–141. DOI: 10.1016/j.jinf.2016.11.001.

25. Bassetti M, Righi E, Carneuelli A. Bloodstream infections in the Intensive Care Unit. Virulence 2016;7(3):267–279. DOI: 10.1080/21505594.2015.1134072.

26. Bharadwaj R, Bal A, Kapila K, Mave V, Gupta A. Blood stream infections. BioMed Res Int 2014;2014. Article ID 515273. DOI: 10.1155/2014/515273.

27. Khurana S, Bhardwaj N, Kumari M, Malhotra R, Mathur P. Prevalence, etiology, and antibiotic resistance profiles of bacterial bloodstream infections in a tertiary care hospital in Northern India: a 4-year study. J Lab Physicians 2018;10(4):426–431. DOI: 10.4103/JLP.JLP_78_18.

28. Nordmann P, Poirel L. Epidemiology and diagnostics of carbapenem resistance in gram-negative bacteria. Clin Infect Dis 2019;69(Suppl. 7):S521. DOI: 10.1093/cid/ciz824.

29. Alizadeh N, Ahangarzadeh Rezaee M, Samadi Kafil H, Hasani A, Soroush Barhaghi MH, Milani M, et al. Evaluation of resistance mechanisms in carbapenem-resistant enterobacteriaceae. Infect Drug Resist 2020;13:1377–1385. DOI: 10.2147/IDR.S244357.

30. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis 2005;40(9):1333–1341. DOI: 10.1086/429323.

31. El-Sayed Ahmed MAE, Zhong LL, Shen C, Yang Y, Doi Y, Tian GB. Colistin and its role in the Era of antibiotic resistance: an extended review (2000–2019). Emerg Microbes Infect 2020;9(1):868–885. DOI: 10.1080/22221751.2020.1754133.

32. Kale P, Dhawan B. The changing face of community-acquired methicillin-resistant Staphylococcus aureus. Indian J Med Microbiol 2016;34(3):275–285. DOI: 10.4103/0255-0857.188313.

33. Bondarenka CM, Bosso JA. Successful implementation of an antimicrobial stewardship program at an academic medical center. Hosp Pharm 2017;52(7):508–513. DOI: 10.1177/0018578717721535.

34. Patel R, Fang FC. Diagnostic stewardship: opportunity for a laboratory-infectious diseases partnership. Clin Infect Dis 2018;67(5):799–801. DOI: 10.1093/cid/ciy077.