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# **CHAPTER 04**

# DRUG RESISTANCE OF GRAM-NEGATIVE PATHOGENS IN LARGE ANIMALS WITH SPECIAL REFERENCE TO PAKISTAN

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# INTRODUCTION

Non-hazardous bacteria are useful microbes for animals and humans, which help in disease prevention and food digestion (Stark 2010). However, pathogenic bacteria are important disease-causing entities. Of these, endotoxin producing bacteria (gram negative bacteria) are important pathogens in large animals, causing systemic infections. The importance of these pathogens has been augmented after the emergence of antimicrobial resistance, which even can be transmitted between humans and animals (Idrees et al. 2011). Gram negative bacteria can cause intestinal and extra-intestinal infections in animals. Treatment of infections caused by resistant pathogens is costly because treating individuals with alternative drugs is always more expensive than conventional treatment (Burroughs et al. 2003). In addition, no new antibiotics have been developed specifically for multi-drug resistant gram-negative bacteria (Giske et al. 2008). Therefore, the clinical and economic impact of resistant gram negative bacteria is greatly worrisome. Knowing the sources and level of antimicrobial resistance in gram negative bacteria are of dire need.

#### **Gram Negative Bacteria**

Bacteria, a well-known type of micro-organisms, are differentiated traditionally based on the retention of crystal violet stain in a Gram staining method. Gram negative bacteria, owing to lower quantity of peptidoglycans in the cell wall, do not retain the crystal violet and appear pink/red under microscope. This property of bacteria is associated with the amount of peptidoglycans in their cell wall.

### **Antibiotic Resistance**

Since the advent of first antibiotic 'penicillin' by Alexander Fleming, number of new antibiotics introduced, continued to show ineffectiveness against microbial pathogens. This phenomenon is known as antimicrobial resistance (AMR). Drug resistance has come forth as global challenge in the recent decades and it is anticipated to be one of leading causes of death in 2050 and emerging global public health concern that endangers efforts to achieve the 2030 Sustainable Development Goals (SDG). Overuse and misuse of antimicrobials in people and animals, often without professional

oversight, contribute to AMR development. Antimicrobials are commonly misused to treat viral infections in humans and for growth promotion in food animals. Resistant microbes can be found everywhere, in humans, animals, our food and the environment. They are capable of spreading between animals and humans, including through food animal products. Impact of AMR is expected to be quite extensive in developing countries. Pakistan is the first country of the Eastern Mediterranean Regional Office (EMRO) of the WHO to establish the early implementation of the WHO Global Antimicrobial Resistance Surveillance System (GLASS). Furthermore, in line with the five strategic objectives of the WHO Global Action Plan (GAP) for AMR, Pakistan also developed the National Action Plan on AMR for the AMR containment through one health approach. As per recommendations given in NAP for AMR, Pakistan also has developed "national surveillance strategy for antimicrobial resistance in healthy food animals (AHC 2021) and "national surveillance strategy for antimicrobial resistance in bacterial isolates from sick food animals" (AHC 2022). Similar strategies are essential for knowing the status of antimicrobial resistance in different types of bacterial pathogens followed by developing antimicrobial stewardship program in animal health sector. Gram negative bacteria are important public health concern, as their outer membrane protects them from many antibiotics, including penicillin.

#### AMR in Large Animals as one Health Issue

According to one health concept, health of humans is closely related with the health of animals and environment. Resistance is transmitted from animals to humans and vice versa. Due to emergence of zoonotic pathogens, AMR has become an important one health issue. Similarly, resistance in commensals including E. coli, Salmonella spp., Campylobacter and Enterococcus spp. in large animals has also public health importance. These bacterial species have become resistant to even highest priority critically important antimicrobials and reserved antibiotics.

#### Mechanisms of Acquiring the AMR

There are certain mechanisms of acquiring resistance by gram negative bacteria. The bacteria can modify the antibiotic molecules by either chemical / enzymatic alterations or

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destruction of antibiotic molecules by  $\beta$ -lactamases. The permeability of antibiotics is decreased by changes in qualitative functioning or number of pores. This decreased permeability results into limited influx.

(i) Decreased permeability resulting limited influx of the antibiotic substances

(ii) Increased extrusion of substances by efflux pumps.

(iii) Modification of the target site and genetic mutations as well as enzymatic alteration of the target site also help bacteria to acquire resistance.

#### **Pathogens and Resistance**

#### Escherichia coli

Escherichia coli has substantial importance for the antimicrobial resistance studies because this resistance can gauge the levels of resistant bacterial phenotypes in the environment (Anjum et al. 2021). Therefore, E. coli is considered for the monitoring of AMR in surveillance programs of developed nations including WHO GLASS, WHO tricycle, EARS-Net and DENMAP. Similarly, commensal E. coli is chosen as AMR sentinel, as it provides valuable data and constitutes a reservoir of resistance genes, which can spread horizontally to zoonotic and other bacteria (EFSA and ECDC 2019). With the passage of time, the magnitude of resistance is being increased. Two decades earlier, E. coli isolated from cattle were resistant (<5%) to all the tested antibiotics including ampicillin (3%); chloramphenicol, cephalothin, and nalidixic acid (2.3% each); ciprofloxacin, cefoxitin (1.5%); and trimethoprimsulfamethoxazole, and amoxicillin-clavulanic acid (0.1% each) (Schroeder et al. 2002). Lower resistance pattern was also observed at Switzerland in 2003 where none of the E. coli isolates from cattle showed resistance to amoxycillin-clavulanic acid, cephalothin, cefoperazone, enrofloxacin and Polymyxin B while chloramphenicol was resistant to 10% isolates and ampicillin, streptomycin and sulfonamide were >20% resistant (Lanz et al. 2003). As the human illness due to E. coli is linked with meat source (Schroeder et al. 2002) so the increasing level of resistant E. coli in humans and animals are analogous. In addition to showing 9% resistance to ampicillin and 66% resistance to streptomycin by bovine E. coli isolates in 2004, 68% of the isolates had multi-drug resistance (MDR) (Wilkerson et al. 2004). E. coli can acquire the co-resistance due to use of other types of antibiotics in animals, as the selection of chloramphenicol resistant E. coli is associated with the administration of dihydrostreptomycin and trimethoprim to the animals (Harada et al. 2006) and it is assumed that irrespective of the antibiotics use in calves, there is coselection of tetracycline resistance due to unknown mutation (Walk et al. 2007). The increased resistance in E. coli commensals isolated from cattle is also attributed to earlier Salmonella infection and similarly the higher MDR was seen in isolates from such animals (DeFrancesco et al. 2004). Apart from systemic and enteric infections, E. coli also causes mastitis (predominantly sub-clinical) in the ruminants and has shown a high resistance to highest priority critically important, high priority critically important and highly important antimicrobials, and producing even fluoroquinolone resistance and extended-spectrum  $\beta$ -lactamase (Su et al. 2016). There is another fact that E. coli isolates from large animals were comparatively higher resistant to tested antibiotics than isolated from humans (Wilkerson et al. 2004; Mora et al. 2005).

Although animals are considered as source of resistant E. coli to humans (Tanih et al. 2015), but there is another thought that milk can't be the source of transmission (Botrel et al. 2010).

#### Salmonella

Salmonella is one the major foodborne pathogens in humans, worldwide. According to United States Centers for Disease Control and Prevention (CDC), United States Department of Agriculture (USDA), University of Minnesota, and the National Institute of Health, Salmonella is 3rd most important zoonosis in Pakistan (CDC 2017). Multi-drug resistant Salmonellosis is endemic in humans in Pakistan, with the varied prevalence of Salmonella (Butt et al. 2005; Mirza and Khan 2008), Salmonella meleagridis, Salmonella montevideo, and Salmonella typhimurium are frequently recovered from faeces of cattle. Humans can acquire the infection from ruminants due to households' contamination or utilizing as food source. Similarly, humans can acquire the resistant bacteria from animals and Salmonella may acquire resistance during treatment with antibiotics for any other disease, due to its potential selective pressure. Salmonella had shown variable resistance to most of the antibiotics including cephalosporins over the longer which is thought to be attributed periods. to occurrence/emergence of different serotypes in an area (Davis et al. 1999; Frye et al. 2007; Hong et al. 2016). This is why, the resistance pattern appears uneven in surveillance programs for Salmonella. Like E. coli, Salmonella species show the higher phenotypic resistance in animals than humans (Davis et al. 1999). The effective choices against Salmonella infections include chloramphenicol and fluoroquinolones (Anderson 1968; Piddock 2002). Salmonella species isolated from cattle highly resistant ampicillin, streptomycin, are to chloramphenicol and tetracycline (Davis et al. 1999; Poppe et al. 2006; Marrero-Ortiz et al. 2012). All isolates of Salmonella from meat in Pakistan showed resistance to ampicillin and evidence of resistance evolution in Salmonella spp. are found in livestock. Before 2000, Salmonella from bovine species were highly susceptible to the antimicrobials; now the situation is opposite i.e., high resistance including to the extended spectrum cephalosporins.

## Campylobacter

The commensal species of Campylobacter in bovines are C. jejuni and C. coli which induce diarrhea. However, C. fetus (previously known as Vibrio fetus) causes venereal disease, Campylobacteriosis in cattle causing infertility. C. fetus can be transmitted through male during coitus and have even been isolated from seminal vesicle of the bull (García et al. 2021). Unlike other commensals, isolation of Campylobacter spp. is difficult due to its anaerobic and other requirements. Unlike Salmonella and E. coli, the critically important antibiotics are different for Campylobacter. Resistant Campylobacter can be transmitted to humans from livestock species (Noreen et al. 2020). Moreover, its zoonotic potential makes it more important. Fluroquinolones and macrolides including erythromycin, clarithromycin, or azithromycin are considered the drugs of choice against Campylobacter infections but high resistance against these drugs has become public health concern. Additionally, Campylobacter coli and C. jejuni have developed high resistance for tetracyclines, beta-lactams, aminoglycosides, and lincosamides as well (Hull et al., 2021).



Fig. I: Mechanisms of acquiring resistance by gram negative bacteria.

The resistant is possibly transmitted from animals to humans. Campylobacter has emerged as resistant to florfenicol and linezolid (Zhao et al. 2019).

#### Helicobacter

Helicobacter pylori is a spiral gram-negative bacillus that infects mostly the gastric lining of different animals. Most of the infections caused by Helicobacter are silent, causing ulcers related to the stomach and intestine, thus contributing to significant levels of morbidity and mortality and also can cause lymphoma and adenocarcinoma. Helicobacter also play role in thrombocytopenic purpura and anemia related to iron and B12 deficiency. Transmission routes of Helicobacter species are not confirmed, but there is evidence of fecal-oral and gastro-oral transmission. AMR of Helicobacter is an emerging issue related to its treatment. Helicobacter has shown high resistance against tetracycline and metronidazole, which results in treatment failure. Growth in antimicrobial resistance against these drugs is due to an increasing rate of treated patients and the growing usage of antibiotics. Other antibiotic drugs like clarithromycin, furazolidone and amoxicillin are better choices to treat Helicobacter infections (Bahrami et al. 2011). Different antibiotic drugs show resistance to several species of Helicobacter. Metronidazole is an antimicrobial having nitroreductases as an active part. In case of Helicobacter, process of resistance is more complex. Factors like decrease in antibiotic uptake, increase in penetration of the drug through the bacterial cell wall and reduced action of nitro reductases are contributing to the non-activation of metronidazole. Levofloxacin, fluoroguinolones are also used as treatment therapy to control Helicobacter infection. This drug hinders DNA gyrase and causes disturbance in the synthesis of DNA. Mutation in A or B subunits of DNA gyrase are contributing to causing resistance by Helicobacter against this drug. Clarithromycin is a bacteriostatic drug used for the treatment

of different Helicobacter species. Different point mutations in the 23S rRNA gene decrease the ability of ribosomes for the antibiotic. In this way, Helicobacter becomes resistant (Alba et al. 2017). Helicobacter pylori is a vital pathogen responsible for increasing antimicrobial resistance and causing a serious threat related to health. Resistance can be single, multiple, or hetero drug. Mechanisms involved in AMR are the mutational transformation of chromosomes and disturbance in the cellular activities of drugs. Growing AMR rates result in a considerable decrease in the efficacy of treatment related to different species of Helicobacter, globally (Tshibangu and Yamaoka 2021). Tetracycline-linked resistance is attained through protecting ribosomal proteins. These proteins enhance the resistance by minimizing the efficiency of ribosomes for this drug or by escaping the antibiotic from the ribosome in bound form. Activation of enzymes of tetracycline and point mutations linked to genes having 16 rRNA, also play role in causing resistance. Due to area-wise variation in incidences of antimicrobial resistance and clinical status of decreased treatment protocols, there is dire need to check the proportion of antimicrobial resistance of local drugs. This action helps in the selection of suitable antibiotic solutions and in changing the views of consultants about AMR, before ultimate treatment. These strategic protocols help in the reduction of treatment failures and the eradication of waves of increasing treatment resistance related to different Helicobacter species, in different populations of the world (Thung et al. 2016).

#### Proteus

Proteus mirabilis is a motile bacillus of Enterobacteriaceae family, normal inhabitants of intestines. However, six species of Proteus including P. vulgaris, P. cibarius and P. terrae are most commonly identified from clinicals samples related to different infections. These are opportunistic pathogen of vital

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importance and present in soil, water and also in mammalian intestinal tract (Li et al. 2021). It acts as major cause of urinary tract infections in different animals. Biofilm production by P. mirabilis has become an emerging issue of much concern. Bacteria isolated from animals having diarrhea showed high resistance to ampicillin and doxycycline (Ghazay et al. 2019). Biofilm producing bacteria (Proteus), with higher rate of genes expression, are significantly more resistant to cefoparazone, piperacillin, and imipenem than non-producers (Schaffer and Pearson 2015). Biofilm production is linked with expression of certain genes like rsmA, hmpA, ureC, atfA and pmfA, showing resistance to kanamycin, tetracycline, doxycycline and cephalothin with almost 3/4th of the MDR and XDR isolates (Alabi et al. 2017). MDR in isolates of P. mirabilis is a growing health concern now a days and also has a serious threat for animals and humans. P. mirabilis isolated from intestines of large animals carry resistant genes of blaOXA-1, blaNDM-1, and blaTEM-1 (Kang et al. 2021). Proteus has shown relation with Salmonella regarding antibiotic resistance, identified based on Salmonellae genomic island 1 (SGII) (Wang et al. 2019). Resistance related to cephalosporins in Proteus species is caused by extended-spectrum  $\beta$ -lactamases (ESBLs) and plasmid related cephalosporinases (Bonnin et al. 2020)

#### Moraxella

Morexella catarrhalis is diplococcus pathogen for infections related to respiratory tract. It causes sinusitis, pneumonia, otitis media and bronchitis (Goldstein et al. 2009), while Moraxella bovis is cause of infectious keratoconjunctivitis in bovines. Although there is low mortality, but morbidity is high with production losses. Antibiotics 'oxytetracycline and tylosin' are widely used for the treating keratoconjunctivitis but tulathromycin has been recognised as rational single dose treatment option (Lane et al. 2006). Other susceptible antibiotic options include ampicillin, ceftiofur, tilmicosin, tylosin, erythromycin oxytetracycline, and gentamicin. Amoxicillin and clavulanate remained drug of choice against Morexella related infections and involving all strains of it (Hsu et al. 2012). A slight decrease has been reported in MICs of cefotaxime and amoxicillin and a significant decrease in minimum inhibitory concentration of drug clarithromycin for mutants acrA, acrB, and oprM as compared to O35E which is a wild type of strain (Spaniol et al. 2015). Polymyxin drug is last approach against different infections caused by gram negative pathogens which are carbapenem resistant.

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