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Detection of Cefepime Resistance Gram Negative Bacteria among Clinical Isolates from Khartoum State Hospitals during July to September at 2018

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ABSTRACT

Introduction: The Gram negative bacteria is leading cause of Varity of infectious e.g. Urinary Tract Infection, Gastro Intestinal Tract infections, dysentery, wound infections, septicemia, bacteremia, and meningitis. Majors organisms contributed for these infections, are E.coli, Klebsiella spp., Proteus, Salmonella, Shigella, Enterobacter and Citrobacter.

Methods: Across sectional study was conducted in Khartoum state hospitals during the period from July to September 2018. 200 clinical isolates of gram negative were collected and identified base on standard microbiological methods, cefepime susceptibility testing was done for detection of cefepime resistant using disc diffusion method.

Result: 200 clinical isolate samples were involved in this study 80 (40%) were male while 120 (60%) were female, common clinical isolates identified as Escherichia coli 114 (57%), proteus 39 (19.5%) klebsiella 33 (16.5%), and pseudomonas 14 (7%). Cefepime resistant isolates were 53 (26.5%), cefepime resistant bacteria commonly detected were pseudomonas aeruginosa (57.1%) followed by klebsiella pneumonia (36.4%), less common by proteus (23.7%) and rarely we detect E.coli (21%).

Conclusion: This study conducted that there is more gram negative bacteria resist cefepime, Pseudomonas aeruginosa were found the most commonly isolate cefepime resistant, correlation of age group the isolates were significant in elderly patient show more resistant than young, there is no significant or correlation of gender cefepime resistant isolate.

Keywords: Cefepime resistant; Gram negative bacteria; Antimicrobial resistant; Sudan

INTRODUCTION

The family Enterobacteriaceae is the largest, most heterogenous collection of medically important Gram's Negative rods. Fifty genera and hundreds of species and imtsubspecies have been described. These genera have been classified based on biochemical properties, antigenic structure, DNA-DNA hybridization, and 16S rRNA sequencing. Despite the complexity of this family, most human infections are caused by relatively few species. Gram negative bacteria are ubiquitous organisms, found worldwide in soil, water, and vegetation and are part of the normal intestinal flora of most animals, including humans. These bacteria cause a variety of human diseases, including one third of all bacteremias, more than 70% of urinary tract infections, and many gastro intestinal tract infections. Some organisms (examples Salmonella serotype Typhi, Shigella species, Yersinia eterocolitica) are always associated with human dis-

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ease, whereas others (e.g., Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis) are members of the normal commensal flora that can cause opportunistic infections. A third group of Enterobacteriaceae exists those normally commensal organisms that become pathogenic when they acquire virulence genes present on plasmids, bacteriophages, or pathogenicety islands [1]

Pathogenesis

Including urinary tract infections, pneumonia, upper respiratory tract infections otitis media otitis externa bacteremia, and sepsis,. They acquire antibiotic resistance. They can invade the debilitated patients when Foley catheters are in the urethra or when a patient aspirates vomits that has been colonized by the enterics. Because of this hospital acquisition, you will often hear them described as the hospital-acquired gram-negatives or nosocomial gram negatives, Examples Escherichia coli, Klebsiella pneumonia Proteus mirabilis, Enterobacter, Serratia, and Pseudomonas aeruginosa [2].

Antimicrobial and resistant

Antibiotic resistance is a growing problem that poses a serious threat to the treatment of many severe illnes, the development of antibiotic resistance there are three key genetic mechanisms by which antibiotic resistance develops: Plasmid-mediated resistance. This occurs when plasmids (portions of genetic information separate from the organism's chromosomal DNA) coding for antibiotic resistance mutations are passed between bacteria Plasmids can be transferred between bacteria by pili, Single or multiple chromosomal mutations Chromosomal mutations (often by chance) can give rise to resistance to antibiotics, Jumping genes or transposons Jumping genes are so named as they can be transposed to different locations in the genome These genes are able to integrate themselves into chromosomal DNA or onto plasmids and are then spread among a species, or even cross species.

Mechanisms of antibiotic resistance: On a molecular level, there are three key mechanisms by which microbes can impair the function of antibiotics and therefore demonstrate resistance:

• **Changing the target site:** The specific area that an antibiotic will target may be altered, often meaning that the antibiotic is less likely to interact with it.

• **Limiting access to the target site:** Access to the specific site where the antibiotic exerts its influence may be limited. This can occur either by allowing less antibiotic to pass through the cell wall or by causing more to leave once it is inside.

• **Antibiotic inactivation:** The organism may start to produce new enzymes that prevent the antibiotic from working (e.g. b-lactamases inactivate the b-lactam ring). [3]

Mechanisms of action: Antimicrobial agents are classified by their specific modes of action against bacterial cells. the modes of action of antimicrobial agents against Gram-positive and an Gram-negative bacteria are very similar and can be divided into five categories: Inhibition of cell wall synthesis, inhibition of protein synthesis, inhibition of nucleic acid synthesis, inhibition of folate synthesis, disruption of the cytoplasmic membrane , Inhibition of cell wall synthesis Agents that interfere with cell wall synthesis block peptidogly can synthesis or cross-linking, they are active against growing bacteria and are bactericidal. Gram-negative bacteria β- lactam antimicrobials enter the cell through porin channels in the outer membrane and bind to Penicillin- Binding Proteins (PBPs) on the surface of the cytoplasmic membrane, This blocks their function, causing weakened or defective cell walls, and leads to cell lyses and death. Gram-positive bacteria lack an outer membrane, so β- lactam antimicrobials diffuse directly through the cell wall and bind to PBPs, which results in weakened cell walls and cell lyses [4]

Cephalosporins

Cephalosporins are closely related to penicillins. They are all active against Gram-positive organisms and later compounds have activity against Gram-negative bacteria including Pseudomonas [5]. The cephalosporins are also β-lactam antibiotics and, like penicillin, are produced by moulds. Also like penicillins, cephalosporins interfere with cell wall synthesis and are bactericidal. The cephalosporins are classified as first, second, third, fourth, and fifth generation cephalosporins, The first-generation agents are active primarily against Gram-positive bacteria, Second-generation Cephalosporins have increased activity against Gram negative bacteria, and third-generation cephalosporins have even greater activity against Gram negatives (including Pseudomonas aeruginosa), cefepime is an example of a fourth-generation cephalosporin with activity against both Gram positives and Gram negatives, including P. aeruginosa). Ceftaroline is a fifth-generation cephalosporin that has expanded activity against aerobic Gram-positive cocci, including Methicillin-Resistant Staphylococcus Aureus (MRSA) and Methicillin-Resistant Staphylococcus Epidermidis (MRSE). Its activity against aerobic Gram-negative bacteria mimics that of the third-generation cephalosporins [6]. Cephalosporins have a mechanism of action similar to that of penicillin. They also active against both Gram-positive and Gram-negative bacteriaContain a β-lactam ring structure that is inactivated by some β-lactamases. Are frequently used to treat patients who are allergic to penicillin [7].

Cefepime: Fourth-Generation There is only one cefepime and it is the only cephalosporin with a fep in its name, cefepime is effective against Pseudomonas aeruginosa [8]. Fourth generation (Cefepime) Spectrum similar to that of third generation compounds, but highly resistant to b-lactamases, hence active against many bacteria resistant to the earlier drugs. P. aeruginosa is also inhibited by cefepime [9].This study aimed to detect Cefepime resistance gram negative bacteria among clinical isolate from Khartoum state hospitals during July to September at 2017.

MATERIALS AND METHODS

Across sectional study was conducted at Khartoum hospitals during the period from July to September 2018, 200 clinical isolates of Gram negative bacteria were collected and identified base on standard microbiological methods, cefepime susceptibility testing was done for detection of cefepime resistant by using disc diffusion method.

Kirby-Bauer technique is an agar diffusion test that provides useful data on antimicrobial susceptibility. In this test, the surface of a plate of special medium was spread with the test bacterium, and small discs containing a premeasured amount

of antimicrobial are dispensed onto the bacterial lawn. After incubation, the zone of inhibition surrounding the discs is measured and compared with a standard for each drug the profile of antimicrobial sensitivity, or antibiogram, provides data for drug selection [10].

Procedure for modified kirby bauer method: In Solid medium with patient's isolate swabbed on the entire plate surface, Multiple paper disks, each with a single dried drug placed on plate, Hydration and diffusion of drug sets up a concentration gradient during incubation and growth of the bacteria, The diameter of the zones of inhibition must be measured to determine significance [11].

RESULTS

A total number of 200 clinical isolates of samples were collected from Khartoum hospitals of which 120 (60%) were from female, 80 (40%) were from male **(Table 1)**.

Table 1: Distribution of cefepime resistant isolated among gender in study population.

Gender	Study population		Cefepime resistant	
	%	N	%	N
Male	40	80	39.6	21
Female	60	120	60.4	32
Total	100	200	100	53

79 (39.5%) bacterial isolated were detected in age group (61-80) less common isolated 26 (13%) were detected in age group (41-60). Most common isolated bacteria were *E.coli* 114 (57%), followed by proteus species 38 (19%) then Klebsiella pnumoniae 33 (16.5%), the least isolates were Pseudomonas aeruginosa 14 (7%). Pseudomonas aeruginosa isolates were the most common cefepime resistant organism account for (57.1%), less common were Klebsiella pneumonia (36.4%), Proteus mirabilis (23.7%), the least were *E.coli* (21%) **(Table 2)**.

Table 2: Distribution of bacterial isolation, cefepime resistant Isolated in study population

	Study population		Cefepime resistant	
Isolated organism	**No**	**%**	**No**	**%**
E.coli	114	57	24	21
Klebsiella pneumonia	33	16.5	12	36.4
Proteus spp	39	19.5	9	23.7
Pseudomonas aeruginosa	14	7	8	57.1

E.coli most common isolated from urine sample (60.5%), while Pseudomonas aeruginosa most common isolated from wound swab (47.1) and ear swab (66.7) **(Table 3)**.

Table 3: Distribution of isolates among clinical samples in study population.

	Urine		Wound swab		Ear swab	
Isolated organism	No	%	No	%	No	%
E.coli	109	60.5	5	29.4	0	0
Klebsiella pneumonia	28	15.6	4	23.5	1	33.3
Proteus spp	39	21.7	0	0	0	0
Pseudomonas aeruginosa	4	2.2	8	47.1	2	66.7
Total	180	100	17	100	3	100

Most common bacteria resist cefepime in urine samples *E.coli* (91.7%), while the most common bacteria resist cefepime in wound swab Pseudomonas aeruginosa (50%) and also in ear swab (37.5%).

DISCUSSION

This study agree with study to investigate cefepime resistance in Pennsylvania they found that Among the 2,529 isolates, 213 (8.4%) exhibited cefepime resistance and 339 (13.4%) exhibited multidrug resistance [12].

This study agree with study to investigate resistance in enterobacteria in Japan ,they found that Among the isolates, 68 (47.9%) were Gram-negative organisms, of which *E.coli* (18.3%), P. aeruginosa (14.8%), and K. pneumoniae (9.2%) accounted for the majority it is same to be [13].

This result was similar to the current research partially agree with study to investigate cefepime-resistant strains and synergy or partial synergy interactions in USA , Among the cefepime resistant strains, synergy or partial synergy interactions were observed in 47.2% of Pseudomonas aeruginosa and 84.2% of Acinetobacter spp [14].

In aim to investigate Efficacy of Cefepime in-the-Treatment they found that cefepime was successfully used in the management of cases of chronic infection that had responded poorly to repeated therapy with imipenem, aminoglycosides, or ciprofloxacin. Eradication of Enterobacter species organisms occurred at 15 (88.2%) of the 17 sites of infection. No emergence of resistance to cefepime was noted in that research result strongly disagree with this research result [15].

This study disagree with the research done to investigate The use of Cefepime for Treating-AmpC-Lactamase they found that of 399 patients meeting eligibility criteria, 96 (24%) had confirmed infections with AmpC β-lactamase–producing organisms. Propensity score matching of patients infected with AmpC β-lactamase–positive organisms treated with cefepime [16].

This study disagree with Cefepime treatment (dosage, 2.0 g intravenously twice daily for 4 to 28 days) was successful in 36 (90%) of 40 infections of the skin and skin structure or wounds and in 16 (84%) of 19 nosocomial urinary tract infections [17].

To treat 28 patients with signs and symptoms of sepsis, 13 patients were prospectively randomized to receive cefepime, 11 of 13 patients treated with cefepime were clinically cured this study disagree with our study [18].

CONCLUSION

This study conducted that there is more resist cefepime, Pseudomonas aeruginosa were found the most commonly isolate cefepime resistant, correlation of age group the isolates were significant in elderly patient show more resistant than young, there is no significant or correlation of gender cefepime resistant isolate. We recommend that more studies with large

sample size together with advanced technique (PCR) should be done to detect cefepime resistant. Standardization of antimicrobial susceptibility testing protocols should be monitor in microbiology lab, progress to discover new antibiotics more effective, control the misuse of antimicrobial agents.

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