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

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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

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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.[4] 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.[5,6]

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.[7] 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%[8], 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

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resistant according to the standardized table supplied by CLSI 2011.[9] 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 (30 µg); cefaclor (30 µg); ceftriaxone (30 µg); cefotaxime (30 µg); cefotaxime + clavulanate (30/10 µg); cefoperazone (75 µg); cefepime (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	N (%)
	Intestinal perforation	38(14.4)
	Diabetic cellulitis	33(12.5)
	Acute appendicitio	32(12.2)
4	Most common surgeries	N (%)
	Open abdomino perineal resection	58(22.1)
	Mesh repair	49(18.6)
	Open appendicectomy	38(14.4)
5	Type of surgery	N(%)
	Emergency	159(60)
	Elective	104(40

Table 2. Frequency of Pre-op Antibiotics Usage

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

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[10], Misra AK et al[11] and a meta-analysis done by Fischer MI et al[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.[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[15] and Chopra et al[16]. According to a study, metronidazole is a preferred SAP before abdominal surgeries to combat anaerobic infections.[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[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.[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.

Surgeries 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

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

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 al[18], 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 Nigeria[19] 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)

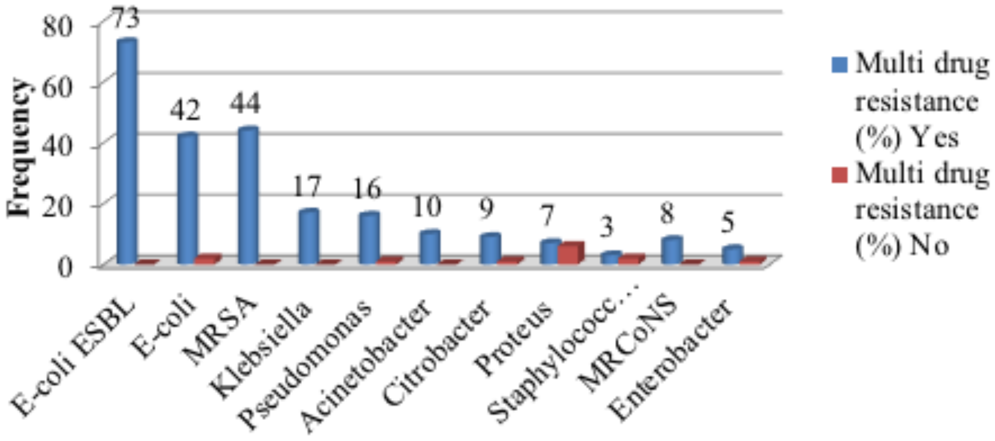

Figure 1. Distribution of MDR-organisms

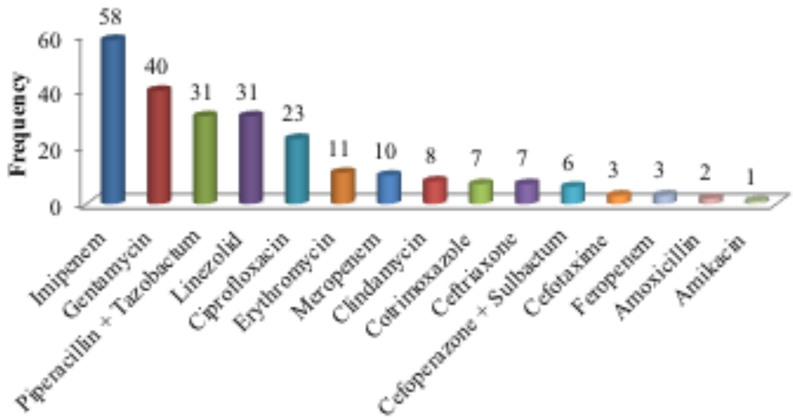

Figure 2. Choice of Antibiotics in the Treatment of SSIs

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.

Table 4. Comparison of Antibiotics Used for Treatment with Those Preferred for Prophylaxis of SSI

Antibiotics preferred for treatment of SSI (N)	Prophylactic antibiotics (N)			
	Cefotaxime	Metronidazole	Amikacin	Piperacillin + Tazobactum
Imipenem (58)	50	45	12	9
Gentamycin (40)	32	25	34	8
Piperacilin+ Tazobactum (31)	29	22	11	2
Linezolid (31)	23	14	1	8
Ciprofloxacin (23)	21	14	17	2
Erithromycin (11)	9	6	0	2
Meropenem (10)	8	8	1	2
Clindamycin (8)	2	2	0	2
Cotrimoxazole (7)	1	5	0	1
Ceftriaxone (7)	2	6	4	2
Cefoperazone+ Sulbactum (6)	2	4	0	2
Cefotaxime (3)	2	3	0	2
Feropenem (30	0	3	2	0
Amoxicillin (2)	0	1	0	0
Amikacin (1)	1	1	0	0

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Conflict of Interest

None declared

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