# Antibiotic Consumption and Development of Resistance among Gram-Negative Bacilli in Hospitalized Patients of King Abdullah University Hospital (KAUH) in North Jordan.

***Karem H. Alzoubi[1] ✉, Nawaf J. Shatnawi[2], Bader M. Al-Sadi[1], Saafan A. Al-Safi[1] and Mustafa A. Abuirjeie[3]***

[1] Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan.
[2] Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan.
[3] Department of Medicinal Chemistry and Pharmacognosy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan.

## ABSTRACT

This prospective study was carried out to investigate the incidence of resistance in Gram-negative bacilli against an injectable form of third generation cephalosprins (Ceftriaxone) and an injectable form of aminoglycosides (Amikacin) in relation to several antibiotics used in King Abdullah University Hospital (KAUH). *Pseudomonas aeruginosa* were most frequently isolated from blood, respiratory tract and wound specimens. *Enterobacter spp* were most frequently isolated from blood specimens. *E. coli* was the most frequent isolate from urine. Ceftriaxone was most frequently used against *E. coli* (19.6%), while Amikacin was most frequently used against *P. aeruginosa* (19.1%). The rate of resistance of *E. coli* for ceftriaxone was 20%, and for amikacin was 40%. For Amikacin, 22.2% of *P. aeruginosa* cases and 33.7% of *Acinetobacter spp* cases were resistant. In conclusion, through analysis of the rates of resistance in KAUH / Jordan, we found that it's worthy to conduct a multicenter / national study studying the incidence of bacterial resistance in Jordan.

**Keywords:** Bacterial resistance, ceftraixone, amikacin, *P. aeruginosa, Acinetobacter spp, E. coli.*

## INTRODUCTION

Gram-negative bacteria remains important hospital pathogens, particularly for critically ill patients. Consequently, appropriate antimicrobial treatment is crucial to decrease morbidity and mortality among hospitalized patients with infections. The propensities for resistance were developed for most available antimicrobial agents[2,3]. Since the discovery of antimicrobial agents, microorganisms have developed virtually unlimited resistance to these agents. Hospitals are an important breeding ground for the development of such resistance. This is attributed to the heavy demand on antibiotic use or due to antibiotic misuse. Moreover, high-density patient populations who are in a frequent contact with health care staff and the risk of cross-infection contributes to the spread of antibiotic-resistant microorganisms[3]. This increases the morbidity and mortality associated with infections, and contributes to rising costs of health care.

Expanded-spectrum cephalosporin (ceftriaxone) and aminoglycoside (Amikacin) are widely used against Gram-negative bacilli[2-4]. Heavy demand and/or inappropriate use of such antibiotics leads to the prevalence of antibiotic resistance[5,6]. In the present

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✉E mail: khalzoubi@just.edu.jo

study, the prevalence of antibiotic resistance among Gram-negative bacilli in KAUH in the injectable form of third generation cephalosprins (Ceftriaxone) and in the injectable form of aminoglycosides (Amikacin) was investigated.

## EXPERIMENTAL SECTION (METHODS)

This prospective study was conducted at King Abdullah University Hospital (KAUH), a major University-affiliated tertiary care facility (>500 beds) located in north Jordan. This study covered the period from July / 2005 until July / 2006. This hospital, which has a fully computerized patient database, provides services in major branches such as surgery, pediatric internal medicine, and service in highly specialized units such as intensive care, neonatal, renal, gynecology, cardiac, and oncology units. From among these units, information about patients, drug and microorganism was collected.

The daily pharmacy records were used to trace all patients admitted to the hospital and taking either third generation cephalosprin (Ceftriaxone) or aminoglycoside (Amikacin) or both. For those patients included in the study, medical records and medication sheets were then reviewed and followed up during patients hospital stay. Information collected from those medical records and medication sheets included age, sex, diagnosis, previous medical illness, antibiotic history and current antibiotic; date of starting antibiotic, duration course, quantities of antibiotic, termination date, complications, and alternative antibiotic use, if any. In addition, for patients included, results of the clinical microbiology laboratory analysis (bacterial culturing and antibiotics susceptibility testing for ceftriaxone and / or amikacin) were traced through the hospital's computerized data system (Medicom).

All samples for bacterial culturing were processed according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Samples were analyzed at KAUH clinical microbiology laboratory using an automated bacterial identification and Antibiotic Susceptibility Testing system (ID/AST; VITEK system, bioMerieux, Inc, NC, USA). Information obtained form the laboratory analysis included culture result before and after using antibiotic, microorganisms resulted from culture, emergence of abnormalities in lab results through using antibiotics, and antibiotics susceptibility patterns.

Included in the study were all patients admitted to the hospital and taking either third generation cephalosprin (Ceftriaxone) or aminoglycoside (Amikacin) or both. Outpatients were excluded from this study. Patients taking antibiotic other than Ceftriaxone or Amikacin and patients taking medication against microorganism other than Gram-negative bacilli were also excluded.

## RESULTS AND DISCUSSION

The frequency of the bacterial isolates and their sites of isolation are shown in Table (1). The most common isolates were *E. coli* (30%), *P. aeruginosa* (20%), *Acinetobacter spp* (12%), and *Enterobacter spp.* (6%). The most common sites of isolation were blood (38%), urine (32%), wounds (12%), respiratory tract (10%), and pus (8%). *Pseudomonas aeruginosa* and *Enterobacter spp* were the most frequent isolates from blood specimens. *Pseudomonas aeruginosa* was also the most frequent isolate from respiratory tract and wounds specimens. *E. coli* was the most frequent isolate from urine (Table 1).

The frequency of the antibiotic usage and their sites of consumption are shown in Table (2). Ceftriaxone was most frequently used against organisms isolated from urine (30.9 %) and blood (28.4%). Ceftriaxone was used in 34.6 % of infections without culturing either as surgical prophylaxis or as a result of finding abnormalities in other lab tests such as finding an increase in WBCs count.

Amikacin was most frequently used against organisms isolated from blood (37.9%), urine (13.6%), and sputum (9%), respectively. Amikacin was used in (28.8%) of infections without doing cultures either as surgical prophylaxis or due to abnormalities in other lab tests.

The antibiotic usage against various Gram-negative bacilli is shown in Table (3). Ceftriaxone was most frequently used against *E. coli* (19.3%). It was used without isolating organism isolated from culture in (69%) of the cases. Amikacin was most frequently used against *P. aeruginosa* (19.1%), *Acinetobacter spp* (12.8%), and *E. coli* (10.6%). It was used without culturing in 29.8% of the cases.

The bacterial susceptibilities and resistance to antibiotics are shown in Table (4). Ceftriaxone was used against *E. coli*; (30%) of the cases were sensitive, (20%) were resistant, and (50%) showed no result when cultured. Only one case of *Pseudomonas aeruginosa* that was sensitive to Ceftriaxone was encountered.

Amikacin was used against *P. aeruginosa* where (66.6%) of the cases were sensitive, (22.2%) were resistant, and (11.1%) with no result for culture. Also, Amikacin was used against *Acinetobacter spp* where (16.7%) of the organisms were sensitive, (33.7%) were resistant, and 50% showed no result from cultures.

During study period, patients received either ceftriaxone or amikacin antibiotic, and were evaluated for development of resistance upon consumption of these antibiotics.

Ceftriaxone was used against *E.coli* infections in ten cases, of which three were sensitive before coming to the hospital and remained sensitive during and after receiving the ceftriaxone. Another two cases were resistant: one developed resistance in advance before coming to the hospital, while the other developed resistance during hospital stay. The latter case received a course of ceftriaxone (about 6mg) for three days, during the first admission to the hospital. During a second admission, two months later, another culture was taken for that case and showed resistance to ceftriaxone.

The results also showed (30%) susceptibility of *E. coli* for ceftriaxone. This is a lower susceptibility compared to the one found in European countries, Canada, and United State[7]. That could be due to a variety of factors including the difference in the bacterial strains between Jordan and developed countries, better patients' compliance and / or practices, better institutional antibiotic handling and more restricted antibiotics prescription strategies employed in these countries. This result may represent the seed for further evaluation and verification both retrospectively and prospectively.

Ceftriaxone was also used against *Enterobacter spp* and Gram-negative bacilli in three cases, which were found to be sensitive to ceftriaxone and remained so after usage of ceftriaxone.

Amikacin was used against *Pseudomonas aeruginosa* infections in nine cases, of which six were sensitive before using Amikacin and remained so after usage. Another two cases were resistant; one of them developed resistance 465 days post the last admission. The other case came resistant to hospital with neither determining quantities of antibiotic used nor determining the date of previous culture, which may have been done in another hospital. The rate of resistance of *Pseudomonas aeruginosa* for Amikacin shown in the present study was comparable to that shown by other previous studies[8].

Amikacin was used against *Acinetobacter spp* in six cases, of which one was sensitive and remained so after using amikacin without developing resistance. Two other cases showed resistance to amikacin before getting hospitalized. Amikacin was also used against *E.coli* infection in five cases, of which two cases were sensitive and remained sensitive after using amikacin. Two other cases showed resistance to amikacin, one was admitted to the hospital several times and received courses of amikacin during hospitalization. Eighty-three days post last admission; the patient was re-admitted, where cultures showed resistance to amikacin. The latter was resistant before hospitalization without determining the quantities of antibiotic used or date of previous culture, which might have been done in other hospitals. Other studies on the aminoglycoside gentamicin, but not amikacin, showed a resistance rate of 25% for *E. coli*[9], which is low in comparison to our results. However, that study was on a different antibiotic (Gentamicin).

In Conclusion, The rate of resistance among Gram-negative bacilli in (KAUH) / Jordan, in relation to antibiotic consumption was either consistent with or higher than rates shown in other countries. Therefore, it may be worthwhile to conduct a multicenter / national study looking into the incidence of bacterial resistance in Jordan.

**Table 1: Types of bacterial strain and site of isolation**

| Microorganism | Sputum n(%) | Urine n(%) | Wound n(%) | Blood n(%) | Pus n(%) | Total n(%) |
|---|---|---|---|---|---|---|
| ***P. aeruginosa*** | 3(30%) | 0(0) | 3(30%) | 3(30%) | 1(10%) | 10 (20%) |
| *Klebsiella spp.* | 0(0) | 1(100%) | 0(0) | 0(0) | 0(0) | 1 (2%) |
| *E. coli* | 0(0) | 14(93%) | 1(7%) | 0(0) | 0(0) | 15 (30%) |
| *Enterobacter spp.* | 0(0) | 1(33.3%) | 1(33.3%) | 1(33.3%) | 0(0) | 3 (6%) |
| *Acinetobacter spp* | 1 (16.3%) | 1(16.3%) | 1 (16.3%) | 3(50%) | 0(0) | 6 (12%) |
| Other Gram-negative bacilli | 0(0) | 1(25%) | 0(0) | 1(25%) | 2(50%) | 4 (8%) |
| Other organisms | 1 (9%) | 1 (9%) | 0(0) | 8 (73%) | 1 (9%) | 11 (22%) |
| All organisms | 5(10%) | 19(38%) | 6(12%) | 16(32%) | 4 (8%) | 50 |
| No growth | 1 | 15 | 2 | 32 | 0 | 50 |

The table contains information about bacterial isolation's site and percentage rate for each site for all isolated organisms. The last row shows the number of specimens with no growth of bacteria during culturing.

**Table 2. Type of antibiotic and site of consumption**

| Culture | Sputum n(%) | Urine n(%) | Wound N (%) | Blood N (%) | Pus n (%) | No culture N (%) | Total N (%) |
|---|---|---|---|---|---|---|---|
| Ceftriaxone | 0 (0) | 25 (30.9%) | 4 (5%) | 23 (28.4%) | 1 (1.1%) | 28 (34.6 %) | 81 (100%) |
| Amikacin | 6 (9%) | 9 (13.6%) | 4 (6%) | 25 (37.9%) | 3 (4.5%) | 19 (28.8%) | 66 (100%) |

The table demonstrates the percentage rate of consumption of each antibiotic in relation to each site of isolation.

**Table 3. Antibiotic usage against various organisms**

| Microorganism | Ceftriaxone | Amikacin |
|---|---|---|
| *P. aeruginosa* | 1(1.9%) | 9(19.1%) |
| *Klebsiella spp.* | 0(0) | 1(2%) |
| *E. coli* | 10(19.3%) | 5(10.6%) |
| *Enterobacter spp.* | 2(3.9%) | 0(0) |
| *Acinetobacter spp* | 0(0) | 6(12.8%) |
| Other Gram-negative bacilli | 1(1.9%) | 3(6.4%) |
| Other organisms | 2(3.9%) | 9(19.1%) |
| No growth | 36(69%) | 14(29.8%) |
| Total | 52 | 47 |

The table describe percentage rate of antibiotic usage against isolated organisms in relation to antibiotic for each organism. Percentages represent total number of each antibiotic used.

**Table 4. Bacterial susceptibilities and resistance to antibiotic**

| | Ceftriaxone | | | Amikacin | | | Total |
|---|---|---|---|---|---|---|---|
| **Microorganism** | **Susceptible** | **Resistant** | **No result** | **Susceptible** | **Resistant** | **No result** | |
| *P. aeruginosa* | 1 (100%) | 0 | 0 | 6 (66.6%) | 2 (22.2%) | 1 (11.1%) | 10 |
| *Klebsiella spp.* | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| *E. coli* | 3 (30%) | 2 (20%) | 5 (50%) | 2 (40%) | 2 (40%) | 1 (20%) | 15 |
| *Enterobacter spp.* | 2 (100%) | 0 | 0 | 0 | 0 | 0 | 2 |
| *S. maltophilia* | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Acinetobacter spp* | 0 | 0 | 0 | 1 (16.7%) | 2 (33.3%) | 3 (50%) | 6 |
| *Proteus mirabilis* | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other Gram-negative bacilli | 1 (100%) | 0 | 0 | 2 (66.7%) | 1 (33.3%) | 0 | 4 |
| Other organisms | 0 | 0 | 2 | 4 (44.4%) | 0 | 5 (55.6%) | 11 |

The table demonstrates the patterns of susceptibility and resistance of the organism to each antibiotic in total number of each organism.

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# استهلاك المضادات الحيوية وحدوث مقاومة بين Gram-negative bacilli في المرضى المقيمين في مستشفى الملك المؤسس عبدالله الجامعي في شمال الأردن

***كارم الزعبي[1]، نواف الشطناوي[2]، بدر السعدي[1]، صعفان الصافي [1] ومصطفى أبو ارجيع[3]***

[1] قسم الصيدلة السريرية، كلية الصيدلة، جامعة العلوم والتكنولوجيا الأردنية، اربد، الأردن.
[2] كلية الطب، جامعة العلوم والتكنولوجيا الأردنية، اربد، الأردن.
[3] قسم الكيمياء الطبية والعقاقير، كلية الصيدلة، جامعة العلوم والتكنولوجيا الأردنية، اربد، الأردن.

## ملخـص

تبحث الدراسة الحالية في تكرار حدوث المقاومة البكتيرية في مجموعة Gram-negative bacilli ضد الحقن لمضادين حيويين هما ceftraixane وAmikacin بالمقارنة مع المضادات الحيوية الأخرى المستخدمة في مستشفى الملك عبدالله المؤسس (KAUH). وجدت الدراسة أن *Pseudomonas Aerugenosa* كانت الأكثر شيوعا في العينات المأخوذة من الدم والجهاز التنفسي والجروح. أما *enterobacter Spp.* فقد كانت أكثر شيوعا في عينات الدم بينما كانت *E. Coli* أكثر شيوعا في عينات البول. استخدم Ceftriaxone في معظم الحالات ضد (19.6%) من *E. coli* بينما استخدم Amikacin في معظم الأحيان ضد *P. Aeragenosa* (19.1%). وجد أن نسبة مقاومة E. coli لـ ceftriaxoneكانت 20% ونسبة مقاومتها لـ Amikacin كانت (40%) ونسبة مقاومة *P. Aerugenosa* لـ Amikacin كانت (22.2%)، بينما كانت نسبة مقاومة *Acinetobactor spp* لـ Amikacin (33.7%). كمحصلة للتحليل الدقيق الذي أُجري في هذه الدراسة لنسبة المقاومة للمضادات الحيوية في KAUH فإن من المهم أن يتم إجراء دراسة وطنية تشتمل عدة مراكز طبية للوقوف على النسبة الفعلية لمقاومة المضادات الحيوية في المراكز الطبية في الأردن.

**الكلمـات الدالـة:** المقاومة البكتيرية، *P. aeruginosa, Acinetobacter spp, E. coli.* ceftraixone, amikacin.

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