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IDENTICAL ANTIMICROBIAL EFFECT OF CEFTRIAXONE AND CEFOTAXIME AMONG DIFFERENT BACTERIAL ISOLATES

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Background: *This study aimed to screen the antimicrobial-resistant profile of these 3rd generation cephalosporins and to identify their similarity and interchangeability.* ***Method:*** *This cross-sectional study, was conducted in all the government hospitals across the Gaza Strip, Palestine. The study started in November 2017 and continued till December 2022. All clinical samples such as wound swabs (pus), urine, sputum, blood, cerebrospinal fluid (CSF), stool, and others in which ceftriaxone and cefotaxime were examined at the same time were collected from hospitalized patients and outpatient clinic attendants. After the identification of the bacterial isolates, a standard disc diffusion technique for drug susceptibility tests was performed. This study was reviewed and approved by The Palestinian Helsinki Committee.* ***Results:*** *In the current study, 24,120 isolates in which ceftriaxone and cefotaxime were examined at the same time were studied. The predominant organisms isolated were, Escherichia coli 9,720 (40.3%), Klebsiella spp. 5,497 (22.8%), Pseudomonas spp. 2,630 (10.9%), and Staphylococcus aureus 1941 (8.0%). Bacterial isolates showed 57.1% and 57.8% resistance against ceftriaxone and cefotaxime, respectively. In this study, 22,404 (92.9%) bacterial isolates were with identical susceptibility test results to ceftriaxone and cefotaxime. The highest match of susceptibility was seen in Acinetobacter spp. 97.3% (770/791), Klebsiella spp. 95.3% (5,241/5,491), and Escherichia coli 94.9% (9,220/9,720). In Staphylococcus aureus it was 90.6% (1,758/1,941).* ***Conclusion:*** *Ceftriaxone and cefotaxime can be interchangeable in most Enterobacteriaceae bacterial species. Ongoing surveillance of different bacterial antimicrobial resistance and multidrug resistance is strongly recommended together with the consideration of implementing antibiotics stewardship programs in all hospitals.*

Keywords: *Bacterial isolates, bacterial resistance, cefotaxime, ceftriaxone, multidrug resistance*

INTRODUCTION

Ceftriaxone and cefotaxime are both broad-spectrum third-generation cephalosporins that were considered to be comparable in safety and efficacy for the treatment of many bacterial infections such as bacterial meningitis[1], lower respiratory tract infections, skin and soft tissue infections, genitourinary tract infections, and bloodstream infections[2], as well as prophylaxis for abdominal surgery[3]. Cefotaxime was discovered in 1976 and after two years in 1978 ceftriaxone was patented. They were approved

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for medical use in 1980 and 1982 respectively[4]. They are active against numerous Gram-positive and Gram-negative bacteria, including several of which are resistant to classic β-lactams such as penicillin[5]. Also, ceftriaxone and cefotaxime do not have useful activity against *Pseudomonas aeruginosa* or *Enterobacter* species[5]. They possess their action by inhibiting bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins. This causes inhibition of the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. So, bacteria eventually lyse due to the ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases). In the absence of cell wall assembly and consequently, bacteria die[6]. Cefotaxime has a short serum half-life (1 hr) because of partial metabolism in the liver to deacetyl-cefotaxime which also has antibacterial activity and a longer half-life in serum (1.7 hrs), allowing dosing every six hrs[7]. Ceftriaxone has a longer serum half-life (6.4 hrs) and can be administered once or twice a day[8]. Cefotaxime has the advantage over ceftriaxone that it can be used safely in neonates hence ceftriaxone can compete with bilirubin and displace it from binding to albumin, increasing the risk of bilirubin encephalopathy. Also, concomitant administration of intravenous ceftriaxone and calcium-containing solutions should be avoided in neonates because this can cause calcium-ceftriaxone precipitations in neonatal lungs and kidneys[9].

For a long time, ceftriaxone and cefotaxime are thought to have possessed similar in vitro susceptibility for many microorganisms. This was documented in the Clinical and Laboratory Standards Institute (CLSI) M100-S28 guideline**. Tables 1A and 1B** state that either ceftriaxone or cefotaxime could be tested against *Enterobacteriaceae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus* spp. (β-Hemolytic Group)[10]. Also, this similarity was seen in susceptibility for *Streptococcus pneumoniae* which is alpha-hemolytic (under aerobic conditions) or beta-hemolytic (under anaerobic conditions)[11]. But for a long time also, it was noticed that changing patterns in microbial resistance suggest cefotaxime may be suffering greater resistance than ceftriaxone[12]. So, it is very important to consider regional microbial sensitivities when choosing any antimicrobial agent for the treatment of infection. Besides, the effectiveness of treatment decisions based on past clinical experience became less effective way since the microbial resistance is currently changing in a continuous unpredicted manner to all approved antimicrobials. This makes the selection of an appropriate antimicrobial agent more challenging. Clinicians become more dependent on data from in vitro antimicrobial susceptibility testing, so this highlights the importance of diagnostic laboratories in clinical practice[13]. So distinguishing and obtaining exact knowledge of the differences between the two widely used antibiotics ceftriaxone and cefotaxime will be valuable work to build exact data on antimicrobial resistance (AMR). This will help clinicians to define the best possible antibiotic treatment of choice for individual patients in empirical therapy practice. Finally, this study will provide signals that could help in identifying the best ways to promote the rational use of antibiotics and its findings will be considered a valuable contribution to healthcare-related knowledge globally. Therfore, the current study, was conducted to determine the identical antimicrobial effect of ceftriaxone and cefotaxime among different bacterial isolates.

MATERIALS AND METHODS

Study design, setting and period

This study was a cross-sectional, and hospital-based study. It was conducted in all governmental hospitals in the Gaza Strip. The duration of data collection was from November 2017 to December 2022. Hospitals provided diverse healthcare services and are located along with all Gaza Strip governorates.

Data collection

Specimen collection

Samples such as wound swabs (pus), urine, sputum, blood, CSF, stool, and others were collected from hospitalized patients and outpatient clinic attendants. Experienced physicians, nurses, and microbiology specialists collected and handled these samples.

Antimicrobial susceptibility testing

Different specimens were collected and processed in the bacteriology laboratory of the Departments of Medical Microbiology in each hospital. Identification of bacteria was based on conventional physiological and biochemical methods (i.e. Gram stain, catalase reaction, coagulase test… etc.). After the identification of the bacterial isolates, a standard disc diffusion technique for drug susceptibility tests was performed as recommended by the CLSI[14]. A standardized data collection sheet was used in the labs. The World Health Organization guidelines were used as a reference in the data collection and analysis for bacterial antibiotics susceptibility and resistance[15]. Specimens were classified by type of organism and characteristics of patients such as gender, age groups, and place of living. Isolates were considered valid if handled properly by the participating hospital laboratories staff and the microorganism's species level was identified as much as possible.

Coordination, monitoring, and quality control

The reliability of the study findings was guaranteed by implementing quality control measures throughout the whole process of laboratory work. Staining reagents, culture media, and antibiotic discs were checked for their normal shelf life before use. All culture plates were prepared following standard manufacturing instructions and were stored at recommended refrigeration temperature. Also, all antibiotic discs which contained 30mcg ceftriaxone and cefotaxime were stored at a suitable temperature as recommended by the manufacturer.

Findings were documented on a daily bases in the laboratories database in addition to the data collection sheets prepared especially for the study. Data were constantly checked for completeness and were cleaned during the study. Each measurement of the inhibition zone diameter was interpreted as 'sensitive', 'intermediate', or 'resistant' according to CLSI standard interpretative charts[14]. Reference strains *S. aureus* (ATCC 27853) for Gram-positive bacteria and *E. coli* (ATCC 25922) for Gram-negative bacteria were used to ensure microbiology quality-control procedures for ceftriaxone and cefotaxime susceptibility test. Finally, all microbiology procedures were done according to standard methods.

Data analysis

Clinical and demographic data variables were keyed into the MS Excel sheet. Data cleaning was performed and then exported to the statistical package for social science (SPSS) software (Version 23) for analysis according to the objectives of the study. Categorical variables were described as proportions and were analyzed to compare the significance of the difference in distribution by using the Chi-square test (χ^2). The standard significant level of $p<0.05$ was considered a statistically significant difference with the respective 95% confidence interval.

Ethical approval and consent to participate

The study protocol was approved by the Palestinian Health Research Council (Helsinki Ethical Committee of Research No. PHRC/HC/382/18). Also, agreement was achieved from the General Diroctorate of Hospitals in the Palestinian Ministry of Health. Furthermore, informed consent was obtained from each participant.

RESULTS AND DISCUSSION

Results

Clinical bacterial isolates and specimens

In this study, 24,120 isolates in which ceftriaxone and cefotaxime were examined in the same cultures have been investigated. The main isolates were *Escherichia coli* 9,720 (40.3%), *Klebsiella spp*. 5,497 (22.8%), *Pseudomonas spp*. 2,630 (10.9%), *Staphylococcus aureus* 1,941 (8.0%), *Coagulase-negative staphylococcus* (CoNS) 1,214 (5.0%), *Proteus spp*. 831 (3.4%), *Acinetobacter spp*. 791 (3.3%), and *Enterobacter spp*. 430 (1.8%). The majority of the isolates came from inpatient wards 17,085 (70.84%) followed by outpatient clinics 6,036 (25.03% %) and emergency departments 996 (4.13% %). Also, the majority of the isolates were from adult patients (more than 12 years) 16,382 (67.9%), children (aged from 1 year to 12) 5,590 (23.2%), while infants (aged from 28 days to one year) contributed to 1,160 (4.8%) and neonates (aged from 0 to 28 days) 985 (4.1%). In total, 12,191 (50.5%) isolates were

obtained from urine specimens, 7,356 (30.5%) from pus, 1,596 (6.6%) from blood, and 1,304 (5.4%) from sputum. **Table 1** shows the distribution of microorganisms in the isolated specimens.

Susceptibility results and identical percentages

Bacterial isolates which were tested for susceptibility showed 53.0% and 53.4% resistance against ceftriaxone and cefotaxime, respectively **(Fig. 1).**

As shown in **Table 2**, the rate of bacterial isolates resistant to ceftriaxone and cefotaxime was the highest in *Acinetobacter spp.* (89.0% and 89.8% respectively) while it was the lowest in *Streptococcus spp.* (26.5% and 30.0% respectively).

Table 1: Distribution of isolated microorganisms in clinical specimens collected from patients.

Isolated Bacteria		Urine	Pus	Blood	Sputum	V.S.	Others	Total
E coli	No	7228	1726	179	136	378	73	9720
	%Specimen	59.3%	23.5%	11.2%	10.4%	45.0%	8.8%	40.3%
Klebsiella spp.	No	2966	1540	266	408	212	105	5497
	%Specimen	24.3%	20.9%	16.7%	31.3%	25.2%	12.6%	22.8%
Pseudomonas spp.	No	626	1383	86	322	30	183	2630
	%Specimen	5.1%	18.8%	5.4%	24.7%	3.6%	22.0%	10.9%
S aureus	No	298	1070	257	26	111	179	1941
	%Specimen	2.4%	14.5%	16.1%	2.0%	13.2%	21.5%	8.0%
CoNS	No	205	428	494	11	16	60	1214
	%Specimen	1.7%	5.8%	31.0%	0.8%	1.9%	7.2%	5.0%
Proteus spp.	No	432	351	10	7	6	25	831
	%Specimen	3.5%	4.8%	0.6%	0.5%	0.7%	3.0%	3.4%
Acinetobacter spp.	No	61	383	132	193	4	18	791
	%Specimen	0.5%	5.2%	8.3%	14.8%	0.5%	2.2%	3.3%
Enterobacter spp.	No	154	169	24	27	16	40	430
	%Specimen	1.3%	2.3%	1.5%	2.1%	1.9%	4.8%	1.8%
Streptococcus spp.	No	42	75	55	86	24	28	310
	%Specimen	0.3%	1.0%	3.4%	6.6%	2.9%	3.4%	1.3%
Enterococci spp.	No	56	51	4	30	16	13	170
	%Specimen	0.5%	0.7%	0.3%	2.3%	1.9%	1.6%	0.7%
Other Bacteria	No	123	180	89	58	27	109	586
	%Specimen	1.0%	2.4%	5.6%	4.4%	3.2%	13.1%	2.4%
Total	No	12191	7356	1596	1304	840	833	24120
	%Specimen	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

V.S.: Vaginal swab, C.S.F.: Cerebrospinal fluid, CoNS: Coagulase Negative Staphylococcus .

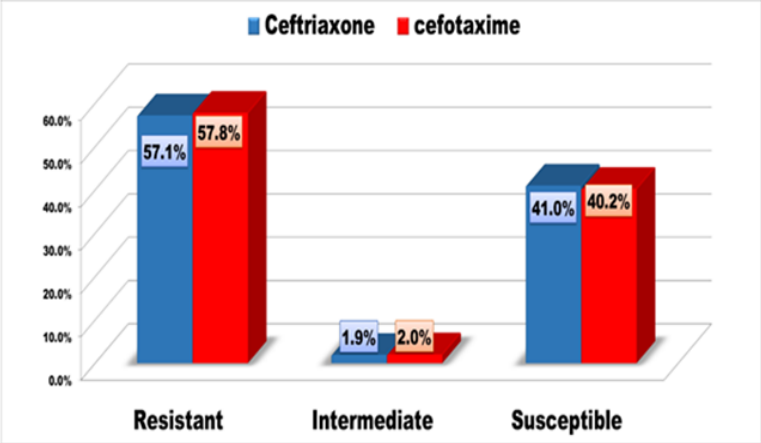

Fig. 1: Susceptibility profile of clinical isolates to Ceftriaxone and Cefotaxime.

Table 2: Susceptibility pattern of the different clinical isolates to ceftriaxone and cefotaxime**.**

Isolated microorganisms	Total	Ceftriaxone			Cefotaxime		
		%R	%I	%S	%R	%I	%S
E coli	9720	53.3%	1.2%	45.5%	53.6%	1.5%	44.9%
Klebsiella spp.	5497	69.9%	1.3%	28.8%	70.5%	1.3%	28.2%
Pseudomonas spp.	2630	62.8%	3.5%	33.7%	66.4%	4.0%	29.6%
S aureus	1941	44.7%	4.7%	50.6%	44.9%	3.5%	51.6%
CoNS	1214	47.4%	2.6%	50.1%	45.8%	2.3%	51.9%
Proteus spp.	831	38.3%	1.7%	60.0%	38.3%	2.5%	59.2%
Acinetobacter spp.	791	89.0%	0.9%	10.1%	89.8%	0.8%	9.5%
Enterobacter spp.	430	57.0%	2.1%	40.9%	56.3%	2.3%	41.4%
Streptococcus spp.	310	26.5%	2.6%	71.0%	30.0%	2.6%	67.4%
Enterococci spp.	170	69.4%	1.2%	29.4%	65.9%	1.2%	32.9%
Other Bacteria	586	33.8%	2.6%	63.7%	34.1%	2.4%	63.5%
Total	24120	57.1%	1.9%	41.0%	57.8%	2.0%	40.2%

R: Resistant, I: Intermediate, S: Susceptible, CoNS: *Coagulase Negative Staphylococcus*.

In this study, 22,404 (92.9%) bacterial isolates were with identical susceptibility test results to ceftriaxone and cefotaxime. The highest match was seen in *Acinetobacter spp*. 97.3% (770/791), *Klebsiella spp*. 95.3% (5,421/5,497), and *E coli* 94.9% (9,220/9,720). The lowest match was in *Pseudomonas spp*. and *Streptococcus spp.* as it was 84.7% (2,228/2,630) and 83.5% (259/310) respectively **(Fig. 2)**.

There were slight differences in identical percentages of results to the same bacterial isolate in different specimens as seen in **Table3**.

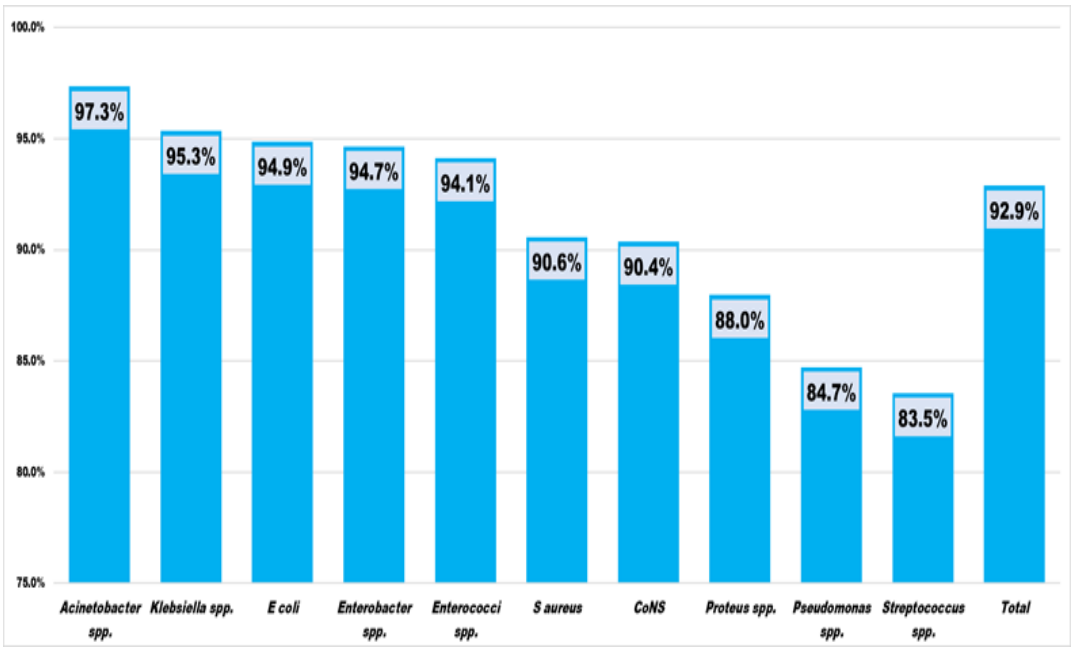

Fig. 2: Identical antimicrobial susceptibility percentages of different microorganisms to Ceftriaxone and Cefotaxime.

Table 3: Differences in identical percentages of susceptibility results to ceftriaxone and cefotaxime among bacterial isolates in different specimens.

Bacteria	Urine	Pus	Blood	Sputum	V.S.	Others	Total	χ2-Value	P-Value
E Coli	94.9% (6857/7228)	94.4% (163/1726)	96.6% (173/179)	95.6% (130/136)	94.4% (357/378)	100.0% (73/73)	94.9% (9220/9720)	6.037	0.303
Klebsiella spp.	94.5% (2804/2966)	95.9% (1477/1540)	98.1% (261/266)	96.8% (395/408)	95.3% (202/212)	97.1% (102/105)	95.3% (5241/5497)	12.815	0.025
Pseudomonas spp	83.1% (520/626)	85.7% (1185/1383)	86.0% (74/86)	86.6% (279/322)	73.3% (22/30)	80.9% (148/183)	84.7% (2228/2630)	8.445	0.133
S aureus	87.2% (260/298)	90.1% (964/1070)	94.9% (244/257)	96.2% (25/26)	91.0% (101/111)	91.6% (164/179)	90.6% (1758/1941)	11.09	0.050
CoNS	82.9% (170/205)	92.1% (394/428)	90.9% (449/494)	90.9% (10/11)	93.8% (15/16)	98.3% (59/60)	90.4% (1097/1214)	19.175	0.002
Proteus spp.	90.5% (391/432)	85.5% (300/351)	100.0% (10/10)	85.7% (6/7)	100.0% (6/6)	72.0% (18/25)	88.0% (731/831)	12.948	0.024
Acinetobacter spp.	95.1% (58/61)	97.4% (373/383)	98.5% (130/132)	98.4% (190/193)	75.0% (3/4)	88.9% (16/18)	97.3% (770/791)	15.488	0.008
Enterobacter spp.	94.2% (145/154)	93.5% (158/169)	95.8% (23/24)	96.3% (26/27)	100.0% (16/16)	97.5% (39/40)	94.7% (407/430)	2.280	0.809
Streptococcus spp.	73.8% (31/42)	85.3% (64/75)	92.7% (51/55)	74.4% (64/86)	95.8% (23/24)	92.9% (26/28)	83.5% (259/310)	16.059	0.007
Enterococci spp.	96.4% (54/56)	92.2% (47/51)	100.0% (4/4)	86.7% (26/30)	100.0% (16/16)	100.0% (13/13)	94.1% (160/170)	5.965	0.310
Other Bacteria	87.8% (108/123)	94.4% (170/180)	87.6% (78/89)	93.1% (54/58)	74.1% (20/27)	94.5% (103/109)	91.0% (533/586)	16.676	0.005

V.S.: Vaginal swab, CoNS: *Coagulase Negative Staphylococcus*; χ^2: Chi-square, Statistically significance ≤ 0.05.

Discussion

In this study which has the advantage of its huge sample size, long duration of data collection, and the variability of types of specimens and microorganisms studied, it is possible to draw a valuable picture of the correct percentage of microbial resistance. Also, it can give us multiple answers about the use of the alternative when one from ceftriaxone or cefotaxime is absent. Although this study misses the therapeutic results it can give the orientations about the use of the appropriate antibiotic for the treatment of susceptible microorganisms in the targeted site of infection. As seen in this study, resistance to both ceftriaxone and cefotaxime was 53.0% and 53.4% respectively.

Cephalosporins are among the most commonly prescribed drugs, especially in hospitals hence they cover a broad range of organisms, are generally well-tolerated, and are easy to administer. Third-generation cephalosporins like ceftriaxone and cefotaxime are marked by stability to the common beta-lactamases of gram-negative bacilli[16,17]. But, the widespread consumption of these broad-spectrum antibiotics has led to an increase in antibiotic-resistant strains of bacteria. This was seen especially in bacteria that can cause common health problems. In this study, it was noticed that more than half of the isolated

bacteria were resistant to either ceftriaxone or cefotaxime antibiotics. This result is in agreement with the global AMR surveillance system (GLASS) Report 2017-2018[18]. On the other hand, the increased AMR in hospitals is thought to be affected by hygiene procedures, the overuse of antimicrobial drugs, and mobile genetic elements that can encode mechanisms of bacterial resistance[17]. The most abundant bacterial isolates in this study were *E coli* and *Klebsiella spp*. which contributed to more than 64% of the total isolates and had also a high prevalence of resistance to both ceftriaxone and cefotaxime. This was in concordance with the worldwide concern about the increasing drug resistance of *K. pneumoniae* and *E. coli* in the last decades[19]. Also, these microorganisms showed a high resistance rates to cephalosporins in clinical isolates of patients from Vietnam[20], Saudi Arabia[21], India[22], and Mexico[23], although the results from this study showed less resistant patterns. Hence, the increased resistance of these organisms may be due to the increased prevalence of Extended-Spectrum β-Lactamases (ESBL) among *Enterobacteriaceae* species found in the Gaza Strip. These species had high resistance against cefotaxime and other beta-lactam antibiotics as found in a recent study done in the Gaza Strip[24].

In the current study, the identical percent of bacterial susceptibility results to both ceftriaxone and cefotaxime was seen to be the highest among gram-negative bacterial isolates in comparison with gram-positive isolates. This was seen especially in *Acinetobacter spp.* in which the identical percent was about 97.3%, which may be due to the high resistance of this microorganism to all antibiotics[25] rather than the high identical effect of the two antibiotics. In *Klebsiella spp*. and *E coli*, the match of susceptibility pattern of ceftriaxone and cefotaxime was high as seen in the Clinical and Laboratory Standards Institute (CLSI) M100-S28 guideline[10] which indicates that they can be interchangeable.

Although some limitations of this study such as the lack of serotyping and genotyping results, which precluded the assessment of the different strains of different bacterial isolates, the uncertain clinical evidence of infections among attendant patients, missing of some exact sociodemographic data of patients, and finally the lack of therapeutic results of using antibiotics, the results of this study can open a road of building evidence-based guidelines based on local antibiotics resistance data.

Conclusion

The results of this study can be valuable for the improvement of guidelines for empiric therapy of different infectious diseases in the Gaza Strip. Ongoing surveillance of different bacterial AMR and multidrug resistance is strongly recommended together with the consideration of implementing antibiotics stewardship programs in all hospitals.

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التأثير المتطابق لمضادات الميكروبات للسيفترياكسون والسيفوتاكسيم بين العزلات البكتيرية المختلفة

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محتوى المقدمة: استهدفت هذه الدراسة فحص مقاومة البكتيريا لهذين المضادين الحيويين من الجيل الثالث للسيفالوسبورينات وتحديد مدى تشابهها وقابليتها للتبادل.

منهجية الدراسة: تمت هذه الدراسة في جميع المستشفيات الحكومية في قطاع غزة في الأراضي الفلسطينية المحتلة، وكانت دراسة مقطعية. بدأت الدراسة في نوفمبر ٢٠١٧ واستمرت حتى ديسمبر ٢٠٢٢. تم جمع جميع العينات السريرية التي تم فيها فحص سيفترياكسون وسيفوتاكسيم في نفس الوقت من المرضى المقيمين في المستشفى وزائري العيادات الخارجية. تم فحص العينات مثل مسحات الجروح (القيح)، والبول، والبلغم، والدم، والسائل النخاعي، والبراز، وغيرها. بعد تحديد العزلات البكتيرية، تم إجراء اختبارات حساسية الأدوية باستخدام تقنية الانتشار القرصي القياسية لاختبار حساسية الدواء. تمت مراجعة وموافقة هذه الدراسة من قبل مجلس البحوث الصحية الفلسطيني ولجنة هلسنكي.

النتائج: في هذه الدراسة، تم دراسة ما مجموعه ٢٤،١٢٠ عزلة تم فيها فحص سيفترياكسون وسيفوتاكسيم في نفس الوقت. وجد أن الكائنات الحية السائدة المعزولة كانت على النحو التالي: الإشريكية القولونية ٩،٧٢٠ (٤٠,٣٪)، كليبسيلا ٥،٤٩٧ (٢٢,٨٪)، الزائفة. ٢،٦٣٠ (١٠,٩٪)، و المكورات العنقودية الذهبية ١،٩٤١ (٨,٠٪). أظهرت العزلات البكتيرية نسب مقاومة تبلغ ٥٧,١٪ و ٥٧,٨٪ تجاه سيفترياكسون وسيفوتاكسيم على التوالي. في هذه الدراسة، كانت ٢٢،٤٠٤ (٩٢,٩٪) عزلة بكتيرية متطابقة في نتائج اختبار الحساسية لكل من سيفترياكسون وسيفوتاكسيم. لوحظت أعلى نسبة حساسية في العصيات الراكدة بنسبة ٩٧,٣٪ (٧٩١/٧٧٠)، كليبسيلا بنسبة ٩٥,٣٪ (٥،٢٤١ / ٥،٤٩١)، و الإشريكية القولونية بنسبة ٩٤,٩٪ (٩،٢٢٠ / ٩،٧٢٠). أما بالنسبة لـ *العنقودية* الذهبية، فكانت النسبة تبلغ ٩٠,٦٪ (١،٧٥٨ / ١،٩٤١).

الخلاصة: تشير الدراسة إلى إمكانية تبادل سيفترياكسون وسيفوتاكسيم في معظم الأنواع البكتيرية المعوية. يُوصَى بشدة بمراقبة مستمرة للمقاومة البكتيرية المختلفة للمضادات الحيوية والمقاومة المتعددة للأدوية، بالإضافة إلى تنفيذ برامج رقابة على المضادات الحيوية في جميع المستشفيات.