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A SYSTEMATIC REVIEW: THE CURRENT STATUS OF CARBAPENEM RESISTANCE IN IRAQ

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Abstract:
In this systematic review, we present the prevalence rates of the carbapenem resistance and carbapenemase genes of 11 articles reported in different regions of Iraq. The highest rates of carbapenem genes were blaOXA-48 (73.8%) followed by blaNDM-1 (67.27%), in Baghdad, in Waist also blaOXA-48 (57.8%) followed by blaNDM-1 (50%) were the highest rates of carbapenem genes. While bla VIM (58.3%) followed by blaNDM-1,2(50%) were the highest rates of carbapenem genes, in Kurdistan region. In Babylon &Karbala, the prevalence of blaOXA-1 gene was 100% and in Al-Diwaniyah, the highest rate of carbapenem genes was blaGES(83.3%).

Keywords: Gram Negative, Carbapenemase Gene, Carbapenem Resistance, Iraq.

INTRODUCTION

Carbapenem resistance (CR) is a serious health concern in the world, this problem is aggravated in developing countries due to deficient surveillance data, lack of awareness about nosocomial infections and poor hygiene. It happens mainly among Gram –ve bacteria such as *Pseudomonas aeruginosa , Klebsiella pneumonia* and *Acinetobacter baumannii*.[1]

Carbapenems are considered from β-lactam antibiotics which consist of a β-lactam ring and a five-membered ring, resistance to carbapenems may be attributed to three major mechanisms: porin-mediated resistance, efflux pumps and acquisition of carbapenemase genes, the most effective and globally spread carbapenemases are IMP, VIM, KPC, OXA-48 and NDM genotypes.[2]Carbapenem resistance causes a wide spectrum of diseases such as urinary tract infections, pneumonia, bloodstream infections, soft tissue and skin infections.[3]This resistance is spread by many factors such as presence of mobile genetic elements, poor infection control practices and misuse of antimicrobial drugs.[4]

Hands of healthcare workers and contaminated medical equipment are the major modes of CR bacteria transmission in healthcare settings[5], in addition to toilets and sink drains are considered as CR transmission source and as an environmental reservoir.[6] Longer hospitalization, admission to ICU, mechanical ventilation, tracheostomy ,neurological disorders, renal dysfunction, nasogastric tube use, urinary catheter use, dialysis implementation, specific use of carbapenems and prior use of any antibiotic considered as risk factors for CR infection and colonization.[7]

This review shed light on the prevalence of carbapenem resistance and the carbapenemase genes isolated from patients and hospital environments in different regions of Iraq, based on Iraqi data published over last 5 years from 2017 to July 2022.This review aid us to obtain deep insight on the carbapenem resistance problem in Iraq and mapping the regional distribution of carbapenemase genes, this significantly encouraged by epidemiologists to enhance surveillance strategies which aid in decreasing the spread of gram -ve bacteria

METHODS

Literature Review

Various Journals (PubMed, ScienceDirect & international) Online databases were searched to July 2022. The search key words used were carbapenemase genes ,carbapenem resistance in Iraq to extract the articles published only in English.

Study Selection Criteria

Only research articles reporting the prevalence of carbapenem resistance and Carbapenemase genes (molecular genotyping frequency) isolated from patients and hospital environment in Iraq were used in this systematic review , review articles and case reports were excluded because it has become conventional. [1,8]

Data Extraction

A database was created by listing the studies (References), cities (studies locations), prevalence of CR with detection methods prevalence (%) , name of the studied bacteria, sample collection period and

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molecular techniques used to identify Carbapenemase genes among the isolates. Table 1.

Results

Prevalence of Carbapeneme resistance among clinical isolates in three different studies conducted in Baghdad by Hussein ,2017; AL-Khafaji et al in 2018 and Hamed & Hasoon in 2019 were 52.73% by using MAST DISCS D70C , 14.03% by using PCR and 95.2% by using sensitivity test respectively[9-11] ,the prevalence of carbapenemase genes were blaNDM-1 (67.27%) & blaIMP (9.1%) detected from *Klebsiella pneumonia* , blaIMP (14%) for *Klebsiella pneumoniae* & *Escherichia coli* and blaOXA-48 (73.8%), blaVIM (54.7%) & blaNDM (4.76%) detected from Gram-negative bacteria respectively. [9-11]

While in Kurdistan region , Carbapeneme resistance were 17.14% by using modified Hodge test and 24% by using Rapidec Carba NP Test; reported by Jamal et al 2020 and Baban 2022 in Erbil respectively[12,13], while the prevalence of carbapenemase genes were blaNDM-1,2(50%) for *Klebsiella pneumoniae* and bla VIM (58.3%), blaNDM (41.7%)& blaIMP (33.3%) for *Pseudomonas aeruginosa* respectively[12,13] , CR were 43% by modified Hodge test & double disk synergy test and 33.3% & 31.7% for imipenem and meropenem respectively by using sensitivity test; reported by Hassan et al 2020 and Oumeri &Yassin 2021 in Duhok respectively[14,15], while the prevalence of carbapenemase genes were blaKPC(10.9%), blaNDM-1(0.9%) and blaOXA-48 (12%) for *Klebsiella pneumoniae* and blaVIM (16 %) for *Pseudomonas aeruginosa* respectively. [14,15]

In Babylon &Karbala, the prevalence of Carbapeneme resistance was 11.8% by using sensitivity test ,while blaOXA-1carbapenemase gene was (100%) for *Klebsiella pneumoniae* reported by Abbas 2021 [16] , in Al-Diwaniyah CR was 24% by using sensitivity test; the carbapenemase genes were blaGES (83.3%), blaSME (79.1%), blaKPC (45.8%), and blaOXA-48 (75%) for *Pseudomonas aeruginosa* , reported by Al-Abedi and Al-Mayahi 2019 [17]. While in Wasit , CR were 44.44% by using IMP-EDTA double disk synergy test & modified Hodge test and 76.3% by using PCR ;reported by Hussein et al 2018 and Al-Mayahie et al 2022 respectively[18,19], while the prevalence of carbapenemase genes were blaNDM-1 (50%) for *Pseudomonas aeruginosa* and blaOXA-48 (57.8%), blaPER (47.3%),blaKPC (15.7%), blaVEB and blaVIM (10.5%, for each) detected from uropathogenic E. coli (UPEC) respectively.[18,19]

Table 1. Review the Iraqi studies data on carbapenem resistance.

Studies (References)	Cities (studies locations)	CR prevalence (%)	Carbapenemase genes prevalence (%)	Name of the studied bacteria	sample collection period	Molecular Techniques
HUSSEIN 2017 [9]	Baghdad / Iraq	52.73% by MAST DISCS D70C	*blaNDM*-1 (67.27%) and *blaIMP* (9.1%)	*Klebsiella pneumoniae* from clinical samples	2015	PCR and Sequencing
AL-KHAFAJI et al 2018 [10]	Baghdad / Iraq	14.03% by PCR	*bla*IMP (14%)	*Klebsiella pneumoniae and Escherichia coli from burn and wound samples*	2018	PCR
Hamed and Hasoon 2019 [11]	Baghdad / Iraq	95.2% to imipenem by sensitivity test	*bla*OXA-48 (73.8%), *bla*VIM (54.7%) & *bla*NDM (4.76%).	Gram-negative Bacteria from clinical samples	2018	PCR
Jamal et al 2020 [12]	Erbil & Mosul / Iraq	17.14% by modified Hodge test	*bla*NDM-1,2(50%)	*Klebsiella pneumoniae* from upper respiratory samples	2018	PCR
Baban2022 [13]	Erbil city, Kurdistan\ Iraq	24% by using Rapidec Carba NP Test.	*bla VIM* (58.3%), *blaNDM* (41.7%), and *bla*IMP (33.3%)	*Pseudomonas aeruginosa from clinical samples*	2019	PCR
Hassan etal 2020 [14]	Duhok city, Kurdistan/ Iraq	43% modified Hodge test and	*bla*KPC(10.9%), *bla*NDM-1(0.9%) and *bla*OXA-48 (12%)	*Klebsiella pneumoniae* from clinical samples	2017	PCR

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		double disk synergy test				
OUMERI and YASSIN 2021 [15]	Duhok city, Kurdistan / Iraq	33.3% and 31.7% for imipenem and meropenem respectively by sensitivity test.	*blaVIM* (16 %)	*Pseudomonas aeruginosa from wound and burn samples*	2020	PCR
Abbas 2021 [16]	Babylon &Karbala /Iraq	11.8% by sensitivity test.	*bla*$_{OXA-1}$(100%)	*Klebsiella pneumonia*e clinical and environmental samples	2015	PCR
Al-Abedi & Al-Mayahi 2019 [17]	Al-Diwaniyah/Iraq	24% by sensitivity test	*bla*$_{GES}$ (83.3%), *bla*$_{SME}$ (79.1%), *bla*$_{KPC}$ (45.8%), and *bla*$_{OXA-48}$ (75%)	*Pseudomonas aerugi nosa from clinical samples*	2018	PCR and Sequencing
Hussein et al 2018 [18]	Wasit Province/Iraq	44.44% by IMP-EDTA double disk synergy test & modified Hodge test	*bla*NDM-1 (50%)	*Pseudomonas aeruginosa* from clinical samples	2017	PCR
Al-Mayahie et al 2022 [19]	Wasit Province /Iraq	76.3% by PCR Carbapenemase genes were detected in 76.3% of B2 isolates.	*bla*OXA-48 (57.8%), *bla*PER (47.3%),*bla*KPC (15.7%), *bla*VEB and *bla*VIM (10.5%, for each)	uropathogenic *E. coli* (UPEC) from urine samples	2019	PCR

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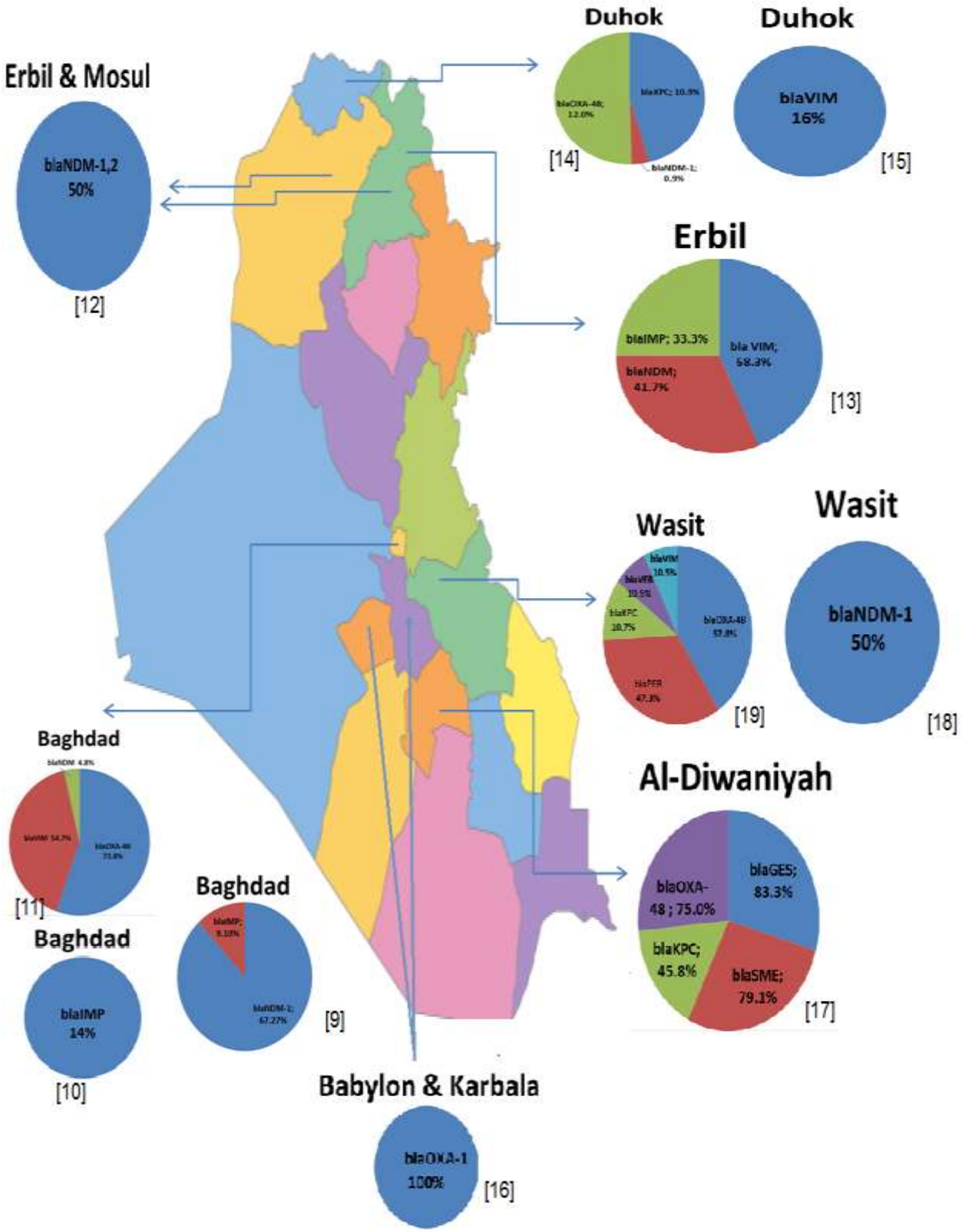

Figure 1 -Molecular distribution of carbapenem resistance genes over Iraq regions.

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DISCUSSION

Carbapenem-resistant gram negative bacteria is a serious health concern and growing threat spreading in Iraq and globally. This dilemma documented in many regions of Iraq and may challenge local health authorities.

The Iraqi studies in different provinces of Iraq reveals different rates of carbapenem resistance bacteria , these differences in the mean prevalence rates among various studies could be related to differences in methods that used in CR bacterium detection ,geographical locations and hygienic practices of the populations.[20-25]

The highest rates of carbapenem genes were blaOXA-48 (73.8%) followed by blaNDM-1 (67.27%), reported among different studies in Baghdad[9,11], in Wasit two different studies also reported blaOXA-48 (57.8%) followed by blaNDM-1 (50%) as the highest rates of carbapenem genes[18,19], the oxacillinase (OXA) enzymes considered from class D carbapenemases, which strongly hydrolyze oxacillin, for which they were named ,the greatest threat of these enzymes is the lack of inhibitors against them [26].

New Delhi MBL (NDM) is an MBL that can give resistance to enteric bacteria, such as *E.coli* and *K. pneumoniae*, making them resistant against β-lactams, including carbapenems but not aztreonam [27]. NDM enzymes are mainly plasmid-encoded, and this facilitate their transmission among different microbial pathogens [28]. While blaVIM (58.3%) followed by blaNDM-1,2(50%) were the highest rates of carbapenem genes , reported among different studies in Kurdistan region[12,13], Verona integron-encoded MBL (VIM) was first isolated in 1999 from a *P. aeruginosa* in Verona/Italy, act on hydrolyzing most β-lactams except for aztreonam [28]. In Babylon &Karbala, the prevalence of blaOXA-1 gene was 100% [16] and in Al-Diwaniyah , the highest rate of carbapenem genes was blaGES(83.3%) [17] , Guiana extended spectrum carbapenemase (GES) is from Class A carbapenemases and several genotypes of the blaGES gene contain a point mutation (G493A), which displays carbapenemase activity. [29] GES carbapenemase considered as plasmid-borne [30].

CONCLUSION

The most prevalent genes responsible in carbapenem resistant strains in Iraq are blaOXA-48 and blaNDM-1. Wide prevalence of these strains submit continuous monitoring and evolving new strategies for antimicrobial resistance control and treatment of infections in addition to that researches must be focus on molecular basis of carbapenem resistance and discovering new drugs.

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