ISSN: 2520-5234

Available online at http://www.sjomr.org

SCIENTIFIC JOURNAL
OF MEDICAL RESEARCH

Vol. 2, Issue 8, pp 166-171, Autumn 2018

ORIGINAL ARTICLE

Antibiotic Resistant Infection of the Bacterial Group ESKAPE

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ARTICLE INFORMATIONS

Article History:
Submitted: 15 August 2018
Revised version received:
8 September 2018
Accepted: 12 September 2018
Published online: x December 2018

Key words:
ESKAPE
Antibiotic-resistant
HAIs
Mosul
Duhok

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ABSTRACT

Objectives: The antibiotic resistant infection of six bacterial species have been designated as 'Red Alert' human pathogens, which are responsible for 2/3 of all hospital acquired infection, they are grouped under acronym ESKAPE which include: 1- *Enterococcus faecim* or *faecalis*, 2- *Staphylococcus aureus*, 3- *Klebsiella pneumoniae*, 4- *Acinetobacter baumannii*, 5- *Pseudomonas aeruginosa*, 6- *Enterobacter* spp. For the first time as group in Mosul and Duhok / Iraq.

Methods: Three hundred and thirty-two samples from different sources as Urine, Blood, Wounds, Burn, High Vaginal Swab (H.V.S.), Throat infection, Nose infection, Cerebrospinal fluid (C.S.F.) and Sputum were collected from hospital patients in city of Mosul and Duhok in Iraq. These samples were cultured on blood and Macconkey's agar. The bacterial colonies were purified and identified to species level using morphological, Biochemical tests , API and confirmed by Vitek 2 System and antibiotic sensitivity was carried out using Vitek 2 System.

Results: Our results showed that 73 isolates 21.98 % were gave growth only and 34.25 % were gram positive and 65.75 % were gram negative and the most isolated number from burns 50 % and the lowest isolated number from C.S.F. 7.69 %.

Fourty eight species were *Kleb. pneumoniae*(13), *A. baumannii*(12), *Pseudo. aeruginosa*(11) and *E. cloacae*(12) and Twenty five species were *Staph. aureus*(17) and *E. faecalis*(8).

The result also showed the most bacterial species within ESKAPE group were resistant for almost antibiotics used under study.

Conclusion: We were isolated ESKAPE bacterial species from acquired hospital infection and they comprise the majority of antibiotic resistance seen in hospital which diagnosed them by Vitek 2 System.

Citation: Khaled D.W. and Abdullah B.A. "Antibiotic Resistant Infection of the Bacterial Group ESKAPE". Sci. J. Med. Res. 2018, 2 (8): 166-171.

INTRODUCTION

There are six organisms that are today considered to be major threats, not because they cause the most devastating illnesses but because they comprise the majority of antibiotic-resistant infections seen in healthcare settings. The ESKAPE include 6 bacterial species: ***E**nterococcus faecium* or *faecalis*, ***S**taphylococcus aureus*, ***K**lebsiella pneumoniae*, ***A**cinetobacter baumannii*, ***P**seudomonas aeruginosa*, and several species of ***E**nterobacter* spp.[1, 2] .

In 2008, Rice grouped the 'top six bugs' for their wide distribution and their ability to escape the effects of antibacterial drugs under the acronym 'ESKAPE'[3].
This microorganisms responsible for two-thirds of all Hospital Acquired Infections (HAIs)[4]. These pathogens were first identified by the Infectious Diseases Society of America (IDSA) in 2004 [5,6]. *Enterococcus faecium* is a commensal bacterium of the human gastrointestinal tract, reported in hospitals in the 1980s and have since been reported in healthcare settings worldwide[7].
The case of the first oxacillin/methicillin- resistant strains of *Staphylococcus aureus* (MRSA) that emerged only a few years after these agents were commercialized in the 1960s [8,9].
Data from the Centers for Disease Control and Prevention (CDC) show rapidly increasing rates of infection due to Methicillin-Resistant *Staph. aureus* (MRSA), Vancomycin-Resistant *E. faecium* (VRE) and fluoroquinolone-resistant *Pseudo. aeruginosa* [10,11].
Ii was noted that *K. pneumoniae* caused several infection like urinary tract infections, nosocomial pneumonia and intra-abdominal infections. One of the most important of it's virulence is the Capsular antigens, of the 77 types of capsular serotypes of *Kleb. pneumoniae*, serotypes K1 and K2 are the most virulent of humans [12].
A. baumannii is an opportunistic pathogen that occurs frequently among people with immunocompromised, especially those who have been hospitalized for more than 90 days. Where it has the ability to colonize the skin and can be isolated frequently from the respiratory and oropharynx secretions of infected individuals, called "red alert" because it caused a warning among the medical staff, especially because of the broad spectrum of antibiotic resistance [13].
Pseudo. aeruginosa found commonly in most hospitals in the world , including those of Kurdistan region in Iraq, it is considered an opportunistic pathogen that causes infection in immune depressed subjects [14].
E. cloacae is responsible for 65 – 75 % of the total infections caused by Enterobacter bacteria in general, and form 5 – 10 % of the total number of infections caused by gram negative bacteria [15,16].
The bacteria have two different strategies to acquire resistance: first, their ability to acquire a new genetic material (DNA) from another source, and the second the ability to mutate their DNA[17].
In addition, these pathogens have advanced defense mechanisms to avoid the effects of antibiotics including: 1)it's ability to pump antibiotics out of the cell due to it's activation of the efflux pumps; 2)it possesses proteins that encode enzymes that act on the hydrolysis β-lactam antibiotics; 3)it's ability to block the protein channels of the bacterial cell selectively [17].
Antimicrobial resistance genes may be carried on the bacterial chromosome, plasmid, or transposons[18]. The genes encoding the ESBLs are found on plasmids and have a great propensity to spread between bacteria [19].
Hemolysin, protease, hyaluronidase, bacteriocin, lipase, aggregation substances (A.S), biofilm, pili , fimbriae, efflux pump, polysaccharides and capsules are the major virulence factors of ESKAPE[20,21].
Some strain like *Staph. aureus* are able to produce Toxic shock syndrome toxin (TSST-1) and Exfoliative [22].

MATERIALS AND METHODS

Sample collection and identification:

Three hundred and thirty-two samples from different sources as : Urine, Blood, Burn, Wound, HVS, Throat infection, Nose infection, C.S.F and Sputum were collected from hospital patients in the city of Mosul and Duhok for the period from September 2015 to December 2015 and then from the period from April 2017 to September 2017.
All the samples were cultured on the blood agar and MacConkey's agar, then was incubated at a 37°C for 24 hours.
The bacterial colonies were purified and identified according to the shape of the colony, color and size, and then the biochemical tests and API were applied, after this we selected 43 isolates to diagnose them by Vitek 2 System, and the sensitivity test was then performed using the Vitek 2 System.

RESULTS

Three hundred and thirty-two samples were collected from patients, 73 isolates (21.98 %) were positive and 259 were negative, 78 % of them did not grow.
The results showed that 34.25 % gram positive and 65.75 % gram negative, as shown in Table 1.

Table 1: **Number and percentage of positive and negative gram stain isolates under study.**

Type of bacteria	Number of positive isolates	Number of negative isolates	Percentage %
Gram positive	25	-	34.25
Gram negative	48	-	65.75
Sum	**73**	**259**	**100**

Table 2 indicate that the most isolated numbers of bacterial isolate were of burns 50 %, the wounds 40 % and the lowest percentage recorded for the presence of bacterial species according to the source of the samples were from the C.S.F. 7.69 %.

Table 2: **Number and percentage of ESKAPE bacterial species isolate according to the source of isolate.**

Source of samples	Number of Samples			Percentage %
	Total	Positive samples	Negative samples	
Urine	180	25	155	13.88
Blood	3	1	2	33.33
Wounds	50	20	30	40
Burn	20	10	10	50
H.V.S	10	3	7	30
Throat infection	7	1	6	14.28
Nose infection	9	2	7	22.22
C.S.F	13	1	12	7.69
Sputum	40	10	30	25
Sum	**332**	**73**	**259**	**21.98**

Bacterial isolates of ESKAPE include: 48 species were identified from gram negative bacteria which included

Kleb. pneumoniae, *A. baumannii*, *Pseudo. aeruginosa* and *E. cloacae* and 25 species were identified of gram positive bacteria which included *Staph. aureus* and *E. faecalis*, depending on the cultural, microscopic and biochemical characteristics as shown in Table 3, the identification was also confirmed by Vitek 2 System.

Table 3: **Gram stain and Biochemical screening test of ESKAPE bacterial group under study.**

Bacterial name	*E. faecalis*		*Staph. aureus*		*Kleb.pneumoniae*		*A. baumannii*		*Psudo. aeruginosa*		*E. cloacae*	
	N. (%)											
Number	8 (10.96%)		17 (23.28%)		13 (17.81%)		12 (16.44%)		11 (15.07%)		12 (16.44%)	
Name of test	+	-	+	-	+	-	+	-	+	-	+	-
Gram stain	8	0	17	0	0	13	0	12	0	11	0	12
Catalase	0	8	17	0	13	0	12	0	11	0	12	0
Oxidase	0	8	0	17	0	13	0	12	11	0	0	12
Indole	0	8	0	17	0	13	0	12	0	11	0	12
Methyle Red	0	8	17	0	0	13	0	12	0	11	0	12
Voges prauskauer	8	0	17	0	13	0	12	0	0	11	12	0
Citrate	0	8	0	17	13	0	12	0	11	0	12	0
Urease	1	7	8	9	13	0	4	8	8	3	5	7
Gelatinase	3	5	17	0	0	13	12	0	8	3	0	12
Co-agulase	0	8	17	0	0	13	0	12	0	11	0	12
String test	0	8	0	17	13	0	12	0	11	0	12	0
TSI	A\K Gas- H_2S-		A/A Gas- H_2S-		A/A Gas+ H_2S-		K/K Gas- H_2S-		K/K Gas- H_2S-		A/A Gas+ H_2S-	

\+ Positive for test - Negative for test

Forty-three species of ESKAPE pathogen are tested it is sensitivity by Vitek 2 System.

Sensitivity was tested for 3 isolates of *E. faecalis* and 12 isolate of *Staph. aureus* against 11 antibiotics , the results showed that the isolates differed in their sensitivity and resistance to antibiotics , as shown in the Table 4.

The sensitivity of the 8 isolates of *Kleb. pneumoniae* and 7 isolates of *E. cloacae* to 18 antibiotics by Vitek 2 System was studied to determine their sensitivity and resistance to these antibiotics to treat different types of human infections .

The sensitivity to 7 isolate of *A. baumannii* and 6 isolates of *Pseudo. aeruginosa* tested against 16 antibiotics also by Vitek 2 System as shown in Table 5.

Table 4: **Percentage of sensitivity and resistance of gram positive bacteria isolates under study.**

The name and the symbol of the antibiotics	The name of the bacteria					
	Staph. aureus			*E. faecalis*		
	%					
	S	**I**	**R**	**S**	**I**	**R**
Gentamicin (GM8,64)	66.66	16.67	16.67	-	-	100
Erythromycin (E1,8)	8.33	33.34	58.33	-	-	100
Tetracycline (TE0.5,2)	75	-	25	-	-	100
Trimethoprim\ Sulfamethoxazole (SXT6\304,32/608)	83.33	-	16.67	-	-	100
Benzylpenicillin (P0.25,64)	-	-	100	66.67	-	33.33
Ampicillin (AM0.5,32)	-	-	-	66.67	-	33.33
Linezolid (LNZ0.5,2)	-	-	-	100	-	-
Daptomycin (DAP0.5,16)	100	-	-	100	-	-
Teicoplanin (TEC0.5,32)	100	-	-	100	-	-
Vancomicin (VA1,16)	91.67	8.33	-	100	-	-
Ciprofloxacin (CIP1,4)	75	-	25	100	-	-
Oxacillin (Ox0.5,2)	41.67	-	58.33	-	-	-
Clindamycin (CM8,64)	66.67	-	33.33	-	-	-

R: Resistance I: Intermediate S: Sensitive

Table 5: **Percentage of sensitivity and resistance of gram negative bacteria isolates under study.**

The name and the symbol of the antibiotics	The name of the bacteria											
	Kleb. pneumoniae			*A. baumannii*			*Pseudo. aeruginosa*			*E. cloacae*		
	%											
	R	**I**	**S**	**R**	**I**	**S**	**R**	**I**	**S**	**R**	**I**	**S**
Ampicillin ($AM_{4,32}$	100	-	-	85.71	-	14.29	100	-	-	-	-	-
Piperacillin/Tazobactam ($TZP_{2/4,48\8}$)	87.5	-	12.5	71.42	-	14.28	-	-	83.33	42.86	14.29	42.85
Amoxicillin/Clavulanic acid ($AMC_{4,32}$)	75	-	25	-	-	-	-	-	-	100	-	-
Cefazolin ($CZ_{4,64}$)	75	-	12.5	71.42	-	-	83.33	-	-	42.85	-	-
Cefoxitin ($FOX_{8,32}$)	75	-	12.5	-	-	14.28	100	-	-	100	-	-
Cefepime ($FEP_{0.25,32}$)	75	-	12.5	-	-	-	-	16.66	16.66	42.85	-	-
Ertapenem ($ETP_{0.03,2}$)	75	-	25	-	-	-	-	-	-	28.57	-	71.43
Meropenem ($MEM_{0.5,12}$)	75	-	25	71.42	-	28.57	-	-	100	28.57	-	71.43
Gentamicin ($GM_{4,32}$)	50	-	50	71.42	-	28.57	16.67	16.67	66.66	57.14	14.29	28.57
Trimethoprim\ Sulfamethoxazole ($SXT_{1/19,16/304}$)	50	-	50	71.42	-	28.57	100	-	-	71.43	-	28.57
Amikacin ($AN_{8,64}$)	50	-	50	-	-	-	-	-	100	-	-	100
Ciprofloxacin ($CIP_{0.5,4}$)	12.5	12.5	75	71.42	-	28.57	33.33	16.67	50	28.57	14.29	-
Cefixime (CFM)	12.5	-	-	14.28	-	14.28	16.66	-	-	28.57	-	28.57
Nitrofurantion ($FT_{16,64}$)	12.5	-	-	28.57	-	-	-	-	-	-	57.14	-
Cefuroxime ($CXM_{2,32}$)	78.5	-	12.5	85.71	-	14.29	100	-	-	100	-	-
Cefuroxime Axetil Ceftin	78.5	-	12.5	85.71	-	14.29	100	-	-	100	-	-
Ceftazidim ($CAZ_{0.25,32}$)	78.5	-	12.5	71.42	-	28.57	16.67	-	83.33	71.43	-	28.57
Ceftriaxone ($CRO_{0.12,16}$)	78.5	-	12.5	71.42	-	28.57	100	-	-	57.14	14.29	28.57
Tigecycline ($TGC_{0.75,4}$)	-	-	-	-	14.28	28.57	-	-	-	-	-	-
Imipenem ($IPM_{1,12}$)	-	-	-	-	-	14.28	-	-	16.66	-	-	57.14

R: Resistance I: Intermediate S: Sensitive

Discussion

Some isolate did not grow because some patients were under the influence of the antimicrobial agents during the culture period or the samples was not cultured under anaerobic conditions or other types were not required in this study.

The results in Table 2 are agreement with what the researchers found [23,24], This difference may be return to the source of the isolate, the case of the pathogenicity and severity of the infection .

The results in Table 3 showed that most bacterial species were resistant for almost antibiotics, this is expected result due to excessive and indiscriminate use of antibiotics as well as the development of resistance mechanisms that this group possesses against most of the antibiotics used in treatment [25,26] .

In the Table 4 most of bacterial isolates were resistance to most antibiotics and this result is expected because the evolution of the resistance mechanisms by this bacteria against most of the antibiotics used in treatment.

The results of this study are consistent with[27] who explained that the resistance of *E. faecalis* to Gentamicin was 100 % while no resistance to vancomycin or linezolid. Another researchers[28] explained that the resistance ratio of this species was erythromycin 95% and tetracycline 97.5%.

Researcher[29] found that *Staph. aureus* resistant to oxacillin 60% and gentamicin 20%.

Gram positive bacterial intrinsically resistant to low levels of aminoglycosides due to inefficient active transport across the cytoplasmic membrane[30]. It's high sensitivity to certain antibiotics, such as vancomycin, indicates that these antibiotics act to prevent the formation of the peptidoglycan layer by binding to the peptide primary elements of the cell wall[31].

The resistance of *Kleb. pneumoniae* may arise for several reasons, including the indiscriminate use of antibiotics without relying on the sensitivity test, which increases the chance of adapting the bacteria and their resistance to these antibiotics or the result of genetic changes in the bacterial cell and so on.

The appearing and distribution of *A. baumannii* and *Pseudo. aeruginosa* resistance to most of the available antimicrobial agents has increased around the world due to the development of antibiotics resistance is a major concern, especially after increased frequency of association with health care, it has become necessary to test it's sensitivity to antibiotics before starting treatment.

The finding in Table 5 is line with the researcher's finding [32]. that the resistance of *Kleb. pneumoniae* to the ampicillin is 100%. The resistance of these gram negative bacteria to these antibiotics may be due to some enzymes produced by the bacteria that break down these antibiotics [33].

The differences between these isolates in the resistance of antibiotics is due to the difference in the use of drugs in hospitals as well as the excessive use of them by patients and remains this situation is not controlled at the hospital and community level and this contributes to the emergence of bacterial strains of multi-drug resistance and failure to eliminate bacterial infections, and that their resistance to antibiotics does not mean that they are produced only enzymes, but may be due to the possibility of a change in the target location of the work of antibiotics or change in the permeability barrier [34].

Conclusions

The presence of ESKAPE pathogens is a major problem of it's high resistance to antibiotics, the results of our study supports the selection of appropriate treatment to target these organisms specifically.

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