Antibiotics in Prevention and Treatment of Multi-Drug Resistant (MDR) Organisms causing Surgical Site Infection (SSI)

Saranya K. Lakshmi1, Hema Narasimhe Gowda1*, Anuradha K2

1Department of Pharmacology, Mysore Medical College and Research Institute
Mysore, Karnataka, India.
2Department of Microbiology, Mysore Medical College and Research Institute
Mysore, Karnataka, India.

Abstract

Antibiotics play a vital role in prevention and treatment of various infections. But inappropriate antibiotic choice could lead to emergence of multi-drug resistance (MDR) among microorganisms. Since, the antibiotic susceptibility pattern of organisms could vary from place to place; forming a local prophylaxis and treatment protocol could hugely reduce this global burden. The primary objectives of the study were to observe the frequency of multi-drug resistant organisms causing Surgical Site Infections (SSIs) and to study the pattern of antibiotic usage for the prophylaxis and treatment of SSIs. A descriptive study was carried out in general surgical wards of KR hospital, Mysore for a period of 18 months (2015-2016). The relevant data was collected from the case sheets of patients who were diagnosed with SSI. Pus samples were collected, and culture-sensitivity was done. Collected data were analyzed using relevant statistical tests. A total of 263 study subjects including both males and females were enrolled in the study. Cefotaxime was the most common antibiotic used for pre-surgical prophylaxis (n=221). Out of 263 pus samples 92% were culture positive. The most common organisms causing SSI were E-coli-ESBL (n=73) and MRSA (n=44). About 95% of organisms showed multi-drug resistance. Imipenem, Gentamicin, Piperacillin-Tazobactum and Linezolid were the most common antibiotics used in the treatment of SSIs. The result of the study is alarming. Overall, there is great rise in the prevalence of MDR organisms causing SSIs. The hospital antibiotic policy should be revised in such a way to decrease the emergence of MDR microbes.

Keywords: Multi-drug resistant organisms, surgical site infection, surgical antibiotic prophylaxis, Antibiotic susceptibility testing

Introduction

Surgical antibiotic prophylaxis refers to the prevention of infectious complications by administering an effective antimicrobial agent prior to exposure to contamination during surgery.1 The principles of appropriate prophylactic antibiotic use for surgical patients begin with the selection of agents that respond well to microorganisms common in surgical wounds.2 However, it has been noted that prolonged antibiotic prophylaxis does not decrease surgical infection and is associated with higher levels of bacterial resistance.3 Although, we have effective guidelines...
proposed for prophylaxis and treatment of SSIs, a constant threat by emerging MDR organisms is alarming. Evidence showed that MRSA and MR-CNS strains isolated from surgical wounds showed multi-drug resistance towards ampicillin, cotrimoxazole, erythromycin, clindamycin, ciprofloxacin, cefotaxime and ceftazidime. In addition, Extended Spectrum Beta Lactamase (ESBL) producing Enterobacteriaceae Sp was shown as one of the major gram-negative organism causing SSI in few studies.

National institute for healthcare and excellence (NICE) suggests using the local antibiotic formulary and always taking into account the potential adverse effects when choosing specific antibiotics for prophylaxis. So, with the aim of forming a local protocol, this present study was undertaken to study the prevalence of multi-drug resistant (MDR) organisms causing SSIs and the choice of antibiotics used for prevention and treatment of SSIs at a tertiary care hospital.

Methods
This observational study was undertaken in surgical wards for a period of 18 months (1st January 2015 – 30th June 2016) to study the proportion of MDR organisms causing SSI and to observe the clinician’s preference of antibiotics in the prophylaxis and treatment of SSIs. Prior to data collection the study protocol with written informed consent form was submitted; and the study was approved by the Institutional Ethics Committee.

The study population included those who were diagnosed with SSI and admitted in the general surgery ward. The type of sampling is the purposive sampling. Using estimation technique with prevalence of SSIs 22%, margin of error at 5% and level of significance 5%, the sample size was found to be 263. The inclusion criteria were the patients older than 18 years of either sex; who had undergone abdominal surgeries and diagnosed with SSI.

After obtaining written informed consent, appropriate data like Socio-demographic details like age, sex, diagnosis, surgery done, details of pre-op and post-op antibiotics used were collected and details on wound infection (soakage of wound dressing, pain, swelling, pus collection and history of fever) were recorded in a Proforma.

Collection and processing of pus sample
After cleaning the wound with saline, the pus or discharge from the surgical wound was collected using a sterile cotton swab. The pus sample was immediately transferred to Microbiology laboratory for further processing. All the samples were processed as per standard guidelines. Smear was prepared and stained by gram’s stain. Specimen was inoculated onto Mac Conkey and blood agar. Isolates were identified by standard protocol.

Antibiotic Susceptibility Testing
Susceptibility testing was performed by Kirby-Bauer disk diffusion technique according to criteria set by Clinical and Laboratory Standards Institute (CLSI) 2011. The inoculum was prepared by picking parts of similar test organisms with a sterile wire loop and suspended in sterile normal saline. The density of suspension to be inoculated was determined by comparison with opacity standard on McFarland 0.5 Barium sulphate solution.

The test organism was uniformly seeded over the Mueller-Hinton agar and exposed to a concentration gradient of antibiotic diffusing from antibiotic-impregnated paper disk into the agar medium, and then incubated at 37°C for 16-18 hours. Diameters of the zone of inhibition around the discs were measured to the nearest millimeter using a ruler and classified as sensitive, intermediate, and
resistant according to the standardized table supplied by CLSI 2011. The discs were selected based on gram positive and gram-negative organisms.

The discs used for gram positive organisms are penicillin G (10 units); amoxicillin (10 µg); cefoxitin (30 µg); erythromycin (15 µg); clindamycin (2 µg); gentamicin (10 µg); ciprofloxacin (5 µg); cotrimoxazole (25 µg); vancomycin (30 µg); teicoplanin (15 µg) and aztreonam (30 µg).

The discs used for gram negative bacteria amoxicillin-clavulanate (30(20/10) µg), cefalexin(30µg); cefaclor(30µg); ceftriaxone (30 µg); cefotaxime (30 µg); cefoperazone (75 µg); cephepine (30 µg); gentamicin (10 µg); ciprofloxacin (5 µg); cotrimoxazole (25 µg); colistin (10 µg); piperacillin + tazobactum (100/10 µg); imipenem (10 µg); tigecyclin (15 µg) and aztreonam (30 µg).

Statistical analysis
Statistical tests applied for data analysis were descriptive statistics, Chi square test and Cramer’s V test. Statistical analysis was done using R-software.

Results
A total of 263 patients who were admitted in the General surgery ward diagnosed with SSI were enrolled in the study. The most common characteristics of the study participants are presented in Table 1. The emergency surgeries were statistically higher when compared to elective ones (p= 0.001).

In our hospital, Cefotaxime, Amikacin, Metronidazole and Piperacillin-Tazobactum were the antibiotics used for pre-operative prophylaxis. All 263 patients were given pre-op surgical prophylaxis and the above mentioned antibiotics were given intravenously before shifting the patient to Operation Theater. In our study, cefotaxime was given to 221 study subjects, metronidazole was used in 161 subjects, amikacin and piperacillin+ tazobactum were given to 43 and 42 study subjects respectively as pre-op surgical prophylaxis.

Table 1: Most Common Characteristics of Study Participants

| No | Patient Characteristics                        | Frequency (%) |
|----|------------------------------------------------|---------------|
| 1  | Most common age group 41-60 years              | 42.2          |
| 2  | Gender:                                        |               |
|    | Male                                           | 58            |
|    | Female                                         | 42            |
| 3  | Most common diagnoses                          |               |
|    | Intestinal perforation                         | 38(14.4)      |
|    | Diabetic cellulitis                            | 33(12.5)      |
|    | Acute appendicitio                             | 32(12.2)      |
| 4  | Most common surgeries                          |               |
|    | Open abdomino perineal resection              | 58(22.1)      |
|    | Mesh repair                                    | 49(18.6)      |
|    | Open appendicectomy                            | 38(14.4)      |
| 5  | Type of surgery                                |               |
|    | Emergency                                      | 159(60)       |
|    | Elective                                       | 104(40)       |
The use of Cefotaxime and Metronidazole as pre-op antibiotics was significantly higher. But the use of Amikacin and piperacillin-Tazobactum was significantly lower as shown in Table 2.

In our study cefotaxime, amikacin, metronidazole and piperacillin+ tazobactum were the antibiotics used for pre-operative prophylaxis of SSIs. Among the above four, a third generation cephalosporin, cefotaxime was used in most patients undergoing surgery which was different from studies done by Alavi SM et al\textsuperscript{10}, Misra AK et al\textsuperscript{11} and a meta-analysis done by Fischer MI et al\textsuperscript{12} where cefazolin was the preferred drug. Moreover, cefazolin, a first generation cephalosporin is the first line recommended drug as per SIGN [Scottish Intercollegiate Guidelines Network] and ASHP [American Society of Health-System Pharmacists] guidelines.\textsuperscript{13,14}

The preference of cefotaxime here is probably due to prevalence of organisms causing SSI with a different susceptibility pattern in our hospital. In our study, intravenous Metronidazole was added to cefotaxime for anaerobic coverage which was like studies done by Khan AKA et al\textsuperscript{15} and Chopra et al\textsuperscript{16}. According to a study, metronidazole is a preferred SAP before abdominal surgeries to combat anaerobic infections.\textsuperscript{17}

In our study, 263 patients were given pre-op surgical prophylaxis which shows irrational prescription of prophylactic antibiotics in case of clean surgeries where SAP is not indicated. These antibiotics were given intravenously before shifting the patient to operation theatre as supported by a study done by Bratzler DW et al\textsuperscript{17}. But the time of SAP administration was not specified in the case records. It is important because ASHP therapeutic guideline recommends administration of the first dose of antimicrobial within 60 minutes before surgical incision.\textsuperscript{11,13}

The percentage of gram negative organisms was significantly higher than that of gram positive organisms in our study (p<0.001). The gram positive bacteria contributed to 23% (n=57) and gram negative bacteria to around 77% (n=190) of the total culture positive cases. The culture report of pus samples shows that around 92% of the total 263 samples were culture positive means that 92% study subjects had proven SSI. The rest 8% showed negative culture or no growth which means that their wounds were not infected.

Surgery like Mesh repair, modified radical mastectomy, excision, splenectomy and sub cutaneous mastectomy were associated with negative culture. This association was proved to be statistically significant in case of mesh repair (p=0.003) and modified radical mastectomy (p=0.001). Also among the four categories of surgery, only clean surgery was significantly associated with no growth (p<0.001) whereas clean-contaminated surgery was not significantly associated

| Pre-Op Antibiotics       | Given | Not Given | p value |
|--------------------------|-------|-----------|---------|
| Cefotaxime               | 221   | 42        | <0.001  |
| Metronidazole            | 161   | 101       | <0.001  |
| Amikacin                 | 43    | 220       | <0.001  |
| Piperacillin-Tazobactum  | 42    | 221       | <0.001  |
with no growth (p< 0.001). Similarly, both emergency and elective surgeries were significantly associated (p< 0.001) with no growth (Table 3).

MDR was seen with 95% of the organisms identified. This was proved to be statistically significant (p<0.001). Organisms were categorized as MDR if they were resistant to ≥3 drug groups. We found that around 95% of organisms that have caused SSI were MDR which is much higher when compared to some studies as follows and among those E-coli (ESBL) and MRSA were the most common ones. This is in contrary to a study done by Bhatt CP et al18, where the MDR was found to be 65.38% and Acinetobacter spp. was the most predominant isolates (32.33%) followed by Pseudomonas aeruginosa (21.80%) etc. In addition, a study done in Nigeria19 found 32% MDR and staphylococcus aureus as the most common organism associated with SSIs. The reason for this variation in results could probably be due to differences in the antibiotic protocol being followed and hygienic measures in that particular hospital. Both Extended spectrum beta lactamase (ESBL) producing E-coli and MRSA were identified as the most common organisms showing significantly higher MDR (p<0.001). Next to them are the E-Coli and Klebsiella respectively. Others showing MDR are Pseudomonas, Acinetobacter, Citrobacter, Proteus, Staphylococcus aureus, MRCoNs and Enterobacter (Figure 1).

Among 241 patients who showed positive culture of the pus sample, around 58 were treated with Imipenem (p<0.001), 40 were given Gentamicin, 31 patients were prescribed piperacillin-tazobactum and linezolid each and 23 were treated with ciprofloxacin (Figure 2).

Among the four antibiotics used for pre-surgical prophylaxis, ceftriaxone (n=3), piperacillin-tazobactum (n=31) and Amikacin (n=1) were used for treatment of SSI as well. There was a change in antibiotic after culture report in majority of the patients (n=210) with a higher preference for broad spectrum ones. The most preferred antibiotics for treatment of SSI are impenem (n=58), gentamicin (n=40), piperacillin-tazobactum (n=31) and linezolid (n=31). (Table 4)

Table 3. Association of Various Surgical Parameters with Negative Culture

| Parameters                     | Total N (%) | Number of Growth, N (%) | Test Statistic  |
|-------------------------------|-------------|-------------------------|-----------------|
|                               |             |                         | Chi-Aquare | p value |
| **Surgeries:**                |             |                         |              |         |
| Mesh repair                   | 49          | 14 (28.6)                | 9.00        | .003    |
| Modified-radical mastectomy   | 14          | 1 (7.14)                 | 10.286      | .001    |
| Excision                      | 12          | 5 (41.7)                 | 0.333       | .564    |
| Splenectomy                   | 1           | 1 (100)                  |             |         |
| Subcutaneous mastectomy       | 1           | 1 (100)                  |             |         |
| **Categories of surgery:**    |             |                         |              |         |
| Clean                         | 79          | 20 (25.3)                | 19.253      | < 0.001 |
| Clean contaminated             | 84          | 2 (2.38)                 | 76.19       | < 0.001 |
| **Time of surgery:**          |             |                         |              |         |
| Emergency                     | 158         | 21 (13.3)                | 85.165      | < 0.001 |
| Elective                      | 83          | 1 (1.2)                  | 79.048      | < 0.001 |
This shows that due to prevalence of MDR organisms in the culture report, the surgeons had to choose the broad spectrum antibiotics (as a last resort) listed above for the treatment of SSIs. In due course, this could result in development of resistance towards these precious antibiotics too which is a major concern today. However, there were only few patients were the same prophylactic antibiotic was continued which could probably be due to any contraindications to the use of broad spectrum antibiotics in those patients. Our study is the first one to report on the post-swab antibiotic preference in treatment of SSIs since there is no similar literature available so far.

The major limitation of our study is that the results cannot be generalized for the whole population. This could be because the study was done in a single centre and the method of sampling is a purposive sampling.

**Conclusion**

Our study concludes that there is a sizeable increase in the development of MDR among organisms causing SSIs in our hospital leading to increased use of broad spectrum antibiotics. So, there is urgent need for an effective local protocol for surgical antibiotic prophylaxis which should be strictly followed by the doctor.
Acknowledgement
I thank Dr. B. M. Parashivamurthy, Professor and Head, Department of Pharmacology, MMC and RI, Mysore for his support and encouragement to carry-out this study. I wish to thank the Professor and Head, Department of Surgery, KR hospital, Mysore, for their support. I would like to thank all the staff members in the general surgery ward for their guidance.

Funding
None

Conflict of Interest
None declared

References
1. World Health Organisation. Global guidelines for the prevention of surgical site infection. 2016; Available from: https://apps.who.int/iris/bitstream/handle/10665/250680/9789241549882-eng.pdf?sequence=8
2. Han HS, Park DJ. Antibiotic Prophylaxis and Surgical Site Infection Prevention. Enhanced Recovery After Surgery. Springer Link. 2020; 259–267.
3. Bharath M, Galagali JR, Mishra AK, Mallick A, Nikhilesh E. Prophylactic use of antibiotics as per SIGN 104 guidelines versus routine antibiotic prophylaxis for prevention of surgical site infection in clean and clean contaminated ENT surgical procedures. International Journal of Otorhinolaryngology and Head and Neck Surgery. 2020; 6(1):106–111.
4. Iyamba JL, Wambale JM, Lukukula CM, za Balega Takaisi-Kikuni N. High prevalence of methicillin resistant staphylococci strains isolated from surgical site infections in Kinshasa. The Pan African Medical Journal. 2014; 18(322)
5. Young B, Ng TM, Teng C, Ang B, Tai HY, Lye DC. Nonconcordance with Surgical Site Infection Prevention Guidelines
and Rates of Surgical Site Infections for General Surgical, Neurological, and Orthopedic Procedures. *Antimicrobial Agents and Chemotherapy*. 2011; 55(10):4659–4663.

6. Sarma J B, Bhattacharya P K, Kalita D, Rajbangshi M. Multidrug-resistant Enterobacteriaceae including metallo-β-lactamase producers are predominant pathogens of healthcare-associated infections in an Indian teaching hospital. *Indian Journal of Medical Microbiology*. 2011; 29(1):22–27.

7. National Institute of Healthcare and Excellence. Preventing and treating surgical site infections. 2020; 1–29. Available at: https://www.nice.org.uk/guidance/ng125

8. Mawalla B, Mshana SE, Chalya PL, Imirzalioglu C, Mahalu W. Predictors of surgical site infections among patients undergoing major surgery at Bugando Medical Centre in Northwestern Tanzania. *Bugando Medical Centre Surgery*. 2011; 11.

9. Sawdekar H, Sawdekar R, Wasnik VR. Antimicrobial susceptibility pattern of bacterial isolates from wound infection and their sensitivity to antibiotic agents at super specialty hospital, Amravati city, India. *International Journal of Research in Medical Sciences*. 2015 Feb; 3(2): 433-439

10. Alavi SM, Roozbeh F, Behmanesh F, Alavi L. Antibiotics Use Patterns for Surgical Prophylaxis Site Infection in Different Surgical Wards of a Teaching Hospital in Ahvaz, Iran. *Jundishapur Journal of Microbiology*. 2014; 7(11): e12251

11. Misra AK, Gupta R, Bedi JS, Narang M, Garg S. Antibiotic prophylaxis for surgical site infection: Need of time. *The Health Agenda*. 2015; 3(3):70-76

12. Isabel FM, Cicero D, Tetelbom SA, Guardiola MN, Isabela H. Antibiotic prophylaxis in obese patients submitted to bariatric surgery. A systematic review. *Acta Cirúrgica Brasileira*. 2014 Mar; 29(3): 209-217

13. Bratzler DW, Dellinger EP, Olsen KM, Peri TM, Auwaerter PG, Bolon MK, Fish DN, Nepolitano LM, Sawyer RG, Slain D, Steinberg JP, Weinstein RA. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *American Journal of Health-System Pharmacy*. 2013; 70: 195–283

14. Madhusudan E, Jakribettu RP, Boloor R, Rao SN. Study of Pre-Surgical Antimicrobial Prescribing Pattern and Correlation with Microbiological Data in a Tertiary Care Hospital. *E-Cronicon Microbiology*. 2015; 2(4):365-373

15. Khan AKA, Mirshad PV , Rashed MR, Banu G. A Study on the Usage Pattern of Antimicrobial Agents for the Prevention of Surgical Site Infections (SSIs) in a Tertiary Care Teaching Hospital. *Journal of Clinical and Diagnostic Research*. 2013; 7(4): 671-674

16. Chopra T, Zhao JJ, Alangaden G, Wood MH, Kaye S. Preventing surgical site infections after bariatric surgery: value of perioperative antibiotic regimens. *Expert Review of Pharmacoeconomics and Outcomes Research*. 2010 June; 10(3): 317–328

17. Lőfmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. *Clinical Infectious Diseases*. 2010; 50 (1): S16–23

18. Bhatt CP, Baidya R, Karki P, Shah RK, Miya R, Mahashate P, Mishra KK. Multi Drug Resistance Bacterial Isolates of Surgical Site Infection. *Open Journal of Medical Microbiology*. 2014; 04(04):203–209.

19. Murphy RA, Okoli O, Essien I, Teicher
C, Elder G, Pena J, Ronat JB, Bernabe KJ. Multidrug-resistant surgical site infections in a humanitarian surgery project. *Epidemiology and Infection*. 2016; 144(16): 3520–3526.