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Antibiotic Use, Cost, and Consumption in Tertiary Hospitals in Lebanon: A Comparative Study Before and After an Implementation of Antibiotic-Restriction Program (ARP)

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AA and SH designed the study, performed the data collection in order to obtain a Master degree in Quality Management. Author IS participated in study design, managed the literature searches, performed the statistical analysis, and wrote the first draft of the manuscript. Authors HS, SS and NS managed the data analyses of the study, and validated the pertinence of data. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To compare the antibiotic use, cost, and consumption before and after an implementation of an antibiotic-restriction program (ARP) in governmental hospitals setting in Lebanon.
Study Design: A retrospective cohort study on hospitalized patients who were prescribed antibiotics prior to, and after the application of the ARP, was conducted over a three month period,

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between March 2013 and June 2013.
Methodology: The studied population included patients on antibiotic therapy. The sample size that was enrolled was equal to 612 patients prior to ARP and 606 patients after ARP.
Results: The average age of the patients was 34.6±23.5 years, 55.6% of whom were females, and 79.2% had no comorbidity. Respiratory diseases, and gynecological surgeries motivated the antibiotics prescriptions. The physicians prescribed combinations of intravenous antibiotics in 91% of the cases. The most frequently ordered antibiotics were second, third- generation cephalosporins, and penicillin derivatives. After ARP, the rate of restricted antibiotic use decreased by 11% (P<.0001), while the use of gentamicin increased with a potential for increased rates of nephrotoxicity and ototoxicity; Prior to and after the ARP, a microbiological exam was done in 12.6% of cases, and 67.3% of the cases of prescribed antibiotics were sensitive. The expenditure of all, and restricted antibiotics decreased by 22.3% and 9% respectively. The cost savings were US$ 8099 per month. The compliance with the ARP by prescribers was very high (>90%).
Conclusion: The ARP reduces the amount of antibiotic usage, cuts down the healthcare expenditure, and may prevent a higher prevalence of some resistant bacterial strains; it is, therefore, in the interest of policymakers to propose an antimicrobial stewardship program based on mHealth system that allows patients, and healthcare providers an on-line and mobile consultation.

Keywords: Antibiotic restriction program; governmental hospital; healthcare cost; pre- and post-intervention; Lebanon.

ABBREVIATIONS

Antibiotic-restriction program (ARP); defined daily dose (DDDs); Infectious diseases specialist (IDS); US dollars (US$).

1. INTRODUCTION

The emergence of antibiotic resistant bacteria is a worldwide problem [1], especially in the southern and eastern Mediterranean hospitals [2]. This escalating evolution of resistance coupled with a diminished antibiotic pipeline, has led some to claim that a post-antibiotic era is eminent [3].

The irrational use (misuse or overuse) of antibiotic drugs is partially responsible for the increasing incidence of resistant microorganisms [1,4-6], increasing health care costs, therapeutic failure, toxicity and drugs interaction [7,8], and increasing threat to global health [1]. It is a common experience in many hospitals where the departments with the highest rates of antimicrobial resistance also invariably have the highest levels of antibiotic use [1,2,6,9]. Such evidence has led to the hypothesis that the selection of resistance during treatment or prophylaxis, rather than transmission from patient to patient, is the key factor in the acquisition of infection caused by a resistant organism [2]. In addition, the wide-spectrum agents, particularly third-generation cephalosporins and quinolones that are normally reserved for serious healthcare-associated infections, were widely used as a first-line empirical treatment [2]. A vicious cycle is created as the multidrug-resistant Gram-negative organism infections force us to rely on additional broad-spectrum antibiotics to treat these infections, leading to more resistance [10]. Broad evidence indicates that approximately 64% of all hospitalized patients receive antibiotic drugs during their hospital stay [8]. The antimicrobials currently account for over 30% of hospital pharmacy budgets in the US [3]. Studies have reported that over half of hospital antibiotic prescriptions are prescribed in an inappropriate manner (indication, dose, dosage, treatment duration) [1,8], especially for upper respiratory tract infections and for urinary tract infections in women [1]. In Lebanon, a study has shown that broad spectrum antibiotics (such as 3rd generation cephalosporins and quinolones) are extensively consumed, where more than 15% of the total national consumption consisted of quinolones [11]. In China, the irrational use of antibiotics is a serious concern where the frequency of antibiotic prescriptions is twice that of the indicator developed by WHO [5]. The consequences are manifold for the individual and the community.

The lack of antibiotic policies and initiatives within the southern and eastern Mediterranean hospitals is relevant in the epidemiology of antibiotic resistant bacteria [2]. The antimicrobial stewardship program is an important but challenging element minimizing the harm from antimicrobial therapy in terms of reducing resistance, preserving the efficacy of the antimicrobial armamentarium particularly for multi-drug resistant gram negative infections emerging worldwide, limiting adverse effects at individual patient level [12], and saving health care costs in the hospital setting [1,2,4,6,8,9,11-14]. It requires a combination of approaches that need to be applied in a disciplined and coordinated manner. Indeed, the rational use of antibiotics was the theme chosen for the World Health Day – 7 April 2011 by WHO under the title "Antimicrobial resistance: No action today, no cure tomorrow" [15]. In Lebanon, under the hospice of the Ministry of Public Health, a working group was established [16].

Little or no information on antibiotic prescribing practices within hospital care has been available on the situation in the southern and eastern countries of the Mediterranean region [2]. Few data are available regarding the antibiotic consumption in Lebanon [11,14], and are mostly restricted to single center studies [11]. Antibiotic stewardship programs are urgently needed [11,17] to answer to the problematic question: "Does the establishment of a multidisciplinary Committee of Antibiotics that initiate an antibiotic restriction program, decreases the consumption and cost of antibiotics in hospital setting?"

The overall objective of this study is to compare antibiotic use, cost, and consumption before and after an implementation of a Committee of Antibiotics that initiate an antibiotic-restriction program (ARP) in two governmental hospitals in Lebanon. The secondary objectives are: (1) to assess the influence of the an antibiotic-restriction program on the consumption of antibiotics, especially restricted antibiotics; (2) to evaluate the impact of the ARP on the cost burden of antibiotic therapy within the hospitals; (3) to evaluate the acceptability, and compliance of the program by prescribers.

2. MATERIALS AND METHODS

A cohort study of patients admitted to two Governmental Hospitals in Lebanon was conducted over a three month period, one prior to the ARP, and one after the ARP. It began in March 2013 and, ended in June 2013. The first hospital is a teaching hospital with 180 hospital beds, localized in Nabatieh Department. It is considered one of the busiest hospitals, receiving referrals from south Lebanon. The second hospital is a general hospital in Iklim al Karroub at Mount Lebanon Department. This study was approved by the directors of the hospitals.

The design used in this study was the pre- and post-intervention, non-equivalent comparison group design. The interventions included the implementation of Committee focused on the use of antibiotics in the two hospitals, and especially applying an antibiotic restriction program (ARP):

- Prior to ARP (Group 1): A retrospective cohort study of patients admitted during the month of March 2013 was conducted. All antibiotics ordered for the hospitalized patients prior to ARP were evaluated.
- After ARP (Group 2): A retrospective study after the application of the Protocol of the ARP was conducted in both hospitals, during the month of May and June 2013 respectively.

2.1 Selection of Patients

The study was conducted in the medical, surgical, pediatric, and maternity wards of both hospitals. The target population included all patients admitted during the period of the study. The studied population included patients on antibiotic therapy. Expecting the rate of antibiotic use is 50% [7], alpha is 5%, margin of error at 5%, and the size of population admitted to the hospitals is 2000 in each group prior to, and after ARP; the minimum recommended sample size worked out to be 323 per group [http://www.raosoft.com/samplesize.html]. The inclusion of data samples was on the basis of the hospitalized patients who have been prescribed antibiotics, either as a treatment or prophylaxis during the period of the study. The selected patients were aged two months and older, receiving at least one antibiotic during the period of the investigation. The inpatients who had not taken antibiotics, neonatal intensive care patients, burn patients, oncology patients, intensive care patients, tuberculosis patients, and patients followed as outpatients were excluded from our sample.

2.2 Sources of Data

The sources of data included medical records of all patients who received antibiotic therapy for infections, and the laboratory test evaluations. Each patient's medical chart was reviewed, data transferred to the data collection sheet and followed up by statistical analysis.

2.3 Data Collection

Data collection included: Patients' related information, and completeness of therapy including demographic data (age, gender, third payers, length of hospital stay, history of patient illness (diagnosis, surgical or medical hospitalization reason, and associated clinical signs: (1) fever, defined as a single oral temperature of 38.3ºC; (2) cough, and (3) diarrhea). The admissions for medical and surgical reasons, are classified into broad categories, each category has several diseases. Comorbidity was assessed by the Charlson (CCI) comorbidity index, which is a comorbidity score used in many clinical studies, validation is based on its prediction of mortality risk associated with pathologies [18]. The CCI scores were categorized into 4 levels: Low comorbidity (2 – 3); Moderate (4-5); High Comorbidity (6-7); and Very high comorbidity >7 [18]. Laboratory values (white blood cells, neutrophils, C - reactive protein, urinalysis), results of microbiological examination, and chest radiography were also assessed. The appropriate use of antibiotics according to microbiological testing was also evaluated.

Antibiotics -related variables: Type, dose, frequency, and route of administration, dosage form, concentration, duration, indication. Antibiotics were divided into eight main antibiotic groups: Penicillin derivative, cephalosporins (first, second, third, and forth generation cephalosporin), carbapenems; aminoglycosides, macrolides, quinolones, parenteral nitro-imidazole derivatives, and others, including glycopeptides, lincosamide, ureidopenicilline, and tetracyclines. The antibiotics use was also divided into 3 categories: Specific or documented (based on culture results); empirical (based on clinical evidence), and prophylactic (without evidence of infection) [7]. The pertinence of the data was validated *a posteriori* by a physician.

In-hospitals, the cost data concerning drugs and antibiotics per patient were expressed by the defined daily doses (DDDs) [19], and the length of stay. To neutralize the effect of variations in the purchase cost of antibiotics over time, all costs were normalized by taking as reference the average purchase price in 2013 of the two hospitals "Cost per patient = DDDs X unit purchase price X length of stay." Lebanese pounds were converted to US dollars (*US$*).

The information concerning the implementation of the Antibiotics Committee, after ARP was also collected: Data concerning the filling of the restricted antibiotics form, the infectious disease specialists' approval prior to dispensing and initiating a course of a restricted antibiotic, change of restricted antibiotics in conformity with the result of the microbiological exams, or an infectious diseases specialist (IDS) consultation, make the antibiotic relay in accordance with the microbiological results, and antibiotic tracking ambulatory relay after the discharge of patients from the hospital.

2.4 Intervention

The Antibiotics Committee team included a multidisciplinary team of physicians (infectious diseases specialist (IDS), internal medicine physician, and surgeon), a microbiologist, a laboratory technologist, pharmacist, nursing and administrative staff.

The main strategies of the Committee on Antibiotics are to optimize the antibiotic usage in hospitals [13], enhance the healthcare cost saving, raise awareness of this problem and affect doctors' prescribing behaviors [1], and improve the quality of care and patient safety [2,7,8,17]. Their objectives are: To establish an ARP, slow-down the development and dissemination of bacterial resistance, develop prescribing guidelines based on the best available scientific evidence [1,8,13,17], estimate the appropriateness of antibiotics drugs use for prophylaxis, and for empiric decision or therapeutic culture-based reasons, intercept a variety of drug-related problems which mainly include non-conformity to guidelines or contraindications, too high doses, DDD and improper administration [20], and limit contacts between physicians and pharmaceutical representatives [13].

The ARP included the following procedures: orders for restricted antibiotics were not honored by pharmacists without a verbal telephone approval by the infectious diseases (ID) attending physician. Prescribing physicians were required to consult the ID attending physician via a dedicated pager to obtain approval, and fill out the antibiotic order form. The approval process included recommendations for dosage and duration of therapy. In case of emergency on weekdays and on weekends, the first doses of restricted antibiotics were dispensed without approval until the ID specialist review orders for appropriateness. The ID specialist could then approve or disapprove the continuation of antibiotic use after further discussions with the physician on the consulting service and, as the microbiological tests results are of decisive importance in the course of the antimicrobial therapy. If the drug was disapproved, the prescribing physician then had the option of responding by requesting a formal consultation by the ID service [8]. The laboratory staff must inform prescribers on microbiological results as soon as possible especially if the antibiotic prescribed does not conform to these results. Finally, parenteral and certain expensive antibiotic could still be prescribed by all specialists just for the first 72 h of treatment but further utilization required the IDS approval [13]. Automatic discontinuance of the antibiotic should be applied by the pharmacist after one week of starting treatment with the same antibiotic restricted, and the prescriber should consult infectious disease again for the continuation of the treatment with the same or an alternative antibiotic [6,8,13,21].

2.5 Data and Statistical Analysis

The different comparisons were based on two pre-conceived hypotheses: (i) ‘Are there differences concerning the consumption of antibiotics, especially restricted antibiotics prior to, and after the ARP (with the initial hypothesis that ARP increases the appropriate use of antibiotics) and (ii) ‘are there differences concerning the cost of antibiotic therapy within the hospitals prior to, and after the ARP?’ (with the initial hypothesis that the ARP decreases the cost).

The method of entry and data analysis was done by SPSS (Statistical Package for Social Sciences) version 22.0. The data for patients receiving antibiotic therapy were presented in both tabulated and graphical forms. The analysis of categorical variables was made by the percentage, the quantitative variable by the mean and standard deviation. Statistical analysis using Chi-square and one-way ANOVA were conducted to examine the association of antibiotics use and costs with sociodemographic factors, diagnosis, comorbidities, and clinical variables. P-value of <0.05 is considered statistically significant.

3. RESULTS

The target population whether with or without antibiotics includes 1,104 patients hospitalized in inpatient services prior to ARP (Group 1), and 1,248 hospitalized after the intervention period (Group 2). The studied population encompasses patients on antibiotic therapy, including 612 patients (55.4%), and 606 patients (48.5%) prior to, and after the intervention respectively. The one third of patients (38.42%) were hospitalized in surgeries wards with no statistically significant difference found between pre and post - intervention period (Table1).

3.1 Sociodemographic Characteristics

The sociodemographic characteristics are presented in Table 1. There were no statistically significant differences in the baseline characteristics between the two groups in this study. The average age of the population studied was 34.7±24.2 years in group 1 and 34.4±22.6 in group 2 [minimum 2.5 months- maximum 99 years]. Fifty five percent were females. More than a half of the population (56.2%) was not registered to the social security, and was treated in charge of the Lebanese Ministry of Public Health. The average length of stay is equal to 2.9±2 days.

3.2 Clinical, Biological, Radiological and Microbiological Results

The reasons for hospitalization are presented in Fig. 1 (a), and (b). Among patients admitted for medical purposes, the pulmonary pathologies motivated the antibiotics prescriptions (55.6% prior to, and 33.5% after the intervention), followed by gastrointestinal diseases (15.5% in group 1, and 18.7% in group 2 ($P<.001$). Concerning the patients hospitalized in surgical wards, the gynecological surgeries motivated the antibiotics prescriptions (32.7% in group 1 and 33.8% in group 2), followed by orthopedic surgeries (20.4%, 19.4%) ($P = .86$).

There were no statistically significant differences in the baseline clinical, biological, and microbiological characteristics between the two groups in this study except for the level of the C-reactive protein in blood, urine analysis results, and respiratory signs (Table 2). The percentage of patients with high level of the C-reactive protein in blood (≥ 6 mg / dl), and high white blood cells in urine increases from 28.6% prior to ARP, to 40.6% after ARP ($P = .03$), and from

17.8% prior to ARP, to 31.5% (*P* <.0001) after the intervention respectively. Neutrophils count was ≥ 70% for 24.9% of patients with no statistically significant difference prior to ARP (25.7%), and after the ARP (24.1%) (*P* =.54). One quarter of patients had a chest x-ray sign of lung infection (*P* < .0001) (Table 2), and 5% had diarrhea. According to Charlson comorbidity index, the majority of the population (79.2%) had no comorbidity, and 20.8% were low risk, moderate risk, or high risk (*P* =.13).

3.3 Data Concerning the Use of Antibiotics

3.3.1 Antibiotics used among patients

For each patient a single, two, and three agents used were examined. In the two groups, 76.4% of patients were treated with a single agent (Table 3).

The antibiotic use for prophylaxis purpose occurred in 55% prior to ARP, and increased to 66% after the ARP. For therapeutic culture-based reasons, antibiotics were prescribed for 4.4 % prior to ARP, vs. 3.6% after the ARP (*P* <.001). Parenteral administration was particularly prevalent where the physicians prescribed combinations of intravenous antibiotics. Unexpectedly, the pre-post gap in the use of injections increased with little decline for the third antibiotics used and even it got worse for the first and second agents used (67.2% prior to ARP, vs. 80.7% after the ARP; *P*<.01) (data not shown in the table). Meanwhile, the overall incidence of parenteral administration was between 60- 96% in the two groups (Table 4).

Table 1. Sociodemographic characteristics of patients prior to, and after ARP implementation (N1 = 612, N2 = 606)

Variable	Total N (%)	Prior to ARP [Group1] N1 (%)	After ARP [Group 2] N2 (%)	*P* value
Age (years)				.06
0.2-5	193 (15.9)	102 (16.7)	91 (15)	
6-15	80 (6.6)	49 (08.0)	31 (5.1)	
16-39	480 (39.4)	221 (36.2)	259 (42.7)	
40-49	135 (11.1)	70 (11.5)	65 (10.7)	
50-59	111 (9.1)	48 (7.9)	63 (10.4)	
60-69	90 (7.4)	46 (7.5)	44 (7.3)	
70-79	88 (7.2)	54 (8.8)	34 (5.6)	
80-99	41 (3.3)	22 (3.7)	19 (3.2)	
Mean ± SD	34.6±23.5	34.8±24.3	34.5±22.6	
Gender				.47
Male	540 (44.3)	278 (45.4)	262 (43.2)	
Female	678 (55.6)	334 (54.6)	344 (56.8)	
Third party payers				.32
Ministry of Health	685 (56.2)	335 (54.2)	350 (57.7)	
Others	533 (43.7)	277 (45.2)	256 (42.2)	
Wards				
Medical	246 (20.20)	128 (20.9)	118 (19.4)	.08
Surgical	468 (38.42)	222 (36.3)	246 (40.6)	.34
Pediatric	264 (21.67)	149 (24.3)	115 (19)	.56
Gyneco & obstetrical	240 (19.70)	113 (18.4)	127 (20.9)	.99
Length of stay (days)				.87
Mean (SD)	2.94 (2.059)	2.95 (2.18)	2.93 (1.93)	
Minimum - Maximum	1 - 30	1 - 30	1 - 19	
Total	1218 (100)	612 (100)	606 (100)	

Notes and abbreviations: "others": National social security fund, army, internal security forces, private insurance, cooperative public servants, the state security, customs police, the international medical community. SD. = standard deviation. Bold indicates statistical significance (p <.05)

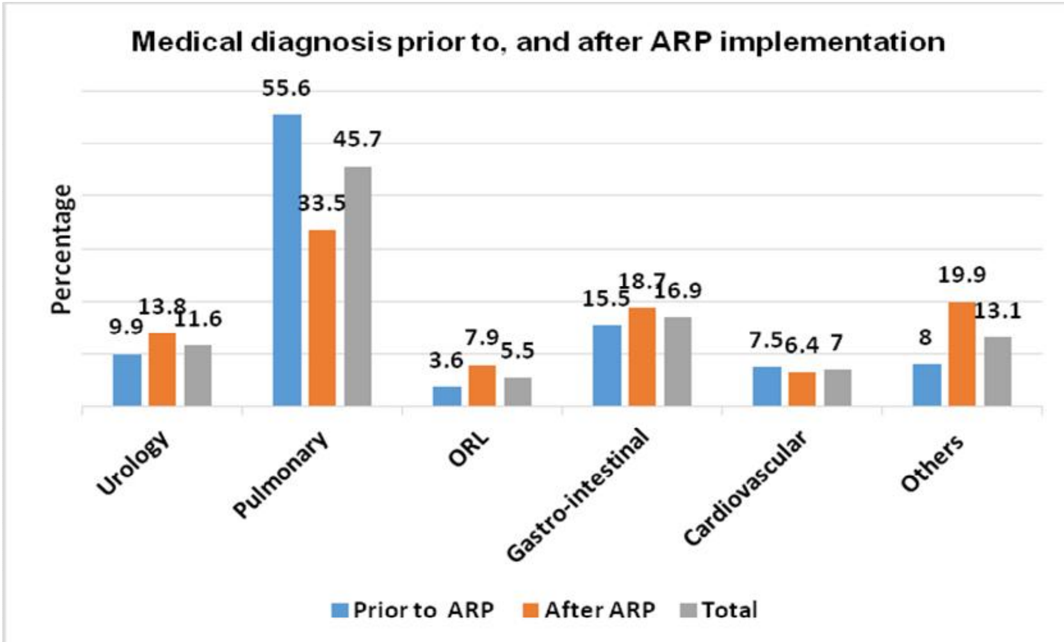

Fig. 1(a). Medical diagnosis prior to, and after ARP implementation (N1=252, N2=202)

Notes and abbreviations: ARP: antibiotics restriction program, ORL: oto-rhino-laryngology, others included the following diagnosis: neurological, orthopedic, gynecological, endocrine, infectious, skin and hematology diseases

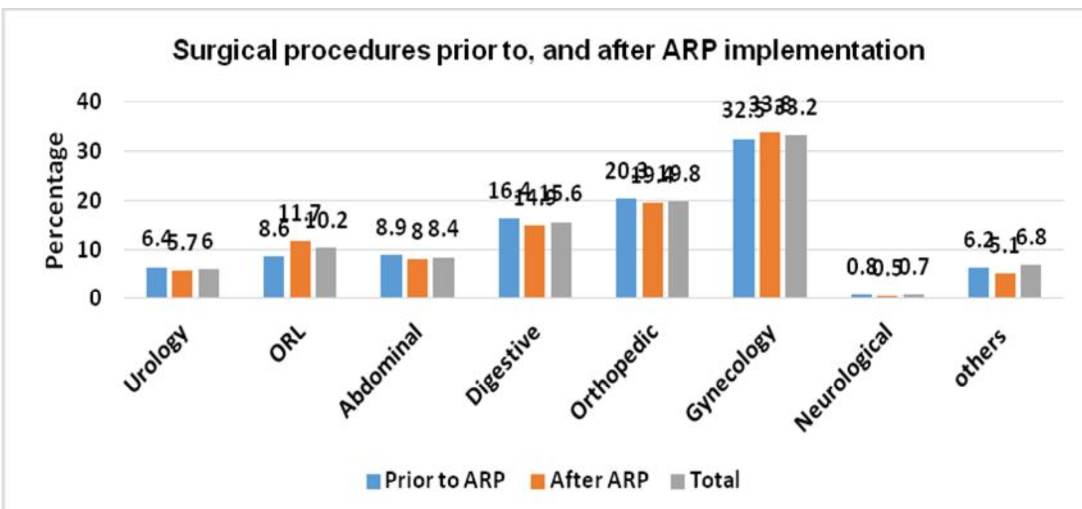

Fig. 1(b). Surgical procedures prior to, and after ARP implementation (N1=360, N2=404)

Notes and abbreviations: ARP: antibiotics restriction program, ORL: oto-rhino-laryngology, others included the following surgical procedures: endocrine surgery (1.4%), ophthalmology (1.0%), skin (1.7%), vascular (0.9%), maxillo facial (0.1%), trauma (0.4%) and plastic surgery (0.4%).p value = 0,81)

The rate of restricted antibiotics was 31.6%. After ARP, the rate of restricted antibiotic use, regardless of one, two or three antibiotics, decreased from 37.1% to 26.1% (*P*<.0001) (Table 3). Among different antibiotics, the most frequently ordered were second generation cephalosporins (26% in group 1, increased to 29% in group 2), penicillin derivatives (24% in group 1 that increased to 28% in group 2), and third-generation cephalosporin. After restriction, the rate of the third-generation cephalosporin use decreased from 19% to 12% (*P*<.001) (Table 4).

The dosage three times per day predominates as regards the frequency of the first antibiotic prescribed (55.7% prior to vs. 54.6% after ARP; *P*<0.0001). The administration of the second agent prescribed at three times per day was 39.5% in group 1 and 56% in group 2 (*P* =.003). The dosage once daily predominated in the frequency of administration of the third antibiotic prescribed (40% prior to, vs.58.4% after ARP; *P* =.66).

3.3.2 Antibiotics relay after patients discharge from the hospitals

At the discharge from the hospital, 24.8% of patients did not have any prescription of antibiotic. Penicillin derivative (36.3%) was the mostly prescribed as an antibiotic tracking ambulatory relay, followed by second- generation cephalosporin (17.2%) (*P* =.08) (Table 3).

Table 2. Clinical, biological, radiological and microbiological characteristics distribution among patient (N1=612, N2=606)

Variable	Total N (%)	Prior to ARP [Group1] N1 (%)	After ARP [Group 2] N2 (%)	*P* value
Charlson comorbidity index				.13
No comorbidity (0)	965 (79.2)	468 (76.5)	497 (82)	
Low comorbidity (2 – 3)	101 (8.3)	59 (9.7)	42 (6.9)	
moderate (4-5)	116 (9.5)	66 (10.8)	50 (8.3)	
High, very high-Comorbidity (≥6)	36 (2.9)	19 (3.1)	16 (2.8)	
Fever (Yes)	208 (17.1)	120 (19.6)	88 (14.5)	.22
Cough (Yes)	154 (12.6)	91 (14.9)	63 (10.4)	**.02**
White blood cells				.16
<12000/ mm^3	990 (81.3)	507 (82.8%)	483 (79.7)	
≥12000/ mm^3	228 (18.7)	105 (17.2)	123 (20.3)	
Reactive Protein C[1]				**.03**
<6 mg/dl	196 (66.2)	120 (71.4)	76 (59.4)	
≥6 mg/dl	100 (33.8)	48 (28.6)	52 (40.6)	
White cells in urine[2]				**.0001**
≤ 5 cu/mm3	446 (76.1)	268 (82.2)	178 (68.5)	
>5 cu / mm3	140 (23.9)	58 (17.8)	82 (31.5)	
Microbiological exam[3]				.10
Yes	153 (12.6)	79 (12.9)	74 (12.2)	
No	1065 (87.4)	533 (87.1)	532 (87.8)	
Type of microbiological exam[3]				**.07**
Urine	98 (64.5)	53 (67.1)	45 (60.8)	
Pus	21 (13.7)	12 (15.2)	09 (12.2)	
Others[4]	34 (21.8)	14 (17.7)	20 (27.0)	
Results of microbiological exam[3]				.80
Negative	104 (68.0)	53 (67.1)	51 (68.9)	
Positive	49 (32.0)	26 (32.9)	23 (31.1)	
Antibiotics based sensitivity test[5]				.35
Yes	33 (67.3)	16 (61.5)	17 (73.9)	
No	16 (32.7)	10 (38.5)	06 (26.1)	
PO antibiotics available based on sensitivity[5]				.36
Yes	37 (75.5)	21 (80.8)	16 (69.6)	
No	12 (24.5)	05(19.2)	07 (30.4)	
Chest x ray results[6]				**.0001**
Normal	570 (74.8)	291 (69.6)	279 (81.1)	
Signs of pulmonary infection	192 (25.2)	127 (30.4)	65 (18.9)	
Total (%)	1218	612 (100)	606 (100)	

Notes and abbreviations: PO= per OS; [1] :(N1=168, N2=128) ; [2] : (N1=326, N2=260) ; [3] : n=153 (N1=79, N2=74) ; [4] :Others" includes sputum, cerebrospinal fluid, blood, peritoneal fluid; [5]:(N1=26; N2=23) ; [6] :(N1=418, N2=344); Bold indicates statistical significance (p <.05)

Table 3. Antibiotics use information

Antibiotic use information	Total N (%)	Prior to ARP [Group1] N1 (%)	After ARP [Group 2] N2 (%)	*P* value
Combination of antibiotics				.57
Single antibiotic	930 (76.4)	475 (77.6)	455 (75.1)	
Two antibiotics	258 (21.2)	123 (20.1)	135 (22.3)	
Three antibiotics	30 (2.5)	14 (2.3)	16 (2.6)	
Purpose of antibiotic use				**.001**
Empiric	431 (35.4)	246 (40.2)	185 (30.5)	
Therapeutic culture-based	49 (4.0)	27 (4.4)	22 (3.6)	
Prophylaxis	738 (60.6)	339 (55.4)	399 (65.8)	
Restricted antibiotics				**<.0001**
Yes	385 (31.6)	227 (37.1)	158 (26.1)	
No	833 (68.4)	385 (62.9)	448 (73.9)	
Antibiotic tracking ambulatory relay				.08
Without antibiotics	302 (24.8)	151 (24.7)	151 (24.9)	
Quinolone	121 (9.9)	60 (9.8)	61 (10.1)	
Macrolide	38 (3.1)	25 (4.1)	13 (2.1)	
Penicillin derivative	442 (36.3)	226 (36.9)	216 (35.6)	
First-generation cephalosporins	05 (0.5)	02 (0.3)	04 (0.6)	
Second-generation cephalosporins	210 (17.2)	96 (15.7)	114 (18.8)	
Third-generation cephalosporins	74 (6.0)	46 (7.5)	28 (4.6)	
Others	26(2.1)	06 (0.9)	19 (3.1)	
Total (%)	1218 (100)	612 (100)	606 (100)	

Bold indicates statistical significance (p <.05)

Table 4. Proportional consumption of the most commonly utilized antibiotic classes prior to and after the intervention (n=1536) (N1=763, N2= 773)

	Total N (%)	Prior to ARP [Group1] N1 (%)	After ARP [Group 2] N2 (%)	*P* value
Antibiotic prescribed				**<.001**
Penicillin derivative	399 (26.0)	184 (24)	215 (28)	
First-generation cephalosporins	28 (01.8)	15 (2.0)	13 (2.0)	
2^{d}-generation cephalosporins	424 (27.6)	197 (26)	227 (29)	
3^{d} -generation cephalosporins	245 (16.0)	149 (19)	96 (12)	
4th -generation cephalosporins	12 (0.8)	8 (1.0)	4 (0.5)	
Carbapenem	20 (1.3)	12 (1.6)	8 (1.0)	
Aminoside	109 (7.1)	51 (7.0)	58 (8.0)	
Macrolide	69 (4.5)	46 (6.0)	23 (3.0)	
Quinolone	108 (7.03)	59 (8.0)	49 (6.0)	
Metronidazole	94 (6.1)	33 (4.0)	61 (7.0)	
Others	28 (1.8)	9 (1.1)	19 (2.0)	
Route of administration				**.04**
Intra venous injection	1402 (91.3)	685 (89.8)	717 (92.8)	
Oral route	134 (8.7)	78 (10.2)	56 (7.2)	
Total N (%)	**1536** (100)	**763 (100)**	**773 (100)**	

Notes and abbreviations: 2^{d}, 3^{d,} 4th: second, third, fourth respectively. Others: glycopeptides, ureidopenicilline, lincosamide, tetracyclines. Bold indicates statistical significance (p < 0.001)

3.3.3 Appropriate use of antibiotics according to microbiological testing

Microbiological testing was done for 79 (12.9%) patients prior to, and 73 (12%) patients after the ARP. Results were positive for 32.9% in group 1 and 31.1% in group 2 without statistical differences between the two groups (*P*=.63).

The appropriate use of antibiotics with evidence of the existence of bacteria found in the patient's body, based on culture and sensitivity test was slightly increased from 61.5% to 73.9% (*P*=.35) (Table 2). The samples for culture and sensitivity depend on the diseases: Blood, urine, sputum, nasal, pleural fluid, and swab of trachea.

Indeed, 39.2% of parenteral administrations were unnecessary as there were better routes available. In 80.8% of patients in group 1 and 69.6% in group 2, according to the results of the antibiogram, there was an antibiotic to which the bacteria was sensitive to be prescribed orally (*P*=.36) and administration by infusion and injections was not required (Table 2).

3.3.4 Cost data

The rate of antibiotics cost represents 33.4% of the total cost of drugs used in hospitals prior to the ARP, which decreased to 23% after the ARP implementation (*P*<.001), and the cost savings were US$ 8,099 per month. After the implementation of the Committee of the antibiotics use, the expenditure of all antibiotics was decreased by 22.3%, (*P*<.001), especially in the departments of surgery, pediatrics, and maternity. In addition, the ratio of cost of restricted antibiotics decreased by 9% (*P* =.02). (Table 5).

3.3.5 Compliance with the ARP activities by prescribers after ARP

The application of antibiotic-restriction program was evaluated according to the attitude and practice of the prescriber towards the ARP activities.

After ARP implementation, among the 158 restricted antibiotics prescribed, 94.4% of prescribers completed the antibiotics restricted form. In 91.8% the prescribers obtained the approval by an IDS before the beginning of treatment or after administering the first dose. Once the IDS determines a deadline to stop the antibiotic, prescribers respected the judgment in 93.7% of cases. In the cases where it was necessary a change of the antibiotic according to the microbiological results, 52.4% did change the antibiotic. In 90.4% of cases, the antibiotic to the relay release was consistent with the microbiological results (Fig. 2).

4. DISCUSSION

The study was designed to compare antibiotic use, cost, and consumption before and after an initiation of an antibiotic-restriction policy in two governmental hospitals.

The findings from the present study support previous research suggesting that the optimization of antibiotic usage reduces the amount of antibiotic usage, and cuts down the healthcare expenditure, may prevent the higher prevalence rates of some resistant bacterial strains, and is associated with the best possible outcome for the patients [5,6,13].

The use of aminosides (amikacin, and gentamycin) increased after the ARP implementation. This study replicates other published data. Indeed, Colligan et al., [12], found that the restrictions on the use of antimicrobials for patients with a high risk of Clostridium difficile infection have increased the use of gentamicin with potential for increased rates of renal toxicity and ototoxicity [12].

Table 5. Data on the expenditure of antibiotics used in the hospitals prior to, and after ARP

Wards	ARP Prior to/ After	Cost of medication *US$* (% of total)	Cost of antibiotics *US$* (% of total)	Cost of restrictive antibiotics *US$* (% of total)	% cost of antibiotics /cost of medication	% cost of restrictive antibiotics /cost of antibiotics
Medical	Prior	51 094 (47.8)	15 287 (42.8)	12 235 (45.8)	29.9%	34.2%
	After	53 762 (44.9)	8 675 (31.4)	7 032 (38.6)	16.1%	25.4%
Surgery	Prior	23 224 (21.0)	10 933 (30.6)	6 461 (24.2)	47%	18.1%
	After	29 358 (24.5)	11 803 (42.7) *	5 396 (29.7)	40.2%	19.5%
Pediatric	Prior	18 579 (17.4)	7 217 (20.2)	7 789 (29)	38.8%	21.8%
	After	20 361 (17.0)	4 600 (16.6) **	5 178 (28.5)	22.6%	18.7%
Gyneco-	Prior	13 934 (13.0)	2 255 (6.3)	213 (0.8)	16.1%	0.6%
obsterical	After	16 250 (13.5)	2 522 (9.1) **	562 (3.1)	15.5%	2%
Total (%)	Prior	106 834 (100)	35 700 (100)	26 700 (100)	33.4%	74.8%
	After	119 733 (100)	27 601(100) ***	18 170 (100)	23%	65.8%*

*Notes and abbreviations: US$ =US dollars; *: p<.05; **: p<.01; ***: p<.001; blanks indicate: not significant*

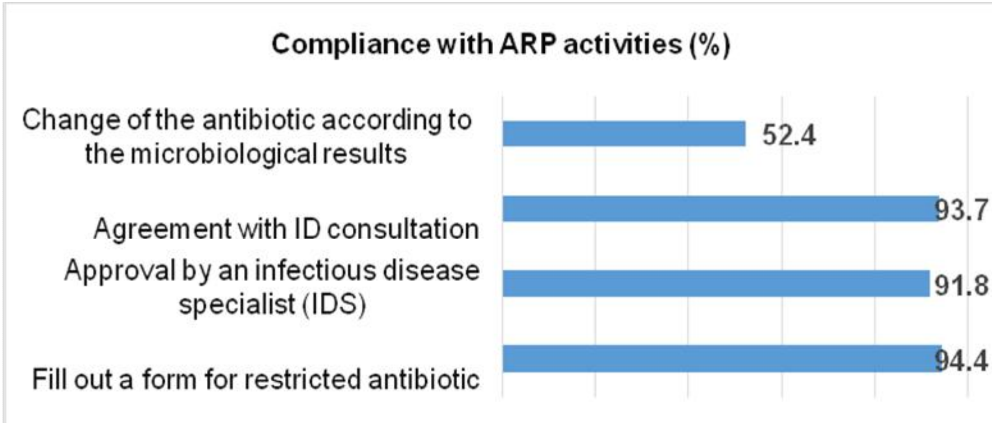

Fig. 2. Compliance with the ARP activities by prescribers after ARP (n=158)

Our study revealed high exposure to penicillin derivative antibiotics (26%). In Singapore, Ling et al. [22], found that many penicillins are significantly independent predictors of Carbapenem resistant Enterobacteriaceae colonization among patients admitted to the hospital [22].

Cephalosporin use in community and hospital settings is prevalent. The overuse of cephalosporins can raises the resistance among bacteria that are considered as an emerging worldwide threat to the favorable outcome of common infections, and leaves the physician with few therapeutic options [9]. Jha et al. [9], reported that resistance to cephalosporins in Gram negative isolates from the community varied from 50% to 64.28% which is much lower than the frequencies observed among the hospital isolates. The restriction of third-generation cephalosporins is nevertheless an effective method for controlling outbreaks of extended-spectrum beta-lactamase producing bacteria. Nevertheless, such measures must be undertaken cautiously [6].

Prior to, and after the ARP implementation, a quarter of patients were treated with two or three agents. According to Tammaa et al. [10], a second antimicrobial agent to treat a Gram-negative organism that is susceptible to a single agent may actually lead to increased antimicrobial resistance, adverse effects, and costs [10].

The combinations of antibiotics were mostly inappropriate. Patients received a combination of antibiotics and even up to three agents, while the culture and sensitivity tests results were negative prior to, and after the ARP implementation. Our therapeutic culture-based results (12.6%) are similar to statistics reported by Restinia et al. [23], where only six (13.64%) patients used antibiotic based on culture and sensitivity test in the hospital setting [23]. The microbiological tests are very indicative, though with possible differences *In vivo/in vitro*, and should be ordered and taken immediately into account by the physicians and the Committee on Antibiotics in each separate case of a hospitalized patient.The surgeons were the most frequent prescribers of antibiotics. The Antibiotic Committee should continuously update data on antimicrobial susceptibility patterns to guide empiric treatment, so that it would help the surgeon in the selection of antibiotics [9].

Parenteral administration was particularly prevalent where the physicians prescribed combinations of intravenous antibiotics. It is in line with the findings reported by Dong, Yan, and Wang in rural areas of Western China [5]. The WHO reported that about 90 % of parenteral administrations are unnecessary as there are better routes available [5]. The overuse of antibiotics and parenteral administration (i.e. infusions and injections) in preference to the oral route are the most prominent manifestations of irrational drug prescription practices, and alarmingly so when many cannot guarantee safety of this route of administration [5].

Our results provide strong evidence concerning the compliance with the policy of restricted antibiotics after ARP by prescribers, especially for the mandatory actions e.g. completion of the antibiotics restricted form, the approval of an IDS about new orders for restricted antibiotics, and the use of stop orders. Indeed, in the case where the physicians had the freedom to provide treatment for patients according to their own decisions, the breakdown of compliance was higher e.g. the changing of the antibiotic prescribed according to the microbiological results was only 52.4%, and the use of prophylactic antibiotic increased after the ARP. It has been reported that the requirement for approval from an IDS is the most effective control method [13]. Meanwhile, the concept of respect for autonomy of physicians involves the capacity to think, decide, and act on the basis of such thought and decision freely and independently, and on the assumption that the decision will not cause harm to others [24]. The role of the infectious diseases specialist should not be overestimated as far as the physician engaged with the patient is to the greatest extent aware and concerned with the patient's treatment. Thus, raising awareness of this problem, and affecting doctors' prescribing behaviors [1], reduce the rate of resistance in bacteria [2], and improve the quality of care and patient safety. In this context, hospital administrators and the Antibiotic Committee teams should build guarantees of safety consciousness and prompt staff to adopt participation in a "culture of safety", wherein everyone commits to personal responsibility for safety [25]. Educational sessions (face-to-face, e-learning, and having a formal education program which is mandatory for specific staff groups [12]) are highly recommended to be utilized by antibiotic boards. Also, the learning with a "*serious game*" is an innovative quick and efficient tool to improve knowledge, and practice of physicians about antibiotics, and patient safety [26]. Finally, the surveillance of antimicrobial use [12] , and the proper record keeping in Lebanese hospitals [11] providing clinicians with feedback based on the data collected, and verbally communicating with prescriber physicians centered around microbiological results and antimicrobial selection [6,8,13,21] are key stewardship activities. The introduction of electronic prescribing across the hospitals will facilitate ward level surveillance [12,17,20]. An informatics supported antibiotic stewardship program to move to desired behaviors without seriously curtailing autonomy is required [27]. A Therapeutic Drug Monitoring for examination of drug plasma levels for certain antibiotics in order to adjust the doses and avoid the side effects is also recommended [23,28].

The development of protocols and guidelines, especially for antimicrobial prophylaxis of surgical-site infections, using controlled language, without ambiguity, may provide a fast knowledge, and timely implementation of the management of antibiotics use in the hospitals [25].

Our study is one of the first interventional studies concerning antibiotics use in governmental hospital settings in Lebanon. There are several limitations in our study. First, we were not able to investigate whether the restrictive use of antibiotics in these tertiary care settings was associated with a change in mortality [13]. Second, the study period after ARP was not long enough to show changes in antimicrobial resistance [13]. Third, as in any sentinel surveillance study, one potential limitation was related to the representativeness of the participating hospitals. This difficulty is always a particular problem in developing countries, where the pool of hospitals capable of partaking in a research project, especially one of a resource intensive nature like this study, is more restricted [2]. Also, our study was unable to determine causal relationships between the antibiotic use, especially the restricted antibiotics, and their influencing factors prior to, and after the ARP. The design used in this study was the pre-post non-equivalent comparison-group design. Since the subjects were not randomly assigned, some threats, e.g. selection bias, to the external and internal validity, were possible. As both groups took the same pre and post drugs, and the intervention covered the same time period for all subjects, the testing and maturation are not internal-validity problems [29].

5. CONCLUSION

The current study evaluated the impact of an interventional program on antibiotic use, and cost savings. A further study of this programmatic approach is needed to evaluate the impact of an interventional program on all antimicrobial use and expenditure, and on antimicrobial resistance in hospital settings. The appropriate use of antibiotics has been initiated by the ARP, and may be addressed by health information campaigns. Rational drug prescribing contributes to global reductions in population morbidity and mortality with consequential medical, social, and economic benefits [5]. The ARP reduces the amount of antibiotic usage, cuts down the healthcare expenditure, and may prevent a higher prevalence of some resistant bacterial strains; It is, therefore, in the interest of policymakers to propose antimicrobial stewardship program based on mHealth system that allows patients, and healthcare providers, especially the physicians, to know more about antimicrobial treatment, and on-line and mobile consultations.

CONSENT

The Directors of hospitals approved this survey, and allowed to collect the data analyzed in this study.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Formoso G, Paltrinieri B, Marata AM, Gagliotti C, Pan A, Moro ML, et al. Feasibility and effectiveness of a low cost campaign on antibiotic prescribing in Italy: community level, controlled, non-randomised trial. BMJ. 2013;347:f5391.
   DOI: 10.1136/bmj.f539
2. Borg MA, Zarb P, Ferech M, Goossens H. On behalf of the ARMed project group. Antibiotic consumption in southern and eastern Mediterranean hospitals: Results from the ARMed project. Journal of Antimicrobial Chemotherapy. 2008;62: 830–836.
   DOI: 10.1093/jac/dkn260
3. Fair RJ, Tor Y. Antibiotics and bacterial resistance in the 21st Century. Perspectives in Medicinal Chemistry. 2014;6: 25–64.
   DOI: 10.4137/PMC.S14459
4. Mouawad R, Afif C, Azar E, Dahdouh E, Masri K, Irani J, Daoud Z. Effect of antibiotic consumption on resistance of *Pseudomonas aeruginosa* isolated from lebanese patients with emphasis on MBL production. Advances in Microbiology. 2013;3:382-388.
   Available:http://dx.doi.org/10.4236/aim.2013.34052 [(Published Online August,2013) (http://www.scirp.org/journal/aim)].
5. Yao Q, Liu C, Ferrier JA, Liu Z, Sun J. Urban-rural inequality regarding drug prescriptions in primary care facilities – a pre-post comparison of the National Essential Medicines Scheme of China. International Journal for Equity in Health. 2015;14:58.
   DOI: 10.1186/s12939-015-0186-7
6. Owens RC, Rice L. Hospital-based strategies for combating resistance. Clinical Infectious Diseases. 2006;42(4): S173–81.
   Available:http://www.sld.cu/galerias/pdf/sitios/apua-cuba/b8-hospital-based_strategies_for_combating_resistance.pdf
7. Ozkurt Z, Erol S, Kadanali A, Ertek M, Ozden K, Tasyaran MA. Changes in antibiotic use, cost and consumption after an antibiotic restriction policy applied by infectious disease specialists. Jpn J Infect Dis. 2005;58(6):338-343.
8. Mansouri MD, Cadle RM, Agbahiwe SO, Musher DM. Impact of an antibiotic restriction program on antibiotic utilization in the treatment of community acquired pneumonia in a Veterans Affairs Medical Center. Infection. 2011;39(1):53–58.
   DOI: 10.1007/s15010-010-0078-0
9. Jha PK, Verma PK, Sayana A. Bacteriological and antimicrobial susceptibility profile of soft tissue infections among hospital and community isolates from a tertiary care hospital. J. Surg. Sci. 2014;4(1):15-18.
   Available:http://lcs2002.com/style/Vol_Mar12.pdf
10. Tammaa PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. Clinical Microbiology Reviews. 2012;25(3): 450-470.
    DOI: 10.1128/CMR.05041-11
    Available:http://cmr.asm.org/content/25/3/450.full.pdf+html
11. Salem SE, Dahdouh E, Daoud Z. Resistance of Gram-Negative *Bacilli* in Lebanon. ISRN Infectious Diseases; 2013.

Available:http://dx.doi.org/10.5402/2013/759208. (Article ID 759208, 6 pages).

12. Colligan C, Sneddon J, Bayne G, Malcolm W, Walker G, Nathwani D. On behalf of the Scottish Antimicrobial Prescribing Group. Six years of a national antimicrobial stewardship programme in Scotland: Where are we now? Antimicrobial Resistance and Infection Control; 2015. DOI: 10.1186/s13756-015-0068-1
13. Altunsoy A, Aypak C, Azap A, Ergönül Ö, Balık I. The Impact of a nationwide antibiotic restriction program on antibiotic usage and resistance against nosocomial pathogens in Turkey. International Journal of Medical Sciences. 2011;8(4):339-344.
14. Eid AJ, Berbari EF. Editorial. The emergence of antibiotic resistance in Lebanon: Reality check and call for action. J Med Liban. 2013;61(3):125-126.
    Available:http://www.lebanesemedicaljournal.org/articles/61-3/editorial.pdf
15. WHO. World Health Day – 7 April 2011; 2011.
    Available:http://www.who.int/world-health-day/2011/en/ (Accessed on September 8,2015 [Online]).
16. Minister Office. Launching of the National Awareness Campaign about the rational use of antibiotics. Lebanese Ministry of Public Health; 2013.
    Available:http://www.moph.gov.lb/Media/Pages/AntibioticsCampaign.aspx (Accessed on September 8,2015 [Online]).
17. Al-Zaagi IA, Al-Dossari DS, Salem SO, Qureshi NA. Medication safety unit programs in King Saud Medical City, 2012 – 2013: Safe medication management and use with a focus on patient safety. British Journal of Medicine & Medical Research. 2015;8(5):384-407.
    Available:www.sciencedomain.org
18. Sabbah I, Sabbah H, Sabbah S, Akoum H, Droubi N. Central obesity and comorbidity risk in hemodialysis patients: A cross sectional study in Lebanon. Open Journal of Nephrology. 2012;2:109-115.
    DOI: 10.4236/ojneph.2012.24018
19. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2015. Oslo; 2014.
    Available:http://www.whocc.no/filearchive/publications/2015_guidelines.pdf
20. Qureshi NA, Al-Dossari DS, Ibrahim Abdulaziz Al-Zaagi, Abdullah Mohammad Al-Bedah, Abdulrahman Nasser Abudalli S, Koenig HG. Electronic health records, electronic prescribing and medication errors: A Systematic review of literature, 2000-2014. British Journal of Medicine & Medical Research. 2015;5(5):672-704. Article no. BJMMR.2015.072.
21. Navas D, Caillon J, Potel G. Bon usage des antibiotiques à l'hôpital: Évaluation des pratiques professionnelles de prise en charge des pneumopathies communautaires. La Presse Médicale. 2005;34:1687–1695. French.
22. Ling ML, Tee YM, Tan SG, Amin IM, How KB, Tan KY, Lee LC. Risk factors for acquisition of carbapenem resistant Enterobacteriaceae in an acute tertiary care hospital in Singapore Antimicrobial Resistance and Infection Control. 2015;4 (26).
    DOI: 10.1186/s13756-015-0066-3
23. Restinia M, Lucida H, Gillani SW. Longitudinal clinical evaluation of antibiotic use among patients with infecton. International Journal of Pharmacy& Life sciences. 2012:3(9):1935-1945.
    Available:http://www.ijplsjournal.com/issues%20PDF%20files/sep2012/1.pdf
24. Alzheimer Europe. Respect for autonomy; 2009.
    Available:http://www.alzheimer-europe.org/Ethics/Definitions-and-approaches/The-four-common-bioethical-principles/Respect-for-autonomy (Accessed on September 8, 2015. [Online]).
25. Sabbah I, Sabbah H, Sabbah S, Akoum H, Droubi N. Occupational exposures to blood and body fluids (BBF): Assessment of knowledge, attitude and practice among health care workers in general hospitals in Lebanon. Health. 2013;5(1):70-78.
    DOI: 10.4236/health.2013.51010
26. Venier AG, Marie S, Duroux T, Bervas C, Parneix P. Teaching good infection control practices with fun: Impact of the serious game Flu.0. Antimicrobial Resistance and Infection Control. 2015:4(Suppl 1):I10.
    Available:http://www.aricjournal.com/content/4/S1/I10
    DOI: 10.1186/2047-2994-4-S1-I10
27. Jones M, Butler J, Graber C, Glassman P, Samore MH, Weir C, Goetz MB. Cognitive perspective of an antibiotic timeout

program. Antimicrobial Resistance and Infection Control. 2015:4(Suppl 1):187. DOI: 10.1186/2047-2994-4-S1-P187

28. Center, Riyadh Poison Control. Therapeutic Drug Monitoring Unit; 2013. Available:http://www.moh.gov.sa/en/Sectors/PCCs/RUH/Departments/Pages/TDM.aspx(Accessed on September 8,2015. [Online])

29. Tran VD. The Effects of cooperative learning on the academic achievement and knowledge retention. International Journal of Higher Education. 2014:3(2). DOI: 10.5430/ijhe.v3n2p131 Available:http://dx.doi.org/10.5430/ijhe.v3n2p131

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