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Evaluation of Tigecycline Use: A Continuous Quality Improvement Study

Al-Shaimaa M. Al-Mehmady, Pharm.D.**, Rahmah A. Al-Harthy,** Pharm.D.**, Abrar F. Al-Subhi,** Pharm.D.**, Hadeel H. Al-Harbi,** Pharm.D., and **Ameen M. Al Mohammadi,** PhD

Department of Clinical Pharmacy, Faculty of Pharmacy,
King Abdulaziz University,
Jeddah, Saudi Arabia
amalmohammadi@kau.edu.sa

Abstract. Tigecycline is the first available agent in the new class of glycylcyclines. It is active against multi-resistant Gram-positive and Gram-negative bacteria. Although it is recently approved, resistance of tigecycline is reported by many strains of bacteria. Moreover, it is one of the most expensive antimicrobials in the market. A retrospective longitudinal study conducted at King Abdulaziz University Hospital, Jeddah. All patients who received tigecycline from March to November 2010 were included in this study. Data regarding indication of tigecycline, monitoring process and the outcome of treatment were all collected *via* patient chart review form, and obtained from patient's file. A total of 92 patients were administered tigecycline in the study period. In 23 (25%) patients, tigecycline was used for unapproved indications and the most common indications of tigecycline were complicated skin and soft tissue infections community acquired pneumonia. The overall outcomes were healing in 50 (54%) patients, infection treated with other drugs in 10 (11%) patients and death was reported in 32 (35%) patients. This study confirmed the high mortality rate associated with tigecycline use, and this should be a reminder to healthcare professional when considering its use in severely infected patients or when to be used as a monotherapy in empirical situation.

Keywords: Tigecycline, Drug use evaluation, Mortality rate, Therapy failure.

Correspondence & reprint request to: Dr. Ameen M. Al Mohammadi
P.O. Box 80260, Jeddah 21589, Saudi Arabia
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Introduction

The increased incidence of resistance to antibiotics led to the discovery of a new class of antibiotics, the glycyclines. Tigecycline is the first agent marketed from this class and it was approved by the Food and Drug Administration (FDA) in 2005. The Tigecycline Evaluation and Surveillance Trial (TEST), a global multicentre surveillance program, documented that tigecycline is highly active against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and *enterococci*; including vancomycin-resistant *enterococci* (VRE). It is also highly active against Enterobacteriaceae, anaerobes and atypical pathogens. Reduced activity of tigecycline has been observed for Proteus species, *Providencia* species and Morganella species, as well as *Pseudomonas aeruginosa*, also not reliably inhibited by tigecycline[1,2].

Even though it is recently approved, resistance of tigecycline is reported from many studies by some strains of bacteria. A study of hospitalised patients in United Kingdom in 2006 showed that many of gram-positive and gram-negative bacteria were resistant to tigecycline such as *Staphylococcus aureus* (*S. aureus*) isolates (7%, n = 2472 of which 39% were MRSA) and *enterococci* (5%, n = 392 of which 17% were VRE)[3]. Generally, most of the rising antimicrobial resistance problem is due to the overuse and misuse of antimicrobials by health care providers and patients[4]. Currently, tigecycline is indicated for complicated skin and soft tissue infection (cSSTI), complicated intra-abdominal infections (cIAI) and for community acquired pneumonia (CAP)[5].

Moreover, it is one of the most expensive antibiotics in the market and in September 2010, the FDA reminded the healthcare professional about the increased mortality risk associated with the use of the tigecycline[6]. Clearly, the drugs use evaluation (DUE), which is a quality improvement method used to ensure and guide the appropriate use of drugs is recommended. Therefore, the aim of this study is to assess the compliance with prescribing guidelines of tigecycline through evaluation of its use, and to identify any deviation of such use.

Materials and Methods

Study design; a retrospective longitudinal study conducted at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The approval from

the Research and Ethics Committee of the hospital was obtained (Appendix 1). All patients who received tigecycline in the period from March 2010 to November 2010 were included in this study. Data collected from patients' files, either the electronic or the manual files. Data recorded include patient addressographs such as: (age, weight, height, gender), diagnosis, indication of tigecycline use and associated co-morbidities. In addition, monitoring parameters such as laboratory tests including liver function tests, complete blood count (CBC), and international normalized ratio (INR) were also collected. Other monitoring parameters are adverse drug reactions and liver disease severity to monitor adjustment in the dosing regimen through the use of Child-Turcotte-Pugh score (CTP score). Data were collected via a specifically designed patient chart review form (Appendix 2). All statistical analysis was performed by using SPSS v. 16.0 programs.

Results

A total of 99 patients were prescribed tigecycline during the study period. Seven (7) patients' files were missed; this has resulted in 92 (93%) patients to be studied. The number of female patients was 49 (53%), while 43 (47%) were male. The mean age with standard deviation was 57 ± 17. The most common co-morbidities are *diabetes mellitus* (DM) in 59 (64%) patients, hypertension in 55 (60%) patients. Seven (8%) patients had a liver disease in which 4 (4.3%) patients classified as Child-Turcotte-Pugh B class (CTP B) and 3 (3.3%) patients classified as Child-Turcotte-Pugh C class (CTP C). Patients' characteristics and co-morbidities are shown in Table 1. The median duration of therapy was 10 days (range 1-29).

Tigecycline was used as empirical therapy in 28 (30.4%) patients and based on culture results in 64 (69.6%) patients. It was used in 28 (30.4%) patients for cSSTI, 28 (30.4%) patients for community acquired pneumonia (CAP), 13 (14.1%) patients for cIAI, and 15 (16.3%) patients for Hospital Acquired Pneumonia (HAP). 5 (5.4%) patients for Ventilator Acquired Pneumonia (VAP), 2 (2.2%) patients for urosepsis and 1 (1.1%) patient for infection of unknown origin (Fig. 1). This has resulted in 23 (25%) patients for which tigecycline was used for unapproved indications, while in 69 (75%) patients it was used according to the approved indications.

Table 1. Clinical characteristics of patients at start of tigecycline therapy.

Patients Demographics	
Number of Patients	92
Gender	**n (%)**
Female	49 (53)
Male	43 (47)
Age	**Years**
Mean + SD	57 ± 17
Co-morbidities	**n (%)**
Diabetes Mellitus	59 (64)
Hypertension	55 (60)
Renal Failure	33 (36)
Liver Disease	7 (8)
Severity of Liver Diseases	**n (%)**
CTP* B	4 (4.3%)
CTP* C	3 (3.3%)

**CTP = Child-Turcotte-Pugh score*

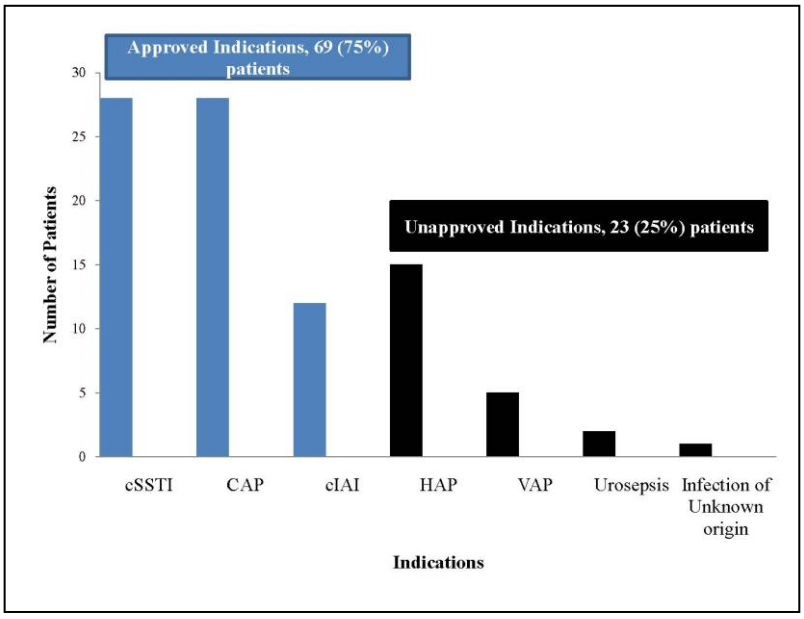

Fig. 1. Indications of tigecycline therapy.

Data of the study showed that 6 (6.5%) patients were not administered a loading dose of tigecycline, while in 90 patients; the maintenance doses were administered as 50 mg Q12hrs IV. Except two pediatric patients (age; two years, thirty-one days, respectively) they were administered a dose of 12.5 mg Q12 hrs and 8 mg Q24 hrs, respectively. Both infants died. According to Child-Turcotte-Pugh (CTP) classification of liver diseases; only 3 patients had liver disease classified as (CTP C) and no dose adjustment performed to the maintenance dose of those patients.

The most common bacteria associated with infections are Acinetobacter baumannii in 51 (56%) patients, followed by *Pseudomonas aeruginosa* in 23 (25%) patients and *Klebsiella pneumoniae* in 23 (25%) patients. All bacteria associated with infections are represented in (Table 2). Most of the patients who had *Pseudomonas aeruginosa* infections were prescribed Tazocin® (Pipercillin/Tazobactam, 3.375 g IV Q6hr or Q8hr according to the type of infection and patient's characteristics) in combination with tigecycline to cover *Pseudomonas aeruginosa* infection. Meropenem, (imipenem/ cilastatin) or colistin were commonly used in the cases that bacteria were not responded to tigecycline.

The reported side effects of tigecycline were nausea, vomiting and diarrhea, which occurred in 3 (4%) patients who were all negative for Clostridium difficile (*C. difficile*) toxin in stool.

Table2. Microorganisms associated with infections.

Bacteria	n (%)
Acinetobacter baumannii	51 (56)
Pseudomonas aeruginosa	23 (25)
Klebsiella pneumoniae	23 (25)
Methicillin-Resistant *Staphylococcus aureus*	10 (11)
Other *Staphylococcus* Species	8 (9)
Enterococcus Species	9 (10)
Stenotrophomonas maltophilia	3 (3)
Escherichia coli	5 (6)
Infection of Unknown Origin	3 (3)
Others	6 (7)
Total	**138 (100)**

The overall outcomes were healing in 50 (54%) patients, infection treated with other drugs in 10 (11%) patients and death was reported in 32 (35%) (Fig. 2). Death was seen mostly in CAP, followed by cSSTI, HAP, cIAI and VAP as presented in (Fig. 3).

However, there was no statistical differences in the overall outcome between patients who prescribed Tigecycline according to the approved indications and those with the unapproved uses (p = 0.940).

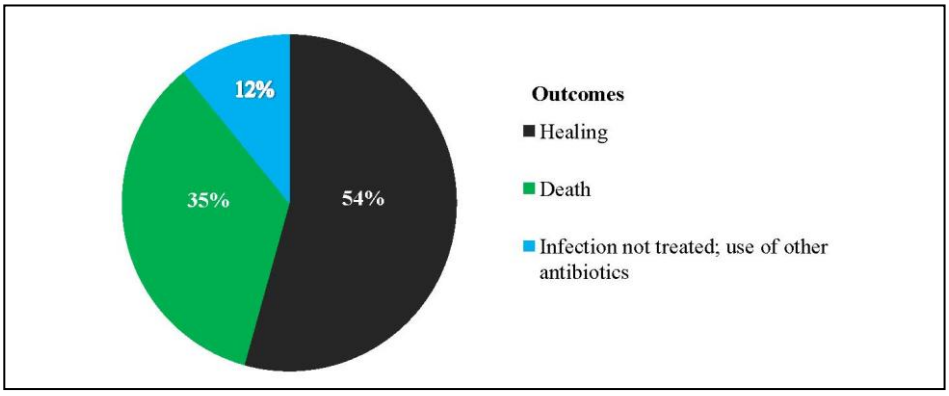

Fig.2. Main outcome after tigecycline therapy.

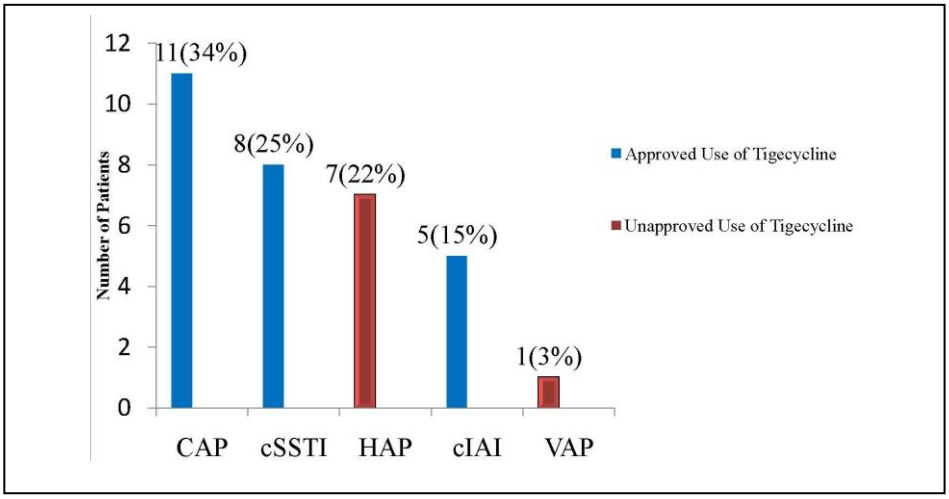

Fig.3. Mortality Rate per Indication after tigecycline therapy.

Discussion

This retrospective study was conducted to evaluate tigecycline use in a real-life clinical practice in a university hospital providing tertiary care health services. In this study, tigecycline was used in four indications not approved by FDA including HAP, VAP, urosepsis, as well as infection of unknown origin (Fig. 1). However, the mortality rate (35%, n=32/92) in this study is about comparable to the mortality rate found in a German study by Swoboda *et al.* (2007), in which the percent of mortality was 30% (n = 21/70)[7] and to that in another British study (41%, n=14/34) by Gordon and Wareham[8]. Interestingly, the results from this study synchronized with a warning from the FDA in September 2010, about increased mortality risk associated with the use of tigecycline compared to other antimicrobials. The increased risk was seen most clearly in patients treated for hospital-acquired pneumonia, especially ventilator-associated pneumonia. Thus, it was also seen in patients with complicated skin and skin structure infections, cIAI and diabetic foot infections[6]. The mortality rate reported in this study is similar to that rate usually reported in severe septic patients. On another hand, critically ill patients, associated comorbidities and unapproved uses may have been contributed to the high mortality rate in this study.

Another issue of concern is that tigecycline was used in infants, who were critically ill, while its safety and efficacy data is not established in pediatric patients younger than 8 years[5]. More studies need be performed to establish more data about tigecycline safety and efficacy in pediatric patients.

In patients with hepatic dysfunction, tigecycline systemic clearance is reduced by 55% and its half-life prolongs by 23%[9]. Therefore, the maintenance dose should be reduced to 25 mg IV Q12hr in case of severe liver impairment (CTP C). However, the results of this study did not show any reduction of the dose of the 3 (CTP C) classified patients.

Study limitations include inability to calculate the APACHE II score to know the severity of illness on patient's condition, because the data required for calculating, the score were difficult to be obtain from the patient's file. Despite of this, the results from this study may be useful for physicians and other healthcare professionals about a newly approved antibiotic for critically ill patients.

Conclusion

This study confirmed the high mortality rate associated with tigecycline use. This should be a reminder to healthcare professionals when considering its use in severely infected patients, or when to be used as a monotherapy in an empirical situation.

References

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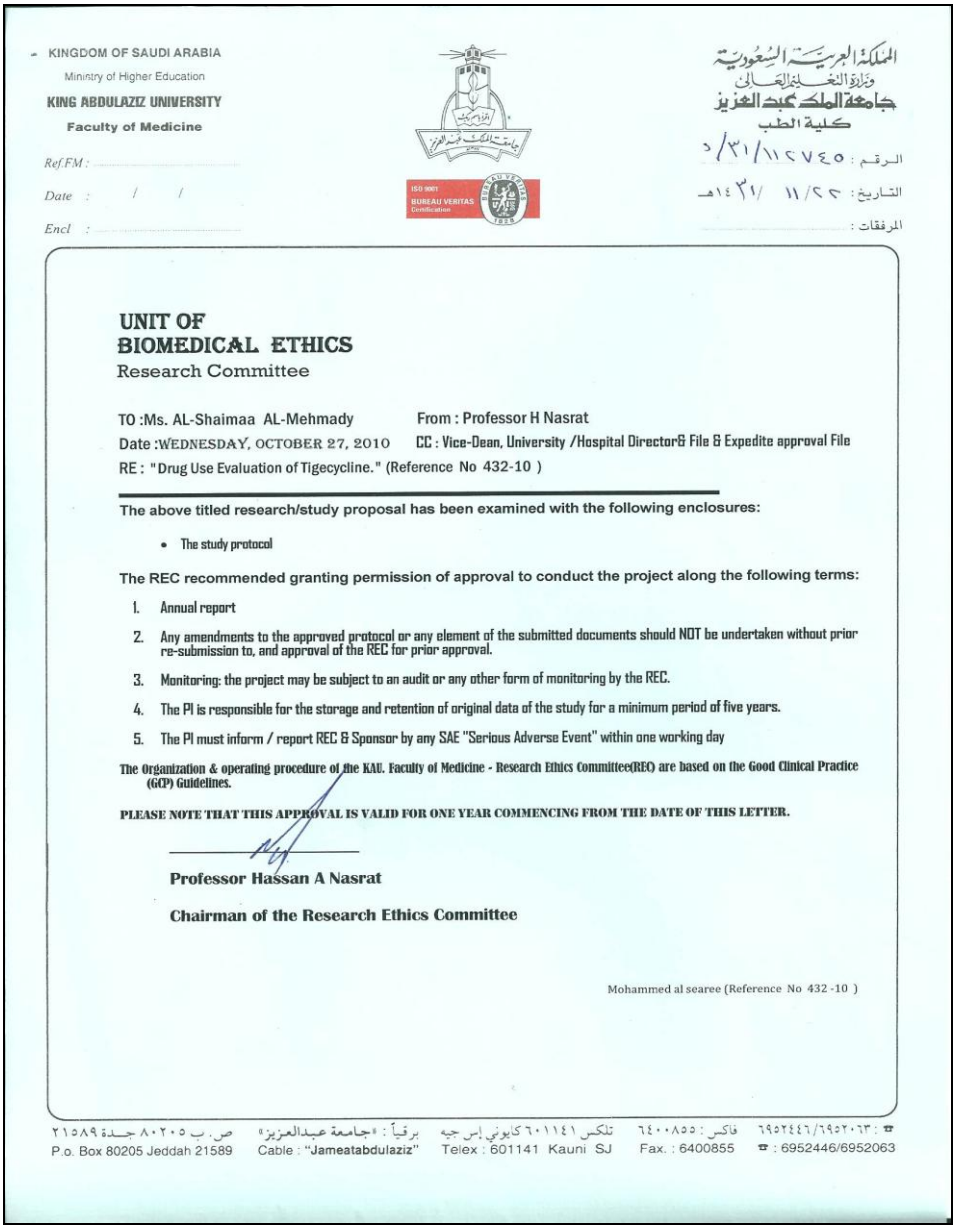
Appendix 1. The approval from the Research and Ethics Committee of King Abdulaziz University Hospital (KAUH).



KINGDOM OF SAUDI ARABIA
Ministry of Higher Education
KING ABDULAZIZ UNIVERSITY
Faculty of Medicine

المملكة العربية السعودية
وزارة التعليم العالي
جامعة الملك عبد العزيز
كلية الطب

Ref.FM : ..... الرقم : د/٣١/١١٢٧٤٥
Date : / / التاريخ : ١١/٢٣ /١٤٣١هـ
Encl : ..... المرفقات : .....

ISO 9001 BUREAU VERITAS Certification

UNIT OF
BIOMEDICAL ETHICS
Research Committee

TO :Ms. AL-Shaimaa AL-Mehmady From : Professor H Nasrat
Date :WEDNESDAY, OCTOBER 27, 2010 CC : Vice-Dean, University /Hospital Director& File & Expedite approval File
RE : "Drug Use Evaluation of Tigecycline." (Reference No 432-10)

The above titled research/study proposal has been examined with the following enclosures:

- The study protocol

The REC recommended granting permission of approval to conduct the project along the following terms:

1. Annual report
2. Any amendments to the approved protocol or any element of the submitted documents should NOT be undertaken without prior re-submission to, and approval of the REC for prior approval.
3. Monitoring: the project may be subject to an audit or any other form of monitoring by the REC.
4. The PI is responsible for the storage and retention of original data of the study for a minimum period of five years.
5. The PI must inform / report REC & Sponsor by any SAE "Serious Adverse Event" within one working day

The Organization & operating procedure of the KAU. Faculty of Medicine - Research Ethics Committee(REC) are based on the Good Clinical Practice (GCP) Guidelines.

PLEASE NOTE THAT THIS APPROVAL IS VALID FOR ONE YEAR COMMENCING FROM THE DATE OF THIS LETTER.

Professor Hassan A Nasrat

Chairman of the Research Ethics Committee

Mohammed al searee (Reference No 432 -10)

ص. ب ٨٠٢٠٥ جدة ٢١٥٨٩ برقياً : "جامعة عبدالعزيز" تلكس ٦٠١١٤١ كايوني إس جيه فاكس : ٦٤٠٠٨٥٥ ☎ : ٦٩٥٢٤٤٦/٦٩٥٢٠٦٣
P.o. Box 80205 Jeddah 21589 Cable : "Jameatabdulaziz" Telex : 601141 Kauni SJ Fax. : 6400855 ☎ : 6952446/6952063

Appendix 2. Patient chart review form.

1. PATIENT DEMOGRAPHICS:

1.1 MRN: ..... **1.2 Name:** ..... **1.3 Sex:** ☐ M ☐ F

1.4 Age: ..... **1.5 Wt:** ..... **1.6 Ht:** .....

1.7 Diagnosis: .....

1.8 CO- MORBITIES:

☐ HTN

☐ Renal Disease *Specify*: .....

☐ Liver Disease *Specify*: .....

☐ Diabetes ☐ Other, *Specify*: .....

1.9 Date of Admission: ...../...../2010

1.10 Date of discharge: ...../...../2010

1.11 Allergy: ..... **1.12 History of ADR:** .....

2. TREATMENT DATA:

2.1 Type of therapy: Empirical ☐ Not Empirical.

2.2 Culture results:

☐ Escherichia coli. ☐ S.aureus (MRSA). ☐ Acinetobacter baumannii.

☐ Klebsiella pneumoniae. ☐ Pseudomonas aeruginosa.

☐ Other. *Specify:* ..... ***(Please write the site & date of sample)***

2.3 Indication of Tigecycline:

☐ cIAI. *Specify:* .....

☐ cSSTI *Specify:* .....

☐ CAP *Specify:* .....

☐ Others *Specify:* .....

Date of adm of LD: / /2010

Date of adm of MD: ( )/ /2010

( )/ /2010

2.4 Dosage:

Loading Dose: Yes, ...mg ☐ No

MD: ☐ Yes, ...mg Q .....hrs Duration.....days ☐ No

2.5 Monitoring:

Side effects	Lab test	ABNORMAL RESULTS (if present)	Drug Interactions	dose
☐ Nausea	☐ CBC		☐ Metronidazole	.....
☐ Vomiting	☐ LFT		☐ Penicillin	.....
☐ Diarrhea	☐ INR		☐ Levetiracetam	.....
☐ Abdominal pain	☐ Other		☐ Sucralfate	.....
☐ Headache	*Specify*.....		☐ Warfarin	.....
☐ Other	.....		☐ Oral contraceptive	.....
Specify.....			*Specify the drug*	
			☐ Other	.....
			Specify the drug	

3. OUTCOMES MEASURES:

☐ Healing. ☐ Recurrence of infection ☐ Death.

☐ Superinfction by; Fungi. Bacteria. *(put a line under the microbe **if present**)* ☐ Re-admission.

☐ Infection is not treated; use of other antibiotic. *Specify:* .....

تقييم استخدام دواءالتيجاسايكلين: دراسة التحسين المستمر للجودة

الشيماء محمد المحمادي (دكتور صيدلاني)، **ورحمة علي الحارثي** (دكتور صيدلاني)، **وأبرار الصبحي** (دكتور صيدلاني)، **وهديل الحربي** (دكتور صيدلاني)، **وأمين المحمدي** (دكتور صيدلاني)

قسم الصيدلة السريرية، كلية الصيدلة ، جامعة الملك عبدالعزيز

جدة – المملكة العربية السعودية

المستخلص. تيجاسايكلين هو أول دواء متوفر في الفئة الجديدة المسماة جلايسيلكلين، وهو فعال ضد البكتيريا متعددة المقاومة الإيجابية والسلبية الغرام. على الرغم من أن الموافقة على استخدامه تمت مؤخرا، إلا أن التقارير أفادت مقاومة التيجاسايكلين بواسطة العديد من السلالات البكتيرية. علاوة على ذلك، هو واحد من أغلى المضادات الحيوية في السوق. أجريت دراسة بأثر رجعي طولي في مستشفى جامعة الملك عبدالعزيز بجدة. وقد تم إدراج جميع المرضى الذين تلقوا التيجاساكلين في الفترة الزمنية ما بين مارس– نوفمبر ٢٠١٠م في هذه الدراسة. المعلومات المتعلقة باستخدامات التيجاساكلين، عملية متابعة الدواء ونتائج علاج جميع المرضى جمعت عبر استمارة جمع بيانات المرضى والحصول عليها من ملف المريض. ٩٢ مريضا تلقوا التيجاسايكلين في فترة الدراسة. في ٢٣ مريض (٢٥٪)، كان استخدام التيجاساكلين في استخدامات غير مصرح بها، والاستخدام الشائع للتيجاساكلين الالتهاب الرئوي المكتسب (كاب). وكانت النتائج الإجمالية الشفاء في ٥٠ مريض

(٥٤٪)، العدوى التي عولجت بأدوية أخرى في١٠ مريض (١١٪)، وتوفي ٣٢ مريض (٣٥٪) خلال الدراسة. أكدت هذه الدراسة ارتفاع معدل الوفيات المرتبطة باستخدام التيجاساكلين، وهذا يجب أن يكون تنبيهًا للمختص عند استخدامه في المرضى المصابين بشدة أو عند استخدامه كعلاج وحيد مبدئيًا.