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ANTIBIOTIC RESISTANCE ISSUES IN CLINICAL PATHOGENS: A REVIEW

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ABSTRACT: Antibiotic resistance in pathogens is on the increase but in the past few decades this problem raised a deepening concern among scientific community in terms of the clinical management of infectious diseases. In this review, the common gram negative clinically significant pathogenic bacteria who have acquired resistance with passage of time like *Shigella dysenteriae, Sh. Boydii, Sh. Flexneri, Listeria monocytogenes, Acinetobacter baumannii, acinetobacter, A. baumannii, Morganella morganii, Enterobacteriaceae, Citrobacter freundii, Citrobacter braakii*, or *Citrobacter amalonaticus*, *P. stuartii*, *Providencia rettgeri*, *P. alcalifaciens, P. rustigianii*, *E. coli, Salmonella. paratyphi, S. typhi, Salmonella enterica,* have been compiled with their plausible ways of causing resistance. We conclude from our literature review that resistance in gram negative bacteria is on the rise and new and advanced antibiotics need to be designed and introduced.

INTRODUCTION: Antibiotics literally means "against life"; in this case, against microbes. There are many types of antibiotics such as antibacterials, antivirals, antifungals, and antiparasitics. Some drugs are effective against many organisms; these are called broad-spectrum antibiotics.

Others are effective against just a few organisms and are called narrow spectrum antibiotics. The most commonly used antibiotics are antibacterial in nature [1]. Ehrlich made the first antibiotic called Salvarsan, now known as Arsphenamine [2, 3, 4].

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Later, the science of antibiotics entered into an age of progress and at the time of penicillin discovery it was thought that soon we would have an upper hand over pathogenic microbes. However in recent past several studies have demonstrated authentically that now these disease causing agents are developed resistance to most of these antibiotics at an alarmingly faster rate and the race once we thought would soon be over after penicillin discovery in 1928 seems had just started [5].

Resistance Mechanisms: There are several mechanisms by which a microbe can get resistant to a particular antibiotic however among them the most studied and frequent one is the horizontal gene transfer between microbes [6]. The antibiotic action against the pathogen can be seen as an environmental pressure; those bacteria which have a mutation allowing them to survive will live on to reproduce. They will then pass this trait to their offspring, which will result in the evolution of a fully resistant colony.

Other four major type of resistance mechanism are; drug inactivation or modification, alteration of target site, alteration of metabolic pathway and reduced drug accumulation [7-8].

Some gram negative bacteria involved in diahorreal infections: As in case of *Shigella i*nfection yet claims for a significant proportion of bacillary dysentery in many tropical and subtropical countries and review of research papers shows the global rise in the growing pattern of resistance of *Shigella* species particularly type-I strains that poses great problem not in antibacterial therapy but also in clinical management all over the world[7]. In Somalia, a studied conducted in which the resistance to conventional antibiotics of 240 *Shigella* strains (like ampicillin, chloramphenicol, streptomycin, tetra cycline, and sulfonamides) and particularly *Shigella dysenteriae* type-I were found to be resistant to more than one drug.

The study also suggested that polymyxin B or M sulfate could be used as they had found effective in in-vivo trails for which have proved to be effective for bacillary dysentery [10]. A similar but a bit at large scale study conducted in London and Wales in which two thousand three hundred and seventy strains of Sh. dysenteriae, Sh. flexneri, and Sh. boydii were tested for resistance to a panel of a dozen of antimicrobial drugs and eighty per cent of strains were resistant to one or more drugs, with significantly sulphonamide resistance was observed, except in *Sh. Soneii* [9].

Another study in Central Isreal over a period of approximately 10 years difference indicated the significantly increased resistance to tetracycline from 23% to 87%, and high resistance to trimethoprim–sulfamethoxazole (94%) and ampicillin (85%) were also noted [9]. In Nepal, a study was conducted with the same aim a couple of years and results indicated that resistance to cotrimoxazole was highest (80.7%), followed by tetracycline (74.7%), gentamicin (55.4%), ampicillin (53%). chloramphenicol (39.7%) and nalidixic acid (31.3%) [12]. In a vast study conducted in Pakistan, where, 79.3% *S. typhi* and 59.9% *S. paratyphi* A were isolated from patients under 15 years of age, with the MDR rate increased in *S.* typhi (34.2 to 48.5% $p<0.001$), but decreased in *S. paratyphi* A (44.5 to 8.6%) in the first line of drugs.

However, Quinolone resistance (MIC>1μg/ml) increased in both *S.* typhi (1.6 to 64.1%) and *S. paratyphi* A (0 to 47%) in older patients. Apart from endemic and sporadic cases, and MDR strains have been responsible for numerous outbreaks on the Asian continent. The Asian isolates, eighteen of 25 isolates of *Salmonella enterica* serovar Typhi were multidrug resistant and contained class 1 integrons with a single cassette, *dfrVII* or *aadA1* on an IncHI1 plasmid. *Salmonella* serovar Typhi could become resistant to broad-spectrum cephalosporins by integrating cassettes, such as *veb-1*, a commntegron-Associated Antibiotic Resistance in *Salmonella enterica* Serovar Typhi from Asia [13].

In an extensive molecular study, seventy-eight Salmonella typhi strains isolated in 1994 and 1995 from patients living in Dhaka, Bangladesh, were subjected to phage typing, ribotyping, IS200 fingerprinting, and PCR fingerprinting. The data indicated a significant number of the S. typhi strains (67%) were demonstrated to be multiple drug resistant (MDR) strains were resistant to chloramphenicol, ampicillin, trimethoprim, streptomycin, sulfamethoxazole, and tetracycline (R type CATmSSuT), that could be conjugated to *Escherichia coli* and resulted in the complete transfer of the MDR phenotype [14].

High resistance, most probably plasmid mediated a serious public health concern and could be responsible for this increased mortality [15]. In a study conducted, *L. monocytogenes* was isolated in 4.5% of fish samples and 8.3% of seawater samples. Multi-resistant environmental strains as 6% of *L. monocytogenes* strains isolated showed multi-resistance to ampicillin, erythromycin, tetracycline, dicloxacillin, and trimethoprim-sulfamethoxazole, that a serious threat to human health [16].

Resistant Nosocomial Infection, A Potential Risk for Health Care Professionals: *Acinetobacter baumannii*, is a worldwide nosocomial pathogen associated with opportunistic infections, community and healthcare-associated infections (HAIs) like pneumonia, urinary tract, bloodstream, skin and soft tissue infections[17]. Thus, it constitutes a major public health problem due to its propensity to develop resistance to numerous drugs [18]. A study was conducted to determine the possible resistant genes in case of MDR acinetobacter starins and found about eight resistance gene determinants the genes

*bla*OXA-23 and *ampC*, resistance to carbapenems and cephalosporins, respectively. However, resistance to quinolones and fluoroquinolones was conferred by an S83L mutation in GyrA and blaTEM-1, which was found, associated to β-lactam resistance, and *strB*, which contributed to aminoglycoside resistance that give rise to the MDR phenotype both in sporadic and epidemic cases [19].

A similar research on a tertiary care 1000 bed hospital in Iran was carried out the results indicated that the *A. baumannii* strains showed high rate of resistance to ceftriaxone (90.9%), piperacillin (90.9%), ceftazidime (84.1%), amikacin (85.2%) and ciprofloxacin (90.9%) however, Imipenem was the most effective antibiotic against *A. baumannii* strains and the rate of resistance for imipenem was 4.5% [20] among various uro-pathogens responsible for urinary infections.

The natural antibiotic susceptibility of 38 *Providencia rettgeri*, 35 *P. stuartii*, 23 *P. alcalifaciens* and 20 *P. rustigianii* strains was examined. MIC values were determined by a microdilution procedure and evaluated by a table calculation programme. P. stuartii was the least susceptible Providencia sp. and was naturally resistant to tetracyclines, some penicillins, older cephalosporins, sulphamethoxazole and fosfomycin and to antibiotics to which other species of Enterobacteriaceae are also resistant. It was naturally sensitive to modern penicillins and cephalosporins, carbapenems and aztreonam [21].

In one of the study on multidrug-resistant *Enterobacteriaceae* (MDRE) in solid-organ transplant patients, as often in compromised hosts, resistant to cephalosporins due to overexpression of their chromosomal β-lactamase found that almost half of patients colonized with MDRE carried one or more cefpodoxime-resistant. *Citrobacter* species are infrequent nosocomial pathogens, and can cause a number of infections due to impairment of immune system [22] and include urinary tract infections, neonatal sepsis, brain abscess, meningitis, bloodstream infections [23]. *Citrobacter freundii*, *Citrobacter braakii*, or *Citrobacter amalonaticus* strains [24].

Our study shows that qnr gene has occurred in Citrobacter freundii isolates from Anhui Province, China. qnr gene was therefore present in both quinolone-resistant and -susceptible isolates and some of them could be transferred by conjugation experiments. qnr positive isolates strains showed multi-resistance and no clone was spread found in these SHV- and TEM-derived extended-spectrum β-lactamases (ESBLs) have also been described for *Citrobacter* species in the context of outbreaks of clonal strains and plasmids [25].

Resistance Cases with some recent clinical importance: *Morganella morganii* is also involved in a number of clinical cases. The different strains of this species are usually resistant to ampicillin, to the amoxicillin-clavulanic acid combination, and to cephalothin, and usually they are susceptible to other antibiotics active against gram-negative bacilli[26]. In some studies, the potential reason behind the resistance his contribution *M. morganii* is the production of extended-spectrum β-lactamases (ESBL) to drug resistance was examined in *Morganella morganii* [27] a high-molecular-weight (49,000) class I cephalosporinase, which contributes in the resistance with ampicillin, carbenicillin, and and broad-spectrum cephalosporins [28].

In the same way, in the hospital of Portugal, a strain of *M. morganii* (FFLM15), isolated from the urine of a neonate, showed resistance to ceftazidime and aztreonam and reduced susceptibility to cefotaxime by the disk diffusion method, however the synergistic results between expanded-spectrum cephalosporins and clavulanic acid was performed, and the positive result indicated the presence of an ESBL producer [29]. Another pathogen, *Citrobacter* species also are infrequent nosocomial pathogens, and can cause a number of infections due to impairment of immune system and cause urinary tract infections, neonatal sepsis, brain abscess, meningitis, bloodstream infections.

In one of the study on multidrug-resistant *Enterobacteriaceae* (MDRE) in solid-organ transplant patients, resistant to cephalosporins due to overexpression of their chromosomal β-lactamase have been noticed and almost half of patients were also resistant with one or more cefpodoxime-resistant *Citrobacter freundii*, *Citrobacter braakii*, or *Citrobacter amalonaticus* strains [22, 23]. Through research, qnr gene found in *Citrobacter freundii* isolates from Anhui Province, China associated with quinolone-resistance and some of them could be transferred by conjugation trials.

Upon screening, plasmid association with resistance, SHV- and TEM-derived extended-spectrum β-lactamases (ESBLs) have also been noted for *Citrobacter* species in case of the outbreaks of clonal strains and plasmids. The susceptibility profile of 38 clinical isolates of *Providencia rettgeri*, 35 *P. stuartii*, 23 *P. alcalifaciens* and 20 *P. rustigianii* strains was examined by a microdilution procedure. *P. stuartii* was the least susceptible among *Providencia* sp. and was naturally resistant to tetracyclines [23]. A total of 238 isolates of *Providencia stuartii* obtained from infected patients in six Dublin hospitals. Both chromosome-encoded and plasmid-coded resistance mechanisms were important and most of the clinical isolates were resistant to several of these antibacterial agents including tetracycline, resistance to penicillin, moreover resistance to polymyxin was also noticed [23].

A total of 238 isolates of *Providencia stuartii* obtained from infected patients in six Dublin hospitals were grouped by using serological and bacteriocin typing methods and tested for sensitivity to a number of antimicrobial agents. Most isolates were resistant to several of these agents. Resistance to tetracycline, resistance to penicillin, resistance to polymyxin, and probably resistance to nitrofurantoin was intrinsic. Plasmid screening coupled with resistance transfer studies showed that both chromosome-encoded and plasmid-coded resistance mechanisms were clinically important. Ampicillin resistance was both chromosomally and plasmid encoded, whereas resistance to kanamycin and resistance to carbenicillin were exclusively plasmid encoded [30].

CONCLUSION: Therefore to encounter these defense mechanisms of resistance, from the pathogens, we need to keep discovering new antibiotics against them so as to cure the diseases. However at the moment perhaps, the biggest problem with antibiotic resistance at the moment is the fact that it's inevitable i.e. no matter how exquisite a new drug is, microbes are going to develop resistance to it in one way or another and yet this matter does not get the kind of attention that other health treats like dengue and bird flu did. Perhaps the biggest obstacle in tackling resistance is the fact that too many people accept it as inevitable.

As Weber explained, "even if drugs were used exquisitely perfectly, the emergence of drug resistance is likely." Also, this problem does not receive much attention compared with other health issues-recent scares, such as severe acute respiratory syndrome (SARS), avian flu and bioterrorism, have clearly overshadowed the distant possibility of bacterial resistance with the short-term fear of imminent danger. However, Levy, who highlighted the dangers of antibiotic resistance more than a decade ago in his book *The Antibiotic Paradox*, feels that public awareness, is slowly increasing. "The message is out there," he said. The next step is overcoming resistance to change.

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