Original Article

Optimizing Antimicrobial Drug Use in Surgery: An Intervention Strategy in A Sudanese Hospital to Combat The Emergence of Bacterial Resistant

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Abstract:

Background: Antimicrobial control programs are widely used to decrease antibiotic utilization, but effects on antimicrobial resistance and outcomes for patients remain controversial. The purpose of this study was to determine the impact of rotation of antibiotic classes used as empirical surgical prophylaxis on the emergence of bacterial resistance organisms and antibiotics drug use when compared with non-rotation period.

Method: Three core, broad spectrum agents (cephalosporins, beta-lactam-inhibitors, and fluoroquinolones) were selected for inclusion in the quaternary rotation for 21 months, based on prior 8 months baseline data from GIT and urology surgical wards in Ibn Sina hospital. Intensive surveillance done for patients admitted to the selected settings.

Results: 1681 surveillance samples obtained from 2359 eligible inpatients admitted to hospital from Jan 2008 to May 2010. A significant reduction in the percentage of positive growth had been observed with antibiotic rotation for both wards from 65% and 49% in baseline to 59% and 33% in rotation (1) and 25% and 33% in rotation (2) in GIT and urology ward respectively ($p \leq 0.0001$). As general there was a divergent effect of the antimicrobial rotation on the prevalence of resistance among G+ve and G-ve bacteria.

Conclusion: We concluded that antimicrobial drug use in surgical departments could be optimized after implementation of antimicrobial cycling policy, and associated in reduction in the incidence of infectious mortality and morbidity but stabilize antibiotic resistance, without significant reduction.

Key words: Antibiotic resistance, antimicrobial cycling, antimicrobial rotation, surgical prophylaxis.

Infection is a common cause of critical surgical illness and also a common complication of surgical care. Because of the inherently invasive nature of surgical therapy, natural epithelial barriers to invasion of the host by potential pathogens (e.g. skin, mucosa) are disrupted routinely, whether by trauma, incision, or catheterization[1]. The prophylactic antibiotic administration is complementary to surgical treatment of site infections, contributing substantially to minimizing of complications, morbidity, and death[2].

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Prophylactic antibiotics must not only be chosen correctly, but also must be dosed correctly in order to have optimal effectiveness. Dosing is a complex set of decisions that involves the characteristics of pathogen, several patient factors (e.g. allergy, organ function), timing of administration and pharmacokinetic parameters of antibiotic[3].

The prolonged use of prophylactic antimicrobials is associated with emergence of resistance bacterial organisms[4]. Resistant organisms pose a grave threat to hospitalized patients as their prevalence increases and antibiotic options narrow, mandating aggressive strategies to control their elaboration and spread. As antibiotic usage has been implicated as a key factor in the development of resistance[5], various techniques of formulary restriction[6], decision support tools[7], antibiotic and antimicrobial

surveillance[8], abbreviated courses of antibiotic therapy[9] and antibiotic cycling or rotation[10] have been advocated as means to control potentially unnecessary and inappropriate antibiotic usage.

There has been increasing interest in antibiotic cycling or rotation, as clinicians seek novel methods to combat the epidemic emergence of resistant organisms in hospitals around the world[11]. This approach remains controversial, as favorable results have not always been achieved in every setting. Moreover, reports to date have been relatively short-term in scope[12].

Through the use of a predetermined quarterly schedule of empiric antibiotics optimally as a prophylactic pre and postoperatively, we hypothesized that rotation could be associated with significant decreases in rates of infection, resistant gram-negative and gram-positive organisms and antibiotics consumption when compared with non-rotation period.

Method:

Study population:

This prospective study was performed in two surgical wards (Gastrointestinal-GIT- surgical ward and Urology surgical ward) in Ibn Sina hospital, 132-beds secondary teaching hospital- Khartoum state capital of Sudan, from Jan 2008 until May 2010. The population of the study was sequential. Patients admitted to GIT and Urology surgical wards in Ibn Sina hospital for ≥ 48 hours were eligible for the study, and followed prospectively until discharge or death. The included inpatients were patients that underwent surgical operations.

Study protocol implementation:

This was a prospective before-and-after study. A detailed account implementation has been previously described[13]. Briefly, antibiotic rotation protocol was implemented in September 1, 2008, as a local hospital policy for antibiotic prophylaxis pre and postoperatively. Baseline data were collected for 8 months (Jan 1 to August 30, 2008). During the baseline period, the prescription of antibiotics for surgical prophylaxis for the antibiotic coverage was at the discretion of the ordering surgeon. After the baseline observation period, an antibiotic-cycling protocol was implemented. Three antibiotics, Cephalosporins (CEF), Co-amoxiclave (AMC) and Ciprofloxacin (CIP) were empirically cycled as primary antibiotics for surgical prophylaxis every 3 to 4 months over a 2-year period. These three cycled drugs were systemically rotated twice, with the cycled drug changing every 4 months in the first year (rotation 1) and 3 months in the second year (rotation 2). The goal of this rotation was to direct quarterly antibiotic class heterogeneity in an effort to avoid resistance –selective pressure.

Data collection and analysis:

Antibiotic susceptibility data for gram positive and gram negative bacteria were collected 8 months before (baseline period), and 21 months after (intervention period), September 1, 2008. Specimen for culture and sensitivity were collected twice times per week from each ward (As surgical operations done twice/week for each ward), from eligible patients as surgical swabs from GIT and urology wards or urine samples from urology ward only and sent to the hospital laboratory for culture and sensitivity tests. Also during this period demographic, clinical and pharmacological data were obtained. The following aspects of antimicrobial prophylaxis were audited: antibiotic choice, duration, dose, interval between doses. Wound class, physical condition of the patient according to classification of the American Society of Anesthesiologist (ASA) was recorded.[1] Adherence to local guidelines for antimicrobial prophylaxis was reviewed for intervention period. Data were collected by infection control practitioner from medical and nursing records, and medication chart, using standardized form. Data collection was validated and entered in WHONET [14] database at monthly base by the primary investigator. The data collected were analyzed using WHONET analysis software, Excel 2007 and SPSS version 16.0. Antimicrobial

drug consumption received by the patients prophylactically was converted into Defined Daily Dose (DDD). Quantitative use was calculated and compared as (DDD/100-bed days).[15] Prior to initiation of the study, ethical approval was obtained from Medical Ethical Committee Ministry of Health and also hospital approval was obtained. Considering the observational nature of the study, the use of conventional antibiotic therapy, so there is no need to obtain informed consent from the patients.

Results:

A total of 2359 patients were eligible to be included into the study according to the study criteria, 2329 (98.7%) of them underwent surgical, 637 (27%) GIT, and 1692 (73%) urological operations. About 68% (1583) of them were male and the mean age ranged between 47 ± 15.2 - 53.4±17.02 for GIT ward 41±22.6 - 44±21.6 for urology ward. There were different reasons for surgical operations and underline diseases for admission to both surgical wards, but the main reasons were stones and cancer of GIT and urology system. The length of stay decreased from pre-intervention period to post-intervention period for each ward, but that was not statistically significant reduction (GIT 13.3± 11.8 Vs 9.6± 8.7 $p \leq 0.229$; Urology 11.9± 12.42 Vs 7.1± 5.5 $p \leq 0.204$). A decrease in the mortality rate was observed when comparing between the two study periods for each ward, but also without significant difference. The detailed and other characteristics of the study populations before and after intervention study periods were shown in Table (1): Total antibiotics used during the study period in GIT ward were 81.4 DDD/100 bed-days and in urology ward were 193.05 DDD/ bed-days. Total protocolized antibiotics used were 47.5 DDD/100 bed-days in GIT ward and 168.6 DDD/100 bed-days in urology ward. However, mean percentage of patients received the protocolized antibiotic decreased in rotation (2) compared to rotation (1) by 20% in GIT and 17% in urology surgical wards. The median duration of antibiotic treatment days increased from 3 days to 4 days in GIT ward, while it was decreased in urology ward from 3 days to 2 days. 1681 surveillance samples were obtained from 2359 eligible inpatients admitted to the Ibn Sina hospital throughout study period from Jan 2008 to May 2010. Of these samples 345 (20.5%) obtained from GIT ward as surgical and wound swabs, 1336 (79.5%) samples obtained from urology surgical ward (1197 urine samples and 139 surgical swabs). Specimen obtained from patients during the post-intervention periods was more than pre-intervention period, but a significant reduction in the percentage of positive growth had been observed with antibiotic rotation for both wards from 65% and 49% in baseline to 59% and 33% in rotation (1) and 25% and 33% in rotation (2) in GIT and urology ward respectively ($p \leq 0.0001$). A substantial variation in incidence of colonization/infection rate was observed between the two surgical wards, while it decreased in GIT ward it increased in urology ward when compared between pre and after intervention periods.

Details of cycled antibiotics consumed in DDD during the non rotation and rotational periods in GIT and urology surgical wards were shown in figures (1). The most frequently prescribed categories of antibiotics throughout the study period were cephalosporins for both GIT and urology wards, and the use of cephlosporins were not completely restricted during any period throughout the study period in both GIT and urology wards, while amoxiclave and quinolones were completely restricted in some cyclic periods in GIT ward (data were not shown). Cefuroxime was the main cephalosporin antibiotic prescribed in GIT surgical ward constituting 47.24%, followed by ceftazidime (27.42%) and ceftrixone (25.34%), while in urology surgical ward the heaviest cephalosporin prescribed was ceftrixone (54.16%), followed by cefuroxime (29.37%) and the lowest was ceftazidime (16.47%). In 58% and 68% of all cases in GIT and urology wards respectively, antibiotics were compliant and prescribed according to the protocol, higher compliance

rate was observed in first rotation compared to second rotation in both wards, with a significant difference (70% vs. 41.5% in GIT ward; P = 0.0001, and 75% vs. 60.5% in urology ward; P = 0.0001). In every cycle (where it is not the on-cycled antibiotics), cephalosporins were the most frequent off-cycle drug to be prescribed in both GIT and urology ward.

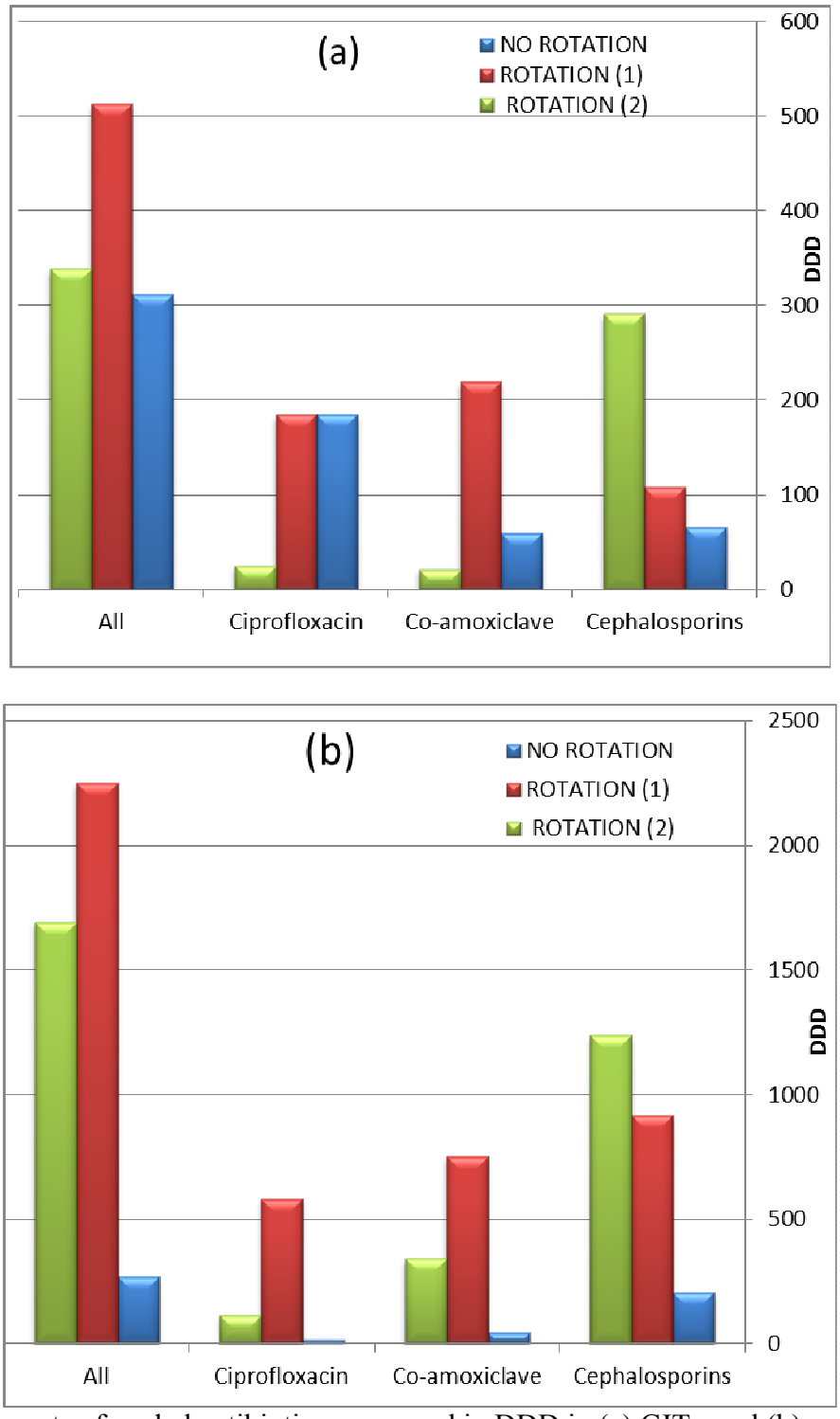

Figure (1): Amounts of cycled antibiotics consumed in DDD in (a) GIT ward (b) urology ward per study periods

Figures (2) and (3) illustrate the diversity of resistant G +ve and G-ve isolated by rotation cycles in GIT and urology surgical wards respectively. Pattern of drug resistance were observed to be different pre and after intervention periods.

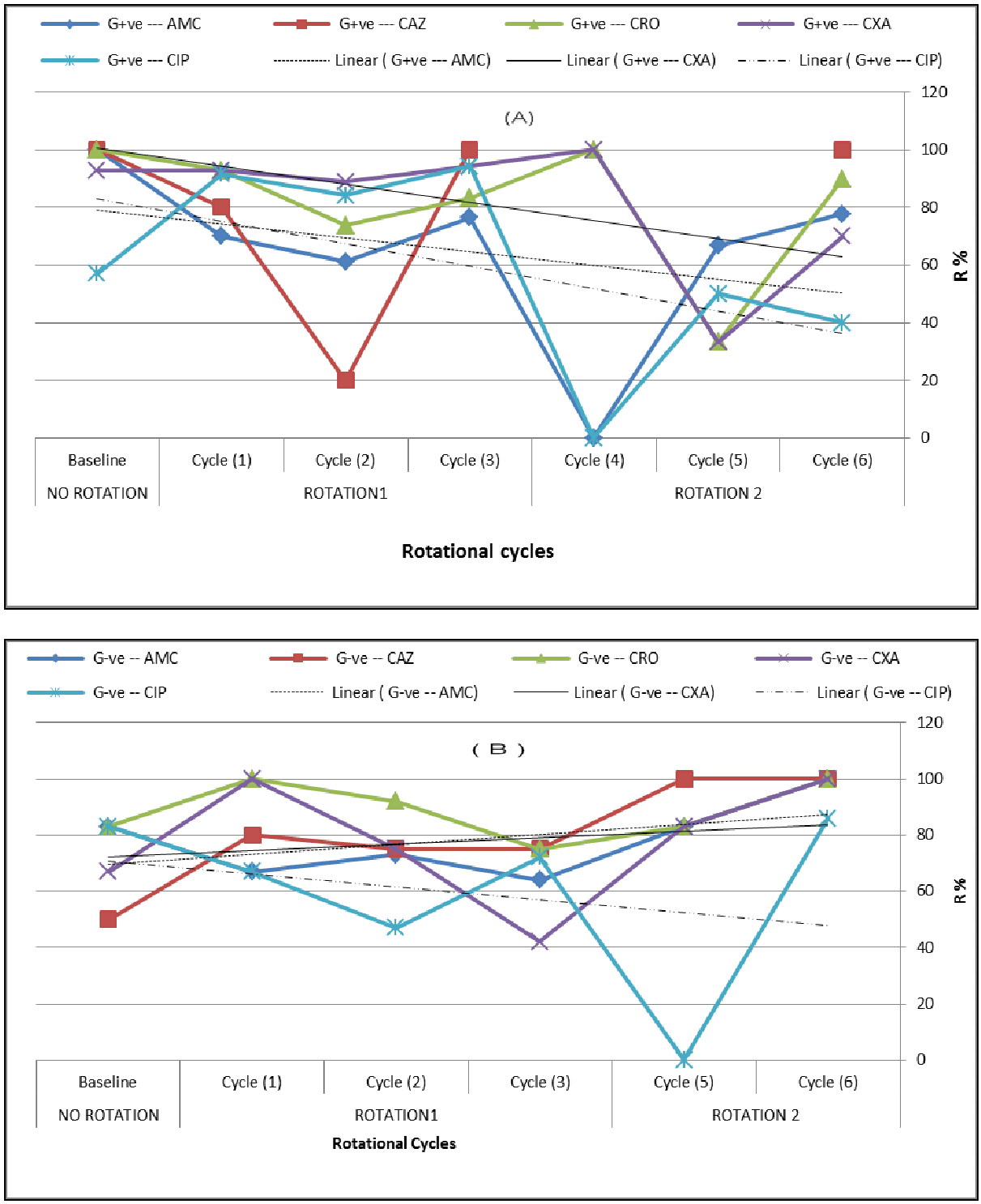

Figure (2) Antibiotic resistance in (A) gram- positive (G+ve) and (B) gram-negative (G-ve) isolates per each rotational cycle in GIT surgical wards. AMC –Co-amoxiclave, CAZ = Ceftazidime, CRO = Ceftrixone, CXA = Cefuroxime, CIP = Ciprofloxacin, Linear = Linear Trendlines of resistance.

In figure 2 (A) there was a trend towards decreasing of G +ve resistance to the three major antibiotic used in GIT ward (indicated as linear trendlines), whereas in figure 2 (B) G -ve resistance increased towards Co-amoxiclave and cephalosporins (represented by cefuroxime), with more dramatic decreased resistance towards ciprofloxacin in the same surgical ward.

Figure (3) Antibiotic resistance in (A) gram- positive (G+ve) and (B) gram-negative (G-ve) isolates per each rotational cycle in urology surgical wards. AMC –Co-amoxiclave, CAZ = Ceftazidime, CRO = Ceftrixone, CXA = Cefuroxime, CIP = Ciprofloxacin, Linear = Linear Trendlines of resistance.

In urology ward the trend suggests an increase in resistance associated with antibiotic used except towards cephalosporins (represented by ceftrixone) where there was a slight decrease in both G+ve and G-ve bacteria as shown in figure 3 (A & B).

Table 1: Demographics and characteristics of patients in GIT and Urology surgical ward before and after intervention periods:

Period	Before intervention Baseline period		After Intervention			
			First rotation		Second rotation	
Surgical ward	GIT	Urology	GIT	Urology	GIT	Urology
Demographic data						
Study length	8 months	8 months	12 months	12 months	9 months	9 months
Study time	Jan 1, 2008 – August 30, 2008		September 1, 2008 – August 30, 2009		September 1, 2009 – May 2010	
Total number of admitted patients	344	577	1154	1441	950	1153
Number of eligible patients for the study	195	365	272	739	177	611
Number of Patients enrolled in surgical operations (%)	188 (97%)	348 (96%)	272 (100%)	733 (99%)	177 (100%)	611 (100%)
Patient / days	3246	4769	11757	15031	8981	9251
Antibiotic Administration						
Number of patient received antibiotics preoperatively (%)	185 (98.4%)	324 (88.8%)	227 (83.5%)	638 (87%)	163 (92%)	588 (96%)
Number of patient received antibiotics Postoperatively (%)	178 (95%)	334 (98%)	247 (91%)	712 (97%)	171(97%)	598 (98%)
Total antibiotic consumption in DDD	311.5	267.6	536.9	2258.1	338.4	1696.6
DDD/100 bed-days	15.9	32.98	38	68.2	27.5	91.9
Mean percentage of patients received the protoclized antibiotic	NA	NA	62%	65%	42%	48%
American Society of Anesthesiologist (ASA) classification						
ASA (1), N (%)	144 (76.6%)	283 (81.3%)	244 (89.7%)	663 (90.4%)	139 (78.5%)	591 (96.7%)
ASA (2), N (%)	44 (23.4%)	64 (18.4%)	28 (10.3%)	70 (9.6%)	36 (20.4%)	20 (3.3%)
ASA (3), N (%)	0 (0%)	1 (0.3)	0 (0.0%)	0 (0.0%)	2 (1.1)%	0 (0.0%)
Wound classification						
Clean wound, N (%)	9 (4.9%)	3 (0.8%)	2 (0.7%)	36 (4.9%)	16 (9.1%)	444 (72.6%)
Clean contaminated wound N (%)	163 (86.7%)	285 (78.1%)	251 (92.3%)	625 (85.3%)	151 (85.3%)	166 (27.2%)
Dirty wound N (%)	16 (8.5%)	60 (16.4%)	19 (7%)	72 (9.8%)	10 (5.7%)	1 (0.2%)
Prevalence of Colonization/infection						
Number of specimen obtained from eligible patients (%)	49 (26%)	93 (26%)	189 (69%)	641 (87%)	107 (60%)	602 (99%)
Number of positive growth from cultured specimens (%)	32 (65%)	46 (49%)	95 (50%)	212 (33%)	27 (25%)	196 (33%)
Rate of prevalence of colonization/infection per 1000 patient/days	9.6	9.7	8.1	14.1	3.0	21.2
P^*			*P1 ≤ 0.0001*	*P1 ≤ 0.0001*	*P1 ≤ 0.0001* *P2 ≤ 0.0002*	*P1 ≤ 0.0001* *P2*≤ 0.7278

P^* = P-value, z-test for proportions. *P1*= P-value between baseline and rotation (1) *P2*= P-value between rotation (1) and rotation (2) NA = Not Applicable

Table (2): Percentage of isolates resistance to cycled antibiotics during the 8 months before and 12 months after (rotation 1) periods.

Organism (G+ve and G-ve) Patient location	No of isolates		Cyclic period (Rotation 1)																	
			Cephalosporins period (CEP)						Co-amoxiclave period (AMC)						Quinolones period (CIP)					
			CEP (R%)		AMC (R%)		CIP (R%)		CEP (R%)		AMC (R%)		CIP (R%)		CEP (R%)		AMC (R%)		CIP (%)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Staphylococcus aureus																				
GIT ward	14	47	97.6%	87.3%	100%	62.5%	72%	90.9%	97.6%	70.7%	100%	61.1%*	72%	84.2%	97.6%	96.7%	100%	78.6%	72%	100%
Urology ward	13	20	100%	100%	100%	100%	92.3%	100%	100%	100%	100%	100%	92.3%	100%	100%	91.7%	100%	75%	92.3%	1.7%
Staphylococcus saprophyticus																				
GIT ward	2	2	100%	100%	50%	100%	0%	100%	100%	NA	50%	NA	0%	NA	100%	NA	50%	NA	0%	NA
Urology ward	2	1	100%	100%	100%	0%	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA
Staphylococcus epidermidis																				
GIT ward	1	2	100%	NA	NA	NA	0%	NA	100%	NA	NA	NA	0%	NA	100%	50%	NA	100%	0%	50%
Urology ward	3	0	77.8%	NA	33.3%	NA	66.7%	NA	77.8%	NA	33.3%	NA	66.7%	NA	77.8%	NA	33.3%	NA	66.7%	NA
Streptococcus sp.	0	2	NA	100%	NA	100%	NA	100%	NA	NA	NA	NA	NA	NA	NA	100%	NA	NA	NA	100%
GIT ward	0	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100%	NA	NA	NA	100%
Urology ward																				
Entercoccus faecalis	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GIT ward	2	3	100%	100%	0%	66.7%	100%	66.7%	100%	NA	0%	NA	100%	NA	100%	NA	0%	NA	100%	NA
Urology ward																				
Escherichia coli	9	16	66.7%	100%	83.3%	100%	83.3%	66.7%	66.7%	90%	83.3%	70%	83.3%	50%	66.7%	87.5%	83.3%	100%	83.3%	66.7%
GIT ward	3	63	100%	96.8%	66.7%	80%	33.3%	85.7%	100%	86.7%	66.7%	80%	33.3%	80%	100%	94.8%	66.7%	85.5%	33.3%	86.2%
Urology ward																				
Pseudomonas aeruginosa	1	6	100%	75%	100%	NA	100%	0%	100%	100%	100%	NA	100%	50%	100%	NA	100%	NA	100%	NA
GIT ward	2	32	100%	100%	100%	100%	100%	100%	100%	83.3%	100%	100%	100%	66.7%	100%	85%	100%	100%	100%	72%
Urology ward																				
Kelebsiella pneumonia	0	3	NA	100%	NA	100%	NA	100%	NA	0%	NA	NA	NA	0%	NA	100%	NA	NA	NA	100%
GIT ward	3	8	100%	75%	100%	100%	100%	50%	100%	100%	100%	NA	100%	0%	100%	100%	100%	100%	100%	100%
Urology ward																				
Non-lactose fermenting G-ve	0	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100%	NA	100%	NA	NA
GIT ward	0	11	NA	NA	NA	NA	NA	NA	NA	100%	NA	100%	NA	50%	NA	95.2%	NA	87.5%	NA	55.6%
Urology ward																				
Serratia marcescens	0	0	NA	NA	NA	NA	NA	NA	NA	100%	NA	100%	NA	50%	NA	NA	NA	NA	NA	NA
GIT ward	1	0	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA
Urology ward																				
Proteus mirabilis	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GIT ward	2	5	75%	100%	100%	NA	0%	0%	75%	75%	100%	100%	0%	100%	75%	NA	100%	NA	0%	NA
Urology ward																				

R% = Resistance % NA = Not Applicable (*) = decrease was significantly difference ($P \leq 0.05$)

Table(3): Percentage of isolates resistance to cycled antibiotics during the 8 months before and 9 months after (rotation 2) periods

Organism (G+ve and G-ve) / Patient location	No of isolates		Cyclic period (Rotation 2)																	
			Cephalosporins period (CEP)						Co-amoxiclave period (AMC)						Quinolones period (CIP)					
			CEP (R%)		AMC (R%)		CIP (R%)		CEP (R%)		AMC (R%)		CIP (R%)		CEP (R%)		AMC (R%)		CIP (%)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Staphylococcus aureus																				
GIT ward	14	13	97.6%	100%	100%	0%	72%	0%	97.6%	33.3%*	100%	66.7%	72%	NA	97.6%	77.8%	100%	87.5%	72%	44.4%*
Urology ward	13	7	100%	100%	100%	100%	92.3%	100%	100%	77.8%	100%	100%	92.3%	33.3%	100%	100%	100%	100%	92.3%	100%
Staphylococcus saprophyticus																				
GIT ward	2	0	100%	NA	50%	NA	0%	NA	100%	NA	50%	NA	0%	NA	100%	NA	50%	NA	0%	NA
Urology ward	2	0	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA
Staphylococcus epidermidis																				
GIT ward	1	0	100%	NA	NA	NA	0%	NA	100%	NA	NA	NA	0%	NA	100%	NA	NA	NA	0%	NA
Urology ward	3	0	77.8%	NA	33.3%	NA	66.7%	NA	77.8%	NA	33.3%	NA	66.7%	NA	77.8%	NA	33.3%	NA	66.7%	NA
Streptococcus sp.																				
GIT ward	0	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100%	NA	0%	NA	0%
Urology ward	0	7	NA	100%	NA	100%	NA	100%	NA	NA	NA	NA	NA	NA	NA	100%	NA	80%	NA	100%
Entercoccus faecalis																				
GIT ward	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Urology ward	2	0	100%	NA	0%	NA	100%	NA	100%	NA	0%	NA	100%	NA	100%	NA	0%	NA	100%	NA
Escherichia coli																				
GIT ward	9	6	66.7%	NA	83.3%	NA	83.3%	NA	66.7%	100%	83.3%	75%	83.3%	0%*	66.7%	100%	83.3%	100%	83.3%	100%
Urology ward	3	61	100%	100%	66.7%	95%	33.3%	95.2%*	100%	93.2%	66.7%	90.9%	33.3%	100%	100%	97.9%	66.7%	100%	33.3%	88%
Pseudomonas aeruginosa																				
GIT ward	1	1	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	100%	100%	100%	100%	100%
Urology ward	2	36	100%	90.9%	100%	100%	100%	33.3%*	100%	92.9%	100%	NA	100%	42.9%	100%	60%	100%	NA	100%	30%
Kelebsiella pneumonia																				
GIT ward	0	1	NA	NA	NA	NA	NA	NA	NA	0%	NA	NA	NA	NA	NA	100%	NA	100%	NA	100%
Urology ward	3	11	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	80%	100%	100%	100%	100%	100%	100%
Non-lactose fermenting G-ve																				
GIT ward	0	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	100%	NA	100%	NA	100%
Urology ward	0	13	NA	100%	NA	100%	NA	50%	NA	100%	NA	100%	NA	NA	NA	100%	NA	100%	NA	72%
Serratia marcescens																				
GIT ward	0	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Urology ward	1	0	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA	100%	NA
Proteus mirabilis																				
GIT ward	0	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	100%	NA	100%	NA	NA	NA	NA	NA	NA
Urology ward	2	1	75%	100%	100%	100%	0%	0%	75%	NA	100%	NA	0%	NA	75%	NA	100%	NA	0%	NA

R% = Resistance % NA = Not Applicable (*) = decrease was significantly difference ($P \leq 0.05$)

Details of gram positive and gram negative antimicrobial susceptibilities before and after intervention periods had been shown in tables (2 and 3). In rotation (1), only one isolate exhibited significant reduction in resistance towards Co-amoxiclave in *Staphylococcus aureus* during Co-moxiclave (from 100% to 61.1%) in GIT surgical ward (table 2). While many isolates exhibit significant reduction in resistance during rotation (2) in both GIT and urology surgical wards (table 3).

Discussion:

From initial review we concluded that antimicrobial drug use in surgical departments could be optimized after implementation of antimicrobial cycling policy. The policy replaced a variety of antimicrobial use regimens, previously chosen on the basis of personal preferences and possibly the result of promotional efforts by pharmaceutical companies. The intervention succeeded in decreasing the mean percentage of patients who received antibiotic prophylactically. Other indicators of satisfactory outcomes with the new policy were a decrease in length of stay and mortality. The number of isolates that were isolated from study of surgical patients increased in rotational periods compared to baseline periods, this was due mainly to the longer rotational period and active surveillance system during those periods. Beside a significant reduction in the percentage of positive growth, we also found a trend favoring a lower incidence of colonization/ infection rate with antibiotic rotation. However, this remains unexplained whereas the reduction in antibiotic pathogenic organisms and infections may be due to antibiotic rotation or other factors. But many studies confirm that altering policy or antibiotic rotation potentially alters an organism's ability to infect the host and decrease the incidence with infection with both antibiotic sensitive and antibiotic resistant bacteria[16-18] .

We have previously shown that there were pronounced reductions in overall antibiotic use and total protocolized antibiotic utilization represented as a reduction in DDD/100 bed-days measurement[19]. This considerable reduction, may actually overshadow any impact of cycling program may have had on the measured outcomes.

Cephalosporins were the most often cycled antibiotics prescribed in both surgical wards during the whole study period. Cephalosporins are frequently used either alone or in combination with metronidazole as surgical prophylaxis. The over use of broad spectrum cephalosporins particularly ceftizidime, cefuroxime and ceftrixone have been implicated in the emergence of multidrug-resistant gram positive and gram negative bacteria[20].

Despite the fact that our study had got some success to lower the amount of utilized antibiotics used, but it seems this reduction is not enough to decrease antibiotic resistance (i.e. still above the threshold point to reduce resistance). Trends of bacterial resistance as a group and by organisms to cycling antibiotics showed no much significant differences between the two years. Although resistant development against β-lactam and flourquinolone antibiotics is based on different mechanism, homogenous exposure to one of these classes did not prevent resistance development to other classes.[21]

Antibiotic cycling has been suggested as a method for decreasing or controlling resistance in microorganisms. In theory, the antibiotic agents that undergo rotation in a given time period, alter resistance pressure in microbial environment. Bacteria with resistance to an agent would lose their growth advantage when the agent is withdrawn from use, and exposure to other class of antibiotics would eliminate these resistant organisms. The present study shows some differences between theoretical considerations and daily clinical practice. However, the theoretical benefits of antibiotic cycling that hold true in daily practice can only be effective by controlling confounding variables. Part of the difficulties in controlling confounding variables arises from the lack of randomization in such quasi-experimental studies (pre-intervention and post intervention). On the other hand high cross-

resistance between cyclic antibiotics and multi-resistance strains carried out by patients admitted to both surgical wards overwhelmingly dominant in the study wards. This is indicated by the persistent multi-resistance profile and absence of significant decrease in antibiotic resistance among most of the cyclic periods for gram positive and gram negative species. The problem of multi-drug resistance may well decrease the potential benefits of antibiotic cycling. Also surgeons' adherence to only the use of the cycled antimicrobial was poor and also erratic and this may have a big role in altering the results of our study. Numerous studies have examined different strategies of rotating an assortment of antibiotic classes, ultimately yielding divergent results[16, 22-25].

Certain limitations exist in our study design. In the first three cycles (rotation 1), cycles were 4 months in the length, while in the second three cycles (rotation 2) cycles were 3 months in length, and this was mainly due to research funding limitations and low adherence and compliance from prescribers at rotation two mainly. In addition to that, the optimal duration of each cycle is not specified in literature. Also we did not link and assessed the infection according to the clinical picture and depended only on colonization and pathogenic isolate cultures and this may over estimate infection rate.

Conclusion:

Antibiotic policy and guidelines were important to optimize antibiotic drug use for surgical prophylaxis. The adherence to such guidelines must be improved, to achieve optimal adherence, antibiotic policy makers should develop evidence-based guidelines in collaboration with surgeons.

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