

Case Report

The Rates of the Unnecessary Antimicrobial Use (UAU) and the Effect of the Infectious Disease Consultations: A Cross-Sectional Study

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Abstract: To measure the rate of unnecessary antimicrobials (UAU), and the effect of the infectious disease consultation. A 17-week multicenter study, patients' records were reviewed for antimicrobials. A predefined UAU definition was developed. Excluded patients were those on prophylaxis and less than 1-year-old. The outcome is the UAU rate. Confounders were adjusted by Charlson index and APACHE 2 score. The analysis was by X^2 and Fischer's Exact Tests and multivariate analysis as appropriate. 662 records were reviewed: 169 qualified the necessary antimicrobial use (NAU) and 493 in the UAU categories. The rate of the UAU was 74.5%. The age means differed (53.85 years for the NAU versus 46.48 years for the UAU, $P < 0.001$) without gender difference ($P = 0.285$). The patients in the UAU category were represented more in UTI, SSTI, BSI, and no infection ($P < 0.05$). The commonest UAU subcategory were non-infectious non-febrile conditions 36.71%, influenza-like illnesses, and viral syndromes 20.08%, combination therapy 17.6%. An infectious disease consultation was significantly associated with less UAU ($P \leq 0.004$), and less mortality ($P < 0.05$). In conclusion: UAU rate was high, and an infectious disease consultation significantly reduced the UAU rate and mortality.

Keywords: Unnecessary Antimicrobial Use, Stewardship, Infectious Diseases Consult, Mortality

1. Introduction

Over the past decades, the wide use of antimicrobials in combating infections saved lives, with a marked reduction in infection-related mortality and complications [1-3]. Due to their perceived benefits in combating infections, an inappropriate message was conveyed on their "miraculous" effects, and their use was inappropriately extrapolated to other

non-infectious ailments. As a result, the unnecessary use of antimicrobials (UAU) emerged in some microbial infections and regrettably conditions other than bacterial infections, adding to the burden of bacterial resistance [4]. The inappropriate utilization of the antimicrobials resulted in an upsurge of the UAU rates, even in systems with antimicrobials restriction where it reached up to 50% [5, 6]. Though the literature is somehow focused on the prescribed antimicrobials in urinary tract infections as necessary-or

unnecessary antimicrobials use, nonetheless, this behavior must be considered in every clinical dilemma where antimicrobials are being used [7]. Here we define the UAU as the inappropriate antimicrobials use in several conditions like influenza, Influenza-like illness (ILI), viral syndromes, non-infectious febrile conditions, non-infectious afebrile conditions, combination antimicrobial therapy including double anti-Pseudomonal coverage [8-11], double anti-anaerobic coverage, extended periods of antimicrobial therapy beyond what is commonly recommended, and treating colonizing microorganisms [12-17]. In Jordan, the antimicrobials are widely used with no antibiotics restriction policies at the national and the hospital levels tempting practitioners for their use in an array of conditions. In an era of a shortage in new antimicrobials, the purpose of this study is to assess the rate of UAU in Jordan, attempting to understand the gravity of the problem and to help in antimicrobials' stewardship through a wise and responsible appropriate prescribing.

2. Materials and Methods

2.1. Study Type and Setting

A 17-weeks cross-sectional multicenter study between 20 November 2019 to 19 March 2020 in compliance with the STROBE statement (STrengthening the Reporting of OBServational studies in Epidemiology) found at (<https://www.strobe-statement.org/index.php?id=available-checklists>). The study was in a three urban Hospitals in Amman – Jordan: The Specialty, Al Khalidi and Jordan hospitals, the hospitals are accredited by the Joint Commission International and the local Health Care Accreditation Council (HCAC), the Specialty and Jordan Hospitals are accredited for training in internal medicine and a few of its subspecialties, as well as surgery, pediatrics, and gynecology/obstetrics. Approval was obtained in each hospital from the institutional review boards/ethics committees. Patients' consent was not obtained as the study was retrospective in nature. The pharmacy records were followed daily for new patients who were started on the antimicrobial agent (s), and on discharge, their medical records were reviewed. The clinical diagnoses of infections and their appropriate treatment were according to the IDSA and CDC guidelines for the diagnosis and treatment protocol, for both community-associated and hospital-related infections. The conduct of studies was confidential and limited to the study team to avoid observation bias among the teams/attending physicians who prescribe antimicrobials during the study period (Hawthorne Effect) [18].

2.2. Definitions of the Unnecessary Antimicrobial Use (UAU)

The following are defined as UAU, and a benefit was not established for the use of the anti-infective agent (s) in the treated infectious condition: The patient has Influenza documented by a nasopharyngeal or BAL sampling. Clinical diagnosis of influenza-like illness (ILI) or "viral syndrome" and no microbiological or serological evidence for bacterial

infection. Non-infectious febrile conditions: a documented fever or a robust clinical suspicion with a laboratory clue (e.g. eosinophils or monocytes on CBC, CPK, positive laboratory tests for rheumatological diseases) indicating a reactive fever, central fever, drug fever or rheumatological illness and no microbiological or serological evidence for bacterial infection. The use of combination antimicrobial agents both active against the treated microorganism, documented by an antimicrobial susceptibility testing (AST) for both antimicrobials, including *Pseudomonas aeruginosa* and double anaerobe coverage [8-11]. The use of antibiotics in noninfectious afebrile patients, e.g. heart failure with or without pulmonary edema. The extended period of antimicrobial use beyond what is recommended. Treatment of colonizing microorganisms reported by the laboratory as a contaminant or judged by the patient attending physician "himself" or an infectious disease physician, and the colonizer microorganism (s) did not correlate with sepsis diagnosis [17, 19].

2.3. Inclusions and Exclusions Criteria

During the study period, records were reviewed, and patients who were prescribed antimicrobials were included. Antimicrobials used outside their labeled indications but used appropriately in infection were considered in the study as necessary antimicrobial use NAU. Patients were excluded if they were on surgical prophylaxis, the patient was not on any antimicrobial, and less than one year of age.

2.4. Outcome Measure

The primary outcome measure is to calculate the UAU rate in our region and to acquire knowledge on some reasons behind UAU by the prescribers, and the impact of infectious diseases consultation. Secondary outcomes include whether the presenting diagnosis, comorbidities, severity index, and the attending specialty will affect the UAU.

2.5. Statistical Analysis

The study team uploaded data onto google form (Google Inc.), transformed into a Microsoft Excel sheet (Microsoft Corporation), the excel sheet was processed into SPSS version 25 (IBM corporation). Patients categorized as UAU and NAU were calculated as proportions (means), confounders were analyzed, like age, gender, the presenting diagnosis, comorbidities, cultured microorganism, mortality, and the reasons behind UAU distributed according to physician's specialty and the patients' presenting diagnoses. Confounders were adjusted by the APACHE II score and comorbidities by Charlson Comorbidity Index. Significance for the comparisons of means was tested by ANOVA. Continuous variables were tested by X2 test, by Fischer's Exact test and adjusted by the Bonferroni method. Within category analysis (APACHE 2, and Charlson comorbidity index) for both categories was assessed by the Log-rank test. Multivariate analysis for confounders by MANOVA. The two-tailed $P \leq 0.05$ was considered significant.

3. Results

Total patients' records reviewed were 662; 169 in the NAU and 493 in the UAU categories. The age means for the two categories differed significantly (53.85 years for NAU versus 46.48 years for the UAU, $P < 0.001$), without gender difference ($P = 0.285$). The rate of the UAU among the patients in the participating hospitals were 51.5% in the non-teaching hospital, and 76.3% and 100% in the teaching hospitals ($P < 0.001$) with an average of 74.5%. The presenting diagnoses: No infection, UTI, SSTI, and BSI, were significantly observed more in patients with UAU ($P < 0.05$). Most comorbidities were similar in both the NAU and UAU patients, except in multiple comorbidities and malignancy they were more in the NAU patients ($P < 0.05$) and the liver

diseases more in the UAU patients ($P < 0.05$). Charlson Comorbidity Index was subdivided into 1 – 2, 3 – 4, 5 – 6, 7-8, and > 8 . It was available for 113 patients in the NAU and 262 patients in the UAU patients. A significant higher Charlson index (≥ 5) among the NAU patients was found ($P < 0.05$). The APACHE II score for patients was subdivided into 4 classes to eliminate a potential within groups suppression of differences: Scores < 10 , 11 – 20, 21 – 30, and > 31 . The only significant difference ($P < 0.05$) noted was in class < 10 , where more patients were in the UAU category. There was a higher proportion of the cultured microorganisms in the patients with NAU compared with the UAU ($P = 0.000$), except for *P. aeruginosa* and the "bacteria not identified". There was a higher proportion of UAU patients with no cultures ordered, 70.6% versus 36.7% for NAU ($P < 0.05$), (table 1).

Table 1. Demographic features and characteristics of patients in the unnecessary antimicrobial use (UAU) study.

Characteristic	Patients with NAU N (%)	Patients with UAU N (%)	P-value
Number			
Total=662	169 (25.5)	493 (74.5)	$< 0.001^*$
Age*	53.85	46.48	0.001*
Gender			
Male	97	259	
Female	74	232	0.285**
Presenting Diagnosis			
Respiratory Tract Infection	64 (37.9)	163 (33.1)	≥ 0.05
No infection	5 (3)	189 (38.3)	< 0.05
Urinary Tract Infection	33 (19.5)	39 (7.9)	< 0.05
Intra-abdominal Infection	17 (10.1)	51 (10.3)	≥ 0.05
Skin and Soft Tissues Infection	24 (14.2)	29 (5.9)	< 0.05
Blood Stream Infection	25 (14.8)	8 (1.6)	< 0.05
Viral	0 (0.0)	10 (2.0)	≥ 0.05
Others	1 (0.6)	4 (0.8)	≥ 0.05
Comorbidities			
None	58 (34.3)	230 (46.7)	< 0.05
Multiple comorbidities	53 (31.4)	98 (19.9)	< 0.05
Diabetes mellitus	13 (7.7)	39 (7.9)	≥ 0.05
Malignancy	12 (7.1)	17 (3.4)	< 0.05
Hypertension	8 (4.7)	20 (4.1)	≥ 0.05
Chronic lung disease	4 (2.4)	12 (2.4)	≥ 0.05
Renal failure	2 (1.2)	12 (2.4)	≥ 0.05
Liver disease	0 (0)	12 (2.4)	< 0.05
Heart failure	3 (1.8)	6 (1.2)	≥ 0.05
Others*	16 (9.5)	47 (9.5)	≥ 0.05
APACHE 2			
$< 10^*$	70 (57.9)	206 (69.8)	< 0.05
11 – 20	36 (29.8)	73 (24.7)	≥ 0.05
21 – 30	11 (9.1)	12 (4.1)	≥ 0.05
> 31	4 (3.3)	4 (1.4)	≥ 0.05
Charlson Comorbidity index			
1 – 2	26 (15.4)	83 (16.8)	≥ 0.05
3 – 4	23 (13.6)	89 (18.1)	≥ 0.05
5 – 6	27 (16.0)	47 (9.5)	< 0.05
7 – 8	17 (10.1)	25 (5.1)	< 0.05
> 8	20 (11.8)	13 (2.6)	< 0.05
Microorganisms			
Enterobacteriaceae	14 (8.3)	8 (1.6)	< 0.05
ESBL producers	14 (8.3)	8 (1.6)	< 0.05
Polymicrobial	11 (6.5)	4 (0.8)	< 0.05
<i>P. aeruginosa</i>	4 (2.4)	4 (0.8)	≥ 0.05
<i>S. aureus</i>	5 (3.0)	2 (0.4)	< 0.05
Acinetobacter spp.	5 (3.0)	1 (0.2)	< 0.05
Enterococci	4 (2.4)	1 (0.2)	< 0.05
Others	9 (5.3)	11 (2.2)	< 0.05
No Microorganism	41 (24.3)	106 (21.5)	≥ 0.05

Characteristic	Patients with NAU N (%)	Patients with UAU N (%)	P-value
Not requested	62 (36.7)	348 (70.6)	<0.05
Mortality	17 (10.1)	13 (2.6)	0.000

UAU: unnecessary antimicrobial use. NAU: Appropriate (necessary) antimicrobial use. ESBL: Extended-Spectrum β -Lactamases.

Blood Stream Infection included 23 Central Line-Associated Blood Stream Infection, 10 Infective endocarditis, and one plus malaria.

Comorbidities: multiple included D. Mellitus plus other conditions.

Microorganisms (others): one Malaria, one CNS infection (undefined), one Dental abscess, and 2 *C. difficile*. Microorganisms (Enterobacteriaceae): not ESBL 14 *E. coli*, 7 *K. pneumoniae*, and one *K. oxytoca*.

Polymicrobial: *P. aeruginosa*, Proteus/Morganella/Providentia, MRSA, Enterococci (*S. faecalis* and *S. faecium*), and *Candida famata*.

P. aeruginosa: 5 were with other bacteria and yeast.

Viral: 5 Influenza by PCR, one H. zoster, one Infectious mononucleosis, one gastroenteritis, and one Adenovirus infections.

P-value is by χ^2 test and the Bonferroni method adjusted, except (*) was tested by ANOVA and (**) by Fischers' Exact Test.

*Others: Chronic lunges, malignancy, scheduled surgeries, and not available.

The rate of the UAU category 493 patients: non-infectious non-febrile conditions 36.71%, influenza-like illnesses and viral syndromes 20.08%, combination therapy 17.6%, extended duration of therapy 8.32%, patients with non-infectious febrile conditions 4.26%, therapy did not cover the treated microorganism 0.81%, elective surgery and colonization 0.6%, fewer patients (11.6%) had more than one reason for the UAU (Table 2). The relative proportion of the

antimicrobial use was higher in the UAU category for the third generation cephalosporins, Quinolones, Carbapenems, β -lactam β -lactamase inhibitor, glycopeptides, Macrolides and Clindamycin, Metronidazole and aminoglycosides ($P < 0.05$), while the proportion was not statistically different for the first/Second Generation Cephalosporines, Tigecycline, antifungals and the fifth Generation Cephalosporines ($P > 0.05$) (Table 3).

Table 2. The reason (definition) behind the unnecessary antimicrobial use (UAU) and frequency. The total UAU in 493 patients.

The Reason (s) for UAU	Frequency (%)
Combination Therapy only	87 (17.65%)
Combination Therapy plus:	
Extended duration	9
Extended duration and colonization	1
Non-infectious non-febrile conditions	7
Influenza-like illness/Viral syndrome	9
Influenza-like illness/viral syndrome/Extended duration	3
Extended duration of therapy only	41 (8.32%)
Extended duration of therapy plus:	
Non-infectious non-febrile conditions	13
Does not cover the treated microorganism	4 (0.81%)
Colonization	3 (0.60%)
Influenza/influenza-like illness/Viral Syndrome only	99 (20.08%)
Influenza-like illness/Viral Syndrome plus:	
Combination	9
Extended	2
Non-infectious non-febrile conditions only	181 (36.71)
Non-infectious febrile conditions only	21 (4.26)
Non-infectious febrile conditions plus: Combination therapy	3
Non-infectious febrile conditions plus: Elective surgery	3
Elective Surgery	3

Table 3. The frequency and the percent of the prescribed antimicrobials in 662 patients categorized into NAU and UAU.

	Number (%)		P-Value**
	NAU	UAU	
Frequency of patients (N=662)	169 (25.5)	493 (74.5)	
The Frequency of the Prescribed Antimicrobial			
Third Generation Cephalosporines	13 (7.7)	228 (46.2)	0.000
Quinolones	10 (5.9)	148 (30)	0.000
Carbapenems	10 (5.9)	108 (21.9)	0.000
β -lactam, β -lactamase inhibitor	3 (1.8)	51 (10.3)	0.000
Glycopeptides	2 (1.2)	37 (7.5)	0.001
Macrolides/Clindamycin	0 (0.0)	26 (15.3)	0.001
Metronidazole	0 (0.0)	21 (4.3)	0.004
Aminoglycosides	1 (0.6)	21 (4.3)	0.023
First/Second-Generation Cephalosporines	2 (1.2)	14 (2.8)	0.382
Tigecycline	0 (0.0)	11 (2.2)	0.075

	Number (%)		P-Value**
	NAU	UAU	
Antifungals	1 (0.6)	6 (1.2)	0.685
Fifth Generation Cephalosporines	0 (0.0)	6 (1.2)	0.346

UAU: unnecessary antimicrobial use. NAU: Appropriate (necessary) antimicrobial use.

Several classes of the prescribed antimicrobials (mostly the third-generation parenteral cephalosporins, carbapenems, Quinolones, and β L- β LI) were in combination with one, two, or three other antimicrobials.

**P-value by Fischer's Exact Test and Bonferroni Method Adjustment.

Exploring the specialties with increased UAU; there were no significant differences among Cardiology, Pulmonary, Internal medicine, Neurology, Pediatrics, Urology, ENT, OB/GYN, and Neurosurgery ($P \geq 0.05$). Gastroenterology and obstetrics/gynecology and orthopedics were significantly in the UAU category ($P < 0.05$). Oncology and nephrology were in the NAU category ($P < 0.05$), but with Tamhane's test (variance assumed not equal) it was not significant ($P > 0.05$). The presence of an Infectious disease consultation had a remarkable difference for being in the NAU category ($P < 0.05$).

A multivariate analysis with a post hoc analysis under the assumption of equal (LSD) or not equal (Tamhane) variances demonstrated a significant more presence in the NAU for the infectious disease ($P \leq 0.004$) with less mortality ($P < 0.05$) (Table 4). The patients who were in the NAU category had shorter hospital length of stay for all APACHE 2 scores ($P = 0.684$ by Log Rank test), while the length of the hospital was longer for patients in the UAU category, and was longest for the high scores ($P = 0.001$ by Log-rank test) except the highest >31 , all died early (Figure 1).

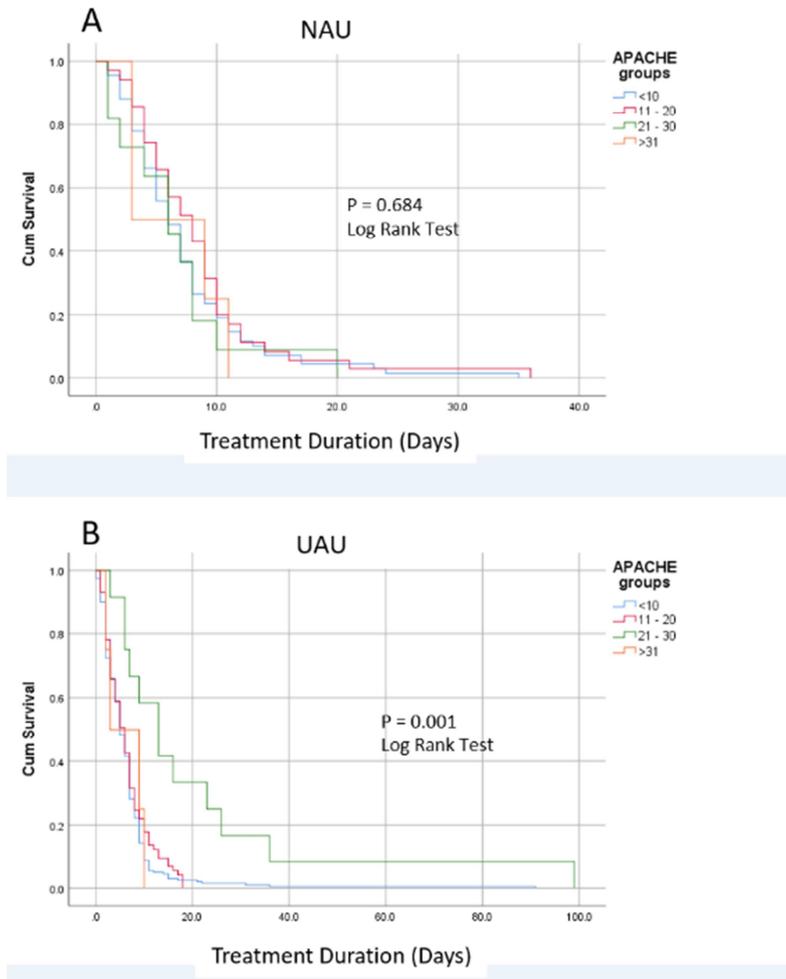


Figure 1. Kaplan-Meier curve demonstrating the duration of treatment for the NAU (A) and UAU (B) categorized patients, grouped according to APACHE 2 scores.

Note: there was no significant difference in the treatment duration grouped by different APACHE 2 severity scores for the NAU, but there was a significant difference in the duration of treatment ($P = 0.001$, by log-rank test) in the UAU category grouped by APACHE 2 score, it was longer with increased severity, but the highest score contained 4 patients and 2 patients died.

NAU: Necessary antimicrobials use. UAU: Unnecessary antimicrobial use.

Table 4. The rates of the prescribed antimicrobials as NAU/UAU classified according to the treating attending specialty and the associated mortality.

Specialty	NAU N (5)	UAU N (%)	P-value *	Mortality (N)	P-value**
Cardiology	18 (10.7)	36 (7.3)	≥ 0.05	4	≥ 0.05
Pulmonary	39 (23.1)	111 (22.5)	≥ 0.05	8	≥ 0.05
Gastroenterology	11 (6.5)	60 (12.2)	<0.05	4	≥ 0.05
Internist	6 (3.6)	25 (5.1)	≥ 0.05	1	≥ 0.05
Neurology	3 (1.3)	15 (3.0)	≥ 0.05	0	≥ 0.05
Nephrology	12 (7.1)	13 (2.6)	<0.05	3	≥ 0.05
Oncology	7 (4.1)	7 (1.4)	<0.05	3	<0.05
Pediatrics	24 (14.2)	58 (11.8)	≥ 0.05	1	≥ 0.05
Infectious Diseases	15 (8.9)	3 (0.6)	<0.05	3	<0.05
Urology	2 (1.2)	10 (2)	≥ 0.05	0	≥ 0.05
General Surgery	20 (11.8)	34 (6.9)	<0.05	1	≥ 0.05
ENT	1 (0.6)	11 (2.2)	≥ 0.05	0	≥ 0.05
OB/GYN	4 (2.4)	50 (10.1)	<0.05	1	≥ 0.05
Neurosurgeon	1 (0.6)	15 (3.0)	≥ 0.05	1	≥ 0.05
Orthopedics	6 (3.6)	45 (9.1)	<0.05	0	≥ 0.05

UAU: unnecessary antimicrobial use. NAU: Appropriate (necessary) antimicrobial use.

*P-values by X2 and adjusted Bonferroni Method. Infectious Diseases consultation and oncology service were associated with significantly less unnecessary antimicrobial use and less mortality, of note, are that most if not all oncology patients with suspected infection receive infectious diseases consultation.

**P-value for the proportion of patients' mortality among those treated by each subspecialty.

4. Discussion

The major objective of the antimicrobial stewardship is the appropriate utilization of antimicrobials, otherwise, their benefit may be deposited by their adverse effects without added therapeutic benefit. In our study, we have high UAU rates (74.5%) due to the lack of policies at the national and hospital levels and was left for the practitioner to decide to cause the unrestricted antimicrobials dispensing. Decreased awareness for the antimicrobials stewardship to curb the UAU was not uncommon. Besides, the high rates may have been due to our "expanded definition" for the UAU. Elsewhere, UAU rates were reported up to 35% in acute care hospitals and 42% from a long-term care facility, with a focus on the urinary system [20, 21]. In our patients, the commonest reasons for UAU were: patients with non-infectious and non-febrile conditions 36.71%, here, the treating surgeons/physicians start patients on an antimicrobial despite the absence of clinical clues for sepsis, laboratory findings, and imaging documentation but solely based on their belief that the presenting patient is "sick". Prescribing antimicrobials for the influenza-like illness or viral syndromes was 20.08%, though there were PCR-documented Influenza patients (N=20) or a reasonably strong clinical scenario for the diagnosis (n=91), the later may have had to increase the bias for the UAU. Though the literature is abundant in studies with opponent and proponent, the combination antimicrobials therapy scored 17.65%, which is not exceedingly high in hospitals with no restriction policies and with high BSI resistance patterns [22], however, this study has low BSI rates (1.6%), and cannot be justified based on the prevalence of resistance patterns from blood cultures alone [23-26]. The extended duration of the antimicrobials contributed to 8.32% of UAU despite the earlier recommendations on the shorter duration, and the wide use of the inflammatory markers like C-RP and procalcitonin in the country to help to attain such goals [27-30] (Table 2). The duration of the antimicrobial treatment was APACHE-2-score

adjusted, it did not reveal a significant difference in the NAU (P=0.684) but was significantly different for the UAU (P=0.001); the higher illness severity-score the longer the unnecessary duration was (Figure 1).

The First-and fifth-generation cephalosporins, as well as the antifungals, did not significantly differ in the two categories possibly due to their uncommon use. All other classes of antimicrobials significantly (P<0.05) were used in the UAU category (Table 3), though their broad-spectrum was not needed, and a narrow spectrum antimicrobial would have done the task [20]. There were no specific presenting diagnoses for patients associated with the adoption of UAU, including patients with the aseptic diagnoses (P<0.05), denoting that the UAU behavior is about the prescriber bias and believes, and was not influenced by a specific diagnosis the patient may have had. Charlson Comorbidity Index-adjusted multiple comorbidities demonstrated a significantly (P<0.05) higher index (≥ 5), while malignancy was significantly higher in the NAU (P<0.05), this have been due to the higher infectious diseases consultations in the patients with multiple comorbidities, except the liver diseases were more in the UAU (P<0.05) possibly due to a medical center dealing with liver diseases and occasional liver transplantation without an infectious diseases coverage. The utilization of cultures was less in the UAU category (36.7% versus NAU 70.6%, P<0.05), notably, NAU had a higher proportion of culture-positive patients (P=0.000), probably due to the confidence in the antimicrobial susceptibility test which directed the treating physicians for a more appropriate regimen.

The specialties that significantly fall in NAU were infectious disease physicians, oncologists and nephrologists, and general surgeons (P<0.05). Obstetricians/gynecologists, orthopedics, and gastroenterologists were significantly in the UAU category (P<0.05): the diagnoses, cesarean section patients, patients with closed fractures, and the gastroenteritis patients respectively placed the respective practitioners in the UAU. The other specialties did not significantly differ between the two categories. Furthermore, a notable (P<0.05)

decrease in the mortality for patients cared for by infectious disease physicians, a phenomenon that keeps on echoing [31-33], oncologists (as admitting physicians) shared the infectious diseases physicians the lower mortality, however, oncologists regularly consult infectious diseases for suspected sepsis/sepsis in the three medical centers (Table 4).

5. Conclusion

In our retrospective study, the UAU rate was high in Jordan, prescribers are mostly not aware of the elements of UAU i.e. when to consider a prescription a UAU, this is possibly due to inadequate physicians' and surgeons' awareness and exposure to the multifaceted stewardship concept. Strategies should be implemented at the country level to curb the high UAU rate, a special emphasis must target the attending physicians and surgeons as decision-makers on the prescription of the antimicrobials. This can be achieved through education, integration in the antimicrobial stewardship, overseeing the prescriptions at the hospital level, feedback, and enforcing antimicrobial restriction at a national and hospital level. Infectious disease consultation must widely be encouraged or at least a change of attitude towards more liberal consultations, this will help in curbing UAU and decreasing mortality [34, 35].

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Conflicts of Interests

Jamal Wadi receives honoraria as a speaker at symposia and webcast meetings by HIKMA, MSD, Pfizer, and Dar Al Dawaa pharmaceuticals, all other authors have no conflict of interest.

Approval

The study was approved by the IRB of the three hospitals.

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