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SYSTEMATIC REVIEW: MECHANISMS USED BY KLEBSIELLA PNEUMONIAE AND ENTEROBACTER SPP TO ACQUIRE THEIR ANTIBIOTIC MULTIRESISTANT AND WHAT TREATMENT ALTERNATIVES EXIST

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Abstract: The management of infections of multiresistant bacterial etiology has become one of the biggest public health problems, both in financial costs and in the cost of human lives.[1] Within these infections, those produced by the Enterobacteriaceae family stand out, being representative *Klebsiella pneumoniae* and *Enterobacter spp*, which have a wide variety of mechanisms that give them the possibility of generating resistance to antibiotics;[2] therefore, there is no standardized treatment management that can be used in this type of infections, which have become a very important public health problem. Therefore, it is necessary to establish treatment alternatives that demonstrate greater efficacy. The purpose of this work then was to describe the mechanisms used by *Klebsiella pneumoniae* and Enterobacter spp. To acquire antibiotic multiresistant and what treatment alternatives exist for these cases.

INTRODUCTION

The development of antibiotics from the beginning has allowed the correct treatment of different infections caused by bacteria that affect the world population. When we look at the past, we find that it was in the 20th century when strong work in the development of antibiotics began, which at that time was not known in this way. One of the first people to work in this field was Paul Ehrlich, a German physician who made great contributions to the world of medicine and was awarded the Nobel Prize for Physiology and Medicine in 1908. One of these great contributions was the concept of "magic bullets" which referred mainly to compounds capable of destroying infectious pathogenic organisms without the need to cause too many side effects, this idea being the basic principle of the function of antibiotics[1]. However, it was Alexander Fleming 1928 who accidentally discovered an antibiotic that saved millions of lives (penicillin), thus ushering in a new era in the development of medicine.

With the emergence of antibiotics such as penicillin, which was introduced into clinical practice in 1941 by Florey and Chain, the door was also opened to the development of resistance by microorganisms. This has been driven mainly by the inappropriate and unscrupulous use of antibiotics, which initially simply represented the presence of resistant strains, today it is one of the biggest public health problems worldwide and organizations such as the WHO have put this problem under the spotlight, since in recent years the number of bacteria that are resistant to antibiotics has increased[2]. The main risk with this problem is the development of multidrug-resistant bacteria that cannot be treated with available antibiotics and, therefore, can lead to great human losses. For this reason, millions of dollars are spent annually to address this problem and promote the development of new antibiotics that can combat multidrug-resistant strains. However, the forecasts are not encouraging; according to official data obtained from the WHO, it was found that at least 700,000 deaths in 2016 were attributed to bacterial multidrug resistance and that by 2050 the figure could reach 10 million deaths if the increase in MDR continues[3].

Additionally, certain types of bacteria such as *Klebsiella pneumoniae* and *Enterobacter spp*. have shown resistance to last-line antibiotics in treatment thanks to different mechanisms. In the case of *Klebsiella pneumoniae*, cases of resistance have been reported against carbapenem antibiotics cataloged as one of the last resources to deal with infections caused by this bacterium[4]. This being so, many of the worldwide efforts are not being implemented.

METHODOLOGY

A literature search in English and Spanish was conducted from February 2, 2021, using PubMed, Google Scholar, SciELO, Medline, and New England Journal of Medicine databases, where the following terms were searched: β-lactamases, *Enterobacter*, *Klebsiella pneumoniae*, resistance, antibiotics, plasmids, genetic mechanism, and treatment. The search was limited to articles published from 2018 to 2022 from which a total population of 160 articles was obtained. Subsequently, the authors independently reviewed titles, abstracts, and conclusions; thus, identifying potentially relevant articles and retaining those containing information related to the mention of intrinsic and extrinsic mechanisms of multidrug resistance of *Klebsiella pneumoniae* and *Enterobacter spp*, description of resistance mechanisms of both *Klebsiella pneumoniae* and *Enterobacter spp*, current treatments and possible therapeutic alternatives in the face of increasing bacterial multidrug resistance, and epidemiological data on multidrug-resistant strains present worldwide. This selection resulted in a significant sample of 50 articles, which were finally compiled in a systematized way. For this purpose, the criteria (serial number, English Name, date, country, authors, abstract, general objective, method, most relevant results, and conclusions) were used to extract the relevant information for each of the specific objectives.

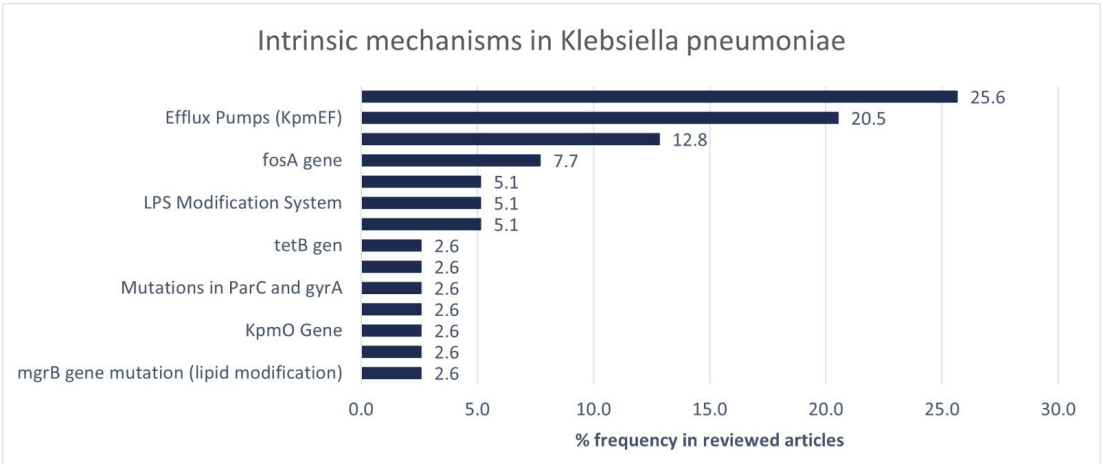
RESULTS

INTRINSIC MECHANISMS OF MULTIDRUG RESISTANCE TO ANTIBIOTICS USED BY *KLEBSIELLA PNEUMONIAE*

Once the review of articles was performed, a great variety of intrinsic mechanisms of multidrug resistance to antibiotics by *Klebsiella Pneumoniae* were found [6, 7,8,9]. Among these mechanisms are several genotypes coding for resistance mechanisms, which were found in several articles. The most prevalent multidrug resistance mechanism (25.6%) was the β-lactamase enzymes, these enzymes give *Klebsiella pneumoniae* special resistance to beta-lactam antibiotics (penicillins, cephalosporins, monobactams, and carbapenems)[10,11,12]. Additionally, it was found that (20.1%) of the articles described efflux pumps (*KpmEF*) as the second most prevalent mechanism.[13,14] Followed by this, is the Alteration of porins (Ompk36) represented with (12.8%); likewise, the presence of the *FosA* gene corresponds (7.6%), while the LPS *RamA* modification system, *oqxA/oqxB* genes represent only (5.13%). Finally, with (2.5%) were found: mgrB gene mutation (Lipid modification), DNA gyrase mutation, *KpmO* gene, *Rpst gene*, *ParC*, and *gyrA* mutations, *BlaSHV-1* gene, *BLAtem-1*, and *tetB* gene. [15,16,17,18]

INTRINSIC MECHANISMS OF MULTIDRUG RESISTANCE TO ANTIBIOTICS USED BY ENTEROBACTER SPP

Very similar results were found concerning *Klebsiella pneumoniae*[19]. For example, the mechanism with the highest prevalence (38.1%) is once again the β-lactamase enzymes, which also provide special resistance to beta-lactam antibiotics (penicillins, cephalosporins, monobactams, and



Graph 1. Intrinsic Mechanism in Klebsiella pneumoniae

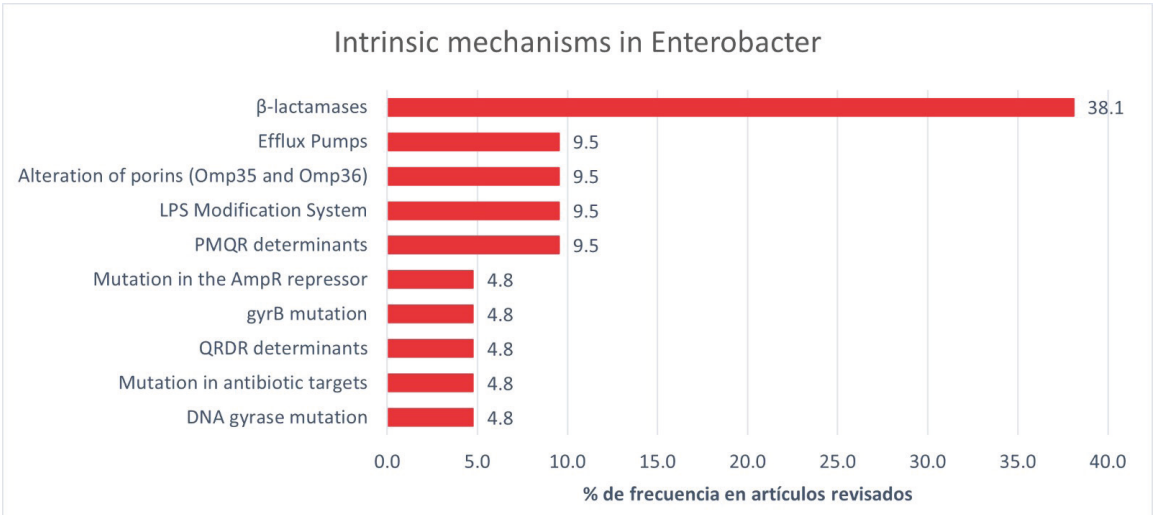
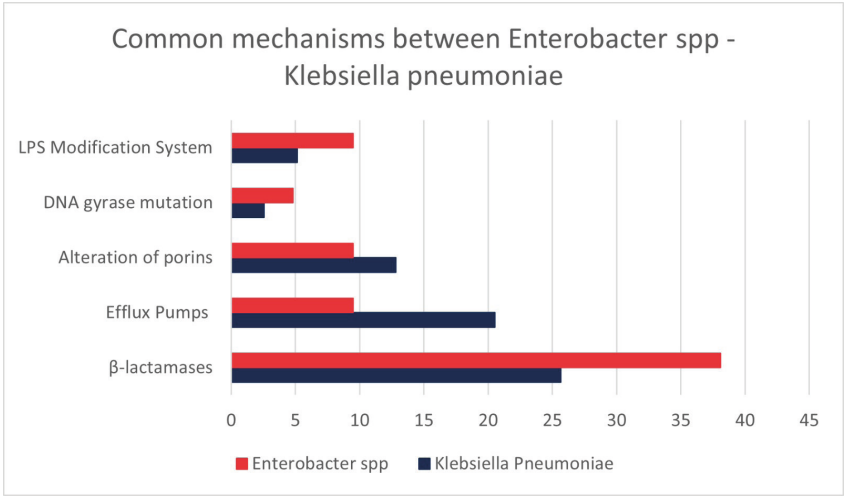
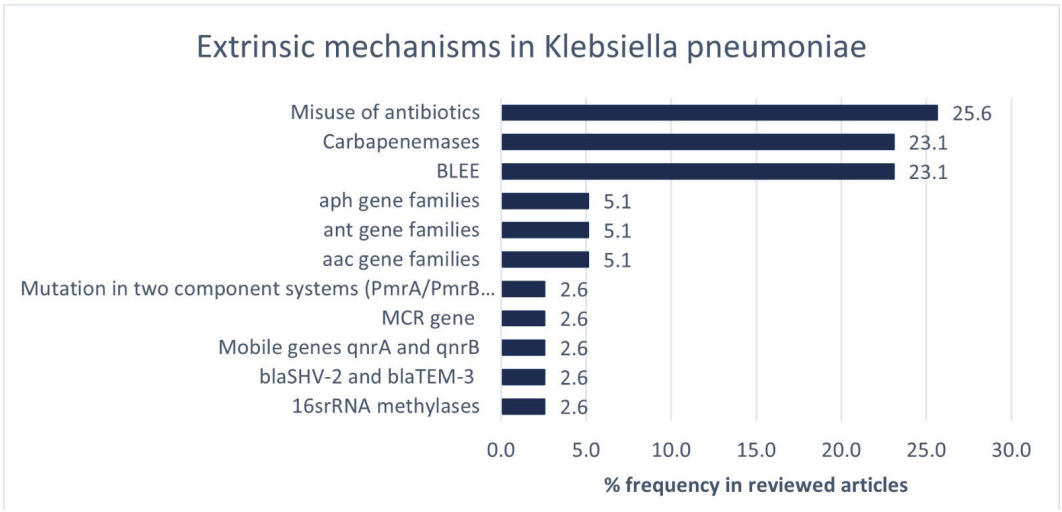


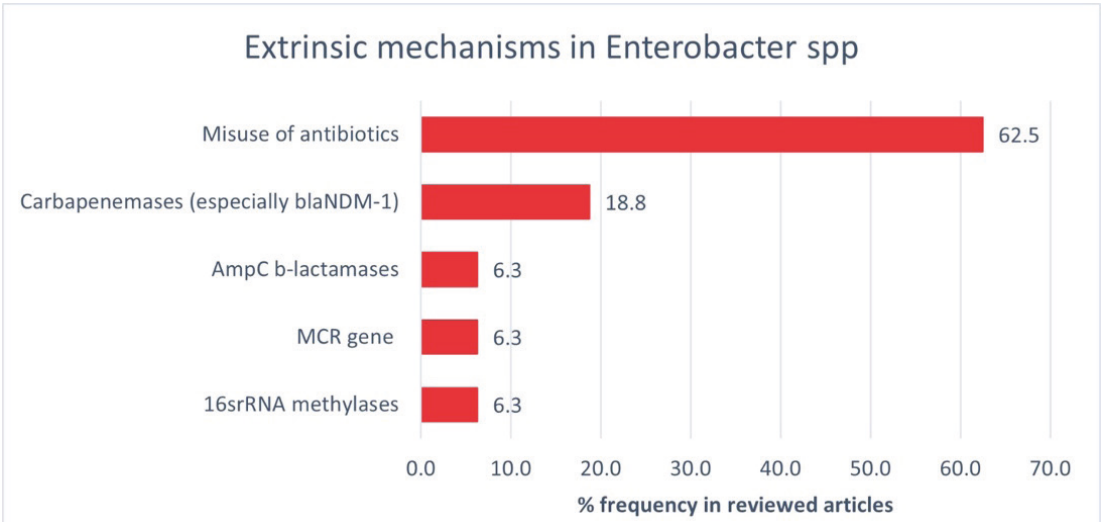
Gráfico 2. Mecanismos intrínsecos en Enterobacter spp.



Graph 3. Common mechanisms between Enterobacter spp and Klebsiella pneumoniae.



***Graph 4**. Extrinsic mechanisms in Klebsiella pneumoniae.*



Graph 5. Extrinsic mechanisms in Enterobacter spp.

carbapenems).[21,22] Likewise, with a prevalence of (9.5%), mechanisms very similar to those described above were found.[23] Among them are: Alteration of porins (Omp35 and Omp36), efflux pumps, LPS modification system, PMQR determinants, and finally with a lower prevalence (4.8%) were found: DNA gyrase mutations, mutation of antibiotic targets, QRDR determinants, *gyrB* mutation and mutation in the A*mpR* repressor[24,25]

It is important to clarify that due to the similarity of intrinsic resistance mechanisms between *Klebsiella pneumoniae* and *Enterobacter spp*. it is necessary to compare them to determine both species' common and predominant mechanisms.[26] In addition, it is necessary to compare them to determine the common and predominant mechanisms in both species.

EXTRINSIC MECHANISMS OF MULTIDRUG RESISTANCE TO ANTIBIOTICS USED BY KLEBSIELLA PNEUMONIAE

This section highlights that the misuse of antibiotics by patients and medical personnel is the most prevalent mechanism causing multidrug resistance in *Klebsiella Pneumoniae* (25.6%).[27,28,29] Likewise, in second place, is the production of extended-spectrum beta-lactamase (ESBL) and carbapenemases (23.1%).[30] As for the genes involved, there is a wide variety of gene families responsible for multidrug resistance:[32,33] *aac* gene family, and gene family, *aph* gene family, which represent (5.1%).[34] Finally, there are 16srRNA methylases, *blaSHV-2* and *blaTEM-3*, mobile genes *qnrA* and *qnrB*, *MCR* gene, and mutation in two-component systems (*PmrA/PmrB* and *PhoP/PhoQ*) with the lowest prevalence (2.6%).[35,36,37]

EXTRINSIC MECHANISMS OF MULTIDRUG RESISTANCE TO ANTIBIOTICS USED BY ENTEROBACTER SPP

Like what has been observed in *Klebsiella pneumoniae*, in *Enterobacter spp*. it was also found that the misuse of antibiotics is the most prevalent mechanism of multidrug resistance (62.5%).[38,39,40] Additionally, Carbapenemases are the second mechanism, but with special attention to *blaNDM-1*, which represents (18.8%).[41] Finally, there are 16srRNA methylases, *MCR* gene, and *AmpC β-lactamases* with (6.3%).[42,43]

POSSIBLE TREATMENTS FOR KLEBSIELLA PNEUMONIAE

A wide variety of treatments for *Klebsiella pneumoniae* were found, among them, the presence of beta-lactamase inhibitors: Ceftazidime-avibactam, Meropenem/vaborbactam, Piperacillin-tazobactam (TZP), Aztreonam-avibactam and Cefepime/zidebactam stand out.[44,45] These, as reviewed were recommended in (20.6%) of the total number of articles discussing the drugs.[46] However, another very frequent therapeutic option was Carbapenems (Meropenem, Imipenem, and Ertapenem) with a recommendation as a treatment option in (13.2%) of the articles. Additionally, Polymyxins and Aminoglycosides were also recommended with a prevalence of (11.8%) and the combination of Aztreonam (ATM) + ceftazidime-avibactam (CAS-AVI), i.e., a Monobactam together with a Cephalosporin and a beta-lactamase inhibitor was recommended in (4.4%) of the articles.[47,48] However, there were many more recommendations with a lower frequency which are mentioned in *Table 1*. However, there was one form of treatment (4.4%) of the articles, which did not include drug therapy. This treatment included bacteriophage-

Possible treatment for Klebsiella pneumoniae			
Family/Group	**Antibiotic**	**Frequency (%)**	**Total per family (%)**
Beta-lactamase inhibitors	Ceftazidime-avibactam	8.8	20.6
	Meropenem/vaborbactam	4.4	
	Piperacillin-tazobactam (TZP)	1.5	
	Aztreonam-avibactam	2.9	
	Cefepime/zidebactam	2.9	
Carbapenem	Meropenem	1.5	13.2
	Imipenem	7.4	
	Ertapenem	1.5	
	Not specified	2.9	
Polymyxin	Polymyxin B	4.4	11.8
	Colistin	7.4	
Aminoglycosides	gentamicin	4.4	11.8
	Amikacin	5.9	
	Not specified	1.5	
Tetracyclines	Tigecycline (In combination with another agent)	5.9	5.9
Monobactame + Cephalosporin + Beta-lactamase inhibitor	Aztreonam (ATM) + ceftazidime-avibactam (CAS-AVI)	4.4	4.4
Treatment with bacteriophages	Pharr, KpNIH-2, vB-KpnM-Teh.1	4.4	4.4
Cephalosporin 4th	Cefepime	2.9	2.9
Phosphonates	Fosfomycin (In combination with another agent)	2.9	2.9
Cephalosporin 2nd	Cefoxitin	1.5	1.5
Chloramphenicol	Chloramphenicol	1.5	1.5
Cephalosporin 6ta	Cefiderocol	1.5	1.5
Rifampicins	Rifampicin	1.5	1.5
Rifampicin + Polymyxin	Rifampicin + Colistin	1.5	1.5
cephalosporin or carbapenem + metronidazole		1.5	1.5
N/A	More studies are needed	13.2	13.2

Table 1. Possible Treatment For Klebsiella Pneumonia.

generating gene therapy. The most frequent bacteriophages were: *Pharr, KpNIH-2*, and *vB-KpnM-Teh-1*.[49] Finally, there was a frequency of (13.2%) where it was mentioned that no treatment was completely optimal and there was a need for further studies.[50] In addition, there was a frequency (13.2%) where it was mentioned that no treatment was completely optimal and there was a need for further studies in this respect.[50]

POSSIBLE TREATMENTS FOR ENTEROBACTER SPP

The treatment found for *Enterobacter spp*. was very similar to that of *Klebsiella pneumoniae*. However, the frequency of antibiotic use was different. [51,52] For this treatment, carbapenems were found to be the first choice with a frequency of (24.4%).[53] In the second place, Betalactamase Inhibitors were found with (12. 2%), contrary to the previous case where beta-lactamase inhibitors predominated.[54] Fourth generation cephalosporins such as Cefepime were mentioned as an important treatment option in (9.8%) of the articles and quinolones in (7.3%). The rest of the drugs had lower frequency and are better specified in *Table 2*. Additionally, treatment with bacteriophages very similar to those mentioned above was also found as an option, but with a lower frequency, i.e. (2.4%). On the other hand, a frequency of (14.6%) was found, which is higher concerning the treatment of *Klebsiella pneumoniae* where it was mentioned that no treatment was completely optimal and there was a need for further studies in this regard. This means that for both species the appropriate treatment is still very uncertain and unspecific.[55.]

DISCUSSION

The increase in bacterial resistance may slow down the progress of medicine. Every day the availability of antibiotics is less and less to fight infections. The detection of resistance mechanisms in the laboratory is not easy, since it depends on their phenotypic expression and this is conditioned by the number of enzymes produced by the bacteria and the presence of other resistance mechanisms and combinations.[1,2,3]

The antimicrobial susceptibility study performed on *E. coli* strains showed high levels of resistance to nalidixic acid and trimethoprim-sulfamethoxazole. This behavior is like those published by Sedighi et al.[3,14,15] These results differ from the data provided by Chiu and Stefaniuk who reported sensitivity values for trimethoprim-sulfamethoxazole of 65.1% and 61.5%, respectively. 6,16 The high sensitivity of *E. coli* strains to nitrofurantoin agrees with national and international publications.[3,7,9,17,18] In the present work, good sensitivity to amikacin was detected. Researchers from China and Iran [6,15] have reported sensitivity percentages of over 75% to this drug.

Analyzing the resistance profile of *K. pneumoniae*, high values of resistance to trimethoprim-sulfamethoxazole were observed. Similar figures were reported by Bartoloni et al.[14,19,20]

The sensitivity of the strains to amikacin in the present work coincides with authors from Bolivia and Venezuela, who published sensitivity figures above 90 %.[14,21] In Cuba, in a national study, resistance values were observed for trimethoprim-sulfamethoxazole (49 %), gentamicin (43 %), and nalidixic acid (38 %).[22.]

Another relevant finding was the high percentages of resistance to the three third-generation cephalosporins. In this regard, recent studies have shown the circulation of uropathogenic strains with high resistance to

Possible treatment for *Enterobacter* spp.			
Family/Group	**Antibiotic**	**Frequency (%)**	**Total per family (%)**
Carbapenem	Imipenem	9,8	24,4
	Meropenem	7,3	
	Ertapenem	2,4	
	Not specified	4,9	
Beta-lactamase inhibitors	Piperacillin-tazobactam (TZP)	4,9	12,2
	Aztreonam-avibactam	2,4	
	Cefepime / zidebactam	2,4	
	ceftazidime-avibactam	2,4	
Cephalosporin 4th	Cefepime	9,8	9,8
Aminoglycosides	Amikacin	7,3	9,8
	Not specified	2,4	
Quinolones		7,3	7,3
Polymyxin	Polymyxin B	2,4	4,9
	Colistin	2,4	
Monobactame + Cephalosporin + Beta-lactamase inhibitor	Aztreonam (ATM) + ceftazidime-avibactam (CAS-AVI)	4,9	4,9
Cephalosporin 6th	Cefiderocol	2,4	2,4
Treatment with bacteriophages	Pharr, KpNIH-2, vB-KpnM-Teh.1	2,4	2,4
Tetracyclines	Tigecycline	2,4	2,4
Phosphonates	Fosfomycin	2,4	2,4
Carbapenem + carbapenem		2,4	2,4
N/A	More studies are needed	14,6	14,6

Table 2. Possible treatment for Enterobacter spp.

ceftriaxone, cefotaxime, and ceftazidime.[3,14,23] In a study conducted by Cuban authors, Quiñones reported a resistance rate of 48-52% for cephalosporins.[22] And in a third-level hospital, Suárez published high percentages of resistance to cephalosporins (47.5 %). [24] However, our results disagree with those published by González, who found in a study carried out in Cuba in isolates of *E. coli*, a resistance of 5.7 % to ceftriaxone and 2.9 % to ceftazidime and in isolates of *K. pneumoniae* the resistance was 14.3 % for ceftriaxone and ceftazidime.[25]

BLEEs are associated with resistance to multiple antibiotics such as aminoglycosides, chloramphenicol, trimethoprim-sulfamethoxazole, and quinolones, which implies that the clinician has few options for the treatment of patients with UTI caused by BLEE-producing strains of enterobacteria.[3,14,18,24]

We consider that the high resistance to nalidixic acid and trimethoprim-sulfamethoxazole in both microorganisms is related to the use of empirically for decades in Cuba for the treatment of uncomplicated UTI in pediatric and adult patients and other infectious diseases. The percentage of isolates resistant to the aforementioned drugs constitutes an important alert for health authorities and shows a notable increase when compared to previous studies in Cuba.[7,9]

The irrational and indiscriminate use of these drugs has undoubtedly led to the appearance of multidrug-resistant isolates. This phenomenon has multiple implications,

the most important of which is the failure in the treatment of the disease by exhausting the therapeutic options, even for the recommended second-line antimicrobials.

The increase in bacterial multidrug resistance is a worldwide phenomenon. The problem of resistance is greater when it involves more than one family of antibiotics; thus, in our work, we observed that multidrug resistance is present in 57.2 % of *E. coli* isolates and 56.4 % of *K. pneumoniae*. The findings of this study coincide with those reported in other studies carried out in Iran, Mongolia, Sierra Leone and Peru, which reported multiresistance percentages between 45.9 % and 93.9 % in *E. coli* and *K. pneumoniae* isolates from urine samples.[15,23-27]

The wide variety of multidrug resistance profiles detected in the present work is also of interest. The drugs comprising most of the patterns are Trimethoprim-sulfamethoxazole, nalidixic acid, gentamicin, and ciprofloxacin. A diversity of antibiotic resistance patterns in uropathogenic *E. coli* and *K. pneumoniae* strains have been reported by international researchers.[2,26-28] The study of antibiotic resistance patterns is a useful tool to guide the empirical treatment of an infection. The results of this work draw attention to the circulation of third-generation cephalosporin-resistant strains in community-acquired urinary tract infections and inform the antibiotics (nitrofurantoin and amikacin) that can be used to combat them empirically in this geographic area.

CONCLUSION

The WHO predicts that there won't be any effective antibiotics available for the treatment of bacterial illnesses by 2050 due to the slow development of new medicines over the past few decades.

Combination therapy is the only method for treating these infections due to the worrisome rise in multidrug-resistant bacteria and the dearth of novel medications for treating them. In standard practice, doctors utilize a variety of medications to treat infections brought on by strains that are resistant to several treatments. Nevertheless, most of the time these combinations are used without understanding their potential benefits or risks, which frequently causes additional selection pressure on the bacteria and worsens the issue of multidrug resistance. Because of its widespread application, in vitro, synergistic testing is required. important in determining the best antibiotic treatments to use and in obtaining positive clinical outcomes. These tests can also help clinicians provide lower and more efficient doses, minimizing side effects from the use of numerous medications and postponing the emergence of antibiotic resistance.

There is a need for programs in the medical curriculum to inform medical students about the gravity of the issue of bacterial multidrug resistance to antibiotics so that, when they enter the workforce, they are aware of the problem's gravity and can take action to help contain it.

REFERENCES

1.Vanegas JM, Jiménez JN. Resistencia Antimicrobiana En El Siglo XXI: ¿hacia Una Era postantibiótica?. Revista Facultad Nacional De Salud Pública, vol. 38, n.º 1, febrero de 2020, pp. 1-6. doi:10.17533/udea.rfnsp.v38n1e337759.

2.Bravo A, Ruiz-Cruz S, Alkorta I, Espinosa M. When Humans Met Superbugs: Strategies to Tackle Bacterial Resistances to Antibiotics. Biomolecular Concepts. 2018;9(1): 216-226.

3.United Nations meeting on antimicrobial resistance. Bull World Health Organ. 2016;94(9):638–9.

4.Organización Panamericana de la Salud. Resistencia Antimicrobiana.https://www.paho.org/arg/dmdocuments/publicaciones/OPSARG_folletoRAM2019Final.pdf

5.Vergé LE, Los-Arcos I, Almirante B. Nuevos antibióticos para el tratamiento de las infecciones por microorganismos multirresistentes. Medicina Clínica Volume 154, Issue 9 2020; Pages 351-357 ISSN 0025-7753. https://doi.org/10.1016/j.medcli.2019.11.002.

6.Hoby JE, Howard-Anderson J, Weiss DS. Hypervirulent *Klebsiella pneumoniae* - clinical and molecular perspectives. J Intern Med. 2020 Mar;287(3):283-300. doi: 10.1111/joim.13007. Epub 2019 Nov 21. PMID: 31677303; PMCID: PMC7057273.

7.Wyres KL, Lam MMC, Holt KE. Population genomics of *Klebsiella pneumoniae*. Nat Rev Microbiol. 2020 Jun;18(6):344-359. doi 10.1038/s41579-019-0315-1. Epub 2020 Feb 13. PMID: 32055025

8.Tamma PD, Doi Y, Bonomo RA, Johnson JK, Simner PJ; Antibacterial Resistance Leadership Group. A Primer on AmpC β-Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. Clin Infect Dis. 2019 Sep 27;69(8):1446-1455. doi: 10.1093/cid/ciz173. PMID: 30838380; PMCID: PMC6763639.

9.Bassetti M, Giacobbe DR, Giamarellou H, Viscoli C, Daikos GL, Dimopoulos G, De Rosa FG, Giamarellos-Bourboulis EJ, Rossolini GM, Righi E, Karaiskos I, Tumbarello M, Nicolau DP, Viale PL, Poulakou G; Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Disease (ESCMID); Hellenic Society of Chemotherapy (HSC) and Società Italiana di Terapia Antinfettiva (SITA). Management of KPC-producing *Klebsiella pneumoniae* infections. Clin Microbiol Infect. 2018 Feb;24(2):133-144. doi: 10.1016/j.cmi.2017.08.030. Epub 2017 Sep 9. PMID: 28893689.

10.Dunn SJ, Connor C, McNally A. The evolution and transmission of multi-drug resistant Escherichia coli and *Klebsiella pneumoniae*: the complexity of clones and plasmids. Curr Opin Microbiol. 2019 Oct;51:51-56. doi: 10.1016/j.mib.2019.06.004. Epub 2019 Jul 17. PMID: 31325664.

11.Qin X, Wu S, Hao M, Zhu J, Ding B, Yang Y, Xu X, Wang M, Yang F, Hu F. The Colonization of Carbapenem-Resistant *Klebsiella pneumoniae*: Epidemiology, Resistance Mechanisms, and Risk Factors in Patients Admitted to Intensive Care Units in China. J Infect Dis. 2020 Mar 16;221(Suppl 2):S206-S214. doi: 10.1093/infdis/jiz622. PMID: 32176790.

12.Aris P, Robatjazi S, Nikkhahi F, Amin Marashi SM. Molecular mechanisms and prevalence of colistin resistance of *Klebsiella pneumoniae* in the Middle East region: A review over the last 5 years. J Glob Antimicrob Resist. 2020 Sep;22:625-630. doi: 10.1016/j.jgar.2020.06.009. Epub 2020 Jun 23. PMID: 32590186.

13.Bernardini A, Cuesta T, Tomás A, Bengoechea JA, Martínez JL, Sánchez MB. The intrinsic resistome of *Klebsiella pneumoniae*. Int J Antimicrob Agents. 2019 Jan;53(1):29-33. doi: 10.1016/j.ijantimicag.2018.09.012. Epub 2018 Sep 17. PMID: 30236960.

14.Alsanie WF. Molecular diversity and profile analysis of virulence-associated genes in some *Klebsiella pneumoniae* isolates. Pract Lab Med. 2020 Jan 9;19:e00152. doi: 10.1016/j.plabm.2020.e00152. PMID: 32055673; PMCID: PMC7005445.

15.Zhang S, Zhang X, Wu Q, Zheng X, Dong G, Fang R, Zhang Y, Cao J, Zhou T. Clinical, microbiological, and molecular epidemiological characteristics of *Klebsiella pneumoniae*-induced pyogenic liver abscess in southeastern China. Antimicrob Resist Infect Control. 2019 Oct 29;8:166. doi: 10.1186/s13756-019-0615-2. PMID: 31673355; PMCID: PMC6819602.

16.Lv L, Wan M, Wang C, Gao X, Yang Q, Partridge SR, Wang Y, Zong Z, Doi Y, Shen J, Jia P, Song Q, Zhang Q, Yang J, Huang X, Wang M, Liu JH. Emergence of a Plasmid-Encoded Resistance-Nodulation-Division Efflux Pump Conferring Resistance to Multiple Drugs, Including Tigecycline, in *Klebsiella pneumoniae*. mBio. 2020 Mar 3;11(2):e02930-19. doi: 10.1128/mBio.02930-19. PMID: 32127452; PMCID: PMC7064769.

17.Xu Q, Sheng Z, Hao M, Jiang J, Ye M, Chen Y, Xu X, Guo Q, Wang M. RamA upregulates multidrug resistance efflux pumps AcrAB and OqxAB in *Klebsiella pneumoniae*. Int J Antimicrob Agents. 2021 Feb;57(2):106251. doi: 10.1016/j.ijantimicag.2020.106251. Epub 2020 Nov 28. PMID: 33259915.

18.Ranjbar R, Fatahian Kelishadrokhi A, Chehelgerdi M. Molecular characterization, serotypes and phenotypic and genotypic evaluation of antibiotic resistance of the *Klebsiella pneumoniae* strains isolated from different types of hospital-acquired infections. Infect Drug Resist. 2019 Mar 20;12:603-611. doi: 10.2147/IDR.S199639. PMID: 31114256; PMCID: PMC6489651.

19.Davin-Regli A, Lavigne JP, Pagès JM. *Enterobacter spp*.: Update on Taxonomy, Clinical Aspects, and Emerging Antimicrobial Resistance. Clin Microbiol Rev. 2019 Jul 17;32(4):e00002-19. doi: 10.1128/CMR.00002-19. PMID: 31315895; PMCID: PMC6750132.

20.Drozdinsky G, Neuberger A, Rakedzon S, Nelgas O, Cohen Y, Rudich N, Mushinsky L, Ben-Zvi H, Paul M, Yahav D. Treatment of Bacteremia Caused by *Enterobacter spp*.: Should the Potential for AmpC Induction Dictate Therapy? A Retrospective Study. Microb Drug Resist. 2021 Mar;27(3):410-414. doi: 10.1089/mdr.2020.0234. Epub 2020 Aug 17. PMID: 32808858.

21.Koren J, Hubenakova Z, Drahovska H, Ozaee E, Markuskova B, Lichvarikova A. Emergence of extended-spectrum β-lactamase (ESBL) and/or carbapenemase producing Enterobacteriaceae (CPE) and their antimicrobial resistance. Bratisl Lek Listy. 2019;120(12):935-940. doi: 10.4149/BLL_2019_157. PMID: 31855054.

22.Alcántar-Curiel MD, Fernández-Vázquez JL, Toledano-Tableros JE, Gayosso-Vázquez C, Jarillo-Quijada MD, López-Álvarez MDR, Giono-Cerezo S, Santos-Preciado JI. Emergence of IncFIA Plasmid-Carrying blaNDM-1 Among *Klebsiella pneumoniae* and *Enterobacter cloacae* Isolates in a Tertiary Referral Hospital in Mexico. Microb Drug Resist. 2019 Jul/Aug;25(6):830-838. doi: 10.1089/mdr.2018.0306. Epub 2019 Mar 5. PMID: 30835632.

23.Nogueira-Miranda Kda S, Palmeiro JK, Conte D, Maia FV, Reason IT, Monteiro CL, Dalla-Costa LM. Detection of extended-spectrum β-lactamase in *Enterobacter spp*.-evaluation of six phenotypic tests. Microb Drug Resist. 2012 Feb;18(1):66-70. doi: 10.1089/mdr.2011.0055. Epub 2011 Nov 1. PMID: 22043805.

24.Alizadeh N, Ahangarzadeh Rezaee M, Samadi Kafil H, Hasani A, Soroush Barhaghi MH, Milani M, Yeganeh Sefidan F, Memar MY, Lalehzadeh A, Ghotaslou R. Evaluation of Resistance Mechanisms in Carbapenem-Resistant Enterobacteriaceae. Infect Drug Resist. 2020 May 12;13:1377-1385. doi: 10.2147/IDR.S244357. PMID: 32494169; PMCID: PMC7229782.

25.Markovska R, Stoeva T, Dimitrova D, Boyanova L, Stankova P, Mihova K, Mitov I. Quinolone resistance mechanisms among third-generation cephalosporin resistant isolates of *Enterobacter spp*. in a Bulgarian university hospital. Infect Drug Resist. 2019 May 28;12:1445-1455. doi: 10.2147/IDR.S204199. PMID: 31213860; PMCID: PMC6549396.

26.Martin RM, Bachman MA. Colonization, Infection, and the Accessory Genome of *Klebsiella pneumoniae*. Front Cell Infect Microbiol. 2018 Jan 22;8:4. doi: 10.3389/fcimb.2018.00004. PMID: 29404282; PMCID: PMC5786545.

27.Wang G, Zhao G, Chao X, Xie L, Wang H. The Characteristic of Virulence, Biofilm and Antibiotic Resistance of *Klebsiella pneumoniae*. Int J Environ Res Public Health. 2020 Aug 28;17(17):6278. doi: 10.3390/ijerph17176278. PMID: 32872324; PMCID: PMC7503635.

28.Hesse S, Malachowa N, Porter AR, Freedman B, Kobayashi SD, Gardner DJ, Scott DP, Adhya S, DeLeo FR. Bacteriophage Treatment Rescues Mice Infected with Multidrug-Resistant *Klebsiella pneumoniae* ST258. mBio. 2021 Feb 23;12(1):e00034-21. doi: 10.1128/mBio.00034-21. PMID: 33622728; PMCID: PMC8545083.

29.Soleimani Sasani M, Eftekhar F. Potential of a Bacteriophage Isolated from Wastewater in Treatment of Lobar Pneumonia Infection Induced by *Klebsiella pneumoniae* in Mice. Curr Microbiol. 2020 Oct;77(10):2650-2655. doi: 10.1007/s00284-020-02041-z. Epub 2020 May 25. PMID: 32451685.

30.Zhang W, Guo Y, Li J, Zhang Y, Yang Y, Dong D, Zhu D, He P, Hu F. In vitro and in vivo bactericidal activity of ceftazidime-avibactam against Carbapenemase-producing *Klebsiella pneumoniae*. Antimicrob Resist Infect Control. 2018 Nov 21;7:142. doi: 10.1186/s13756-018-0435-9. PMID: 30479755; PMCID: PMC6249859.

31.Wyres KL, Holt KE. *Klebsiella pneumoniae* as a key trafficker of drug resistance genes from environmental to clinically important bacteria. Curr Opin Microbiol. 2018 Oct;45:131-139. doi: 10.1016/j.mib.2018.04.004. Epub 2018 May 1. PMID: 29723841.

32.Borsa BA, Demirci M, Gungordu-Dalar Z, Karabiyik G, Aygun G, Kucukbasmaci O. Molecular Mechanisms of Colistin Resistance Among *Klebsiella Pneumoniae* Strains. Clin Lab. 2019 Jul 1;65(7). doi: 10.7754/Clin.Lab.2019.180705. PMID: 31307167.

33.Zhang P, Shi Q, Hu H, Hong B, Wu X, Du X, Akova M, Yu Y. Emergence of ceftazidime/avibactam resistance in carbapenem-resistant *Klebsiella pneumoniae* in China. Clin Microbiol Infect. 2020 Jan;26(1):124.e1-124.e4. doi: 10.1016/j.cmi.2019.08.020. Epub 2019 Sep 5. PMID: 31494252.

34.Marques C, Menezes J, Belas A, Aboim C, Cavaco-Silva P, Trigueiro G, Telo Gama L, Pomba C. *Klebsiella pneumoniae* causing urinary tract infections in companion animals and humans: population structure, antimicrobial resistance and virulence genes. J Antimicrob Chemother. 2019 Mar 1;74(3):594-602. doi: 10.1093/jac/dky499. PMID: 30535393.

35.El Haddad L, Harb CP, Gebara MA, Stibich MA, Chemaly RF. A Systematic and Critical Review of Bacteriophage Therapy Against Multidrug-resistant ESKAPE Organisms in Humans. Clin Infect Dis. 2019 Jun 18;69(1):167-178. doi: 10.1093/cid/ciy947. PMID: 30395179.

36.Candan ED, Aksöz N. Klebsiella pneumoniae: characteristics of carbapenem resistance and virulence factors. Acta Biochim Pol. 2015;62(4):867-74. doi: 10.18388/abp.2015_1148. Epub 2015 Dec 4. PMID: 26637376.

37.Fatima S, Liaqat F, Akbar A, Sahfee M, Samad A, Anwar M, Iqbal S, Khan SA, Sadia H, Makai G, Bahadur A, Naeem W, Khan A. Virulent and multidrug-resistant Klebsiella pneumoniae from clinical samples in Balochistan. Int Wound J. 2021 Aug;18(4):510-518. doi: 10.1111/iwj.13550. Epub 2021 Jan 21. PMID: 33480117; PMCID: PMC8273605.

38.Wengrofsky P, Soleiman A, Benyaminov F, Oleszak F, Salciccioli L, McFarlane SI. *Enterobacter Cloacae* Device Endocarditis: Case Report, Scoping Study, and Guidelines Review. Cardiol Vasc Res (Wilmington). 2019;3(3):10.33425/2639-8486.1050. doi: 10.33425/2639-8486.1050. PMID: 31245792; PMCID: PMC6594712.

39.Meini S, Tascini C, Cei M, Sozio E, Rossolini GM. AmpC β-lactamase-producing Enterobacterales: what a clinician should know. Infection. 2019 Jun;47(3):363-375. doi: 10.1007/s15010-019-01291-9. Epub 2019 Mar 6. PMID: 30840201.

40.Markovska R, Stoeva T, Dimitrova D, Boyanova L, Stankova P, Mihova K, Mitov I. Quinolone resistance mechanisms among third-generation cephalosporin-resistant isolates of *Enterobacter spp*. in a Bulgarian university hospital. Infect Drug Resist. 2019 May 28;12:1445-1455. doi: 10.2147/IDR.S204199. PMID: 31213860; PMCID: PMC6549396.

41.Hong YK, Ko KS. PmrAB and PhoPQ Variants in Colistin-Resistant *Enterobacter spp*. Isolates in Korea. Curr Microbiol. 2019 May;76(5):644-649. doi: 10.1007/s00284-019-01672-1. Epub 2019 Mar 19. PMID: 30891622.

42.Wu W, Wei L, Feng Y, Xie Y, Zong Z. Precise Species Identification by Whole-Genome Sequencing of *Enterobacter* Bloodstream Infection, China. Emerg Infect Dis. 2021 Jan;27(1):161-169. doi: 10.3201/eid2701.190154. PMID: 33350909; PMCID: PMC7774573.

43.Ramirez D, Giron M. Enterobacter Infections. 2021 Jun 30. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 32644722.

44.Shen L, Lian C, Zhu B, Yao Y, Yang Q, Zhou J, Zhou H. Bloodstream Infections due to Carbapenem-Resistant *Klebsiella pneumoniae*: A Single-Center Retrospective Study on Risk Factors and Therapy Options. Microb Drug Resist. 2021 Feb;27(2):227-233. doi: 10.1089/mdr.2019.0455. Epub 2020 Jun 23. PMID: 32584202.

45.Bassetti M, Peghin M. How to manage KPC infections. Ther Adv Infect Dis. 2020 May 14;7:2049936120912049. doi: 10.1177/2049936120912049. PMID: 32489663; PMCID: PMC7238785.

46.Yasmin M, Fouts DE, Jacobs MR, Haydar H, Marshall SH, White R, D'Souza R, Lodise TP, Rhoads DD, Hujer AM, Rojas LJ, Hoyen C, Perez F, Edwards A, Bonomo RA. Monitoring Ceftazidime-Avibactam and Aztreonam Concentrations in the Treatment of a Bloodstream Infection Caused by a Multidrug-Resistant *Enterobacter spp*. Carrying Both *Klebsiella pneumoniae* Carbapenemase-4 and New Delhi Metallo-β-Lactamase-47. Clin Infect Dis. 2020 Aug 14;71(4):1095-1098. doi: 10.1093/cid/ciz1155. PMID: 31802119; PMCID: PMC7428388.

48.Wang Y, Zhong H, Han X, Wang N, Cai Y, Wang H, Yu J, Zhang X, Zhang K. Impact of antibiotic prescription on the resistance of *Klebsiella pneumoniae* at a tertiary hospital in China, 2012-2019. Am J Infect Control. 2021 Jan;49(1):65-69. doi: 10.1016/j.ajic.2020.06.189. Epub 2020 Jun 26. PMID: 32599099.

49.Effah CY, Sun T, Liu S, Wu Y. *Klebsiella pneumoniae*: an increasing threat to public health. Ann Clin Microbiol Antimicrob. 2020 Jan 9;19(1):1. doi: 10.1186/s12941-019-0343-8. PMID: 31918737; PMCID: PMC7050612.

50.Macesic N, Nelson B, Mcconville TH, Giddins MJ, Green DA, Stump S, Gomez-Simmonds A, Annavajhala MK, Uhlemann AC. Emergence of Polymyxin Resistance in Clinical *Klebsiella pneumoniae* Through Diverse Genetic Adaptations: A Genomic, Retrospective Cohort Study. Clin Infect Dis. 2020 May 6;70(10):2084-2091. doi: 10.1093/cid/ciz623. PMID: 31513705; PMCID: PMC7201408.

51.Ramirez MS, Iriarte A, Reyes-Lamothe R, Sherratt DJ, Tolmasky ME. Small Klebsiella pneumoniae Plasmids: Neglected Contributors to Antibiotic Resistance. Front Microbiol. 2019 Sep 20;10:2182. doi: 10.3389/fmicb.2019.02182. PMID: 31616398; PMCID: PMC6764390.

52.Falcone M, Daikos GL, Tiseo G, Bassoulis D, Giordano C, Galfo V, Leonildi A, Tagliaferri E, Barnini S, Sani S, Farcomeni A, Ghiadoni L, Menichetti F. Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase-Producing Enterobacterales. Clin Infect Dis. 2021 Jun 1;72(11):1871-1878. doi: 10.1093/cid/ciaa586. PMID: 32427286.

53.Holsen MR, Wardlow LC, Bazan JA, Fussner LA, Coe KE, Elefritz JL. Clinical outcomes following treatment of Enterobacter species pneumonia with piperacillin/tazobactam compared to cefepime or ertapenem. Int J Antimicrob Agents. 2019 Dec;54(6):824-828. doi: 10.1016/j.ijantimicag.2019.07.008. Epub 2019 Jul 15. PMID: 31319191.

54.Shields RK, Iovleva A, Kline EG, Kawai A, McElheny CL, Doi Y. Clinical Evolution of AmpC-Mediated Ceftazidime-Avibactam and Cefiderocol Resistance in *Enterobacter cloacae* Complex Following Exposure to Cefepime. Clin Infect Dis. 2020 Dec 17;71(10):2713-2716. doi: 10.1093/cid/ciaa355. PMID: 32236408; PMCID: PMC7744991.

55.Brkić S, Božić D, Stojanović N, Vitorović T, Topalov D, Jovanović M, Stepanović M, Ćirković I. Antimicrobial Susceptibility and Molecular Characterization of Carbapenemase-Producing *Enterobacter spp*. Community Isolates in Belgrade, Serbia. Microb Drug Resist. 2020 Apr;26(4):378-384. doi: 10.1089/mdr.2019.0224. Epub 2019 Oct 25. PMID: 31651210.

56.Ghasemi E, Ferdosi-Shahandashti E, Rajabnia M, Sabbagh P, Maali A, Ferdosi-Shahandashti A. Class I integrons among multidrug-resistant *Enterobacter spp*. isolates from hospitalized patients in Babol, North of Iran. Caspian J Intern Med. 2021 Winter;12(1):65-69. doi: 10.22088/cjim.12.1.65. PMID: 33680400; PMCID: PMC7919182.