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COMBATING ANTIMICROBIAL RESISTANCE: NOVEL STRATEGIES AND THERAPEUTIC INTERVENTIONS

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ABSTRACT

The growth of antimicrobial resistance (AMR) has severely hampered the utility of these antibiotics, despite the fact that they have been vital in expanding the life expectancy of humans and improving their health. As a result of antimicrobial resistance, the efficiency of antimicrobials has decreased, which makes it more difficult to treat infections and significantly increases the chance of disease transmission, severe illness, and death. This is the most significant impact due to antimicrobial resistance. Note that antimicrobial resistance may manifest itself in a variety of ways. Due to the fact that a rising number of infections are exhibiting multi-drug resistance (MDR), the treatment landscape is getting significantly more challenging. Traditional therapies, on the other hand, are almost worthless when it comes to combating organisms that are either pan-resistant (PDR) or extensively drug-resistant (XDR). Antibiotics and other antimicrobial medications are losing their efficacy as a result of antimicrobial resistance (AMR), which makes it more difficult, if not impossible, to treat a wide variety of illnesses. Furthermore, the World Health Organization (WHO) has confirmed the existence of this truth. At its 75th general session, which took place in May 2007, the international committee of the World Organization for Animal Health (OIE) unanimously approved the endorsement of Antimicrobial Agents of Veterinary Importance.

Keywords: *Multi-Drug Resistance (MDR), Antimicrobial Agents, Antimicrobial Medications.*

INTRODUCTION

Antimicrobial resistance (AMR) is responsible for significant pharmacoeconomic costs. As an illustration of the financial impact that antimicrobial resistance (AMR) has on the Medicare population in the United States, a study conducted by the Infectious Disease

Society of America (IDSA) discovered that in 2017, infections caused by bacteria that were resistant to various antibiotics resulted in a total of $1.9 billion in healthcare costs, 400,000 hospital days, and 10,000 fatalities among the elderly population. Prior to this, in 2014, Lord Jim O'Neill presided over the United Kingdom Review on Antimicrobial Resistance, which discovered that each year infectious diseases that are resistant to antibiotics claim the lives of 700,000 people. Antimicrobial resistance is one of the most important and complicated health concerns that the world is now facing. It is driven by interconnected dynamics in the fields of human, animal, and environmental health. All of these misappropriations, when paired with a variety of epidemiological settings and a limited pipeline for new antimicrobials, contribute to the propagation of bacteria that are resistant to multiple drugs. This problem is likely going to get much more severe in the near future. Antibiotic resistance is a widespread problem that affects people all around the globe, both in general and in particular. When a single country takes certain actions, such actions may have either a positive or a negative impact on the other nations. In order to limit the formation of organisms that are resistant to antibiotics and, as a result, enhance overall management, it is vital to implement preventive measures and coordinated efforts that are specifically directed. Because of this post, readers have been provided with extensive knowledge on a variety of tactics that have the potential to be used in order to slow down the development and spread of antibiotic resistance around the globe.

CONDUCT IMPACTING THE RESISTANCE TO ANTIBIOTICS

A simple method to discover acts that can worsen AR symptoms is to think about situations that require the use of antibiotics. Although it is not my purpose to present an exhaustive list, this is one way to identify behaviours that might provoke AR symptoms. However, despite the fact that I am just discussing the behaviours of laypeople in this instance, there are a number of national and international entities participating in the administration of augmented reality.

Community usage of antibiotics

A key contributor to the development of AR is the use of antibiotics. The vast majority of antibiotic prescriptions in human medicine are written for patients who are treated in outpatient settings. When compared to the hospital sector in Europe, the community sector uses ten times more antibiotics than the hospital sector does. Because the usage of antibiotics, particularly when they are administered in the appropriate manner, exacerbates AR, the situation is becoming even graver.

It is common for prescribers to make the presumption that patients desire antibiotic prescriptions; nevertheless, patients have the ability to influence their prescriptions by indicating that they are looking forward to receiving antibiotic treatment. When the patient makes a specific request for antibiotics or when the physician has reason to assume that the patient anticipates receiving them, antibiotics are prescriptions that are more often given. Pharmacists in countries where antibiotics are effectively accessible over the counter express anger because patients in these countries often request drugs despite the pharmacists' lack of trust in their ability to provide them. In spite of the fact that these routines may be altered, it

is essential to have an understanding of how intricate they are. Individual characteristics such as socioeconomic class and demography are not the only variables that influence antibiotic consumption; contextual and societal factors also play a role. Consider the case of antibiotics; for reasons that are both cultural and historical, it seems that some patients place a greater amount of faith in the medications than they do in the recommendations made by their doctors and chemists.

In the context of antibiotic use, the socioeconomic position of a population is a significant influence. Existence in precarious situations and living in economically disadvantaged areas are two examples of socioeconomic disadvantages that may explain and influence the use of antibiotics without proper judgement. On the other hand, in the majority of instances, these features are only proxies for other variables, such as the ones that induce infectious diseases that need antibiotics. Patients are eager to resume their normal activities as soon as they begin to feel better, whether it is at their place of employment or at their residence. Because they are unable to pay to see a physician, some individuals make an effort to self-medicate by either getting antibiotics without a prescription or by taking antibiotics that are already available to them. Therefore, in order to limit the amount of antibiotics that are used, it is vital to implement social interventions and welfare programmes, which include workplaces and social support systems. Having this in place is very necessary in order to cultivate an atmosphere in which people are able to engage in antibiotic conduct that is responsible

If nothing is done to address the issue, it is anticipated that by the year 2050, the number of deaths would have increased to 10 million per year, resulting in a loss of economic production of one hundred trillion dollars. 1.27 million of the 4.95 million deaths that have been connected to bacterial antimicrobial resistance are attributable to antimicrobial resistance, according to the first-ever comprehensive assessment of the global burden of antimicrobial resistance, which was based on statistical analysis of the data that was available in 2019 from 204 nations globally. It was projected that the region of sub-Saharan Africa will have the highest number of deaths due by antimicrobial resistance (AMR), while the region of Australasia would have the lowest number.

It was also estimated that methicillin-resistant Staphylococcus aureus (MRSA) was responsible for half a million deaths, while the six pathogens Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa were responsible for between fifty thousand and one hundred thousand deaths.

Misuse and abuse of antibiotics

Misuse and abuse of antibiotics are the primary factors that lead to the development of multidrug resistance in bacteria. Multidrug-resistant bacteria (MDR) are able to develop resistance to antibiotics through horizontal transfer of mobile genetic elements and sequential genetic mutations. This renders the majority of antibiotics ineffective, including those that are considered to be the last line of defense. As a result, there is an increased demand for improved antimicrobial agents. Furthermore, conventional antibiotics have a detrimental

effect on the commensal microbiota of people and eliminate beneficial bacteria without making any distinctions between them. Consequently, this highlights the need of developing novel approaches that make use of several bactericidal processes in order to battle medicine resistance.

Other takes on the fight against Antimicrobial Resistance

Over the course of many decades, a vast range of antimicrobials have been developed and distributed with the intention of accomplishing a single objective: to treat and cure infections of varied degrees of severity. An accidental discovery of the drug in the late 1920s led to the discovery of numerous new antimicrobials, one of which being penicillin, a breakthrough antibiotic. Penicillin was one of several new antimicrobials found. In the past, some diseases, like as AIDS, were very impossible to treat; but, as a result of research, new anti-viral treatments have made a return. Along the same lines, anti-parasitic and antifungal (or anti-mycotic) medications have emerged as crucial weapons in the battle against infection.

OBJECTIVES

1. To the study of combining antimicrobial drugs with alternative treatments that are licensed by the FDA and are just as effective
2. To the study of The identification of the identity of K. pneumoniae and the biochemical characterization of the bacteria isolated from diverse clinical specimens.

METHODOLOGY

Various computational methodologies and tools were used in order to investigate potential lead compounds that have the potential to operate as β lactamase inhibitors, hence revitalizing the bactericidal capabilities of conventional antibiotics. The following provides information on the in-silico programme that is currently being used. The single isolated colony of the bacterial culture was sub-cultured on MacConkey agar (BD), EMB agar (HI Media), Chrome agar (HI Media), and Klebsiella Chromo Select agar (HI Media) in order to verify the viability and purity of the clinical strains. This was done in order to ensure that the patients received the best possible care. This was then followed by biochemical assays for the purpose of identifying and characterizing K. pneumoniae.

DATA ANALYSIS

Evaluation of Indole

Following the cultivation of the test bacterial cultures for a period of one night, four milliliters of tryptophan broth that had been sterilized was collected and injected with the cultures. After an incubation period of twenty-four to twenty-eight hours at 37 degrees Celsius, 0.5 milliliters of Kovac's reagent were applied to the broth culture. The data were interpreted in a manner that was determined by whether or not a ring was present.

Sugar-iron test: three tests

At the same time as the triple sugar iron agar (TSI) slants were being created, a sterile inoculation needle was being used to inoculate them with the bacterial culture that had developed over the course of the previous night. First, the needle was penetrated into the middle of the medium until it reached the bottom, and then it was streaked along the surface of the slant using the needle. During the incubation period, the slants that had caps randomly inserted were kept at 37 degrees Celsius at room temperature for a period of 18 to 24 hours.

Find out whether you have Simmons Citrate (SC).

The Simmons citrate agar slants were made in the test tubes that had been maintained in sterility. In order to spatter the newly generated culture across the slant surface, a sterile needle was used and the process was carried out overnight. At a temperature of 37 degrees Celsius, these slants were incubated for 18 to 24 hours using an aerobic process. It was observed that the hue changed to blue, which indicates the presence of alkalinization.

Table1.1: Specific characteristics of Klebsiella pneumoniae colonies grown on a variety of media

Biochemical Test and Differential Media	Features of the bacteria Klebsiella pneumoniae
MacConkey Agar	Huge encapsulated, mucoid, glossy, dark pink colonies
Agar with Klebsiella Chromo Select	Mucoid colonies and purple-magenta ones
Chromo Agar	Klebsiella spp. strains resistant to carbapenem are characterized by Metallic Blue colonies.
EMB Agar	Big, pink to purple, lactose-fermenting, acid-producing mucoid colonies without a metallic green shine
The TSI Exam	Big, pink to purple, lactose-fermenting, acid-producing mucoid colonies without a metallic green shine
Citrate Test by Simmons	Positive growth and a shift in the medium's color from green to blue
Test of Indole	layer that appears yellow in color and does not generate tryptophanase

For the purpose of conducting future study on the single isolated colonies of all pure cultures of K. pneumoniae, glycerol stocks were generated by storing twenty percent of the glycerol in

Cation-adjusted Muller Hinton broth (CAMHB) in vials. These vials were then stored at a temperature of at least eighty degrees Celsius.

KLEBSIELLA PNEUMONIAE ISOLATED FROM CLINICAL SPECIMENS: IDENTIFICATION AND BIOCHEMICAL CHARACTERISATION

Between the years 2014 and 2019, a total of 14,273 clinical isolates of Enterobacteriaceae were obtained from the five diagnostic labs and centres. There was a total of 14,273 clinical isolates, 3834 of which were identified as Klebsiella pneumoniae. Out of these clinical isolates, 171 were eliminated owing to contamination. For the purpose of the subsequent research, a total of 3663 clinical isolates of K. pneumoniae were taken into consideration.

In order to identify the presence of K. pneumoniae, several types of materials, including blood, urine, sputum, pus, fluids, semen, endotracheal (ET) secretion, bronco-alveolar lavage (BAL), and others, were examined utilising screening techniques. Both the number of distinct specimens and the proportion of those specimens are presented in table 4.1 and figure 4.1, respectively, according to the year. The kind of specimen that was collected the most frequently was urine (1228/33.63%), followed by pus (333/9%) and blood (299/5%) respectively. The number of sputum and ET samples, as well as their percentages, were as follows: 7% (266), 4% (132 & 150) for swabs, 2% (71) for fluids, 1% (28) for semen samples, and different sorts of samples. Out of the entire clinical specimens that were obtained, 9% (346) and an undetermined 16% (530) are being gathered.

Table 1.2 : The quantity of clinical isolates based on collections from 2014 to 2019

Specimen	Number of specimens (Year wise)						Total
	2014	2015	2016	2017	2018	2019	2014-2019
BAL	23	43	47	37	0	0	150
Blood	62	62	52	58	21	44	299
ET	69	76	51	65	2	3	266
Fluid	13	22	17	15	0	4	71
Others (stool etc.)	28	80	150	76	1	11	346
Pus	64	71	97	67	8	26	333
Semen	6	7	5	6	0	4	28
Sputum	40	72	83	65	6	14	280
Swabs	29	31	39	23	0	10	132
Unspecified	62	45	21	32	257	113	530

Urine	225	248	335	219	37	164	1228
Total	621	757	897	663	332	393	3663

*BAL- Bronchoalveolar lavage, ET- End tracheal secretion.

A two-dimensional checkerboard test with the purpose of combating multi-drug resistance has been developed

According to the findings of this research, the two-dimensional checkerboard tests were utilised to investigate sixteen distinct double-drug combinations consisting of meropenem and colistin, together with eight other antimicrobial drugs belonging to seven other classes.

Through the use of meropenem in combination trials, only additive effects were detected, and there was no interaction observed. It can be concluded that there is no synergy between the combinations of MEM + AZT, MEM + CTX, MEM + TET, MEM + SOL, and MEM + AMP (FICI 2), MEM + LEV (1), MEM + NIT, and MEM + TIG (1.4) because the FICI for all of these combinations was more than 0.4.

The combination research of colistin, on the other hand, revealed that it had synergistic action with six out of eight other antimicrobial drugs. There was a twofold reduction in the minimum inhibitory concentration (MIC) of NIT when it was combined with colistin. Additionally, there was a fourfold reduction in the MIC of AZT (8 mg/L to 2 mg/L), CTX (8 mg/L to 2 mg/L), LEV (4 mg/L to 1 mg/L), and TIG (4 mg/L to 1 mg/L), and an eightfold reduction in the submaximal inhibitory concentration (SOL) (>8 mg/L to 1 mg/L). The minimum inhibitory concentration (MIC) of colistin was reduced by a factor of two when using TET (4 mg/L to 2 mg/L), and by a factor of four when using AZT, CTX, LEV, NIT, AMP, TIG, and SOL (4 mg/L to 1 mg/L). With the FIC indexes of 0.4, 0.4, 0.4, 0.38, 0.24, and 0.4 correspondingly, the synergistic effects were seen in the combinations of COL+AZT, COL+CTX, COL+LEV, COL+TIG, COL+SOL, and COL+AMP. These combinations were found to have different combinations. Combinations of COL and TET (FICI 1) and COL and NIT (FICI 0.74) were found to have additive effects compared to other combinations. This study did not uncover any evidence of hostile action.

Table 1.3: Meropenem combination research with 8 antimicrobials utilising 2-Drugs checkerboard tests

S. No.	Antibiotics		Alone MIC (mg/L)	MIC (mg/L) in Combination		FIC		FICI
				Drug A	Drug B	FICA	FICB	FICA+FICB
1	Aztreonam		>8	>8	>16	1	1	2
2	Cefotaxime	Drug A	>8	>8	>16	1	1	2

3	Levofloxacin		>4	2	8	0.4	0.4	1
4	Tetracycline		>8	>8	>16	1	1	2
4	Nitrofurantoin		>16	16	8	1	0.4	1.4
6	Tigecycline		4	4	8	1	0.4	1.4
7	Solithromycin		>8	>8	>16	1	1	2
8	Ampicillin		>8	>8	>16	1	1	2
9	Meropenem	Drug B	>16					

*FIC (fractional inhibitory concentration) estimates the interaction between two or more drugs intended to be used in combination. It is calculated by using the MIC of drug alone as denominator and MIC in combination as numerator. Drug A = Aztreonam, Cefotaxime, Levofloxacin, Tetracycline, Nitrofurantoin, Tigecycline, Solithromycin and Ampicillin, Drug B = Meropenem.

OVERCOMING K. pneumoniae's multidrug resistance (MDR)

The same as in this work, we discovered MDR clinical isolates of K. pneumoniae that were resistant to antimicrobial drugs belonging to more than five different classes. As a result, we investigated the synergistic effects of antimicrobial medications and one unique chemical (MMV674968) in order to treat infections that were caused by MDR isolates.

CONCLUSION

To a greater degree, antimicrobial susceptibility testing is helpful in evaluating the treatments that are provided by healthcare facilities and government programmes for the management of infectious illnesses and for the prevention of these infections. K. pneumoniae frequently affects immunocompromised persons such as newborns, old people, diabetics, alcoholics, or patients with other illnesses such as cancer. It is also responsible for a variety of infections, including sepsis, which is one of the diseases that it causes. We evaluated the data from Enterobacteriaceae over a period of five years (2014-2019), and we found that K. pneumonae was the second most frequent pathogen prevalent in community- and hospital-acquired (nosocomial) infections, behind E. coli. K. pneumoniae is the pathogen that was isolated from the majority of the clinical specimens related to both community and nosocomial infections. This was the case for both types of infections. It was shown that urine was the most common form of clinical specimen examined. Pupil, blood, sputum, stool, semen, endotracheal

secretion, bronchoalveolar lavage, and other clinical specimens were also submitted for examination.

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