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Effect of Antibiotics on the Pathogenic Bacteria (*K. pneumonia* and *P. aeruginosa*) Isolated Around the Dental Implant Area

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ABSTRACT

In this study, the bacterial isolates (36) were obtained from total 52 samples were taken Twenty K. pneumonia and sixteen P. aeruginosa isolates were found in the dental implant region of individuals of varying ages and sexes who visited a single dental clinic. It was determined what kind of bacteria had been identified by culture, microscopic characteristics and biochemical tests. The resistance and sensitivity of isolates to eight antibiotics (Ceftazidime CAZ, Amikacin Ak, Ciprofloxacin CIP, Chloramphenicol C, Meropenem MEM, Gentamycin GN, Imipenem IMI, Amoxicillin Clavulanate AMC) were studied, with depending on the diameter of the inhibition on Muller-Hinton Agar medium and its comparison with the standard ratios in the Clinical and Laboratory Standards Institute (CLSI, 2018). The results showed that the highest percentage of resistance *K. pneumonia* bacteria was to Ceftazidime and Amoxicillin Clavulanate, which reached (100% ,90%), respectively. It was followed by Gentamycin (77%), Ciprofloxacin (67%) and Amikacin was (40%). While the lowest percentage of resistance to the antibiotics (Imipenem, and Meropenem) were (25%) and Chloramphenicol was (20%). As for bacteria. aeruginosa the highest percentage of resistance was to the antibiotic Ceftazidime (93%), followed by the antibiotic Amikacin by (71%), Chloramphenicol (58%), Gentamycin (47%), Meropenem (42%), then the antibiotic Imipenem (40%) While the lower percentage of resistance to the antibiotic Amoxicillin Clavulanic (39%) and Ciprofloxacin (20%). This review provides a complex effect of antibiotics to understand of mechanism and effects of the antibiotic is the base for the new approaches in clinical treatments by which can effectively fight the groups of the resistant pathogens, in patients who are at high risk specially when undergo dental procedures.

Keywords- Antibiotics, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, dental implant.

I. INTRODUCTION

Infection of the oral cavity have been linked to the oral bacteria specially the gram-negative bacteria outnumbered every other organism (Hoen and Duval 2013). Patients were given antibacterial prophylaxis before dental treatments. Recent years have shown that Gram-negative organisms (particularly Pseudomonas aeruginosa and Klebsiella Pneumonia) are the primary causes of multidrug-resistant oral bacterial infections, which have been recognized as a significant global concern during the last several decades. Pseudomonas aeruginosa is one of the most common opportunistic diseases since it is resistant to many medications and has a low nutritional need to survive (Vessillier et al, 2001). Some bacteria are more dangerous than others because of a combination of characteristics, including those called virulence factors that help the bacteria colonize and promote infection by evading the host's immune defenses and secreting toxins that may lead to either localized or systemic illness (De Nies et al, 2021). K. pneumonia, a member of the family Enterobacteriaceae, has long been recognized as a pathogenic bacterium. It is a kind of gram-negative, rod-shaped bacterium that is encased in a capsule, and it is one of the most important virulence factors found in bacteria, as it helps them

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escape from the host's immune system (Al-Jubouri, 1990). The primary target of interaction of antibiotics - bacterial that induce cell death is concerned on the inhibition of the essential cellular functions. In general, the antibiotics classified depend on the system they affect or the cellular component, they whether inhibit cell growth (bacteriostatic antibiotics) or induce cell death (bactericidal antibiotics) that mainly inhibit cell membrane, protein, DNA, and RNA synthesis (Walsh, 2003). Antibiotics are mandatory in the treatment of infectious diseases, including periodontitis but their side effects strongly determine these antibiotics to be used especially, the bacterial resistance development (Soares *et al.,* 2012). An important promoting factor in increasing antibiotic resistance is the higher disproportionately rates of use of antibiotics among the general population especially children and elderly (Ready *et al.,* 2004). Amikacin is an antimicrobial with activity against more resistant gram-negative bacilli such as *P. aeruginosa* (Sizar, *et.al* 2021). Amikacin interferes with and inhibit the protein synthesis. Amikacin, when combined with penicillin, can have an additive effect on specific microorganisms. The routine clinical use of the Amikacin should be reserved for treating difficult and serious infections because of its synergistic or additive effects when combined with other types of antibiotics (Block, and Blanchard, 2022). As the Amikacin is nephrotoxic the frequent user of should always and regularly check renal function. Amoxicillin/clavulanate in medicine is used heavily, also in dentistry, at present, is prescribed frequently as chemoprophylaxis and recommended for the 'higher risk' group infective endocarditis prior to any specific dental (Limeres *et al.,* 2016). In 1981, in the United Kingdom, a combination of amoxicillin and clavulanic acid was introduced under the brand name Augmentin due to its efficacy against a wide variety of bacteria when taken orally. As was the case at its inception, amoxicillin/clavulanate continues to play a vital role in the treatment of a wide variety of community-acquired infections thanks to the development of novel high-dose regimens and pharmacokinetically improved formulations (Geddes et al. 2007). By combining amoxicillin with clavulanic acid, the antibiotic's usefulness was increased (White et.al., 2004). Ceftazidime with Avibactam: CAZ-efficacy AVI's against Gram-negative bacteria is maintained despite P. aeruginosa's resistance. Resistance to CAZ-AVI is most often caused by changes in genes involved in the production of -lactamase. CAZ-AVI should not be used clinically for bacteria that have developed a resistance to it, although it might be useful in conjunction with other antibacterial drugs. (Wang *et al.,* 2020). Ciprofloxacin is a synthetic broad-spectrum bactericidal type of antibiotic agent and effective in the treatment of a wide range of infections. It is active against both gram-negative bacteria and certain gram-positive bacteria while most of the anaerobic bacteria are not sensitive (Silva, *et al.,* 2016). Gentamicin is dependent highly on the concentration of the antibiotic to result misreading of messenger RNA and protein synthesis in inhibition, so it is considered as powerful antibiotic. (Wei, *et al.,* 2019). More effective outcomes are obtained clinically and therapeutically from using the encapsulated type from Imipenem when compared with using the current administered formula in the hospitals (Shaaban, *et al*., 2017). Meropenem is a carbapenem antibacterial agent that has is more antimicrobial activity against Gram-negative, less active against Gram-positive and anaerobic micro-organisms (Hurst and Lamb, 2000).

II. AIMS OF THE STUDY

The aim of the research is to detect pathological bacteria present in the gums around the area of dental implants and diagnose it by culture, microscopic and biochemical tests and to know the effect of the antibiotics used against bacteria (*K. pneumonia and P. aeruginosa*). And finding any of these antibiotics is more sensitive or resistant to them for use in treating infections that affect areas of dental implants or the entire oral cavity

III. MATERIALS AND WORKING METHODS

Ethical approval

Patient information and samples from locations with dental implants were reviewed and approved by the Duhok Health Directorate's Ethics Committee. (Reference number: 07122022-9-3).

Samples collection

The samples 36 from total 52 were collected from patients attending dental clinic by taking swabs using cotton swab around the dental implant area. The swabs were cultured on Nutrient agar medium. Different types of germs and microbes where present in the area around dental implant, in this study only two types of bacteria were selected (*K. pneumoniae* and *P. aeruginosa*) as they repeated in most samples. Bacterial isolates were cultured on Nutrient agar and Nutrient broth medium to cultivate bacterial isolates and store them safely in the fridge until they are needed. The agricultural media was ready per the supplier's specifications.

Microscopic examination

The microscopic examination of the cells of bacterial isolates was carried out by transferring part of a young colony by a loop and mixing it with a drop of water on the surface of a clean glass slide, then spreading it on the surface of the slide and leaving it to dry and fixing with heat, then the gram stain was applied, and the specimen was studied under a microscope to determine the types of bacteria present, how they were arranged, and what colors they produced when exposed to the dye (Jawetz, et al., 2019).

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Diagnosis

Cultured, microscopic, and biochemical properties of bacterial isolates were used to make diagnoses. Growth in MacConkey and blood agar media was examined to learn more about the culture features. The samples were cultivated using the streaking technique on a blood agar medium. Each petri dish was placed in an incubator set at 37 degrees Celsius. To determine whether bacterial isolates can create a haemolysin, a rich media for bacterial growth, the medium was made according to the manufacturer's instructions and incubated at 37 degrees Celsius for 24 hours (Ferbes et al, 2007). To identify bacteria capable of fermenting lactose sugar without fermentation, the colonies were transferred to a MacConkey agar medium. Colony features like as size, shape, texture, and smell may be used in a laboratory setting to help narrow down a bacterial diagnosis (Jawetz et al., 2019).

Biochemical Test:

The capacity of the isolates to create the catalase enzyme, which decomposes hydrogen peroxide into water and oxygen gas, was tested, as was the ability of bacterial colonies to produce the oxidase enzyme. These tests were among the biochemical analyses performed. The approach included a homolysis test, a test of the bacteria's capacity to generate the enzyme urease, which catalyzes the conversion of urea into ammonia and carbon dioxide gas, and a gelatine liquefaction test (Forbes et al., 2007).

Resistance and Sensitive of bacterial isolates to Antibiotic

Isolate bacteria's susceptibility to eight antibiotics prepared from Bioanalyse Company (Turkey) (Ceftazidime CAZ, Amikacin Ak, Ciprofloxacin CIP, Chloramphenicol C, Meropenem MEM, Gentamycin GN and the Imipenem IMI and Amoxicillin Clavulanate AMC) were tested using Kirby- Baure method according to (Vandepitte *et al*., 2003), where a lube campaign of young bacterial colonies was transferred to a tube containing 5 ml of normal saline. After some adjusting, McCulland's solution 0.5 now has a turbidity of 1.5 x 108 cells/ml. After removing any excess inoculum with a sterile cotton swab by rotating and pressing it against the inner sides of the tube, the bacteria were spread on Agar-Muller Hinton by spreading the bacteria several times while rotating the Petri dish by 45 degrees after each spread. The antibiotic disk was distributed uniformly over the surface of the culture media at the doses listed in (Tab.1), and the dishes were incubated at 37 ° C for 24 hours. Dimensions of the Inhibition Zones around the disks were recorded in millimetres, then the results were compared with standard disks according to whether they are sensitive, moderately sensitive, or resistant to antibiotics, depending on the Clinical and Laboratory Standards Institute (CLSI, 2018).

Table 1: Antibiotic disk used against bacterial isolate

No.	Antibiotic	Code	Antibody Concentration µg/disk
1	Ceftzidime	CAZ	30
2	Amikacin	AK	30
3	Chloramphenicol	C	30
4	Ciprofloxacin	CIP	5
5	Gentamycin	GN	10
6	Meropenem	MEME	10
7	Imipenem	IMI	10
8	Amoxicillin Clavulante	AMC	10

Statistical analysis:

The computer program SPSS version 25 was used to do the statistical analysis. The proportion of K. pneumoniae and P. aeruginosa that are resistant to various antibiotics was compared using a significant difference test. The cutoff for long-term significance was a P value of 0. 05.

IV. RESULTS AND DISCUSSION

Isolation and diagnosis of samples

Twenty K. penumonia and sixteen P. aeruginosa isolates were found in the dental implant region of patients of varying ages and sexes who visited a single dental clinic. Bacteria were cultured, analyzed microscopically, and subjected to biochemical testing to determine their identity. When Klebsiella bacteria were cultured on blood agar medium, they produced colonies of the non-hemolytic blood type, or -hemolytic type (Fig. 1a), while on MacConkey agar medium, the bacteria fermented lactose in the medium, resulting in colonies that looked large, mucoid, and smooth and had a pink color. After being stained with gram, the cells could be seen to take the shape of long, gram-negative bacilli under microscopic inspection. The findings mirrored those of (Goldman and Green, 2009) and (Al-Jader and Ibraheem, 2022).

Isolates of Pseudomonas were identified on nutrient agar plates by their characteristic large, rounded, colonies with flat edges and a grape-like odor; on MacConkey agar plates, the colonies were pale because they had not fermented to the sugar lactose, which is

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consistent with the findings of previous studies and the observations of the authors cited above (Baron et al., 2007; Al-Mimari, 2018). Colonies on blood agar media showed hemolytic blood and so-called -hemolytic mucopoly, as shown in (Fig.1b), which is consistent with the earlier discussion (Qin et al., 2003, Al-Mimari, 2018). Since the bacterial isolates produced gelatinase when cultured in the nutrient medium, the bacterial cells themselves were gelatinized during cultivation (Baron et al, 2007). The findings are consistent with those found by Gram-negative bacilli staining and microscopic inspection (Al-Tikriti, 2021: Procop et al., 2017).

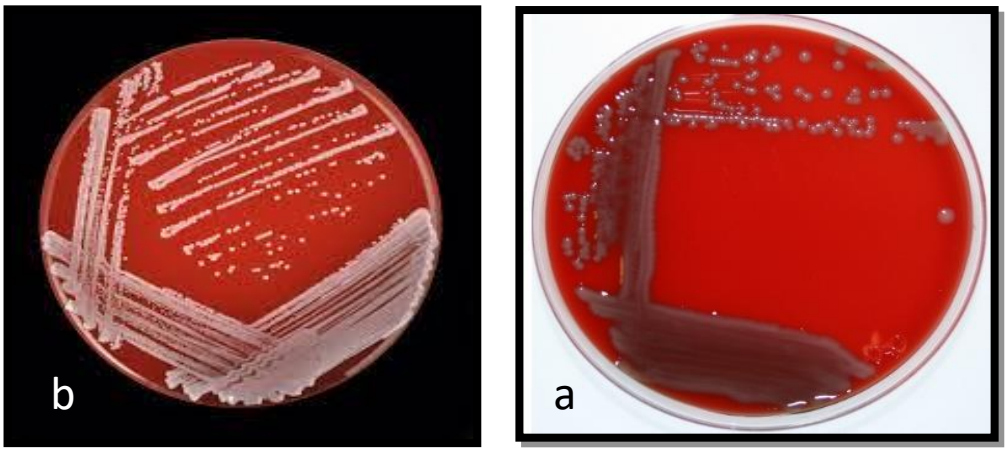

Figure 1: Colonies on agar blood medium a- *K. pneumoniae* bacteria, b- *P. aeruginosa* bacteria

The Biochemical tests

The results of the biochemical tests conducted on all the isolates under study showed that all bacterial species (K. pneumonia, P. aeruginosa) showed a positive result in the catalase test, where oxygen gas bubbles appeared on the test slide as a result of the bacteria's ability to produce the catalase enzyme, which works on the dissolution of hydrogen peroxide into water and oxygen gas; and that P. aeruginosa showed a positive result in the oxidase test, where the violet color of the test appeared within 5-10 K. pneumonia, on the other hand, passed the gelatine dilution test and showed a positive result for the urease production test when the medium's color changed from yellow to pink, indicating the bacterium's ability to produce the urease enzyme. This enzyme catalyzes the decomposition of urea into ammonia and carbon dioxide. These findings corroborate those of (Al-Mimari, 2018; Al-Tikriti, 2021; Al-Jader and Ibraheem, 2022) and show that P. aeruginosa bacteria generate the hydrolysed gelatinase enzyme (Tab. 2).

Table 1: Diagnostic and Biochemical tests results

Bacteria		Biochemical test						
		Gram stain	β-hemolysis	MacConkey agar	Catalase test	Oxidase test	Urease test	Gelatinase test
K. pneumoniae	K1	-	-	+	+	-	+	-
	K2	-	-	+	+	-	+	-
	K3	-	-	+	+	-	+	-
	K4	-	-	+	+	-	+	-
	K5	-	-	+	+	-	+	-
	K6	-	-	+	+	-	+	-
	K7	-	-	+	+	-	+	-
	K8	-	-	+	+	-	+	-

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	K9	-	-	+	+	-	+	-
	K10	-	-	+	+	-	+	-
	K11	-	-	+	+	-	+	-
	K12	-	-	+	+	-	+	-
	K13	-	-	+	+	-	+	-
	K14	-	-	+	+	-	+	-
	K15	-	-	+	+	-	+	-
	K16	-	-	+	+	-	+	-
	K17	-	-	+	+	-	+	-
	K18	-	-	+	+	-	+	-
	K19	-	-	+	+	-	+	-
	K20	-	-	+	+	-	+	-
	P1	-	+	-	+	+	-	+
	P2	-	+	-	+	+	-	+
	P3	-	+	-	+	+	-	+
	P4	-	+	-	+	+	-	+
	P5	-	+	-	+	+	-	+
	P6	-	+	-	+	+	-	+
	P7	-	+	-	+	+	-	+
	P8	-	+	-	+	+	-	+
	P9	-	+	-	+	+	-	+
	P10	-	+	-	+	+	-	+
P. aeruginosa	P11	-	+	-	+	+	-	+
	P12	-	+	-	+	+	-	+
	P13	-	+	-	+	+	-	+
	P14	-	+	-	+	+	-	+
	P15	-	+	-	+	+	-	+
	P16	-	+	-	+	+	-	+

Resistance and Sensitive of bacterial isolates to Antibiotic

The emergence of different mechanisms of bacterial resistance led to an effect on the effectiveness of the drugs used for treatment and the length of hospitalization, which necessitated a sensitivity test for bacterial isolates, which include (8) antibiotics on (*K. pneumonia* and *P. aeruginosa*) species, with depending on the diameter of the inhibition on Muller-Hinton Agar medium and its comparison with the standard ratios in the Clinical and Laboratory Standards Institute (CLSI, 2018). From the (Fig. 2), appendix (1) it can be seen that the percentage of *K. pneumoniae* bacterial resistance for different antibiotics, as the resistance to the antibiotic Ceftazidime was (100%) while the percentage of resistance to the antibiotic Amuxicillin-Clavulanate reached (90%) and this is due to the bacteria's production of β-lactamase enzymes that work to cause hydrolysis of a ring In addition, the genes encoding the enzyme beta-lactamase are present on plasmids, which leads to easy transfer between resistant bacterial strains. overexpression of efflux-pumps and changing the permeability of the outer membrane also affects the increase in resistance. The resistance to the antibody was Gentamycin (77%), while the percentage of resistance to Ciprofloxacin (67%) and Amikacin was (%40). This is

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due to the influx pumps of antibiotics and changing the permeability of the outer membrane, as well as the excessive use of these antibiotics. While the lowest percentage of resistance to the antibiotics (Imipenem, and Meropenem) were (25%) and Chloramphenicol was (20%) which belongs to the phenicol family. This sensitivity is due to the influx of the antibiotic out of the bacterial cells through the flow systems, these results agree with (Hidalgo *et al*., 2018 and Mofolorunsho *et al*., 2021) have obtained in terms of bacteria *K. pneumoniae* sensitivity to the same antibiotics.

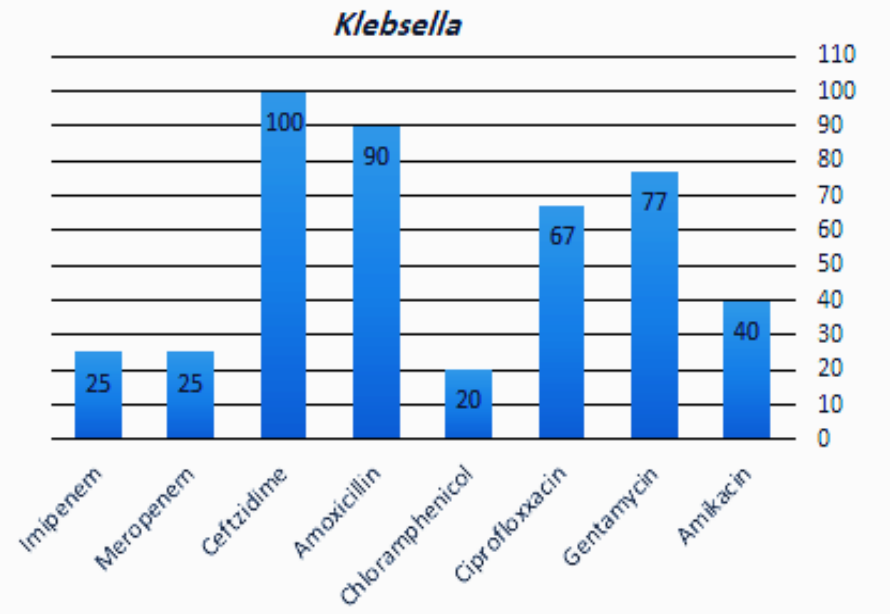

Figure 2: Percentage of resistance of *K. pneumoniae* to different antibiotics, according to the inhibition diameter of Müller-Hinton's medium

The resistant of *P. aeruginosa* bacteria for the antibiotics was different, (Fig. 3). appendix (1), the highest percentage of resistance was to the antibiotic Ceftazidime (93%), followed by the antibiotic Amikacin by (71%), Chloramphenicol (58%), Gentamycin (47%), Meropenem (42%), then the antibiotic Imipenem (40%) and Amoxicillin Clavulanic (39%) While the percentage of resistance to the antibiotic Ciprofloxacin was very low (20%).

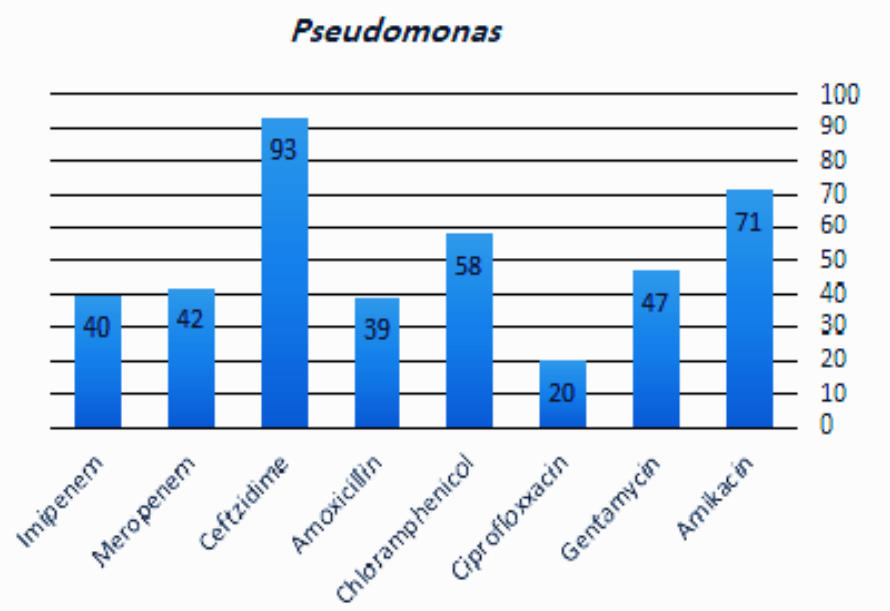

Figure 3: Percentage of resistance of Pseudomonas aeruginosa to different antibiotics, according to the inhibition diameter of Müller-Hinton's medium

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One of the causes of *P. aeruginosa* 's resistance to the antibiotic Ceftazidime, which belongs to the third-generation cephalosporin family, is due to the bacteria' production of Beta- lactamase enzymes that work to cause the hydrolysis of the β- lactamase ring of the antibiotic. β -lactams are present on plasmids, which lead to easy transmission between resistant bacterial strains. The mechanisms of overexpression of efflux-pumps flow systems and changing the permeability of the outer membrane also affect the increase in resistance. Also, the bacteria were resistant to the antibiotic Amikacin, which belongs to the aminoglycoside family of antibiotics causing mutations in the 30S ribosomal subunit, which inhibits the binding of the antibiotic to the subunit and affects the protein synthesis process. Flow regimes or changing the permeability of the outer membrane may play a role in increasing the resistance to the antibiotic Chloramphenicol also, while the resistance of bacteria to the antibiotic Ciprofloxacin, which belongs to the family of Ciprofloxacin Quinolones have several mechanisms of resistance, including mutations in the target site Quinolone Resistance Determining Region (QRDR), and to the transfer of resistance genes to the plasmid, as well as to flux regimes and change of outer membrane permeability. The antibiotics Meropenem and Imipenem, which are belong to the family of Carbapenems the resistance mechanism is also due to the efflux-pumps systems that act on the outflow of antibiotics and to a change in the permeability of the outer membrane (Rida *et al*., 2018) these results are in agreement with (Rocha *et al*., 2019) where the researcher used the same antibiotics to test the sensitivity and resistance of *P.aeruginosa* bacteria, and the results showed close proportions. These results were also close to the results of the researcher (Al-Tikriti, 2021) when he used the same antibiotics to find the sensitivity of bacteria to them and other gram-negative bacteria.

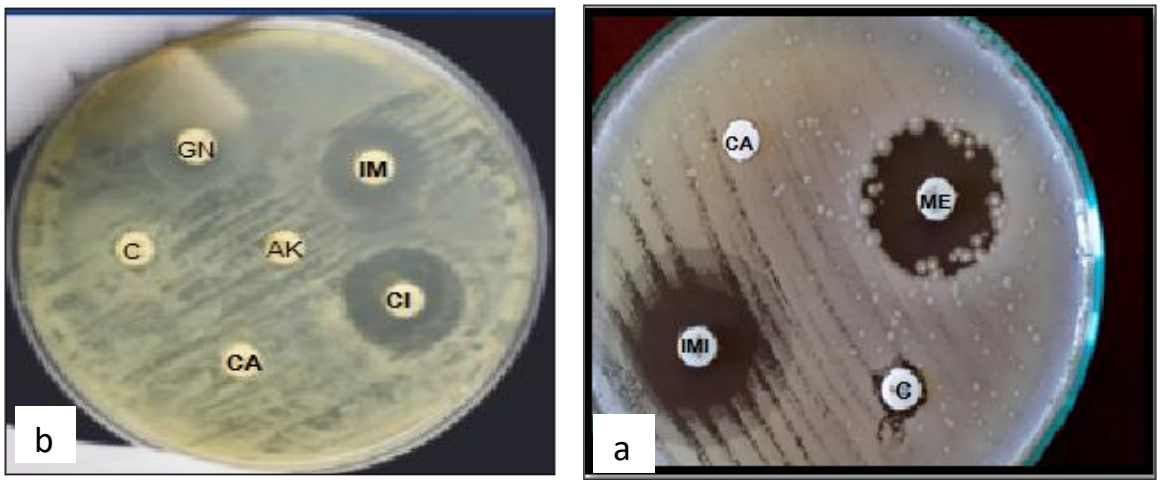

Figure 4: Resistance and Sensitive of bacterial isolates to antibiotic a-*K. pneumonia*. b- *P.*

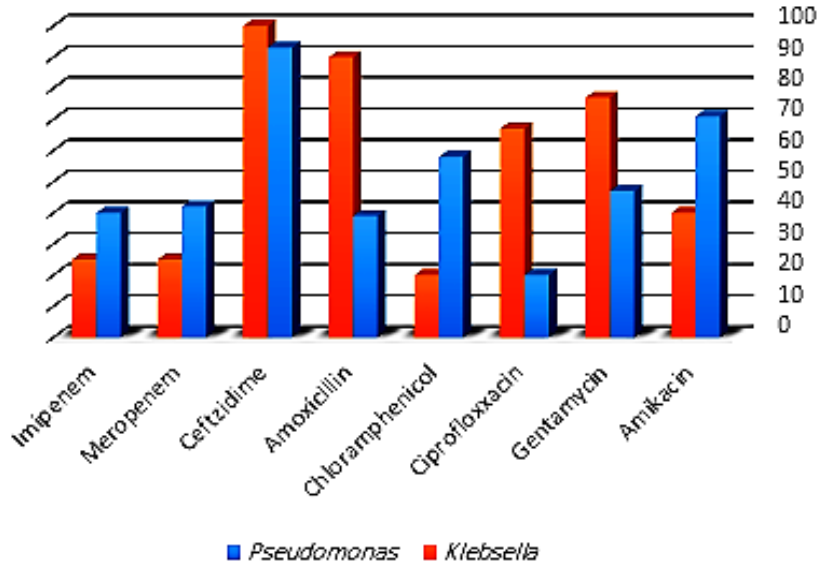

Figure 5: Comparison of bacterial isolates (*K. pneumonia*, P. *aeruginosa* concerning their resistance to antibiotics

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From (Fig. 5) it can be seen that there is a difference between the resistance of *K*. pneumonia bacteria and *P*. aeruginosa bacteria to the same antibiotic, where the percentage of resistance of *K*. pneumonia bacteria to the antibiotic Chloramphenicol was (20%), which is a very small percentage compared to the percentage of resistance of *P*. aeruginosa bacteria for the same antibiotic about (58%), as well as for the antibiotic Amikacin, where the resistance of *K*. pneumonia bacteria was less than that of *P*. aeruginosa bacteria. On the contrary, the resistance of *K*. pneumonia bacteria to the antibiotic Amoxicilin was higher, reaching (90%), while the resistance of *P*. aeruginosa bacteria reached (39%), as well as the case with the antigens (Gentamycin, Ciprofloxacin). This discrepancy between bacteria in their resistance and sensitivity to antibiotics the vitality may be due to the difference in the physiology of bacterial species, where *K*. pneumonia contains a capsule that surrounds the bacterial cell and its absence in *P*. aeruginosa, which is one of the important virulence factors found in bacteria, which helps the bacteria to escape from the immune system of the host organism (Al-Jubouri, 1990). It may be due to the presence or absence of the gene responsible for resistance in a particular type of bacteria without the other type. It may be due to the repeated or wrong use of an antidote against a type of bacteria, or it may be due to the enzymes modifying the antibody. Modification of the target site, or reduced permeability (Castañeda-Garc´ıa, *et al*., 2013).

V. CONCLUSION

The major problem today in the health sector is the Drug-resistant bacterial infections and have worsened as a result of the introduction of a small number of additional medicines in recent years. Patients at high risk, especially those undergoing dental procedures where prophylactic antibiotics are recommended due to the difficulty in treating infections caused by these organisms as a bacterial resistance to different types of antibiotics are discussed in this review.

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Appendix 1: Results of testing resistance and sensitivity of bacterial isolates to antibiotics

Bacteria		Antibiotic							
		Ceftazidime	**Amox Clavula**	**Amikacin,**	**Gentamycin**	**Ciprofloxacin**	**Meropenem**	**Imipenem**	Chloramphenicol
K. pneumonia	K1	R	R	R	S	S	R	R	**R**
	K2	R	R	R	R	S	R	R	**R**
	K3	R	R	R	S	R	S	R	**S**
	K4	R	R	S	S	R	R	S	**S**
	K5	R	R	S	R	R	S	S	**S**
	K6	R	R	R	R	R	S	S	**S**
	K7	R	R	S	R	R	S	S	**S**

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	K8	R	R	R	R	R	S	S	**S**
	K9	R	R	R	R	R	S	R	**R**
	K10	R	R	R	R	R	S	S	**S**
	K11	R	S	S	S	S	S	S	**S**
	K12	R	R	S	R	S	R	S	**S**
	K13	R	R	S	R	S	S	S	**S**
	K14	R	R	S	R	R	S	S	**S**
	K15	R	R	S	R	R	S	S	**S**
	K16	R	R	S	R	R	S	S	**S**
	K17	R	S	S	S	R	S	S	**S**
	K18	R	R	S	R	S	S	S	**S**
	K19	R	R	R	R	S	R	R	**R**
	K20	R	R	S	R	R	S	S	**S**
	P1	R	R	R	S	S	R	R	**S**
	P2	R	R	R	S	R	R	R	**S**
	P3	R	S	R	R	S	S	S	**R**
	P4	R	S	S	S	S	S	S	**R**
	P5	S	S	S	S	R	R	S	**R**
	P6	R	S	R	R	S	R	R	**R**
	P7	R	S	R	R	S	R	R	**S**
	P8	R	R	S	R	R	S	R	**S**
	P9	R	S	S	S	S	S	S	**S**
P. aeruginosa	P10	R	R	R	R	S	S	S	**S**
	P11	R	S	R	S	S	S	S	**R**
	P12	R	S	S	S	S	R	R	**R**
	P13	R	R	R	S	S	R	S	**S**
	P14	R	R	R	R	S	S	S	**R**
	P15	R	S	R	R	S	S	S	**R**
	P16	R	S	R	R	S	S	S	**R**