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PATTERNS OF ANTIMICROBIAL USE AND PREVALENCE OF ANTIBIOTIC RESISTANT BACTERIA

STUDY AT AIN-SHAMS UNIVERSITY

SPECIALIZED HOSPITAL (ASUSH)

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ABSTRACT

Introduction: Antibiotics are prescribed for treating bacterial infections. However, Excessive use of antibiotics leads to the development and spread of multidrug resistant bacteria, currently regarded as a global public health crisis threatening our ability to treat common infectious diseases, resulting in prolonged illness, disability and death.

Aim of the work: To analyze the use and prescribing patterns of antimicrobials by physicians at Ain-Shams University Specialized Hospital (ASUSH) for inpatients among different infections and to determine the prevalence of different types of bacterial resistance among hospital infections.

Subjects and methods: A cross- sectional study was conducted at (ASUSH). A total of 339 microorganisms isolated from several samples types were identified and studied using VITEK® 2 system. Physicians' attitudes and knowledge were assessed using a questionnaire about antibiotic resistance problem.

Results: Among (339) bacterial isolates Klebsiella pneumoniae was the most common isolate n=92 (27.1%), followed by E-coli n=60 (17.7%), Staph coag –ve (SCONs) n= 43 (12.7%) and Methecillin resistant staphylococcus aureas (MRSA), Pseudomonas aeruginosa and Acinetobacter baumanni n=33 (9.7%)

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for each. In this study, the majority of physicians had good knowledge about the antibiotic resistance meaning and the magnitude of that problem, with a positive attitude towards prescribing antibiotics.

Conclusion: Strategies for control of resistant bacteria should consider variations among sample types, wards, and antibiotic resistance variability. There is a need to specifically address staff training and communication procedures for infection prevention and control with respect to drug resistant bacteria.

Keywords: antibiotic policy, Multi Drug Resistance, physicians' knowledge and attitude, Antibiotic Susceptibility.

INTRODUCTION

There is no doubt that antimicrobials have played a revolutionary role in healthcare systems worldwide. From the discovery of the first antibiotics in the 1930s and1940s, these medicines have saved countless lives through reducing morbidity and mortality rates for a number of infectious diseases that were once a principal cause of death. (Nichol., *et al* ., 2018).

Antibiotics have not only saved patients' lives, they have played a pivotal role in achieving major advances in medicine and surgery. They have successfully prevented or treated infections that can occur in patients who have chronic diseases such as diabetes, end-stage renal disease, or rheumatoid arthritis; or who have had complex surgeries such as organ transplants, joint replacements, or cardiac surgery.(Gould and Bal., 2013 ; Atif, *et al* ., 2017).

New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases. (Tyers and Wright, 2019; WHO, 2018). It leads to increased morbidity and mortality, increased hospital stay, and costly and toxic alternatives. However, while

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resistance rates continue to rise, the rate of antibiotic discovery has dropped substantially. (Laxminarayan, 2014; Hernando-Amado, et al., 2017).

Antimicrobial resistance (AMR) happens when microorganisms (such as bacteria) change when they are exposed to antimicrobial drugs they became less sensitive to the drug and sometimes completely insensitive to the antibiotic. As a result, the medicines become ineffective and infections persist in the body, increasing the risk of spread to others (WHO, 2018).

A number of factors are thought to be associated with this rapidly developing AMR bacteria but inappropriate consumption of antimicrobial (either prescribing antimicrobials when not required or prescribing a broad-spectrum agent when a narrower spectrum agent would be adequate) is still the main determinant of AMR (Atif., *et al* ., 2017).

Globally, between 20 to 50% of antimicrobial consumption is inappropriate, causing significant impact on the quality of care, cost of therapy and incidence of adverse drug (Centers for Disease Control and Prevention, 2013). Inappropriate consumption of antimicrobial is not the only reason for antibiotic resistance, there are many other reasons leading to this crisis like the overuse of antibiotics & the extensive agricultural and veterinary use of it. (Ventola, CL. 2015).

Inappropriate attitudes and lack of knowledge towards the use of antibiotics, patients' demands, lack of culture and selling antibiotics without prescription are also some of the most common contributors towards

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antibiotic resistance and considered as a high-risk factor contributing to the rise of AMR cases. (Zulu, et al., 2020)

As a result, the WHO recommends continuous surveillance of antibiotic use as a strategy for improving antibiotic use among patients and also for controlling antibiotic resistance and minimizing patient harm, so accurate information on the use of antibiotics are crucial to address the problem of antibiotic overuse and resistance. (Labi, *et al* ., 2018).

We aimed to analyze the use and prescription patterns of antimicrobials by physicians at (ASUSH) for inpatients with different infections and to determine the prevalence of different types of bacterial resistance among hospital infections

SUBJECT AND METHODS

Patient and sample characteristics

Records from August 2018 to January 2019 from inpatients with MDR infections attending ASUSH were analyzed. A total number of 339 MDR-positive samples were identified. Demographic data (sex, age group) is summarized in Table (1). They were isolates from pus, urine, blood, respiratory and cerebrospinal fluid (CSF) samples; sample type information and Bacterial species identified for each sample type are summarized in Table (2).

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Identification and Antibiotic susceptibility testing

The identification was carried out by the automated *VITEK® 2* system ((bioMérieux. Marcy l'Etoile, France) which used for species identification and susceptibility testing of the bacteria, which accommodate the colorimetric reagent cards that are incubated and interpreted automatically.

Physicians' survey

A questionnaire was distributed to (90) physicians at ASUSH from different departments, positions and with different years of experience to determine their knowledge and understanding of MDR infections and the procedures in place to identify and contain these infections in their institution.

STATISTICAL METHODS

IBM SPSS statistics (V. 25.0, IBM Corp., USA, 2017-2018) was used for data analysis. Date were expressed as both number and percentage for categorized data. The following tests were done:

- Descriptive statistics using Cross-tabulation including count and absolute percentage.

- Chi-square test to study the association between each two variables or comparison between two independent groups as regards the categorized data.

RESULTS

Sample type

In this study a total number of 339 isolates of MDR bacterial infection were isolated mainly from males (n= 210 (61.9%)) while females accounted for (n=129(38.1%)). The distribution of those resistant pathogens mainly found in age range (51-70 years) with (51.6%), then from (31-50 years) with (22.7%), which is demonstrated in table (1).

Bacterial species

Bacterial species distribution of the 339 MDR isolates and sample distribution is shown in Table (2). The total number of isolated pathogens were (339) among which Klebsiella was the most common isolate n=92 (27.1%), followed by E-coli n=60 (17.7%), Staph coag −ve (SCONs) n= 43 (12.7%) and MRSA, Pseudomonas and Acinetobacter n=33 (9.7%) for each.

Klebsiella and E_coli were frequently isolated from urine samples 32.14% and 29.7% of all isolated microorganism from urine sample respectively.

Antibiotic resistance profiles

The resistance and sensitivity profile for each microorganism in table (3) and table (4) revealed that Antibiotic resistance profiles were not uniform across bacterial species or sample types; these factors should be considered for informing antibiotic stewardship programs within the hospital. As expected, there were overall high levels of susceptibility to carbapenems. E.coli showed the lowest resistance pattern to most antibiotics unlike

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klebsiella which was the Most frequent isolate in our study showed moderate resistance to Meropenem (51.9%) and Amikacin (53 %) and was highly resistant to Ceftriaxone (96.5%) followed by Ceftazidim (95.8%) and Levofloxacin(71.4%). Table (3)

None of MRSA nor SCONs were resistant to linezolid nor vancomycin. However, MRSA showed higher sensitivity against teicoplanin, tri/sulpha and erythromycin than SCONs. Table (4)

Physicians' knowledge

When they were asked about the meaning of antibiotic resistance and the magnitude of this problem the majority (85.6%) Knew the meaning and felt that it's a very important problem

Overuse of broad spectrum antibiotics considered to be the most Important factor that lead to antibiotic resistant (100%) followed by Widespread use of antibiotic (98.9%) and inappropriate use of antibiotics (82.2%). The least important factor was companies promote antibiotic use & inadequate hand washing (36.7%).

Physicians thought that prolonged Treatment (74%) and increased cost (68%) were the most frequent complications related to antibiotic resistance and Death is the least complication (7%).Table (5)

Physicians thought that Educational program to physicians considered to be the most useful factor in containing the problem (78%) followed by culture prior to antibiotic choice (70%) & Antibiotic cycling the least useful factor (44%) as summarized in table(5).

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Physicians' practice

The highly prescribed Antibiotic (empiric antibiotic) were Meropenem (26.7%), Amp/sulb (17.8), levofloxacin (15.6%), Ceftriaxone (11.1%), Ceftazidime (7.8%), Ciprofloxacin (5.6%), Amikacin (5.6%), Dalacin (4.4%), Tazocin (3.3%), and Salyprazone (2.2%) .Table (6)

The majority 92.2% would stop the antibiotic if the culture report indicate resistance to that antibiotic and 7.8 % would add another antibiotic to which the microorganism is sensitive.

And 68.9% would continue using the antibiotic, although the culture showed that microorganism is sensitive to another narrow spectrum antibiotic and only 31.1% would change to the other narrow spectrum antibiotic.

Table (1): demographic data

Gender	n (%)
Male	210 (61.9%)
Female	129 (38.1%)
Age	
<1	17 (5%)
1-15	10 (2.9%)
16-30	15(4.4%)
31-50	77 (22.7%)
51-70	175 (51.6%)
71-98	45 (13.3%)
Total	339(100%)

Table (2): Bacterial distribution

Microorganism	Urine N (%)	Sputum N(%)	Pus N(%)	**Blood** N(%)	Drain N(%)	Wound N(%)	Central line N(%)	**Stool** N(%)	Endotracheal N(%)	**Count** (%)
klebsiella	27(32.14%)	18(29%)	14(24.1%)	5(10.6%)	6(20%)	10(34.4%)	4(33.3%)	5(50%)	3(42.8%)	92(27.1%)
E-coli	25(29.7%)	6(9.6%)	12(20.6%)	4(8.5%)	6(20%)	4(13.7%)	0	3(30%)	0	60(17.7%)
Staph coag –ve	4(4.7%)	3(4.8%)	5(8.6%)	25(53.1%)	0	2(6.8%)	4(33.3%)	0	0	43(12.7%)
MRSA	3(3.5%)	7(11.2%)	13(22.4%)	6(12.7%)	0	4(13.7%)	0	0	0	33(9.7%)
Pseudomonas	7(8.3%)	6(9.6%)	7(12%)	0	10(33.3%)	1(3.4%)	1(8.3%)	0	1(14.2%)	33(9.7%)
Acinetobacter	3(3.5%)	18(29%)	2(3.4%)	2(4.2%)	2(6.6%)	2(6.8%)	2(16.6%)	0	2(28.5%)	33(9.7%)

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Cont. Table (2): Bacterial distribution

Microorganism	Urine N (%)	Sputum N(%)	Pus N(%)	**Blood** N(%)	Drain N(%)	Wound N(%)	Central line N(%)	**Stool** N(%)	Endotracheal N(%)	**Count** (%)
ENTEROCOCCI	4(4.7%)	0	2(3.4%)	2(4.2%)	2(6.6%)	3(10.3%)	1(8.3%)	0	0	14(4.1%)
Proteus	2(2.3%)	2(3.2%)	0	0	0	3(10.3%)	0	0	0	7(2.1%)
non.hemol strepto	5(10.4%)	0	2(3.4%)	0	2(6.6%)	0	0	0	0	9(2.7%)
staph aureus	0	2(3.2%)	1(1.7%)	3(6.3%)	0	0	0	0	1(14.2%)	7(2.1%)
Citrobacter	4(4.7%)	0	0	0	2(6.6%)	0	0	2(20%)	0	8(2.4%)
Total	84(100%)	62(100%)	58(100%)	47(100%)	30(100%)	29(100%)	12(100%)	10(100%)	7	339(100%)
MRSA: Methecillin Resistant Staphylococcus Aureas										

Table (3): Sensitivity and resistance pattern of most significant bacteria among antibiotics used:

	E_coli		Acinetobacter		Klebsiella		Pseudomonas	
Antibiotic	R%	S%	R%	S%	R%	S%	R%	S%
Nitrofurantoin	9.5%	90.5%						
Ceftazidim	81.5%	18.5%			95.8%	4.2%	93.3%	6.7%
Amikacin	16.4%	83.6%	75.9%	24.1%	53%	47%	65.5%	34.5%
Impenem	63%	37%	88.9%	11.1%	76.4%	23.6%	77.3%	22.7%
Tri/sulpha	82.5%	17.5%	83.3%	16.7	93.6%	6.4%		
Amp/sulbactam	93%	7%	90%	10%	95.5%	4.5%		
Ceftriaxone	91.5%	8.5%	100%	---	96.5%	3.5%		
Pip/tazo	46.9%	53.1%	90.9%	9.1%	71.4%	28.6%	93.3%	6.7%
Cefipime	72.7%	27.3%	95.7%	4.3%	91.9%	8.1%	93.3%	6.7%
Meropenem	28.8%	66.7%	77.4%	22.6%	51.9%	48.1%	75.9%	24.1%
Amox/clav	79.5%	20.5%			91.5%	8.5%		
Tetracycline	77.4%	22.6%			64.3%	35.7%		
Cefotaxime	94.3%	5.7%	100%	---	95.5%	4.5%		
Gentamycin	28.6%	71.4%	81.5%	18.5%	61.3%	38.6%	63%	37%
Ciprofloxacin	68%	32%	96.9%	3.1%	81.8%	18.2%	79.3%	20.7%
Levofloxacin	70.2%	29.8%	95%	5%	71.4%	28.6%	87%	13%
R: Resistant			S: Sensitive					

Table (4): Sensitivity and resistance pattern of most significant bacteria among antibiotics used:

Antibiotic	SCONs		MRSA	
	R%	S%	R%	S%
Erythromycin	76.2%	23.8%	26.9%	73.1%
Cefopid	100%	------	100%	------
Ceftazidim	100%	-------	100%	-------
Impenem	100%	------	100%	------
Tri/sulpha	54.1%	45.9%	12%	88%
Amp/sulbactam	100%	------	100%	------
ceftriaxone	100%	------	100%	------
Pip/tazo	100%	------	100%	------
Cefipime	100%	------	100%	------
Meropenem	100%	------	100%	------
Amox/clav	100%	------	100%	------
Cefotaxime	100%	------	100%	------
Cefuroxime	100%	------	100%	------
Teicoplanin	10%	90%	3.8%	96.2%
Vancomycin	------	100%	------	100%
Linezolid	------	100%	------	100%
R: Resistant S: Sensitive SCONs: staph coagulase -ve MRSA: Methicillin Resistant Staphylococcus Aureas				

Table (5): physicians' questionnaire

Factors can lead to antibiotic resistance: (can choose more than one answer)				
Factors	very Important	Moderately important	Minimally Important	Don't know
widespread use of antibiotic	%98.8	1.2%	0	0
overuse of broad-spectrum antibiotic	100%	0	0	0
inappropriate use of antibiotic	82.2%	17.7%	0	0
inappropriate choice of antibiotic	66 %	28.8%	4.4%	0
lack of guidelines	72.2%	26.6%	1.2%	0
patient Demand for antibiotics	50%	34.4 %	11.1%	4.4%
companies promote antibiotic use	36.6	23.3%	40%	0
inadequate hand washing	36.6	11.1%	51.1%	1.2%
Complications related to antibiotic resistance (can choose more than one answer):				
Complication	More likely	Moderately likely	Less likely	Don't Know
prolonged treatment	82.2%	17.7%	0	0
increased cost	75.5%	23.3	1.2%	0
organ failure	30%	41.1%	28.8%	0
Death	7.7%	30%	54.4%	7.7%
factors are useful in containing resistance : (can choose more than one answer)				
Factors	Very important	Maybe	Not important	don't Know
educational program	86.6%	13.3%	0	
access to lab reports	68.8%	25.5%	5.5%	
Consultation	71.1%	27.7%	1.2%	
antibiotic guidelines	71.1%	23.3%	5.5%	
culture prior to antibiotics use	77.7%	21.1%	1.2%	
public educational programs	62.2%	28.8%	8.8%	0
antibiotic restriction	61.1%	33.3%	4.4%	1.2%
Antibiotic cycling	48.8%	48.8%	0	2.2%

Table (6): The most frequent antibiotic prescribed (Empiric antibiotic)

Antibiotic	Count	%
Meropenem	24	26.7%
Ampicillin/sulbactam	16	17.8%
Levofloxacin	14	15.6%
Ceftriaxone	10	11.1%
Ceftazidime	7	7.8%
Ciprofloxacin	5	5.6%
Amikacin	5	5.6%
Dalacin	4	4.4%
Tazocin	3	3.3%
Salyprazone	2	2.2%
Total	90	100.0%

DISCUSSION

The widespread of MDR pathogens is becoming a serious challenge in public health. Recently, therapeutic options against them have become limited, causing morbidity and mortality in hospitalized patients. Inappropriate use of antibiotics in hospitals and communities has resulted in an increasing resistance to various antibiotics (Awad and Aboud, 2015).

In this study the total number of isolated pathogens was (339) among which Klebsiella was the most common isolate (27.1%), followed by E_coli (17.7%), Staph coag −ve (12.7%) and MRSA, Pseudomonas and Acinetobacter (9.7%) for each. Similar to our study results, literature also reports Klebsiella pneumoniae as the most common resistant isolates, followed by Escherichia coli and/or Enterobacter species. (Sodhi, et al., 2020)

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and also similar to a study conducted at tertiary care hospital in Egypt by (Hassan, et al., 2020).

The distribution of those resistant pathogen mainly found in age range (51-70 years) with (51.6%) then from (31-50 years) with (22.7%) which support that aging is one of the main predisposing risk factors for HAIs with resistant pathogens , this was in agreement with Feng, *et al*., (2019).

In our study E.coli showed the lowest resistance pattern to most antibiotics specially gentamycin and amikacin unlike A.baumanni & P. *aeruginosa* which were highly resistant to the same antibiotics. However the highest sensitivity of E.coli was recorded to nitrofurantoin (90%) as found in other study by *(Aguilar-Santelises, et al., 2020).*

Klebsiella which were the Most frequent isolate in our study unlike E.coli showed moderate resistance to meropenem (51.9%) and amikacin (53 %) and were highly resistant to ceftriaxone (96.5%) followed by ceftazidim (95.8%) and levofloxacin(71.4%). Another study at largest hospital's NICU in Minia by Hassuna, et al., (2020) showed higher degree of resistance towards antibiotics with (100%) resistance against ceftriaxone, while unlike our study they found none resistant against levofloxacin.

According to the results none of MRSA and SCONs were resistant to linezolid nor vancomycin. However, MRSA which was the dominant bacterial species isolated from pus showed higher sensitivity against teicoplanin, tri/sulpha and erythromycin unlike SCONs which was the dominant bacterial species isolated from blood showed moderately higher

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resistance against them which was consistence with other studies byHashemizadeh, *et al., (2019) and* Nicolosi,D., et al.,(2020).

Antimicrobial stewardship programs (ASPs) have emerged as a strategy to manage or contain the problem of AMR, which considered as a systematic approach to improve the prescribing pattern of antibiotics through a variety of interventions and have been proven to be cost-effective. ASPs should afford educational and effect changes in prescribing behaviors of healthcare providers. (Labricciosa, F. et al., 2018)

In this context, a questionnaire was conducted to analyze the use and prescribing pattern of physicians working at the same departments from which the resistant pathogen were isolated at the same period of time from which isolated pathogens were collected. The total number of physicians who filled the questionnaire were (90) physician of different specialties and years of experience from which (55.6%) male and (44.4%) female.

In this study, the majority of physicians (85.6%) have good knowledge about the antibiotic resistance meaning and the magnitude of that problem which was in agreement with a study conducted at national liver institute in Egypt by Tahoon, et al., (2020) who found that (85%) of physician were familiar with antibiotic resistance. another study by Tegagn et al., (2017) found that 81.3% of healthcare professionals were familiar with antibiotic resistance meaning.

According to the conducted survey Overuse of broad spectrum antibiotic considered to be the most Important factor that lead to antibiotic resistant

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(100%)followed by Widespread use of antibiotic (98.9%) and inappropriate use of antibiotic (82.2%) These results are close to previous study from Italy Napolitano F, et al., (2013) also showed that wide spread use of antibiotics is the most important cause of this problem.

Most Physicians thought that prolonged Treatment (74%) and increased cost (68%) were the most frequent complications related to ANTIBIOTIC resistance and Death is the least complication (7%) which was similar to another survey by Nichol, , et al,. (2018) at a tertiary care institution in the Caribbean.

The majority of physicians (78%) considered periodic Educational programs to be the most useful factor in containing the antibiotic resistance problem as a tool to improve antibiotic prescription pattern of them. Furthermore, the majority considered taking cultures prior to ANTIBIOTIC choice (70%) as other important factor against the spread of MDR bacteria. Antibiotic cycling considered to be the least useful factor with (44%) which is correlate with a study in UAE by John , et al., (2012)and other study in Khartoum by Kheder . ,(2013).

This results shows that there is a need to follow infection control measures and to increase the restrictions of antibiotic use in the current antibiotic policy to slow down the emergence and spread of antibiotic resistant bacteria in the health care setting.

CONCLUSION

Infections can be transferred between and within hospitals, facilitated by sub-optimal infection prevention and control measures, as well as between the community and healthcare facilities.

Hence, the importance of cooperation between clinical and microbiology laboratory staff in determining antibiotic resistance profiles and implementation of effective antibiotic stewardship programs in controlling selection and use of antibiotics.

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الأنماط المختلفة لاستخدام المضادات الحيوية ومدي انتشار البكتريا المقاومة للمضادات الحيويه – دراسة بمستشفي عين شمس التخصصي

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المستخلص

لا يوجد مجال للشك بأن المضادات الحيويه تلعب دورا ثوريا فى النظام الصحى عالميا". فمنذ الإكتشاف الأول لها عام ١٩٣٠ و١٩٤٠ والمضادات الحيويه تنقذ أعدادا" لا حصر لها من الأرواحمن خلال الحد من معدلات الإصابه بالأمراض والوفيات فى عدد الأمراض المعدية التى كانت في يوم من الأيام سبباً رئيسياً للوفاة. ومع ذلك، يؤدي الاستخدام المفرط للمضادات الحيوية إلى

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تطوير وانتشار البكتيريا المقاومة للمضادات الحيويه، والتى تُعتبر حاليًا أزمة عالمية للصحة العامة تهدد قدرتا على علاج الأمراض المعدية الشائعة.

الهدف من البحث: التعرف على أنماط استخدام ووصف المضادات الحيويه من قبل الأطباء فى المستشفى التخصصى – جامعة عين شمس وذلك للمرضى الخاضعين للرعايه بالمستشفى بسبب الإصابه بعدوي بكتيريه و توصيف البكتريا المقاومه للمضادات الحيويه المختلفه .

الحالات وطرق البحث: أجريت هذه الدراسه بالمستشفى التخصصى – جامعة عين شمس بالقاهره. حيث تم دراسة ٣٣٩ بكتريا مقاومه للمضادات الحيويه تم فصلها من مرضى مقيمين بالمستشفى فى الفتره من أغسطس ٢٠١٨ الى يناير ٢٠١٩ كما تم عمل استبيان للأطباء العاملين بالمستشفى فى نفس الفتره لتقييم مدي إدراكهم لمشكلة مقاومة البكتريا المضادات الحيوية والعوامل التى تؤثر بالسلب وتزيد من فرص حدوث مقاومه بكتيريه.

النتائج : هناك عدد من العوامل المرتبطة بمقاومة البكتريا للمضادات الحيويه، ولكن الاستهلاك غير الملائم للمضادات الميكروبية (إما عن طريق وصف مضادات الميكروبات عند عدم الحاجة إليها أو وصف مضاد حيوي واسع المجال عندما يكون هناك أخرا" ضيق المجال كافياً) يعد أحد الأسباب الرئيسيه.

الخلاصه: لابد من مراقبة استخدام المضادات الحيوية كإستراتيجية لتحسين استخدام المضادات الحيوية بين المرضى وأيضاً للسيطرة على مقاومة المضادات الحيوية والتقليل من الضرر الواقع على المريض.

الكلمات الرئيسيه : البكتريا المقاومه للمضادات الحيويه، أنماط وصف المضادات الحيويه.