Patterns of inappropriate use of meropenem as antibacterial

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Abstract

Introduction: The development of antibiotic resistant organisms is related to inappropriate use of antibiotics, especially in developing countries where broad spectrum antibiotics can be purchased without prescription. Some of the common causes that contribute to the development of antimicrobial resistance are unnecessary use of antimicrobial drugs, inappropriate dose, inadequate duration of therapy. **The aim of the study:** The present study aiming to focus light on the inappropriate use of meropenem a lone, as it is one of the preserved last choices of antibiotics and is under restricted regulations for description and dispensing by ministry of health in Iraq. **Materials and methods:** This study was carried out in Tertiary –care hospital. Hundred and thirty patients received meropenem had included in this study. The meropenem administration was followed up regarding dose, frequency, duration, indication. The bacteria were isolated and identified by standard conventional methods in addition to Api20E systems. Antibiotic sensitivity testing carried out by Kirby-Bauer disc diffusion method. **The result:** Collectively 54% of the patients included in this study recieved meropenem inappropriately. The antibiotics sensitivity test by the hospital was inadequate. The most common bacteria isolated from the study were gram negative bacteria (72.7%). *E.coli* was the most predominant isolated bacteria (32%). **Conclusion:** The abuse of antibiotics is very common especially because antibiotic sensitivity test is almost neglected in Iraq. Fundamental changes are required to solve this problem. For the future of the next generations let us start a new policy in prescribing and dispensing antibiotics in Iraq.

Key words: Meropenem, inappropriate, antibiotics.

انماط الاستخدام الغير ملائم للميروبنيم كمضاد بكتيري

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الخلاصة

المقدمة: ظهور الاحياء المجهرية المقاومة للمضادات الحيوية لها علاقة بالاستخدام الغير ملائم للمضادات الحيوية ، خاصة في البلدان النامية حيث من الممكن شراء المضادات الحيوية واسعة الطيف بدون وصفة طبية . بعض الاسباب الشائعة التي لها علاقة بظهور المقاومة المضادات الحيوية هو الاستخدام الغير ملائم للمضادات الحيوية ، بجرعة غير ملائمة ،لمدى غير كافي . هدف الدراسة: نهدف في الدراسة الحالية ان نسلط الضوء على الاستخدام الغير منطقي للميروبنيم كواحد من الخيارات الاخيرة المحفوظة للمضادات الحيوية .لان هذا المضاد الحيوي بالذات يخضع لضوابط مشددة بالوصف والصرف من قبل وزارة الصحة العراقية. المواد و الوسائل: هذه الدراسة اجريت في مستشفى ابن سينا التعليمي العام في مدينة الموصل /العراق. مائة وثلاثون مريضا كانوا يتعاطون ا دواء الميروبنيم تم تضمينهم في الدراسة الحالية. اعطاء الميروبنيم تمت متابعته بما يخص تكرار الجرعة ، مدة الاعطاء و استخدامه الغير ملائم للحالة المرضية، واذا ما كان هناك مضاد حيوي اخرلاستخدامه قبل البدء باعطاء الميروبنيم. وتم جمع العينات من المرضى(حسب الحالة المرضية) وثم عزلت البكتريا وعرفت بالوسائل القياسية بالاضافة لنظام APIE20. اختبار حساسية المضادات الحيوية للعزلات البكتيرية انجزت بطريقة الاقراص المشبعة. النتائج: اجمالا 54% من المرضى المشمولين بالدراسة الحالية اخذوا الميروبنيم بدواعي غير ملائمة . اختبارحساسية المضادات الحيوية الذي تجريه المستشفى كان غير كافي .العزلات البكتيرية الاكثر شيوعا في هذه الدراسة كانت سالبة الگرام (72,7%). الايشيريشيا القولونية كانت الاكثر هيمنة في هذه الدراسة بنسبة32% من العزلات البكتيرية. الاستنتاج:اساءة استخدام المضادات الحيوية شائع جدا في العراق (واحد اهم اسبابه هو عدم التقييد بعمل اختبار حساسية المضادات الحيوية قبل صرف اي مضاد حيوي). ولهذا تغييرات اساسية مطلوبة لحل هذه المشكلة. لاجل مستقبل الاجيال القادمة لنبداء سياسة جديدة في وصف وصرف المضادات الحيوية في العراق منها الاستخدام الروتيني لاختبار حساسية المضاد الحيوي قبل صرفه.

الكلمات المفتاحية: ميروبنيم، غير ملائم،مضادات حيوية.

Introduction

The emergence of worldwide antibiotic resistance is a major public health problem, impacting patient treatment and outcomes. Antibiotic resistance continues to increase among bacteria that cause community and hospital acquired infections [(1)]. The development of antibiotic resistant organisms is related to overuse and/or inappropriate use of antibiotics, especially in developing countries where antibiotics can be purchased without prescription and broad spectrum antibiotics can be prescribed by any clinician[(2)]. Rational use of drugs is based on use of right drug, right dosage at right cost by the definition of the world health organization (WHO) " definition: Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, at the lowest cost to them and their community"[(3)]. Some of the common causes that contribute to the development of antimicrobial resistance are unnecessary use of antimicrobial drugs, inappropriate dose, inadequate duration of therapy, use of irrational antimicrobial fixed dose drug combinations [(4)].The problem of antibiotics – resistance is shared responsibility need group effort to be solved because as a problem it has a significant impact not only on the present time but also it will effect on the future. It is reported earlier, 'the slow pace with which new molecules of antimicrobials are introduced into the market is inadequate to meet the needs of this global threat [(5)].The real solution of this problem requires continuous education of prescribers and patients, which needs to be supported by high quality evidence linking antimicrobial use to the emergence of resistance[(6)] .

The aim of the study

The present study aiming to focus light on appropriate/inappropriate use of meropenem a lone as it is one of the preserved last choice antibiotics.

Materials and methods

This study was carried out in Tertiary-care hospital (Ibn-Senna general teaching hospital) at Mosul city\Iraq (Neinava-health directory). During December 2012 to June 2013, carried out intermittently due to the intermittent supply of the meropenem. Demographic information's was reported for each patient including: patient age, gender, primary diagnosis. Hundred and thirty patients who were taking meropenem had included in this study regardless of the age, sex and medical condition then they were categorized into groups later. The meropenem administration was followed up regarding dose ,frequency, duration ,indication (weather it was inappropriate for the medical condition) and if there were other antibiotics to use before starting with meropenem. The samples were collected with proper aseptic precautions before administration of meropenem. Each sample was cultured aerobically and anaerobically. The isolates were identified by standard methods, including colony morphology, gram stain, bacteriologic and biochemical methods [(7, 8, 9,10)]. After the isolation of bacteria, antibiotic sensitivity testing was done by Kirby-Bauer disc diffusion method on Muller Hinton agar [(10,11)].Api20E systems(bioMerieeux , France) was also utilized according to the manufacturer´s instructions .

The results

The patients in the present study were first divided according to age into two main groups, as in figure(fig) 1:

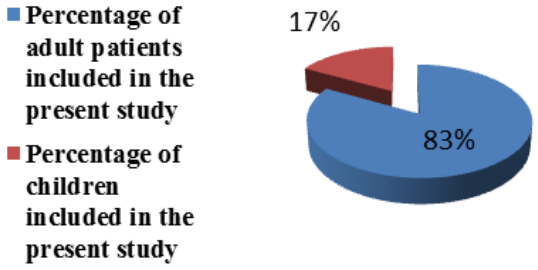


Fig.(1):- The distribution of patients included in the study according to the age.

The diagnosis of the pediatric patients who were taking meropenem was listed in table number (no.) 1, as follows:

Table (1):- The distribution of pediatric patients according to the reported hospital diagnosis.

The diagnosis	The number
Brain abscess	1
Septecemia	19
Meningitis	1
Pneumonia	1
Total	22

At first we will illustrate the inappropriate use of meropenem in pediatrics. In fig. 2 we would represent the percentage of inappropriate use according to age, as follows:

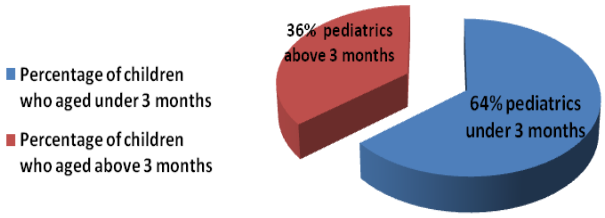


Fig.(2):-The distribution of pediatrics taking meropenem according to age.

The percentage of inappropriate pediatrics dose frequency was represented in fig.3, as follows:

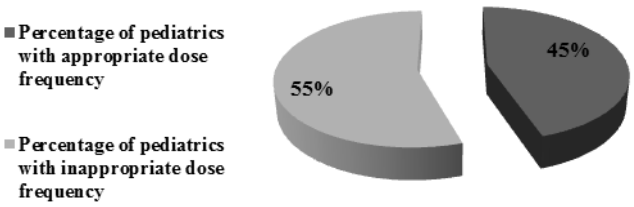


Fig.(3):-The distribution of pediatrics according to the dose frequency of meropenem.

The inappropriate duration of meropenem in pediatrics included in this study was represented in fig.4 and fig.5

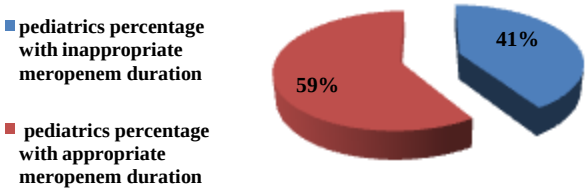


Fig.(4):- The distribution of pediatrics according to duration of meropenem therapy.

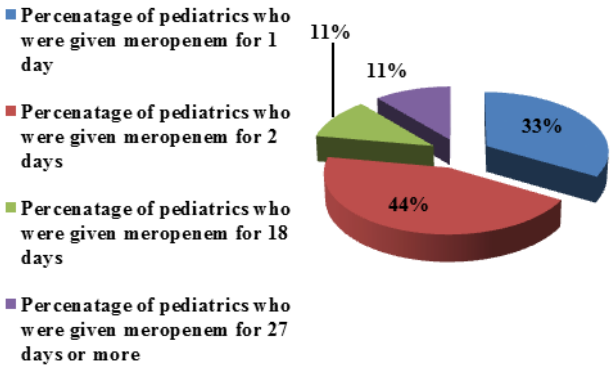


Fig.(5):-The distribution of pediatrics according to the inappropriate duration of meropenem therapy(equal to 41% in fig.5).

The distribution of pediatrics included in the study according to the antibiotics sensitivity test performed by the hospital was represented in fig.6:

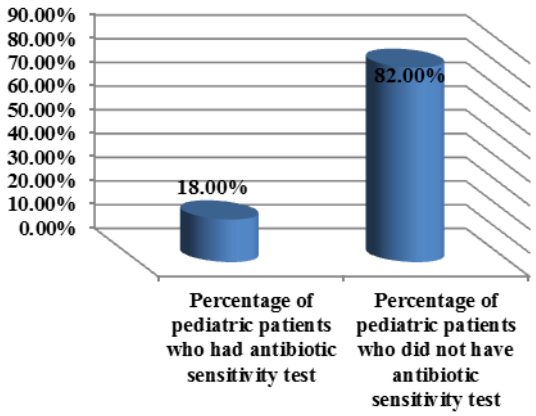


Fig.(6):-The percentage of pediatrics who was given meropenem without antibiotics sensitivity test.

The administration of meropenem required creatinin clearance test to evaluate renal function of the patients .The percentage of pediatric patients who had this test represented in fig.7.

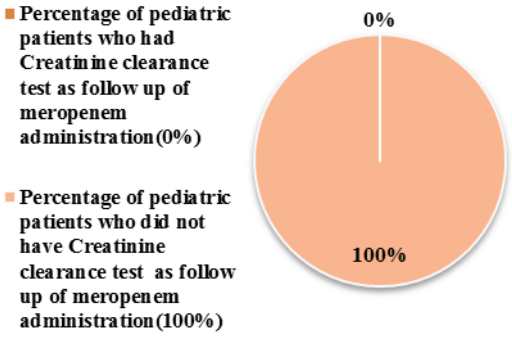


Fig.(7):-The percentage of pediatrics having creatinin clearance test as meropenem follow up.

The no. of patients who aged between 13years - ≥70years and received meropenem included in the study was 108. Their distribution according to the hospital report diagnosis represented in table 2; as follows:

Table (2):-The distribution of adult patients according to the hospital report diagnosis.

Non-haematological diseases	
The diagnosis	No.
Bronchitis	4
Pneumonia	5
Gangrene	1
Discitis	5
Septecemia	11

Hypertention	**2**
Urosepsis	**3**
Hepatitis	**1**
Urinary tract infection(UTI)	**2**
Meningitis	**4**
Pancreatitis	**1**
Chronic renal failure	**2**
Bilateral renal failure	**1**
Anemia	**6**
Hematological diseases	**60**
Total	**108**

The distribution of adult patients included in this study according to sex was represented in fig.8

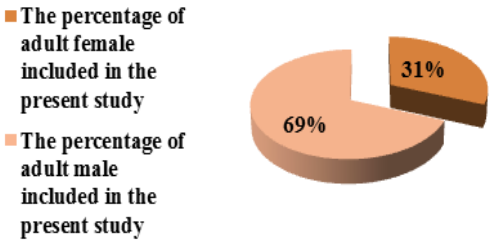


Fig.(8):- The distribution of adult patients included in the present study according to sex.

The percentage of inappropriate meropenem dose frequency for adult patients was represented in fig.9

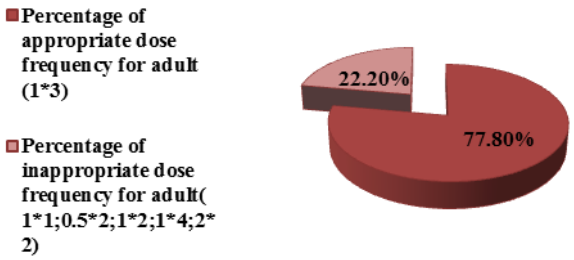


Fig.(9):-The percentage of inappropriate meropenem dose frequency in adult patients.

The percentage of inappropriate meropenem duration in adult patients represented in fig (10,11):

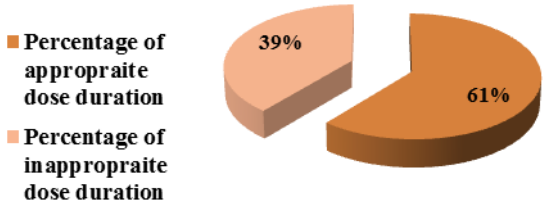


Fig.(10):-The distribution of adult patients included in this study according to inappropriate meropenem duration.

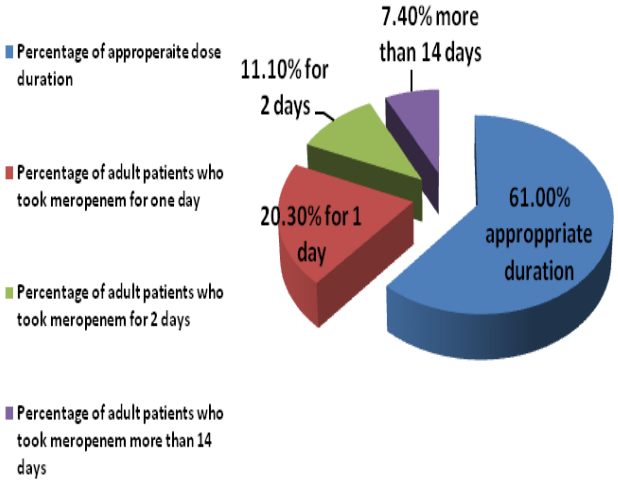


Fig. (11):-The percentage of adult patients included in this study according to inappropriate meropenem duration.

The percentage of adult patients who were taking meropenem without antibiotic sensitivity test by the hospital was represented in fig. 12**.**

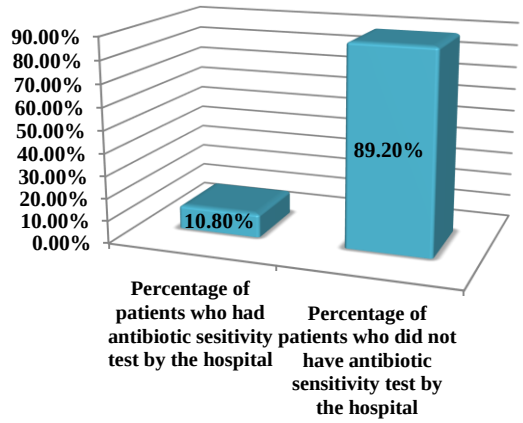


Fig.(12):-The percentage of adult patients who taking meropenem and have antibiotic sensitivity test by the hospital .

The percentage of adult patients who were taking meropenem without creatinin clearance test as follow up was represented in fig 13:

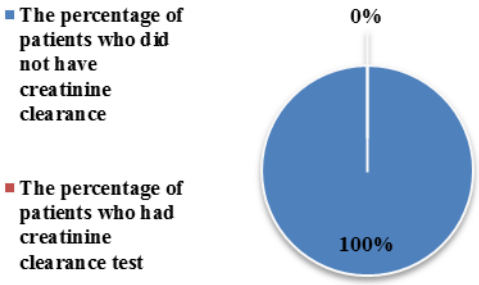


Fig.(13):-The percentage of adult patients who were taking meropenem and don't have creatinin clearance as meropenem follow up measurement.

We made bacterial culture for all patients (130) included in this study. The percentage of patients had positive bacterial culture was 68.5%(89/130) Three percent of the patients had *candida albicanas* infection(4/130).One patients was unidentified(1/130).Twenty-eight percent (36/130) of the patients included in this study had negative microbial infection.The distribution of the patients according to our positive bacterial culture represented in fig. 14:

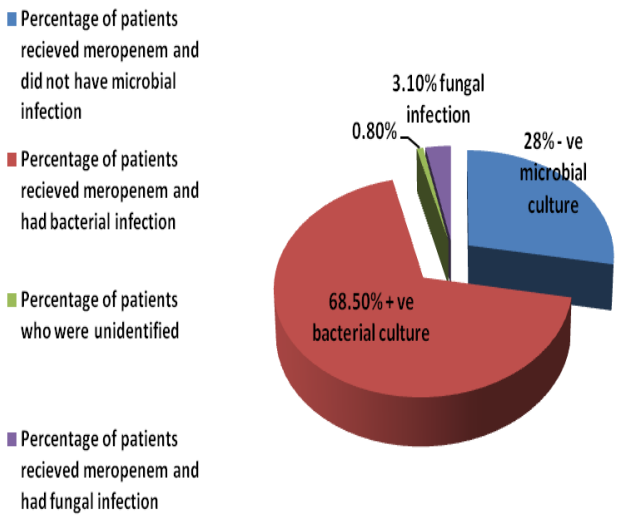
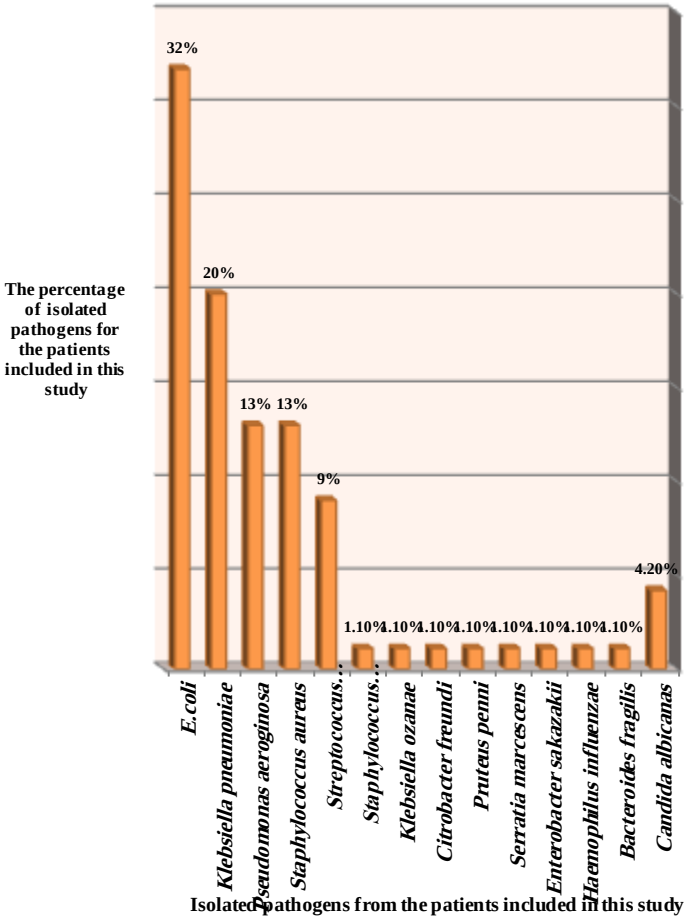


Fig.(14):-The distribution of patients according to our bacterial culture.

We identified the bacteria isolated from the patients included in this study and the results was



represented in fig.15

Fig.(15):-The percentage of isolated bacteria for patients in present study.

We made antibiotic sensitivity test for our isolates and the results were represented in table 3 and 4, as follows:

Table (3):-The antibiotic sensitivity test for gram positive isolates against selected antibiotics.

The isolated gram-positive bacteria (no.)	Ceftazidim	Cotimoxazole	Erythromycin	Vancomycin	Gentamycin	Cefoxitim	Cephalothin	Augmantin	Penicillin	Ampicillin
Staphylococcus aureus (12)	25%	42%	42%	100%	58%	58%	50%	67%	17%	25%
Staphylococcus epidermidis(1)	100%	0%	100%	100%	100%	0%	100%	100%	0%	100%
Streptococcus pneumonia(8)	75.%	37.5%	87.5%	100%	25%	75%	87.5%	87.5%	87.5%	87.5%

Table (4):-The antibiotic sensitivity test of gram negative bacteria against selected antibiotics.

The isolated gram-negative bacteria(no.)	Amikacin	Co-trimoxazol	Ciprofloxacin	Gentamicin	Pipercillin	Pipercillin/ Tazobactam	Cephalothin	Cefoxitim	Ceftazidime	Augmentin	Ampicillin
E.coli (30)	87%	37%	67%	60%	47%	93%	27%	63%	60%	33%	17%
Klebsiella pneumonia (19)	58%	37%	74%	53%	32%	89%	26%	68%	42%	42%	11%
Pseudomonas aeroginosa(12)	58%	25%	75%	42%	67%	92%	17%	25%	58%	25%	8%
Klebsiella ozanae(1)	0%	0%	100%	100%	0%	100%	0%	100%	100%	0%	100%
Citrobacter freundi(1)	100%	0%	100%	0%	100%	100%	0%	100%	100%	0%	0%
Pruteus penni(1)	100%	0%	100%	0%	100%	100%	0%	100%	100%	0%	0%
Serratia marcescens(1)	100%	0%	100%	100%	100%	100%	0%	0%	100%	0%	0%
Enterobacter	100%	100%	100%	0%	100%	100%	0%	0%	100%	100%	0%

***sakazakii*(1)**											
***Haemophilus influenza*(1)**	100%	100%	100%	0%	0%	100%	0%	100%	100%	0%	100%
***Bacteroides fragilis*(1)**	100%	100%	100%	0%	0%	100%	100%	100%	100%	100%	100%

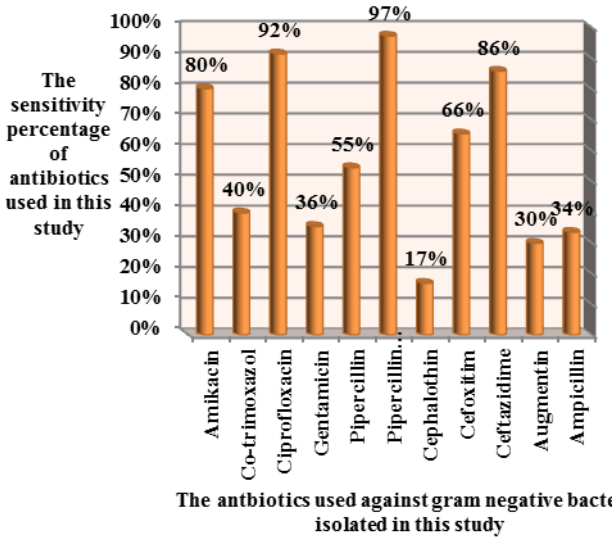


Fig.(16):-Total sensitivity testing for overall antibiotics used against gram negative bacteria isolated in this study.

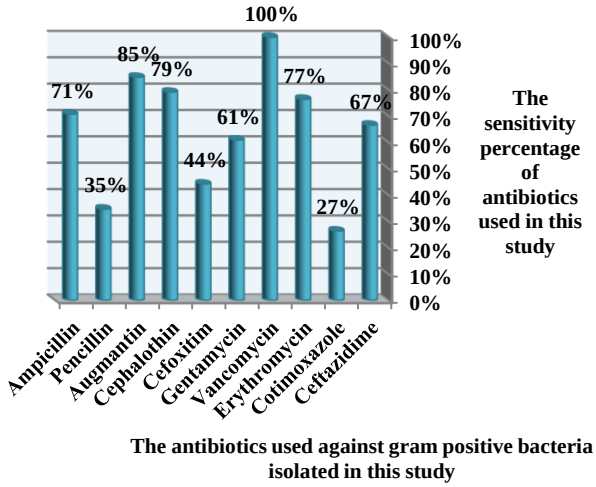


Fig.(17):-Total sensitivity testing for overall antibiotics used against gram positive bacteria isolated in this study.

Discussion

Inappropriate and indiscriminate use of antimicrobials and their combinations is a global problem causing a substantial economic burden on health care systems. Over prescribing is associated with increased side effects, excessive cost of therapy, moreover it leads to emergence of resistant

organisms, whereas under prescribing gives rise to treatment failure and emergence of resistant organisms [12,13,14]. In the present study we concentrated on meropenem and its inappropriate use in pediatrics, neurosurgery, internal medicine, haematology departments at a tertiary care hospital in Iraq because this antibiotic is under restricted dispensing regulations by MOH /Iraq. By concentrating on single antibiotic (meropenem) which has restricted MOH regulations (theoretically) in prescription - dispensing and some of its inappropriate use, we hope that light will be focused on the abuse of other antibiotics that don't have restricted MOH regulations in prescription and dispensing as meropenem. In order to examine the meropenem prescription carefully and to concentrate on the details we first divided the patients into two main groups (according to the hospital regulations): the pediatrics (age 1 day-12years) 17% and adult (13 years-≥70year)83% (fig.1).The distribution of pediatrics and adult patients according to the hospital diagnosis was represented in tables 1 and 2. All patients was discussed in term of dose frequency, duration, indication (weather it was appropriate /inappropriate for the medical condition), and if there was other antibiotics to use before starting with meropenem. The percentage of pediatrics took meropenem and aged less than 3 months was 36% (fig.2). The use of meropenem in pediatrics under 3 months of age is not licensed by FDA, meropenem leaflet's, BNF C and many other references [15,16,17,18,19] as the effect of which is not fully evaluated and further study is needed. Although BNF C had mentioned the dose of meropenem for these young age but" not licensed for use in children under 3months" as BNF C itself. In this study some of these infants aged 1 day - 4 days. Why such risk , why the risk in these innocent lives despite that the antibiotic sensitivity test done by us indicate the availability of alternative antibiotics with more safety range ,less side effects and cheaper at the hospital . Is this decision for the benefit of the patient or a competition from the physician to ensure their ability to break the ministry regulations on the expense of human life quantity or at least future life quality of those patients. Fifty-five percent of the pediatrics (fig.3) and 22.2% of adult patients (fig.9) had inappropriate dose frequency according to many references [15,16,17,20,21]. The decision of this inappropriate dosing is not related to renal function test as none of the patients included in this study were having creatinin clearance test as follow up (fig8 and fig13 for pediatrics and adults respectively) not during or after the treatment with meropenem. The use of meropenem is inappropriate for renal failure patients and if it is necessary the dose should adjusted. Although there are 3 patients were having renal failure but they were given meropenem without adjustment or follow up. The bacterial culture for those 3 patients was made before the administration of meropenem and the results came negative for bacterial growth. Again why such adventure in giving meropenem for such patients. Of the patients (pediatrics and adults) with inappropriate dose frequency of meropenem 12.2% had 1*4 dose frequency. Again what are the references or guidelines that justify such frequency. This unauthorized frequency will have many undesirable effects as; wasting the nursing time that might be needed for other patients, this frequency will increase the cost of treatment, expose the patient unnecessarily to the side effects of the drug without medical benefit. Also 1*1 dose frequency in a percent of 4.4% was reported in this study. The standard duration of meropenem for each case included in this study was determined according to many references [16,17,22,23,24,25,26,27,28,29,30,31,32] and was compared to the real duration of meropenem therapy in the hospital (if bacterial infection does exist) for all patients in the study. Accordingly 41% of pediatrics had inappropriate duration (fig4&5).Thirty-three percent of these pediatrics had taken meropenem for one day and 44% of them took meropenem for 2 days. While the percentage of adult with inappropriate duration was 39% (fig11 &12) of them 20.3% with one day duration and 11.1% had taken meropenem for only 2 days. This short

duration of antibiotics administration was reported by Jumaa *et al* [33].The short duration and inadequate antimicrobial therapy is considered as one of the most important factors in the emergence of bacterial resistance [34] and result in treatment failure[12,13,14]. The percentage of pediatrics who received meropenem without hospital antibiotic sensitivity test is 82% (fig 6). The adult patients without antibiotic sensitivity test is 89.2 %(fig 12). This was almost agreed by Jumaa *et al* [33] and much higher than that reported by Joshi *et al* [35] .The prescription of meropenem without antibiotic sensitivity test is against MOH/Iraq regulation for dispensing meropenem. This is almost agreed with previous study carried out in Iraq which found that the physician directly prescribed the more new and the more costly antibiotic without antibiotics sensitivity test and without order for cultures "follow their own guidelines"[33]. According to worldwide regulations for antibiotic prescription" meropenem should be used as specific antibiotic therapy directed against significant isolates cultured from appropriate specimens, and should be prescribed according to the results of antibiotic susceptibility testing because meropenem provide limited cover for gram positive infections therefore it is not suitable to be the first line empirical antibiotic therapy"[30,36]. In order to evaluate this aspect of dispensing meropenem in the hospital, bacterial culture was done to all the patients included in the study then they were identified according to standard bacteriological methods [7-11] (tables 3&4) .There was no bacteria that resist all antibiotics available in the hospital .This was against MOH regulations for meropenem and increases the cost of treatment. The medical conditions for the patients in this study was multiple and variables (tables 1&2). The most common bacteria isolated from the study was gram negative bacteria (72.7%) . The most common gram negative bacteria were belonging to the *Enterobacteriaciae* in a percentage of 57.5% (fig 14). *E.coli* was the most predominant isolated bacteria in a percentage of 32% (30/93), followed by *Klebsiella pneumonia* in a percentage of 20%(19/93) and *Pseudomonas aeroginosa* in a percentage of 13%(12/93). While gram positive bacteria isolated in this study from 23.1% of the patients. *Staphylococcus aureus* was the most common isolated gram positive bacteria in a percentage of 13%(12/93) followed by *Streptococcus pneumoniae* in a percentage of 9%(8/93). *Candida albicanas* was isolated from 4.2% (4/93) of the positive isolates in this study .Thirty-six (28%) patients had negative culture and one patients was unidentified (severely ill old female patients with meningitis). The most common bacteria isolated from septecemic patients was *Staphylococcus aureus* (9 patients) followed by *E. coli* (7 patients).This result was the same as Asghar [37] .In general the gram negative bacteria was overcome the gram positive bacteria as a cause of septicemia in this study(14 vs12) . The gram negative bacteria as the main cause of septicemia was agreed by Nwadioha *et al* [38,39]. This result was inagreement with that of Karchmer [40]. The most common bacteria isolated from patients with pneumonia was *Streptococcus pneumoniae* (3 patients).This was agreed by many study [41,42]. The most common bacteria isolated from UTI and patients with urosepsis was *E.coli* .This was agreed by Nicolle [43].The most effective antibiotic against gram positive bacteria was vancomycin and the least effective is co-trimoxazole while the most effective antibiotic against gram negative was pipercillin/tazobactam and the least effective was cephalothin. The antimicrobial sensitivity patterns differs indifferent studies as well as at different times in the same hospital. This is due to the emergence of antibiotics resistance as a result of discriminate use of antibiotics [44]. In this study the collection of the patients was according to meropenem uptake regardless to the medical condition that is the reason for such variability in the isolated bacteria and their antibiotics sensitivity profile. The obsession in the use of any new antibiotic without consideration to its impact on future is simply wrong because the excessive use of new antibiotic has disastrous effect not only on the present time but it would extend to the

future and it will at some point influence the excellent outcome of infectious diseases therapy . For the life and future of our children let us start a new policy in prescribing and dispensing antibiotics in Iraq. Twenty –three percentage of the positive bacterial culture patients had gram positive bacteria, of these 13% had *Staphylococcus aureus* infections (table4). As we mentioned meropenem has limited cover against gram positive bacteria specially *Staphylococcus aureus*[30,36]. Meropenem is an antibacterial this mean there should be a bacterial infection in order to prescribe it. In this study 31% of patients didn't have bacterial infection (3.1% had fungal infection+28% had negative microbial culture-fig.14) this mean 31% of the patients included in this study received meropenem for no reason at all. The administration of antibacterial unnecessarily will only increase the bacterial resistance to this antibiotic ,increase the cost of therapy , expose the ill patient to chemical compound and its side effects without any benefit. Also disperse the attention from the real cause of the patient suffery (it is not due to bacterial infection, what are the cause of the patient illness).In addition to all the above, the meropenem dispensing unnecessarily decreases the availability of meropenem for other patients who have bacterial infection and need it .This is particularly important because meropenem quantity in the hospital is limited and supplied into the hospital intermittently. By describing meropenem for patients without bacterial infection we deprive the patient with the right infection and to him meropenem may be live savior. Collectively 54% of the patients included in this study took meropenem without appropriate indication for the use of meropenem. The abuse on antibiotics that is very common in Iraq had many causes : The microbial culture and antibiotic sensitivity test is not done routinely for patients who suspected to have infection before initiation of antimicrobial therapy . Most of physicians prescribe antibiotics without ordering antibiotic-sensitivity test and refuse to follow the national recommendations and guidelines for prescribing and dispensing antibiotics. Most of physicians tend to take the easy decision in prescribing the most expensive and the newer antibiotic, refusing to discuss their decision with the clinical pharmacist (take any objection as a personal attack) .Also because clinical pharmacist does not have a documented authority from MOH to review and fix the error(s) in prescribing(in this study) meropenem. Also MOH has the ability to provide more restricted regulations for antibiotic prescription and dispensing not only for meropenemn. The regulation of meropenem is also has some defect for example :meropenem dispensed for life threatening conditions without antibiotic sensitivity test which provide a door to abuse ;as physician may dispense meropenem for simple UTI and justify it by saying life threatening . To reduce the human error such decision should be according to consultant of physician, clinical pharmacist and microbiologist. This will eliminate the abuse in antibiotic. Public education to the hazardous of use antibiotic without culture and antibiotic sensitivity test and its rule in the emergence of antibiotic resistance and how this will affect the future generations.

Recommendations

1. MOH/Iraq should provide the clinical pharmacist with a documented authority to review the prescribed antibiotics in general and provide him with the ability to order laboratory test(s) to evaluate the medical condition completely and provide the most suitable treatment.

2. MOH must provide a uniform guideline for antibiotics and other therapeutic agents for all hospitals in Iraq with intranet to be easily accessed by all physicians and pharmacists.

3. The dispensing of newer broad spectrum antibiotics should be dispensed by a clinical consultant committee consisting of the responsible physician, clinical active pharmacist, and clinical microbiologist. This will help in deciding the most appropriate antibiotic.

4. Similar study can be done by other hospitals to give the complete picture for

abuse of antibiotics in Iraq. Meropenem can be the standard to measure the abuse in other antibiotics .By this MOH can know where is the defect and in future when MOH activate the complete regulations for all antibiotics both in government and private institutions can fix the defects in the past regulations. For example the life threatening conditions must be discided by a clinical consltant in addition to the responsible physician to optimize the effect of antibiotics.

5. Public education of the hazardous impact of dispensing antibiotic(s) without culture and antibiotic sensitivity test.

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