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The role of Normal flora in emergence and spread of antimicrobial resistance

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ABSTRACT

Antibiotic resistance is increasing dramatically in all parts of the world. New resistance factors are responsible to spread antibiotic resistance microorganism over the world and makes difficult to treat common infectious diseases. While antibiotics become less effective most infection disease becoming life treating. The irresponsible use of antibiotics in several dedicates is associated with emergence of antibiotic resistance in micro-organisms, destroying the normal flora gives the chance for multiplication of infections and the other microbes with the resistant genes. The antibiotics have lethal effect on normal flora and decrease the colonization, thus microorganisms are possess resistance genes can grow and spread among the normal flora and pathogens, and this rise the number of resistance micro-organism. In recent years due to the decline in the approval of new drugs, abuse and misuse of antibiotics , especially in hospitals, and community, and uses as a growth factor in live stocks, creating a crisis of antibiotic resistance. Normal flora is one of the most agents which are responsible for the transportation of resistance genes by with spread between the other Normal flora, and pathogenic bacteria in hospital, community and in animal, and it is more responsible for hospital acquired resistance infections. The Resistance emerges by changing the environmental conditions, Thus normal flora is the resource of genes which has antibiotic resistance characteristic and most dependable the increase of antimicrobial resistance.

1. Introduction

Antimicrobial agents defined by world health organization as a natural substance, synthetic or semi-synthetic which exhibits lethal effects or inhibitory effects against bacteria, viruses, protozoa and fungi [1]. As the WHO described antibiotics as an important option for treatment of infection disease, but unfortunately resistant microorganisms to antimicrobial agents is increased and causing life- threatening infection disease, today Emerging of resistance to Gram-negative bacteria becomes a common health problem, and several factors contributed to increase the resistant organism these factors can be, irresponsible Use of antimicrobial agents, in animals as growth promoter and in human as empiric therapy, so for the synthesis of new antibiotics is also decreasing day by day and there will be no more effective classes of antimicrobial to eliminate the bacteria [2]. If we considering these life threatening resistance organism are emerges and spreads to all over the world by some specific genes, like metallo- β-lactamase also called NMD-1, which is newly emerge and spread which is known as one of major public health problem related with the multi-drug resistance[3,4]. Urinary tract infection is one of these health problem witch mostly caused by *E. Coli* and *Klebsiella pneumonia,* and presence of metallo- β-lactamase genes in *Klebsiella pneumonia* strain and *Escherichia coli*, associated with the complicated urinary tract infection and caused the resistance pathogens, this resistance may transport to other *Enterobacteriaceae* species [4]. *E. coli* isolated from poultry and pigs, carried out the gene of spectrum β-lactamase (ESBL). *E. coli* is a bacteria which is exists universally with different types, some types are important in pathogenesis in human and animal. Some strain of *E. coli* which can cause the diarrhea and urinary tract infections, are more infectious as compare to *Salmonella* and *Campylobacter* [5].The resistant gens can transferred from *E. coli* to another normal flora and pathogens, like resistant genes which is responsible for resistance to *Carbapenem* found in *Enterobacteriacae* of pets have capability to transfer from these organism to other members of *Enterobacteriacaes*spp and other pathogenic organisms [6].The patient with such a resistant infection genes difficult to cure and some time it is life threatening, because these gens easily can transfer to other normal flora or pathogens. Hens this study helps to find out the spread factors of resistance genes among the normal flora and other pathogenic organisms.

1.1 Emergence of antibiotic resistance microorganisms

First antibiotic “penicillin” discovered by Alexander Fleming in 1945. On that time it was the most effective antibiotic, and by later on by use of penicillin in infection disease the resistance organisms are developed against penicillin and this resistance passed to other bacteria, thus infection disease like septicemia and pneumonia did not treat with penicillin moreover. Analysis of 30000 year aged DNA indicates that, the resistance genes can code proteins which could degrade the β-lactams, tetracycline and glycopeptide antibiotics, So resistance to antibiotic is a natural phenomenon[7].The improper use of antibiotics dose (low and high concentration) for treatment of infectious disease in human, animals, and agriculture associated with the emergence of resistant bacteria [8]. The AMP genes can transfer by aquatic environment and the transportation mostly occurs by plasmids from one bacteria to other bacteria and this plasmid some time can easily captured by bacterial pathogen that can contributed as resistant infection in human [9].

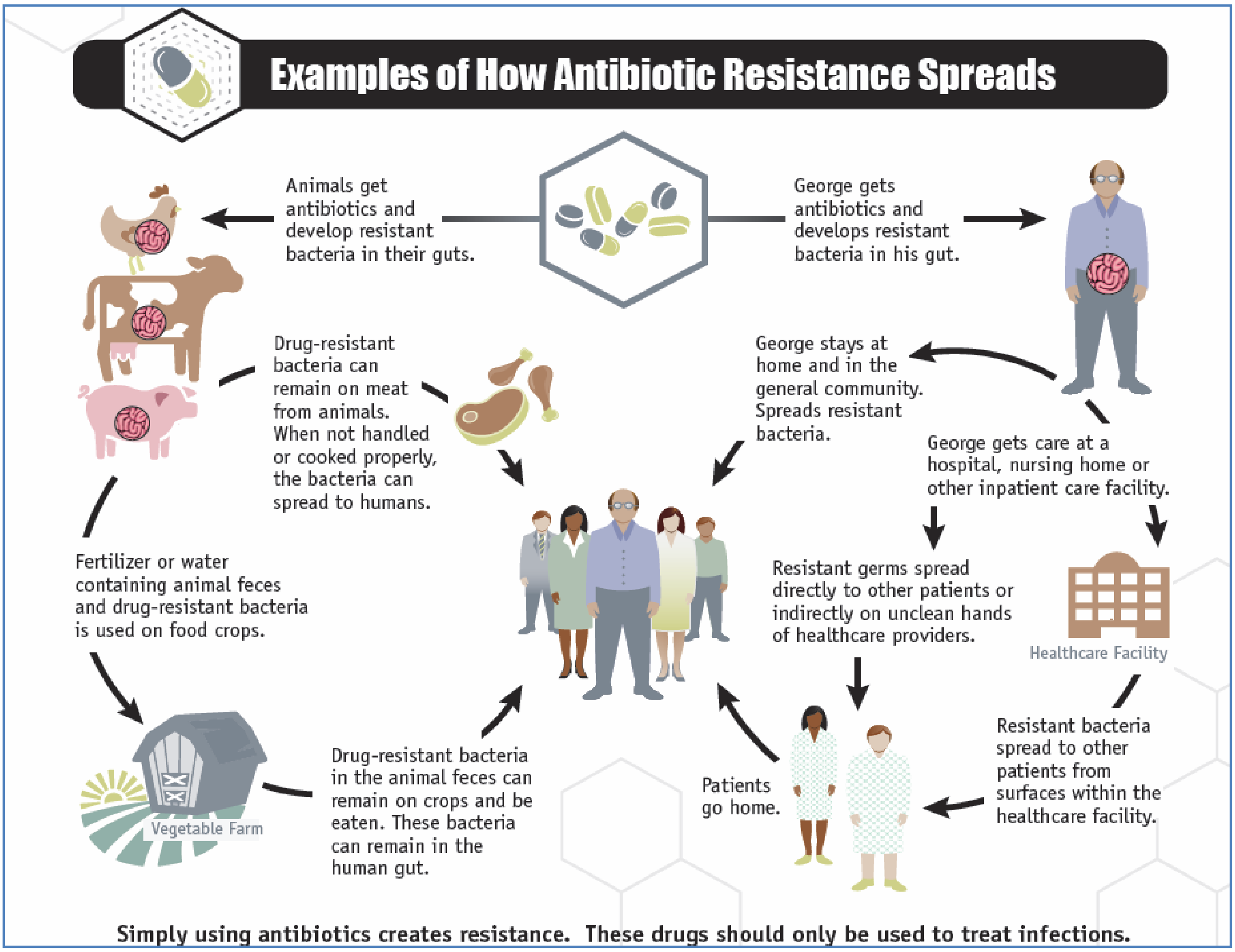
1.2 Relationship between antibiotic utilization and antibiotics resistance

Different studies indicate that emergences of antibiotics is related to the use of antibiotics. A comparison usage reports of antimicrobials from different countries demonstrated the relationship between higher antibiotics user and elevated resistance.A tudy in relationship between antibiotic utilization and emergence of resistant organisms in nine European countries from 2005 and 2011 showed important difference in concentration of antibiotic and production of meat. Thus these countries use antibiotics as growth promoters. Investigation on resistance rate in these countries had shown significant relationship between use of penicillin, Tetracycline's, *Quinolones* and *Macrolides* antibiotics and emergence of resistant organisms, except the emergence of resistant organisms against Cephalosporins. And also there is evidence of relationship between usage of *Avoparcin* as a food additives in production of meat and emerging of resistance normal flora in poultry [10]. And also there is the evidence that usage of tetracycline in pigs emerge the tetracycline resistance *E.coli* [11].

1.3Extend of resistance microorganism against antimicrobial

During treatment of human and animal infectious disease the normal flora also exposes to lethal effect of antibiotics and most of organisms killed and susceptible one is replaces to resistant. The microbe with resistance gene disseminates in to inorganic substance and living bodies, and can transfer this resistance genes to other normal flora and pathogenic bacteria. There is evidence that The resistance gens spread easily among the *salmonella, campylobacter, listeria, E coli,* and by them to the environment and cause food born infection**[12]**,The graph (Figure 1) describes the linkages of human and healthcare systems, food production and animal, and shows the path spread of antimicrobial resistance The antimicrobial resistance genes in bacteria can transfer by horizontal gene transformation between normal flora and food borne bacteria and this process leads to obtain antimicrobial resistance in the receiver strains **[13].** In one study indicate that antimicrobial resistant to several antibiotics, found from normal flora of gut in newborns in first week of life, which has been no longer exposed to antibiotics **14].**

Figure 1 Examples of spread antibiotic resistance



Most Studies focused on the emergence of new resistance, and some others focused on spread of resistance, each of them important factors for causal crisis emergence of resistant organisms [15]. Some other risk factors also contributed like Economic situation and societal factors are related to increasing the level of antimicrobial resistance, [16].

1.4 Cross-resistance, innate resistance, Co-resistance, Co-selection

'We have different types of resistance properties. Cross-resistance and co-selection, In case of innate resistance of microorganism, the microorganism expose to the antibiotics and the antibiotic molecule normally "without any developed resistance mechanism" could not reach to the targets metabolic pathway or the antibiotic will not be effective any more "resistance owing to a native mechanism [17].In case of Cross-resistance a bacteria species may have broad-spectrum resistance mechanisms in addition of having innate resistance against a specific antimicrobial agent, this is known as "cross-resistance" or Cross-resistance – a single resistance mechanism confers resistance to an entire class of antibiotics. An example is the aminoglycoside-modifying enzymes which may confer resistance to several members of the aminoglycoside family. Cross resistance can also occur across different classes of agents - a result of either overlapping drug targets as is the case with macrolides and lincosamides or if there is a drug efflux pump with a broad range of activity (i.e. capable of exporting different classes of drugs. Co-resistance refers to the presence of resistance to more than one class of antibiotics in the same bacterial strain as might occur on a plasmid. This concept is also concern in emergence of resistant organisms by mutation under the pressure of specific antibiotics, and resistant occurs against to this specific antibiotics, and it is also possible when this types of resistance occurs it may shows resistance properties to other antimicrobials agent which has not been exposed to this microbe anymore [27]. Like multi-resistance cfr gene in Gram-positive bacterial is responsible for antimicrobial resistance against to *cloramphenicols, lincosamides, pleuromutilins, streptogramin* antibiotics and as well as *macrolids* and *linezolids* [18]. Co-selection is the selection of multiple antibiotic resistance genes when one of these genes is selected. The most elegant example of this is the integron which is a cassette of antibiotic-resistance genes that areunder the control of a single promoter. As a result, these genes are expressed in a coordinate manner, although the most downstream gene may not be as efficiently expressed as the gene next to the promoter. These cassettes are now found in both Gram positive and negative bacteria. Since they are a form of transposon they can become a part of the bacterial chromosome or plasmid and can then be transmitted among different strains. [17].

1.5 Mode of antimicrobial resistance

Several mechanisms of antibiotic resistance are present in resistance microorganisms.

- *Alteration of cell membrane in bacteria avoids the entering amount of antimicrobial into the bacterium.*
- *Antimicrobial exit from cell wall by active efflux pumps.*
- *Reduce availability of antimicrobial due to changes in target site.*
- Production of enzymes inside the bacteria can degrade or inactivate the antimicrobial.
- Changing of enzymatic pathways alters in metabolism of antibiotic agent and cause change approximately among those embattled or inhibited by the antimicrobial.
- By changing some molecules in bacteria the antibiotic bind to altered molecule instead the target side and limit the activity of antibiotic.
- Alter the antimicrobial activation due to loss or alteration in enzymes of those which are pro-drugs "cannot convert to active form".

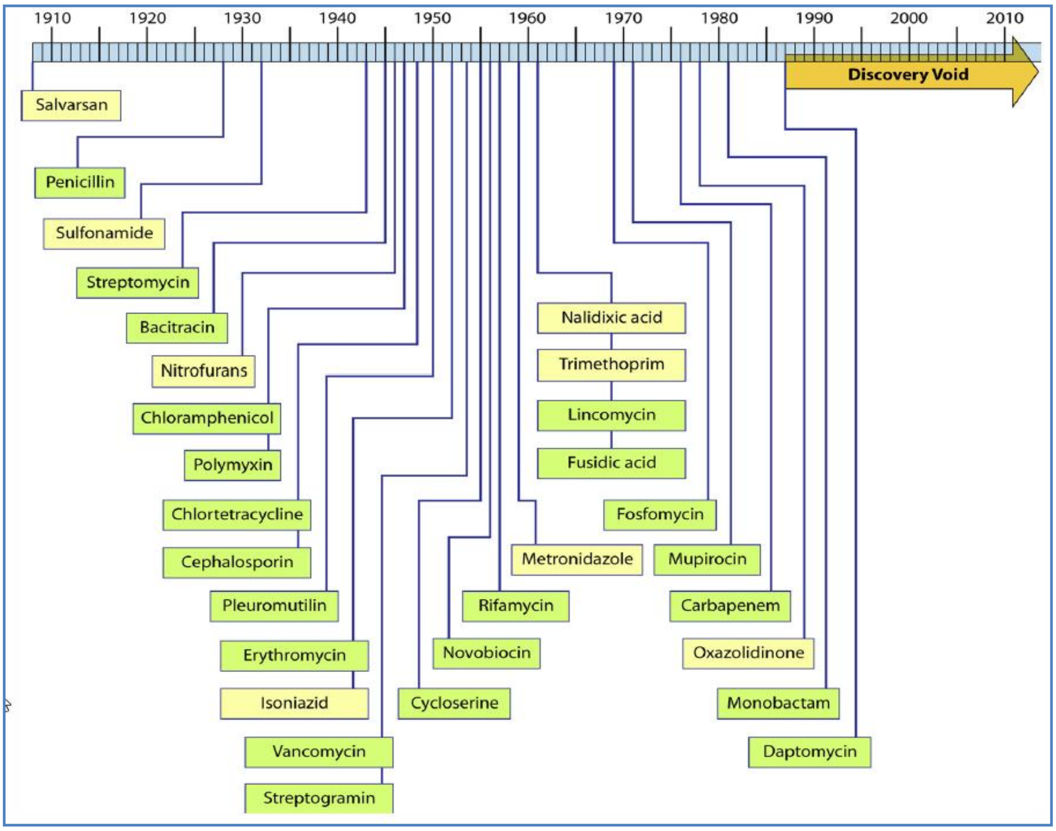
Some bacterial resistance mechanisms have an appropriate biological propriety, as a result of increased metabolism, use of an alternative chemical route. Sensitive bacteria are vulnerable and the bacteria that are resistant to the metabolic process are less effective.

However, other changes in biological properties do not effect on bacteria, some resistance directions have been changed even the biological preparation of bacteria, and in some cases, and bacteria over time can provide other mechanisms for balancing biological cost and produce resistance. **[19].**thusother mod of resistance, mutation in genetic level in bacteria and, obtaining of resistance gene can spread between each bacteria and sometime combination of these two mechanism responsible for emergence of resistance **[20].** Mechanisms of resistance against *fluoroquinolonces* in Gram-positive and Gram-negative bacteria are exhibit alteration in binding sit of antibiotic molecule in cell wall, which these alteration of permeability and activation of efflux pump caused by mutation **[21].**

1.6 Incentive of novel Antibiotic

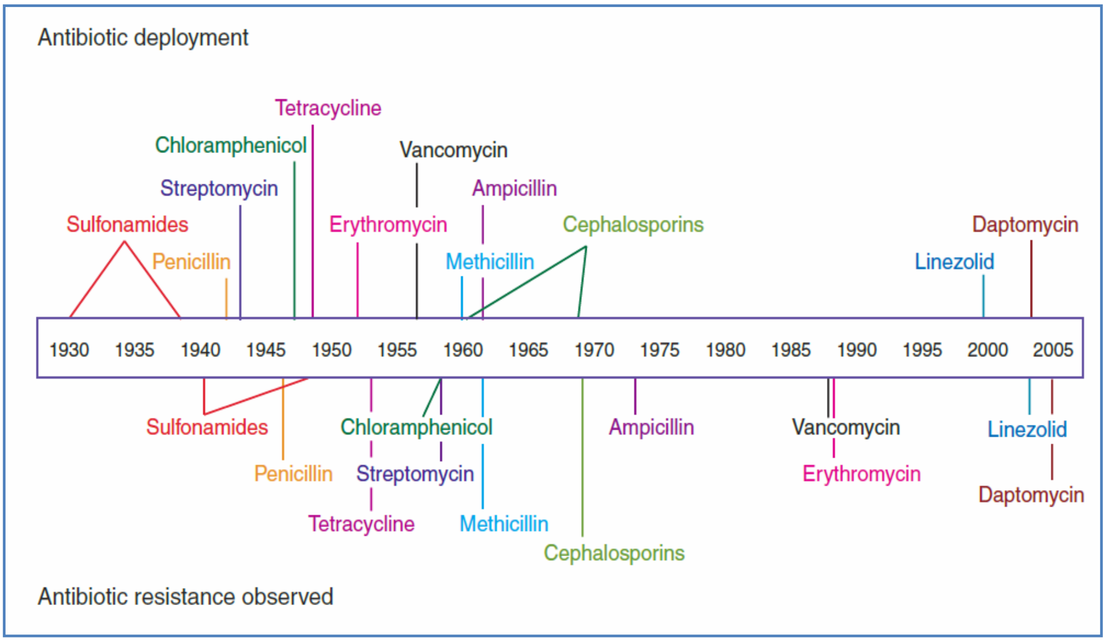
There is no such an incentive in pharmaceutical industry to provide a new antibiotic, due to some reason such, fence economic and regulation. Eighteen major pharmaceutical companies that previously developed antibiotics decreased up to fifteen titles **[22].** As a timeline indicate in Figure 2, the result of scientific discoveries of distinct classes of antimicrobial in last decades shows decrease number of new discoveries since 1987, which different factors contributing in this area [23].

Figure 2 Dates of discovery of antibiotics classes and void discovery



And also the emergence of antibiotic resistance increasing and new antibiotic discoveries decreasing (see Figure 3) **[24].**

Figure 3 Emergence of antimicrobial resistance and new antibiotics time line



However some antibiotic development and production process shows analogue compounds against multi-drug resistance Gram-negative bacteria **[25].**

One of major public health concern in many countries is emergent of resistance genes encoding resistance to *Carbapenemases* which is related with the multi-drug resistance**[26].**

1.7 Reverse proceeding of resistant microorganism against antibiotics

To overturn the inclination of antimicrobial resistance must set priorities, such threats to human health, animal health and sustainability of food product and trade. For same case of high resistance required for effective antimicrobials, such 3th generation of *cephalosporins* and *fluoroquinolones*, and some element of antibiotic utilization required to be careful, contain the time of use of antibiotics, indication and how to use them are important **[13].**Due to the number of animal species, types of insects, a range of bacteria involved the limitations of existing antimicrobial classes and a variety of resistance mechanisms, antimicrobial resistance is a major problem in veterinary **[27].**

1.8 Reducing antibiotic utilization

Use of antibiotics has been targeted to reduce in some countries, particularly in veterinary.

For example, in France the strategy of EcoAntibio in veterinary medicine is reduced the use of antibiotic and decreased by 25 percent in 5 year **[28].**

For the reduction of total antibiotics the strategies should maintain.

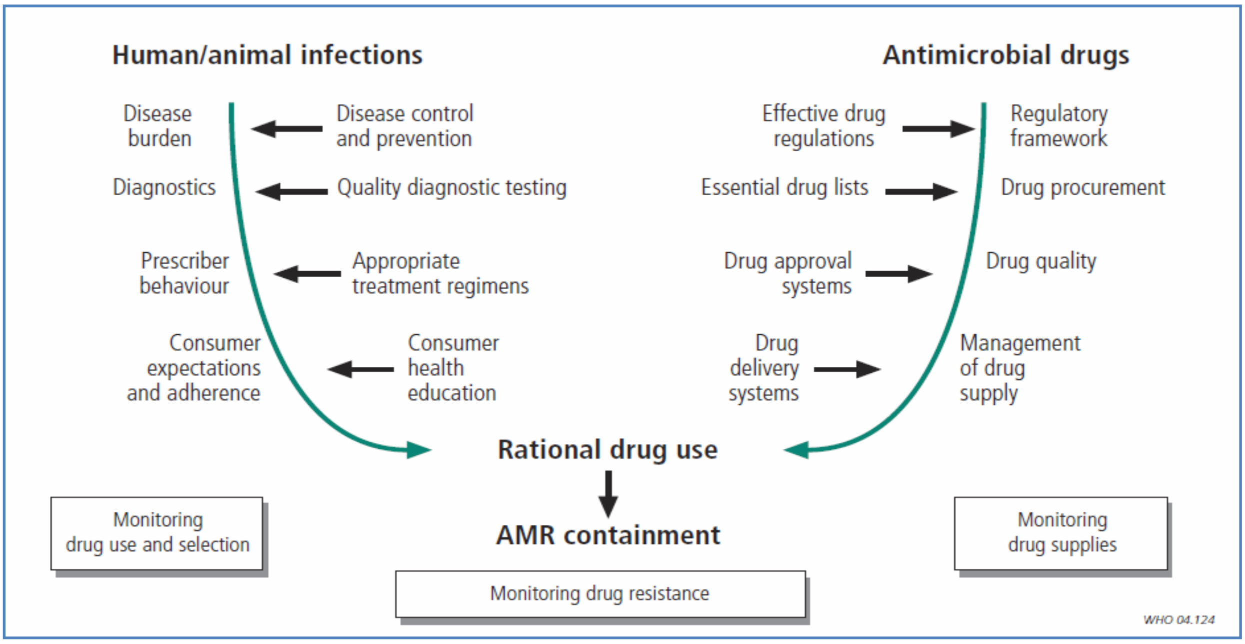
With programs, training and other programs that work to get better the wellbeing of humans and animals and the sustainable industries.

Strategies must be maintained to reduce the use of antibiotics, with programs, tutorials to improve the health of humans and animals and sustainable industries.

World Health Organization Bulletin shows a simple plan for discovering and describing the program, elements requires to maintain antimicrobial resistance (see Figure 4).

There is requirement of coordination strategy between animal and human health and product systems, to monitoring the antibiotics resistance and use of antibiotic, as the graph in (Figure 4) shows there are some specific component present to help us in monitoring system and diagnoses of resistance**[29].**

Figure 4 Elements of antimicrobial resistance control and observation



2. Conclusion

Normal flora is one of the most important agents which is some time contribute and responsible for the transportation of resistance genes, by with spread between the other Normal flora, and pathogenic bacteria in hospital, community and in animal, and it is more responsible for hospital acquired resistance infections, like genes of metallo- β-lactamase which emerge and spread which is one of the lives threatening concern in public health such as responsible for chronic UTIs. And the *Klebsiella pneumonia* strain also shows the presence of metallo- β-lactamase genes. This type of resistance also found in *Escherichia coli*, and it may responsible for transport of genetic material between *Enterobacteriaceae* species, and the enzyme metallo- β-lactamase also called NMD-1, and this enzyme related with the multi-drug resistance .There is significant relationship between use of *penicillin, Tetracycline's, Quinolones* and *Macrolides* antibiotics and emergence of resistance organism, but there are no significant relationship for *cephalosporin's*, but there is significant relationship between uses of*Avoparcin* as a food additive in production of meat and emerging of resistance normal flora in poultry, Use of tetracycline in pigs emerge the tetracycline resistance *E. coli* And also some *E. coli* strain which is isolated from poultry and pigs, and from patient with serious infection carrying gene of spectrum β-lactamase (ESBL). Thus these strains are important in pathogenesis in human and animal. These resistance strains of *E. coli* which can cause the diarrhea and urinary tract infection are more infectious as compare to *Salmonella* and *Campylobacter*. The resistant gens transferred from *E coli* to another commensal and pathogens, like resistant to *Carbapenem*found in *Enterobacteriacae*of pets. The patient with such a resistant infection gens difficult to cure and some time it is life threatening, because these gens easily can transfer to other normal flora organisms or pathogens species. The Resistance microorganisms emerging by changing the environmental conditions, the isolation and identification of resistant organisms are difficult but the detection of genes are possible among the normal flora. Thus we can conclude normal flora is the resource of genes which may have antibiotic resistance genes and characteristic and most dependable the increase of antimicrobial resistance.

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