ISSN: 2834-5274

Research Article

Journal of Surgery Care

The Prevalence of Multidrug-Resistant Organisms in Patients with Surgical Site Infections in Riyadh, Saudi Arabia: A Cross-sectional Study at a Tertiary Care Hospital

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Submitted: 2023 , Sep 13 ; **Accepted**: 2023,Oct 06; **Published**: 2023, Oct 20

Citations: Alazmi, M., Alsabahi, T., Algwizani, A., Alqunaibet, A., Alabdan, L.., et al. (2023). The Prevalence of Multidrug-Resistant Organisms in Patients with Surgical Site Infections in Riyadh, Saudi Arabia: A Cross-sectional Study at a Tertiary Care Hospital. *J Surg Care, 2*(1), 59-67.

Abstract
Background: *Multidrug-resistant (MDR) infections are a threat in patients undergoing surgery. This study was undertaken to determine the prevalence and possible predictors of MDR infections over a two-year period in patients with surgical site infection (SSI) at a tertiary care hospital in Riyadh, Saudi Arabia.*

Methods: *We conducted a cross-sectional study from April 2016 to April 2018 by reviewing hospital records of patients with a diagnosis of SSI based on a physician report and laboratory findings. The isolation of MDR organisms (MDRO) from SSI was the primary outcome variable as well as other risk factors.*

Results: *SSI was diagnosed in 55 out of 77 patients under study, with MDRO prevalence rate of 44%. Previous antibiotic use and hospitalization in the last 90 days were strongly associated with developing MDRO infection often due to ESBL producing Gram-negative bacterial pathogens. Superficial and deep incisional SSI were more frequent in patients compared to organ/space SSI. History of diabetes mellitus, duration of surgery and bacterial colonization at other body site also increased the likelihood of MDRO. Factors such as trauma, obesity, general anesthesia, and wound types were not found to increase the risk for MDRO.*

Conclusions: *Our study identified recent antibiotic use and hospitalization as major risk factors for MDRO surgical site infections. Other predisposing factors include diabetes mellitus, duration of surgery and bacterial colonization. MDRO isolated include E. coli and Pseudomonas aeruginosa. Bacterial pathogens harboring multiple resistant mechanisms can complicate SSI adversely affecting clinical outcomes following routine surgical procedures.*

Keywords: Surgical-Site Infections, Multidrug-Resistant Organisms (MDRO), Antibiotics, ICU, Surgical Procedure.

1. Introduction
The emergence of multidrug-resistance (MDR) organisms is a threat in healthcare which adversely affects hospitalized patients [1]. Many antibiotics previously effective against common infections are no longer active due to antimicrobial resistance in bacterial pathogens. The World Health Organization (WHO) estimates that by the year 2050, about 10 million people will die annually due to antimicrobial resistance [2]. WHO also reported that the burden of antimicrobial resistance is a critical human and animal health issue requiring international cooperation [3]. MDRO colonization occurs in critically ill patients in ICU [3]. Such organisms also colonize health care workers (HCW) and often contaminate the hospital environment, with transmission to susceptible patients [4,5].

The health care system in Saudi Arabia is facing a similar challenge caused by MDRO. Recent studies suggest that MDR infections caused by Enterobacterales bacteria and non-fermenting Acinetobacter, and Pseudomonas species were common and increased morbidity and mortality in hospitalized patients [6,7]. Worldwide, the burden of antimicrobial resistance increases mortality rate and morbidity in ICU patients [8]. Studies from Saudi Arabia have identified bacterial infections and antimicrobial resistance mechanisms in hospital acquired infections. For example, staphylococci and pneumococci species have shown widespread resistance against cell wall antibiotics. In this regard, a national action plan successfully reduced MDR bacterial infections [9].

The National Healthcare Safety Network, USA reported that approximately 30% of cases of outbreaks are related to multidrug-resistance organisms [10]. The widespread use of antibiotics in the hospital affects up to 50% of hospitalized and 70% of ICU patients receiving at least one antibiotic during their stay [11, 12]. A study of 15, 202 patients worldwide reported that 21% of ICU patients had a hospital acquired infection associated with higher in-hospital mortality compared to community acquired infections [12].

A surgical-site infection (SSI) is defined by the CDC as infection that occurs within 30 days after an NHSN defined operative procedure involving only the skin and subcutaneous tissue of incision [13]. NHSN classifies SSI risk index category from 0 (lowest risk) to 3 (highest risk). The CDC SSI definition further requires presence of one of the following criteria in affected patients: a purulent discharge, identification of a bacterial pathogen, a superficial wound that is deliberately opened by a medical practitioner with features of inflammation and diagnosis of SSI by a physician or surgeon.

The causes of SSI are multifactorial involves length of hospital stay, patient co-morbidities, obesity, duration and complexity of surgical procedure, administration of general anesthesia, and a higher wound contamination classification [14, 15]. The CDC classifies surgical wounds based on their level of contamination, beginning from the Clean class 1 which are non-infective wounds with no inflammation to Dirty class 4, which are old traumatic wounds containing devitalized tissue with clinical infection or perforated viscera [16].

In a meta-analysis, SSI occur in up to 60% of patients undergoing surgery worldwide [17]. A US study reported that the healthcare costs for SSI are two times higher than the costs for treating an unaffected patient after a surgical procedure [18]. A systematic review of SSI in Europe demonstrated that SSI increased hospital length of stay and costs, require reoperation, readmission, and increased mortality [19]. While the impact of SSI on clinical outcomes and healthcare cost in Saudi Arabia have not been investigated, a 10-year study of SSI rates in Eastern province of Saudi Arabia noted a general decline in such infections caused by Gram-negative bacterial pathogens, mainly due to better infection control measures [20]. Interestingly, the authors of this study identified hospital accreditation as major factor, possibly due to improved practices.

Risk factors that predispose to SSI MDR infections in have not been investigated in our region. The existence of such data will facilitate preventive strategies to reduce the burden of MDR in SSI. This is particularly important after the Covid-19 pandemic during which the incidence of MDR has increased. Our aim was to determine the prevalence of MDRO and risk factors for SSI, thus facilitating improved patient management during the post-operative period.

2. Methods

2.1 Study Design and Test Procedures

We conducted a cross-sectional study from April 2016 to April 2018 at a tertiary care hospital in Saudi Arabia. Wound specimens from patients suspected of SSI were collected in sterile swabs in aseptic manner. Bacterial cultures were performed according to standard microbiological techniques. Antibiotic susceptibility tests (AST) were performed as per Clinical Laboratory Standards Institute (CLSI) guidelines. The final identification and AST results were verified and reported to physicians about MDRO including MRSA, ESBL, VRE and other MDR.

2.2 Study Population and Outcome Variables

The study population comprised all patients diagnosed with an infection in postoperative period. This was based on physicians' report, laboratory results and met the CDC-National Healthcare Safety Network definition of SSI. The total of 77 patients were identified with SSI during the above period. Cases of SSI that were not laboratory-confirmed were excluded. The MDRO were considered as the dependent variable in the study. Independent variables included age, gender, surgery type, duration, time between surgical procedure and the infection, wound classification, risk index category, obesity, diabetes mellitus and bacterial colonization.

2.3 Statistical Analysis

A descriptive statistic for characterizing the study population is presented in frequency tables and appropriate graphs indicated below. The prevalence of MDRO was estimated by dividing the number of MDROs by the total number of patients with surgical site infection. All prevalence estimates are presented with a 95% CI as a measure of precision. To identify associated factors with MDRO, the logistic regression analysis was used (both at the univariate and multivariate levels) to assess potential risk factors: patient age, gender, surgical procedure, duration, the time between surgery and SSI, wound classification, ASA class, risk index category, obesity, diabetes mellitus, pathogen colonization with MDRO. We used a p-value of less than 0.05 as a cut off for a significant variable. Relevant data were analyzed using SPSS version 19.

3. Results

3.1 Social and Demographic Characteristics of Participants

Table 1 below lists the demographics of the study participants as 59 males (76.6%) and 18 females (23.4%). Majority were adults (93.5%) while children were 6.50%. There were 12 diabetic patients representing 15.6% of the study population. 31 (40.30%) patients had a BMI that was considered as either normal or underweight while equal proportions were overweight and obese (30% in each group). Patients who were admitted to the hospital were 71.40% (n=55) while ICU admissions were 28.60% (n=22). Assessment of the period between surgery and an SSI event revealed that most patients developed a bacterial infection in a period of 10 days or less following surgery-54.50%

(n=42), while 45.5% (n=35) developed an infection after 10 days of surgery. The time between hospitalization and surgical procedure was 2 days or less in 66.20% (n=51), while 33.80% (n=26) of patients underwent a surgical procedure more than 2 days after hospital admission. Approximately 58.40% (n=45) of patients did not have a history of previous hospitalization (duration of > 5 days); in contrast, 41.60% (n=32) of patients who had a history of previous hospitalization. We noted that 53.20% did not have a history of receiving antibiotics in the last 90 days (n=41) compared to 46.80% (n=36) who received antibiotics in the same period.

Characteristic	n	(%)
Gender Male	59	76.6%
Female	18	23.40%
Age Pediatric	5	6.5%
Adult	72	93.50%
Diabetes Mellitus No	65	84.4%
Yes	12	15.60%
Receiving antimicrobial therapy within last 90 days		
No	41	53.20%
Yes	36	46.80%
Previous hospitalization within last 90 days		
No	45	58.40%
Yes	32	41.60%
Previous hospitalization for 5 days or more		
No	45	58.40%
Yes	32	41.60%
BMI Underweight or normal	31	40.3%
Overweight	23	29.90%
Obese	23	29.90%
Time b/w surgery and SSI		
10 days or less	42	54.50%
More than 10 days	35	45.50%
Time b/w hospitalization and surgery		
2 days or less	51	66.20%
More than 2 days	26	33.80%

Table 1: The demographics of study participants

3.2 Clinical Characteristics of Study Participants with SSI

The clinical characteristics of the study participants are presented in Table 2 below. For the risk index category (based on National Nosocomial Infections Surveillance-NNIS system of US Centre of Disease Control-CDC), majority were scored as risk index 1 (45.5%), followed by patients who were scored as 2 (40.3%), while the highest risk index 3 was the least common type of procedure (13%) in our study. As general anesthesia is a risk factor for SSI, we reviewed the proportion of patients who received a general anesthetic; these were 98.70% (n=76) compared to those who did not receive general anesthetic (1.30%). To assess wound types, we assessed if a specific wound class is associated with SSI. Most patients in our study had clean wounds (54.50%, n=42), while clean-contaminated type of wounds was found in 42.90% (n=33). Since trauma predisposes to SSI, we found no history of trauma in most patients 76.60% (n=59), while those with a history of trauma were 23.40%. Emergency surgery, a risk factor for SSI, was performed in 70.10% (n=54) compared to non-emergency surgery in 29.90% (n=23) of patients. Laparoscopic surgery was not performed in majority of cases (96.10%) in our study.

Of the total, 71.40% (n=55) patients were diagnosed with SSI before discharge from hospital vs. after discharge-23.40% (n=18) and fewer following readmission (5.20%, n=4). Laparotomies (28.60%) and appendix related surgery (20.8%) were more frequently performed, while open reduction of fractures (20.80%) and other types were fewer (29.90%).

Surgical procedures below average duration was 67.50% (n=52) compared to 32.50% that were above the average period.

Clinical characteristic	n	(%)
Risk Index Category		
0	1	1.30%
1	35	45.50%
2	31	40.30%
3	10	13.00%
General Anesthesia		
No	1	1.30%
Yes	76	98.70%
Wound type		
Clean wound	42	54.50%
Clean-contaminated		
wound	33	42.90%
Contaminated wound or		
dirty/infected Wound	2	2.60%
Trauma		
No	59	76.60%
Yes	18	23.40%
Emergency surgery		
No	23	29.90%
Yes	54	70.10%
Laparoscopic procedure		
No	74	96.10%
Yes	3	3.90%
SSI diagnosis		
Before discharge	55	71.40%
After discharge	18	23.40%
On readmission	4	5.20%
Type of surgery		
Appendix surgery	16	20.80%
Open reduction of fracture	16	20.80%
Laparotomy	22	28.60%
Others	23	29.90%
Duration of surgery		
Below average	52	67.50%
Above average	25	32.50%

Table 2: Clinical Characteristics of Study Participants

3.3 Univariate Analysis of Factors Associated with MDRO

A univariate regression analysis of MDRO as the dependent variable and other independent variables included the following. Age, gender, type of surgery, duration of surgical procedure, time between surgical procedure and infection, wound classification, risk index category for obesity, diabetes mellitus and bacterial pathogen colonization. The results in Table 3 below indicate that females had lower odd of MDRO infection compared to males (OR = 0.68, [95% CI:0.225-2.059]). Similarly, risk index categories 2 or 3 were significantly less likely to be associated with MDRO SSI compared to category 0 or 1 (OR= 0.293, [95% CI: 0.113-0.76].

Risk of MDRO infection increased with duration of surgery, diabetes mellitus, and colonization with gram-negative bacteria at another body site, although these lacked statistical significance. Contaminated wounds did not increase the risk of developing an MDRO compared to clean wounds. Likewise, a history of trauma was not associated with MDRO infection. Patients receiving antibiotics in 90 days previously were three times more likely for MDRO infection vs. patients not receiving antibiotics (OR= 3.409, [95% CI:1.314-8.847]). Further, patients hospitalized in the last 90 days were twice likely to develop an MDR infection compared to non-hospitalized patients (OR= 2.51, [95% CI: 0.982-6.413]); however, this was not statistically significant (p = 0.55). Gram negative bacteria were more likely to be the cause of MDRO compared to Gram positive bacterial pathogens.

The following outcomes were not significantly associated with MDRO: history of emergency surgery, time to SSI diagnosis after discharge, admission in the wards/ICU, adult patients, body mass index, the time between surgery and SSI, laparotomy, duration between hospitalization and surgery and type of surgery.

Characteristics	Ref.	p value*	OR	95% C.I.	
				Lower	Upper
Female Gender	Male	0.495	0.68	0.225	2.059
Risk index category 2 or 3	category 0 or 1	0.012	0.293	0.113	0.761
Duration (above average)	below average	0.865	1.088	0.408	2.902
DM	no	0.914	1.071	0.307	3.741
Colonizing organism at another body site	no	0.19	1.882	0.731	4.847
Gram positive bacteria	no	0.608	0.782	0.305	2.003
Gram negative bacteria	no	0.112	2.516	0.806	7.855
Wound class-contaminated	clean	0.02	0.315	0.119	0.83
Trauma	no	0.028	0.221	0.058	0.846
Emergency	no	0.895	1.069	0.394	2.901
Antibiotic in last 90 days	no	0.012	3.409	1.314	8.847
Hospitalization in last 90 days	no	0.055	2.51	0.982	6.413
SSI diagnosis-after discharge	before discharge	0.273	1.75	0.644	4.758
Ward	ICU	0.273	0.571	0.21	1.554
Adult	pediatric	0.358	2.857	0.304	26.86
Overweight	underweight or normal	0.123	0.41	0.132	1.274
Obese	underweight or normal	0.221	0.5	0.165	1.517
Time b/w Surgery and SSI-more than 10 days	10 or less	0.966	0.98	0.393	2.447
Time between hospitalization and surgery-more than 2 days	2 days or less	0.818	0.893	0.339	2.348
Open reduction of fracture	Appendix surgery	0.695	0.733	0.156	3.45
Laparotomy	Appendix surgery	0.159	2.64	0.685	10.181
others	Appendix surgery	0.442	1.692	0.443	6.467

p value: < 0.05 considered significant; OR: odds ratio; CI: confidence interval

Table 3: Factors associated with an MDRO surgical site infection

3.4 Multivariate Analysis for Possible Predictors of MDRO
To determine if multiple independent variables affected MDRO, we conducted a multivariate regression analysis. As in Table 4 below, the risk index categories 2 or 3 have lower odds of an MDRO after adjusting for other factors; however, this was not significant vs. category 1 (OR= 0.399, 95% CI: 0.116-1.37]). Similarly, contaminated wounds had also a lower odd ratio (adjusted) of developing MDRO SSI compared to clean wounds (OR= 0.467, 95% CI: 0.134-1.627]) without significance. Previous hospitalization in the last 90 days had 25% higher odds of MDRO SSI but this insignificant compared to patients not hospitalized. A positive history of trauma was inversely associated with MDRO SSI compared with no past trauma (OR= 0.14, [95% CI: 0.032-0.624]). Lastly, the receipt of antimicrobial therapy in the last 90 days of SSI had more than 4-fold greater likelihood of developing an MDRO infection compared to those who did not receive antimicrobial therapy (OR= 4.487, [95% CI:1.015-19.83]).

Predictors				95% CI for OR	
	Comparator	p value*	AOR**	Lower	Upper
Risk index category	Category 0 or 1	-	-	-	-
	Category 2 or 3	0.144	0.399	0.116	1.37
Wound class contaminated	Clean wound	-	-	-	-
	Contaminated	0.232	0.467	0.134	1.627
Trauma	No	-	-	-	-
	yes	0.01	0.14	0.032	0.624
Previous hospitalization in last 90 days	No	-	-	-	-
	yes	0.763	1.258	0.283	5.603
Antibiotic in last 90 days	No	-	-	-	-
	yes	0.048	4.487	1.015	19.83

p value: < 0.05 considered significant; AOR: adjusted odds ratio; CI: confidence interval for odds ratio

Table 4: Possible Predictors associated with an MDRO surgical site infection

4.5 Analysis of MDRO SSI Bacterial Isolates

The types of wounds associated with SSI were superficial SSI-42.90%, deep incisional SSI were both 42.90%, while the organ/space SSI were 14.30% (see Figure 1 below). The total number of patients identified with MDRO were 34 out of 77 in our study. Most bacterial isolates (55.8%; n=46) were sensitive to routinely reported antibiotics compared to 44.2% which were MDRO (see Figure 2 below). Gram-negative bacteria caused 72% of SSI, while Gram-positive bacteria were 28%. The bacterial resistance mechanisms included Extended-Spectrum Beta-Lactamase (ESBLs)-22.1%, methicillin-resistant staphylococcus aureus (MRSA) and MDR-10.4% (Figure 2); vancomycin resistant enterococcus (VRE) was 1.3%.

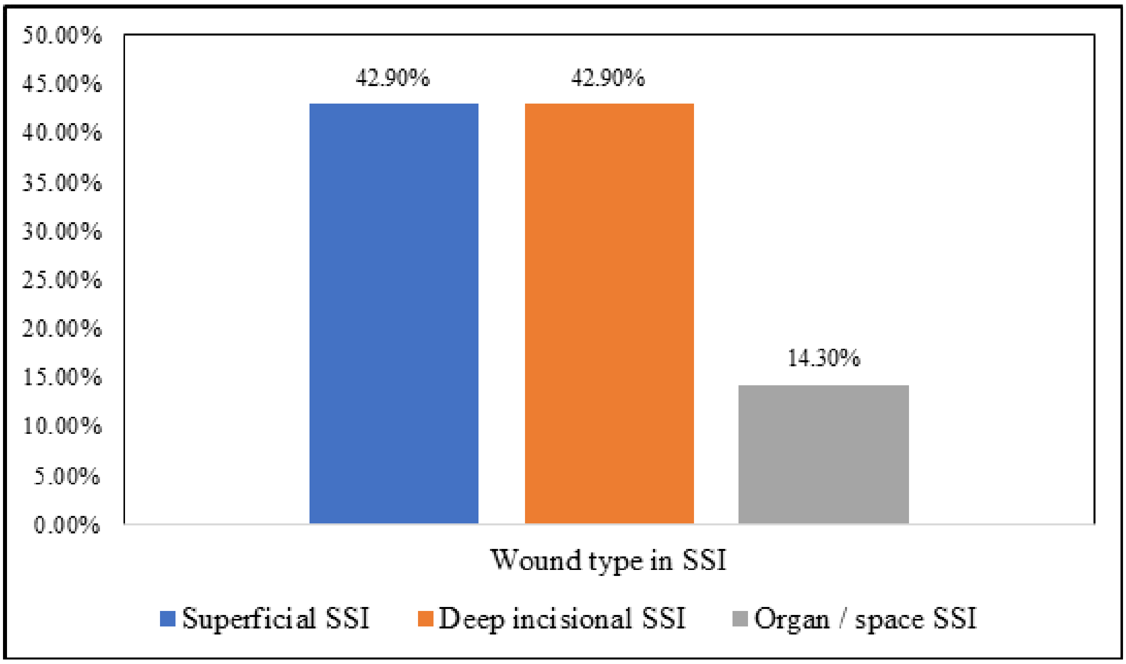

Figure 1: Wound types in Surgical Site Infections (n=77)

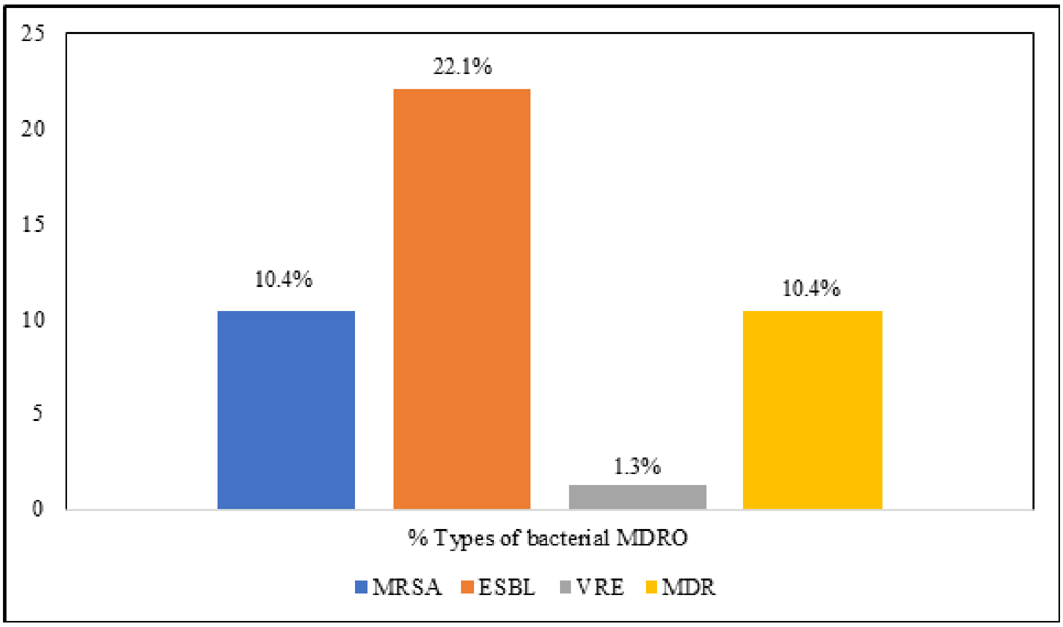

Figure 2: Mechanisms of Resistance in MDRO (n=77). MDRO include MRSA, ESBL, VRE and MDR (others).

Bacteria isolated in SSI were *E. coli* 15%, *Pseudomonas aeruginosa* 8%, Coagulase-negative staphylococci 5%, C. albicans 4% and *Klebsiella pneumoniae* 4%. Other isolates including Serratia marcescens, *Streptococcus constellatus and Staphylococcus aureus* were each identified in 3% of SSI. *Enterobacter cloacae and Acinetobacter baummanii* were 2% while other types represented 51% (see Figure 3 below).

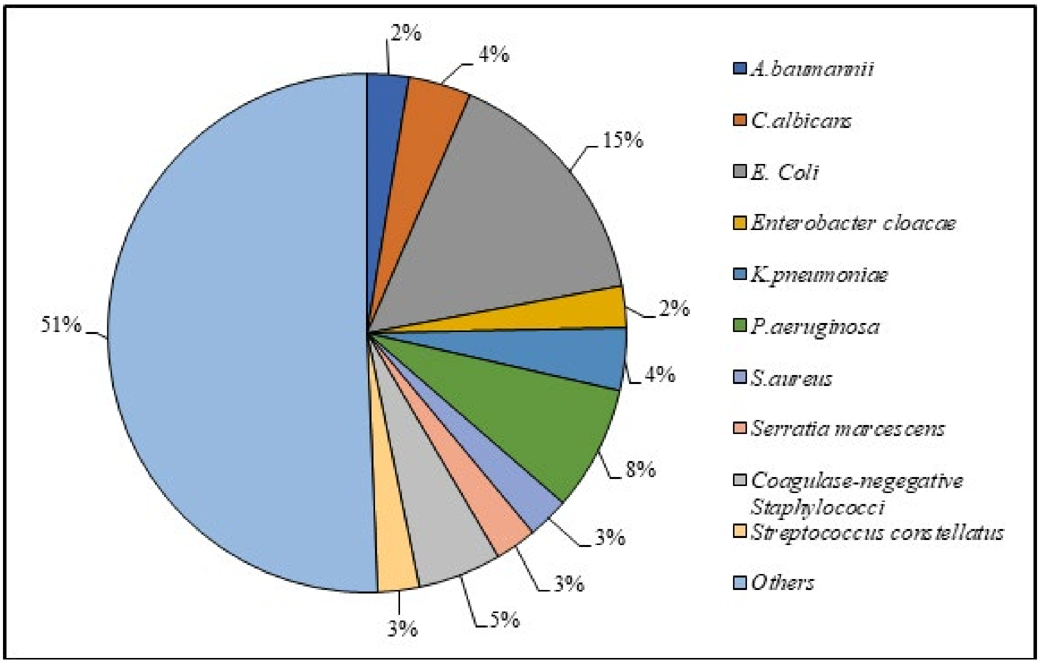

Figure 3: Types of Bacterial Pathogens Identified in Surgical Site Infections (n=77)

5. Discussion

In this study, we found that the prevalence rate of MDRO as 44% in SSI over a two-year period. Such infections more commonly involved surgical procedures performed on superficial and deep incisional body sites. Our data contrast with a 10-year multi-hospital study by El-Saed A et al, who reported a lower rate of superficial and deep SSI (37%) compared to organ/space SSI (38.5%) [21]. These differences may be due to variation in surgical procedures, environmental and patient related factors. We found that adult patients develop SSI more commonly than other age-groups, possibly explained by underlying comorbid conditions e.g., diabetes mellitus. Studies on SSI conducted globally have also demonstrated an increased risk of SSI in elderly patients [22].

The prevalence of MDRO in our study (44%) was generally lower compared to other reports that investigated SSI. In an eight-year study of device associated infections, the authors observed that the device associated hospital acquired infection (HAI) rate of 62.5% [23]. Another ten-year study of SSI in multi-hospital system found and SSI rate of 60% of which MDR Gram-positive isolates were approximately 28% while Gram-negative isolates accounted for 16% [21].

Taken together, these studies which were conducted over a longer period suggest the risk of SSI and MDRO have increased significantly in hospitals. We investigated risk factors and some possible predictors of MDRO in SSI. Administration of antibiotics in the last 90 days increased the risk of SSI due to MDRO up to 4-fold. This finding likely reflects selection of resistant clones of bacteria following previous antibiotic use. Patients who experienced trauma demonstrated a relatively lower risk of SSI, possibly because this occurred in a younger population involved in road accidents in our study. Hospitalization in the last 90 days also increased the risk of MDRO. While this finding lacked significance there was an association ($p = 0.055$). An earlier study reported a higher SSI incidence among diabetic patients and while diabetes mellitus increased the risk of MDRO in our study, this was not a significant factor [24].

We found that 55/77 patients developed SSI before discharge, 18 patients with SSI some days after discharge, and 4 on readmission. These data are comparable to a study by Prospero et al. in which 17 patients were identified with SSI after discharge [25]. In a US study, Avato and Lai reported that 40% of SSI occurred upon patient readmission, 28% during hospital stay, and 28% during follow-up [26]. These findings possibly reflect local epidemiology of HAI, differences in surgical procedures, patient factors and community acquired infections.

The major finding in our study is that previous antibiotic administration increases the risk of MDR in patients undergoing surgical procedures. Misuse of antibiotics contributes to MDRO in health care settings [27]. Antimicrobial stewardship programs reduce unnecessary use of antibiotics which ultimately impact HAI and MDRO. Antimicrobial stewardship is defined as "the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance [28]. The incidence of MDR infections limits treatment options and increases healthcare costs [29]. In the US, each SSI increases the length of hospital stay by approximately 9.7 days and costs up to US $20,842 per admission [30]. While such quantitative data are not available locally, the rise of MDRO has created an alarming burden on health care system in our region [23, 21].

The WHO global action plan promotes awareness about antimicrobial resistance (WHO: https://www.who.int/antimicrobial-resistance/global-action-plan/en/). Consistent with this initiative, the Saudi MOH launched a national strategy to combat antimicrobial resistance in the country (Saudi MOH: http://extwprlegs1.fao.org/docs/pdf/sau171813.pdf.). A recent study reported that implementation of this plan helped to reduce bacterial infections and HAI [9]. Since most MDROs were acquired in hospital settings, infection control practices need to be reviewed and best practices adopted. The authors of this study recommend a multi-disciplinary approach with key stake holders for combatting healthcare associated antimicrobial resistance.

Unexpectedly, we noted that contaminated wound types and high-risk category of SSI events were not associated with MDRO. This may be attributed to the practice of antibiotic coverage before surgical procedures are performed in such patients. Other possibilities include a small sample size of our patients and inability to follow up this group of patients over longer time-period to assess colonization.

6. Conclusions

This is the first study in our region which investigated the prevalence and risk factors for MDRO in SSI. We determined prevalence rate of 44% and identified antibiotic administration and hospitalization as important risk factors. A limitation of our research is its cross-sectional design and lack of temporal relationship between various factors. The use of molecular tests and strain typing, which were unavailable, could have provided a better understanding of resistance mechanisms, bacterial relatedness, and infection source. Finally, a small sample size in our study influenced the outcome variables and limited the significance of our findings. Larger multi-center studies in future may help to increase our understanding of MDRO especially after the Covid-19 pandemic.

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