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Evaluation of antibiotic utilization pattern and economic outcomes associated with surgical site infection in surgical department of tertiary care hospitals Karachi, Pakistan

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Abstract: Surgical Site Infection (SSI) has an enormous impact on patients' quality of life. SSIs further stresses on allocation of different health care resources and contribute significantly in terms of high cost of care. This was a prospective study carried out in tertiary care hospitals of Karachi, Pakistan, involving abdominal surgeries and few other surgeries, in patients having 20 years of age and above, were admitted from June 2016 to May 2017. Total number of 554 patients were included. Data was collected in all relevant areas including utilization pattern of antibiotics, cost in term of infected and uninfected patients, the duration of patient stay etc. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software. P value less than 0.005 was taken as significant**.** Single therapy of co amoxiclav or along with metronidazole and third generation cephalosporin were the most common prescribed antimicrobial groups. Amikacin most commonly used to treat post-surgical wound infection. Economic cost was high in terms of SSI patients. Duration of stay was found longer in infected patients**.** It can be concluded that SSI, may prolong length of hospitalization, cause morbidity, upsurge the health care cost, and even may lead to mortality.

Keywords: Surgical site infection, economic burden, antibiotic pattern, length of hospitalization.

INTRODUCTION

Postoperative SSIs can be quite lethal and remain a major source of morbidity or a less frequent cause of mortality in surgical patients. From the estimated 2 million nosocomial infections approximately one-quarter account for SSI annually. Furthermore, SSIs cause an increase treatment cost, bed occupancy in hospital ward and prolong patient’s hospital stay. In developing countries, due to inadequate resources, even basic life-saving procedures like cesarean sections and appendectomies are linked with high rate of infections of wounds and cause mortality (Sattar *et al.,* 2019).

Multi drug resistance (MDR) poses a greater challenge to surgeons to treat post wound infection with antibiotics reported to be high (Tariq *et al.,* 2017). Patients who acquired resistant infections are at greater risk for morbidity, mortality, longer duration of hospital stays, and catastrophic health expenditures (Velin *et al*., 2021).

For Surgical antibiotic prophylaxis (SAP) it is essential to choose an antibacterial agent having narrowest spectrum in turn to decrease the emergence resistivity and there may be wide spectrum of antibiotics required later in case (Rehan *et al.,* 2009). Furthermore, poor selection of antibiotic is linked with the significant increase in mortality. Approximately 30-90% of prophylactic antibiotic used in hospital found to be inappropriate (Rahman *et al.,* 2015). Furthermore, adherence to the guidelines or recommendation in selecting the type and timing of antibiotic administration for prophylaxis is not always followed. It was also observed that in many of the cases, prophylactic antibiotics prescribed for longer duration than suggested in guideline, this situation has brought to higher occurrence of antibiotic resistance globally, which has a considerable impact on public health issues, mainly on treatment outcomes. Surgeons frequently used a broad/wide-spectrum antibiotic prophylaxis prior to surgical procedure or that does not comply with the guidelines/suggestions that have been recommended (Radji *et al.,* 2014; Kulkarni *et al.,* 2005). Therefore, to improve the prescribing pattern of antimicrobial prophylaxis, it is essential to know the trends used for prescribing antibiotics along with the adherence to the recommendations of the guidelines (Ahmed *et al.,* 2022)

Pharmacoeconomic is considered as the significant part of health economics. The study of pharmacoeconomic approximates the cost (monetary terms expressions) and effects (articulated in terms of fiscal value, effectiveness or improved quality of life) of a pharmaceutical manufactured goods. Numerous disciplines of pharmacoeconomic estimation encompass cost-benefit, cost-minimization, cost- utility and cost- effectiveness

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analysis. Such studies provide a guide for optimal allocation of healthcare resource in a scientifically and consistent manner (Jayanthi *et al.*, 2014; Turner *et al.*, 2021).

The development of a Surgical Infection causes a considerable upsurge in the clinical as well as economic burden in surgical discipline. The fiscal burden of surgery is amplified due to the direct costs sustained by prolonged length of hospitalization in patient, diagnostic procedure or tests, and treatment. Some patients may also need to reoperate after the contraction of an SSI, which is directly related with significant additional costs (Badia *et al.*, 2017).

Overall, Surgical site Infection may result in $1–$10 billion in direct and indirect medical costs annually, however, costs and outcomes secondary to SSIs can vary by location and type of surgery (Perencevich *et al.*, 2003). While, Inappropriate usage of antibiotic could lead to increased hospital financial costs, emergence of resistant microbes, and super-infections and amplified adverse drug reaction (ADR). In developing nations, antimicrobials expense shares higher budget as compare to the other category of drug (Ayele and Taye 2018).

The economic impact/influence of SSIs is still under-recognized, limited research studies exist to quantify the expenses/costs to manage these infections or the financial elements that significantly contribute to those costs. In the light of above facts this study was performed to evaluate the prescribing pattern of antibiotic (Prophylaxis/Empiric) in surgical department along with their management in case of surgical site infection, Furthermore, SSI-related direct costs of care were also calculated and these results were compared with a non-SSI group.

MATERIALS AND METHODS

This was a descriptive, observational and cross-sectional study conducted between May 2016 to April 2017 among patients undergone surgery in tertiary care set up of Karachi, Pakistan. After obtaining the approval of the Ethical Review Committee (ERC) of hospital (Ref No: 0211015ATPHARM), according to the criteria of inclusion data were collected, i.e both male and female patients above 20 years of age, found to have definite SSIs, admitted in different units of hospital settings. Exclusion criteria include the ambulatory patient and infections over the incision sites after complete resolution. 554 patients' undergone surgical procedures were incorporated in the present study. Standardized data collection form comprised of multiple section was used to record information included; prescribing variables/ antibiotics with respect to diagnoses, administered dose, duration of treatment, frequency of administration, were elucidated. For this medication records hospital pharmacies records were also investigated. Comparison of Length of hospitalization between SSI and non-SSI patients were also observed. The last section of questionnaire was designed to collect the data related to economic outcomes. For this purpose, cost data for control and case patients were obtained from the computerized internal cost and activity accounting database from the hospital's finance department. This hospital database directly associated with internal hospital costs with patient charges. Hospital costs reflected the costs incurred/utilized during a specific hospitalization period and were calculated on the basis of reference prices for each type/particular type of treatment used. For quality assurance and data analysis study tool was elucidated in depth before application. In order to defend the correctness (accuracy) of outcomes, all questionnaires were under direction of the consultants, reviewed and checked/assessed cautiously before they were collected.

STASTICAL ANALYSIS

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) software (Version 22). To evaluate the significant level of outcome variables to all categorical variables, Chi- square test was executed. *P* value less than 0.05 was considered statistically significant. For comparison of total cost of SSI with international bench mark, t-test was performed

RESULTS

Study population and demographic characteristics

A total no of 554 patients with different surgical procedures were included in this study. Of these 554 patients, 333 (60.1%) operations were performed on female and 221 (39.9%) on male patients. 116 patients (20.93%) were in the age group of 21-30 years, 192patients (34.6%) were in the age group of 31-40 years, 116 patients (20.93%) were in the age group of 41-50 years, 94 patients (16.97%) were in the group of 51-60 years, 19 patients (3.4%) were in the age group of 61-70 years, while 17 (3.06%) were 71-80years of age

Antibiotic utilization pattern in various surgical procedures

Antibiotic utilization pattern (Prophylaxis/Empiric) in terms of frequency of antibiotics prescribed with respect to specific surgeries were incorporated in table 1. Prophylactic antibiotic was also noted with respect to their dose and frequency along with the strength & WHO define daily dose of the prescribed antibiotics in various surgical procedures as described in table 2. Duration of antibiotics was recorded in terms of SSI and Non-SSI along with their mean no of antibiotic as shown in table 3. Specific antibiotic in case of treatment/management of Surgical Site Infection, was mentioned in fig.1.

Table 1: Antibiotic utilization pattern in various surgical procedures

Type of Surgery	Antibiotic	Patients (N)	Patients Prescribed (N)	Frequency (%)
Cesarean section	Co-Amoxiclav	119	50	42.0%
	Ceftriaxone		4	3.3%
	Co-Amoxiclav +Metronidazole		54	45.37%
	Ciprofloxacin+Metronidazole		4	3.3%
	Ceftriaxone+Metronidazole		7	5.8%
Cholecystectomy	Ceftriaxone	116	57	49.1%
	Ciprofloxacin		21	18.1%
	Amikacin		6	5.1%
	Ceftriaxone +Metronidazole		4	3.4%
	Ciprofolaxcin+Metronidazole		7	6.03%
	Ciprofloxacin +Gentamicin		4	3.4%
	Ceftriaxone+Gentamicin		12	10.3%
	Imipenem+Cilastatin		5	4.3%
Appendectomy	Ciprofloxacin	60	12	20%
	Ciprofloxacin+Metronidazole		40	66.6%
	Cefuroxime		6	10%
	Imipenem/Cilastatin+Metronidazole		2	3.3%
Laparotomy	Ceftriaxone	88	37	42.0%
	Ciprofloxacin		21	23.8%
	Ceftriaxone+Metronidazole		12	13.6%
	Imipenem/Cilastatin +Metronidazole		9	10.2%
	Ceftrixone+Gentamicin		3	3.4%
	Ceftrixone+Gentamicin +Metronidazole		6	6.8%
Hernia repair	Co-Amoxiclav	66	38	57.5%
	Cefuroxime		15	22.7%
	CoAmoxiclav+Cefuroxime		9	13.6%
	Co-Amoxiclav+Cephadrene		2	3.0%
	Cephadrene		2	3.0%
Other surgical procedures	No Prophylaxis	105	10	9.4%
	Co-Amoxiclav		30	28.57%
	Co-Amoxiclav+Metronidazole		24	22.8%
	Co-Amoxiclav+Cefuroxime		3	2.85%
	Amikacin		14	13.3%
	Ceftriaxone +Metronidazole		8	7.6%
	Ceftriaxone		2	1.9%
	Ciprofloxacin		3	2.8%
	Ciprofloxacin+Metronidazole		2	1.9%
	Teicoplanin		2	1.9%
	Co-Amoxiclav+ Imipenem/Cilastatin +Metronidazole		7	6.6%

Table 2: Prescribed dose and frequency of antibiotic in various surgical procedures

Antibiotic	Prescribed dose	Prescribed Frequency	WHO Define Daily Dose
Co-Amoxiclav	1.2g	TDS	3g
Metronidazole	500mg	TDS	1.5g
Ciprofloxacin	400mg	BD	0.5g
Ceftriaxone	2g	OD	2g
Amikacin	500mg	BD	1g
Imipenem/Cilastatin	500mg	TDS	2g
Gentamicin	320 mg	OD	0.24 g
Cefuroxime	750mg	TDS	3g
Cephadrene	2g	OD	2g
Teicoplanin	200mg	OD	0.4g
Colistin	3-9 million units	TDS	3 million units
Sulzone (Cefoperazone / Sulbactam)	2 g	BD	4g/1g
Imipenem+Cilastatin	500mg	TDS	2g
Vancomycin	1g	OD	2g
Linzolid	600mg	BD	1.2g
Pipercillin/Tazobactum	4.5g	TDS	14g

Table 3: Number and duration of antibiotics in different surgical procedures

No of Antibiotics	No of cases.	Mean No	Std. Deviation	Minimum No. of Antibiotics	Maximum No. of Antibiotics	P value
SSI	81	3.8519	1.53388	2	7	0.000
Non SSI	473	1.4101	0.52969	1	3	
Duration of Antibiotics	No of cases.	Mean (days)	Std. Deviation	Minimum No of days	Maximum No. of days	P value
SSI	81	8.0494	3.28596	3	16	0.000
Non SSI	473	3.4419	1.33297	1	12	

Table 4: Comparison of length of hospitalization in days between infected & uninfected patients in various surgical procedures

Comparison Between SSI/Non SSI	No of cases	Mean (days)	P value	Std. Deviation	Minimum (days)	Maximum (days)	Std. Error of Mean
Cesarean Section							
SSI	6	6.50	0.000	1.643	5	9	0.670
Non SSI	113	4.34		0.942	3	8	0.088
Cholecystectomy							
SSI	12	7.00	0.000	2.662	3	10	0.768
Non SSI	104	3.72		1.396	2	9	0.136
Appendectomy							
SSI	12	6.00	0.004	3.692	3	12	1.066
Non SSI	48	3.75		0.785	3	5	0.113
Laparotomy							
SSI	30	10.60	0.000	3.756	5	17	0.685
Non SSI	58	6.13		3.075	3	14	0.406
Hernia Repair							
SSI	6	7.50	0.000	0.547	7	8	0.223
Non SSI	60	3.43		0.963	2	7	0.124
Wound Debridement							
SSI	3	15.66	0.072	1.154	15	17	0.666
Non SSI	4	10.50		0.577	10	11	0.288
Incision and drainage							
SSI	9	10.66	0.005	2.000	8	12	0.666
Non SSI	6	5.33		1.861	3	7	0.760
Abdominal Hysterctomy							
SSI	3	7.33	0.000	1.154	6	8	0.666
Non SSI	36	4.66		0.925	3	6	0.154

Table 5: Comparison of economic cost between infected & uninfected patients associated with different surgical procedures

Type of Surgical Procedures	Cost of SSI Mean (PKR)	Cost of SSI Mean ($)	No of Cases (SSI)	Cost of NonSSI (PKR)	Cost of Non SSI ($)	No of Cases (NonSSI)	P value (PKR)
Cesarean section	70289.5	671.2	6	65633.68	626.81	113	0.000
Cholecystectomy	159187.5	1520.2	12	77226.84	737.53	104	0.000
Appendectomy	141344.5	1349.8	12	61886.47	591.02	48	0.000
Laparotomy	246241.1	2351.64	30	106935.86	1021.25	58	0.000
Hernia Repair	64214.0	613.25	6	51525.13	492.07	60	0.000
Wound debridement	184666.6	1763.60	3	93765.00	895.47	4	0.072
Incision& drainage	170626.3	1629.51	9	101956.0	973.69	6	0.01
Abdominal hysterectomy	183284.6	1750.40	3	88702.83	847.12	36	0.000

Note: Average dollar rate between June 2016- May 2017=104.71PKR (1 $=104.71PKR)

Table 6: Comparison of total cost of SSI with International Bench Mark (Wijeratna *et al.,* 2015*;* Edwards *et al., 2015;* Gili Ortiz *et al., 2015;* Shepard *et al., 2013)*

Comparison of study outcome of total cost (Dollars) with different studies reported							
Parameter	N	Mean	Std. Deviation		Std. Error Mean		
Total Cost Dollars	81	1702.7051	1083.72819		120.41424		
Studies reported	Test value	t - value	df	Sig.(2-tailed)	Mean Difference	95% Confidence Interval of the Difference Lower	Upper
Wijeratna *et al.,* 2015	15576	-115.213	80	0.000	-13873.29494	-14112.9269	-13633.6630
Edwards *et al.,* 2008	25940	-201.283	80	0.000	-24237.2944	-24476.9269	-23997.6630
Gili Ortiz *et al.,* 2015	33533.4	-264.343	80	0.000	-31830.69494	-32070.3269	-31591.0630
Shepard *et al.,* 2013	58822	-474.357	80	0.000	-57119.29494	-57358.9269	-56879.6630

Length of hospitalization & economic burden

Over all comparison of length of hospitalization between SSI and non-SSI shown in fig. 2, while economic burden was illustrated in fig. 3. Length of hospitalization in relation to specific surgeries were also noted in terms of SSI or non-SSI as shown in table 4. Economic outcomes related to specific surgical procedures were also noted in terms of average cost between infected and uninfected patient as shown in table 5. A one-sample t-test was run to determine whether the total cost of SSI obtained from tertiary care hospital in Pakistan is statistically different to the cost of SSI calculated in different countries as described in table 6.

DISCUSSION

Surgical site infections are the most commonly occur health care associated infections and account for an approximate of $3.2 billion additional cost of care per year in various tertiary care setups (Zimlichman *et al.,* 2013). Despite current efforts to reduce surgical infections, these complications continue to be a serious and costly problem across worldwide, resulting in increased length of hospital stay, readmissions, outpatient visits, mortality and health care financial costs (Hou *et al.,* 2023). The objective of this study was to determine the pattern of antibiotic utilization for surgical site infection prophylactically/empirically and also evaluate the economic burden as well as length of hospitalization associated with surgical infected patients.

In surgical practice it is very common to use prophylaxis antibiotic in order to avoid complications of surgical infection. However, inappropriate use of antibiotics can lead to multiple problems including an increase in the emergence of resistant micro-organisms and elevated cost of care. Table 1 depicted the utilization pattern of antibiotic with respect to specific surgeries. In lower segment section Co amoxiclav was most commonly prescribed antibiotic in, which is parallel to the study conducted by Rehan *et al*., in 2009. The success rate of co amoxiclav as a single therapy or along with metronidazole was most commonly observed among antimicrobial groups which are concordant with the study conducted by Wloch *et al.,* in 2012. However, metronidazole has beneficial effect and it has been recommended as a combination in the surgical prophylaxis, to provide an appropriate anaerobic cover (Segura Egea *et al.,* 2017).

Table 1 also shows that the practice of co amoxiclav and second generation cephalosporin as monotherapy or in combination, was observed in cases of hernia repair but, however The European Hernia Society(EHS) does not suggest routine practice of prophylactic antibiotic for elective procedure of inguinal hernia repair (using a mesh)in those patients who are at low risk, but recommend prophylaxis consideration if there is having patient-related risks for instance old age, immunosuppressive patients and recurrence or procedure-related risks like long duration of surgery. In contrast, the latest randomized controlled trial, indicates that antibiotic utilization prophylactically is effective for the prevention of surgical site infection which is found concordant with our study (Mazaki *et al.,* 2014). The success rate of ciprofloxacin with metronidazole was observed in case of appendectomy in our study, which is almost similar to the value of the other studies (Oriaifo and Oriaifo, 2013; Saha *et al.,* 2008)

Similarly in patient who underwent in surgical procedure of cholecystectomy and laparotomy third generation cephalosporin i.e., ceftriaxone was most frequently used prophylaxis antibiotic as a single therapy or in combination with metronidazole which is similar to study of Mohamoud *et al.,* in 2016 but it found inappropriate as per *American Society of Health*-System *Pharmacists* and *Scottish Intercollegiate Guidelines Network* (SIGN), according to these guideline or recommendation for surgical prophylaxis, it is essential to choose an antibiotic having narrowest antibacterial spectrum in order to decrease the development of resistance and because broad spectrum antibiotics may be required in future incase serious sepsis develop by the patient. Therefore, it is suggested that the practice of third generation cephalosporins should be avoided in surgical prophylaxis (Rehan *et al.,* 2009).

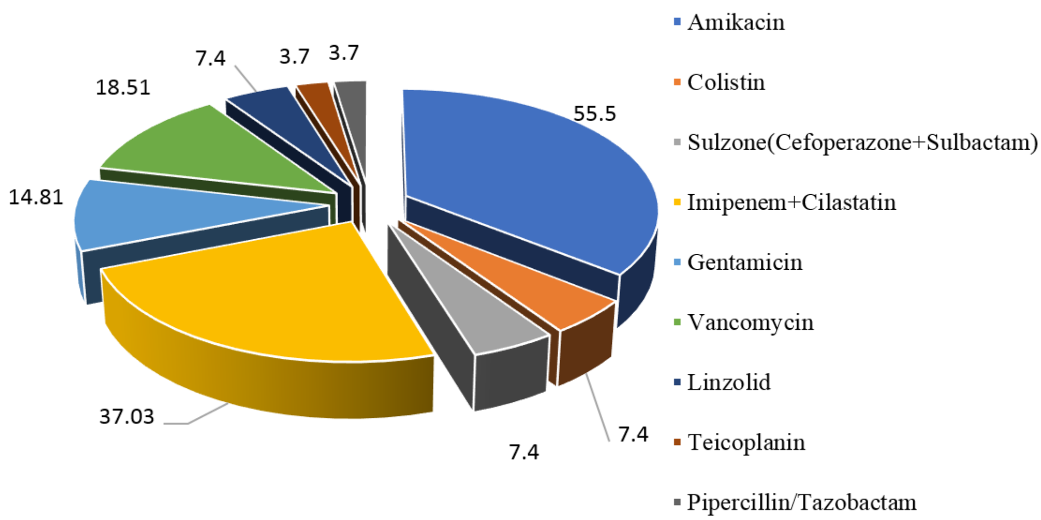

Fig. 1: Management of SSI

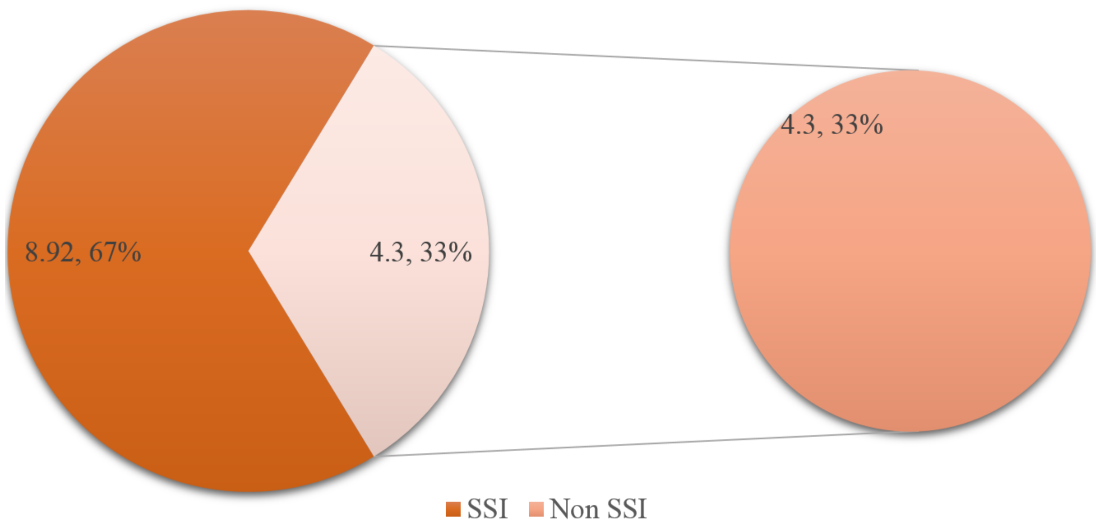

Fig. 2: Length of hospitalization between SSI and Non SSI patients

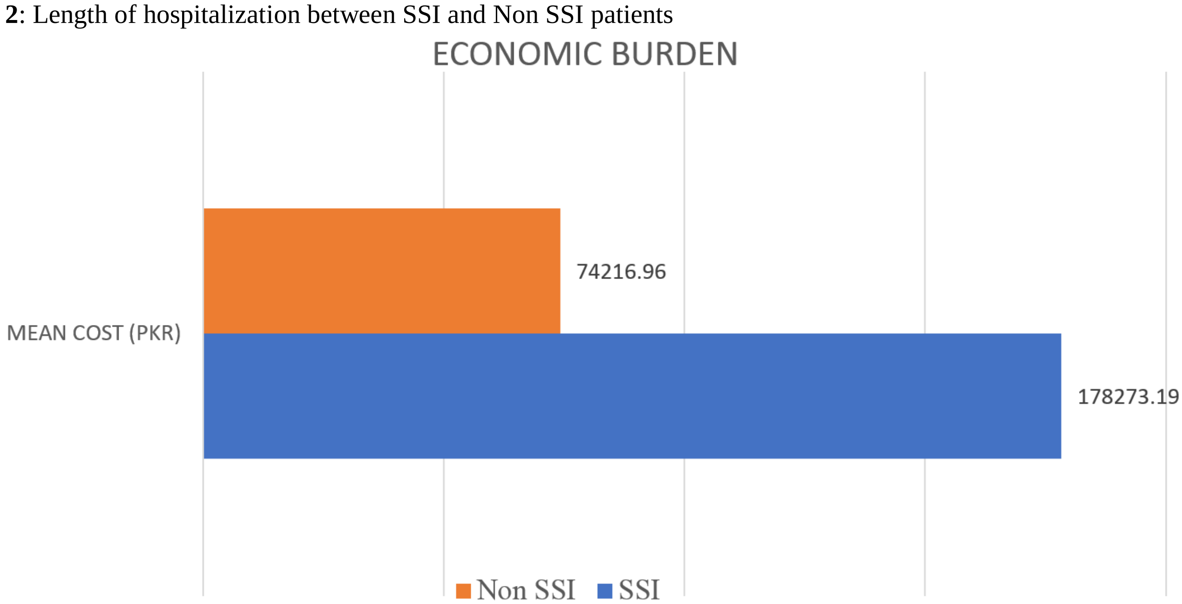

Fig. 3: Total economic cost associated with surgical infected and uninfected patients

In this study it was also observed that in some surgical procedures the combination of third 3rd generation cephalosporins like cefotaxime or ceftriaxone with metronidazole is used along with gentamicin in case of three drug combination required, which is parallel to the study conducted by Heethal *et al.,* in 2010. In present investigation half of the patients received amikacin to treat post-surgical wound infection. While imipenem + cilastatin is prescribed in 37.03% patient. This is highly supported by the study conducted by researcher demonstrated that amikacin is the most sensitive antibiotic against *E. coli* and *Pseudomonas* (Anita *et al*., 2014).

The decision on which antibiotics to use for surgery can greatly differ according to type of surgery, associated factors of patient, and identified resistance pattern against various clinical isolates. Utilization pattern of antibiotic in surgical procedures are required as prophylactic bases or specific need to prevent or treat surgical site infections. Antibiotic choices are mainly based on numerous factors including tissue penetration profiles, drug half-life, side effects or toxicity spectrum and mode of action. It is evident in table one that more frequently prescribed antibiotics in contaminated and dirty procedures are mostly given in combination in comparison to procedures where surgeries were with less risks of infections. In these cases, some narrow-spectrum antimicrobials were prescribed. Moreover, institutional protocols and guidelines and Surgeon's preferences and recommendations also influence the selection and utilization of antibiotics in different surgical procedures

For each antimicrobial agent/drug and their route of administration, the WHO Collaborating Centre for Drug Statistics and Methodology describe the Daily Define Dose (DDD) as "the assumed average maintenance adult dose per day for the main indication/use of this agent and maintains updates". However, the defined daily dose is an international unit/standard that can be used for global or regional comparisons of usage of antibiotic primary care setup and in hospitals (Dahlén *et al.,* 2023). In this study antibiotics which were prescribed with respect to specific surgical procedures were found parallel to the WHO define daily doses.

The average number and duration of antibiotic was also observed and compared between SSI and non-SSI patient. This study shown that average number of antibiotics increased in patient having SSI as compared to non-SSI patient. A similar study reported by *Giri et al.,* in 2008 found the mean number of antibiotics was 3.51 ± 1.80 in SSI patients than non-SSI patients 2.02 ± 1.26.

In this study the mean length of stay for patients having SSI was be significantly longer when compared with patients having no SSI which is found parallel to the study conducted by Labib *et al.,* 2012.

Fig. 2 shows that length of hospitalization (LOH) was found to be more in SSI patient as compared to non-SSI patient, which is found to be parallel with the study conducted by Hirani *et al.,* in 2022, reported a significant increase in the length of hospitalization in patients with incisional surgical site infection (ISSI). Patients with ISSI were estimated to have an average hospital LOS of 10 days longer than the control group.

In this study over all hospital costs for patients having SSI were found to be greater than for non-SSI patients as shown in fig. 3, found to be parallel with other study that reported costs associated with patients having SSI to be almost double as compared to non-SSI patients and mainly driven by additional length of hospitalization (Fenny *et al.,* 2020). In addition the mean average cost associated with SSI for various surgical procedures like cholecystectomy, appendectomy, laparotomy and lower segment caesarean section were also reported to be 159187.50 PKR (1520.27$), 141344.50 PKR (1349.86$), 246241.10 PKR (2351.64$), 70289.50 PKR (671.27$) respectively, which is found to be two fold higher in comparison with the average cost of the control patients undergone above mentioned procedures which is found concordant with the study of Schweizer *et al.,* 2014 who calculated the average costs for patients with and without SSI and it was found to be $52,620 and $31,580 respectively. The associated cost was 1.43 times greater in patients with SSI. A considerable portion of the increased charges was due to hospital accommodation costs and the need for additional medicines (Schweizer *et al.,* 2014).

Similar study conducted by Kaye *et al.,* in 2009 determined the charges of hospitalization during the 90 days after surgery (including readmissions to the hospital as well) which were significantly increase for patients with SSI than for uninfected patient ($94,564, IQR $84,942-104,186 and $44,080, IQR 34,219-53,940, respectively, *P*<.001).

A one-sample t-test was run to determine whether the total cost of SSI obtained from tertiary care hospital in Pakistan is statistically different to the cost of SSI calculated in different countries. In this regard the costs calculated by number of investigators for SSIs were compared with the tertiary care hospital SSI total cost of the present study and it has been illustrated from the above findings that the cost associated with surgical site infection was higher in developed countries as compare to Pakistan.

CONCLUSION

Surgical site infections (SSI) could be minimized with the number of interventions. With these encouraging result or outcomes, the good practices should be sustained and promulgated. Such an SSI prevention program should be included in the work processes linked with surgical disciplines. This study may be helpful in development of a multi factorial approach to improve patient's safety and medical outcomes. Furthermore, these findings may be beneficial for appropriate therapeutic strategies and will also be helpful to minimize the patient's burden in terms of cost due to prolonged length of hospital stay due to SSIs.

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