Indian J. Vet. Med. Vol. 39, No. 2, 2019 pp. 1-5

Invited Review Article

An overview on antimicrobial resistance in veterinary practice and holistic approach for its mitigation

Sarnarinder Singh Randhawa[1], D.K. Gupta[2] and S. Sharma[2]

[1]Ex Director of Research & Professor, [2]Department of Veterinary Medicine, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana

Antimicrobials are among the most commonly prescribed drugs in human and veterinary medicine; and antimicrobial resistance against major bacterial pathogens is one of the most serious and rapidly emerging problems across the globe. Livestock sector plays a critical role in the welfare of India's rural population. India ranks first in global livestock population with a population of 199.1 million cattle, 105.3 million buffaloes, 71.6 million sheep and 140.5 million goats. A widespread antibiotic use in livestock for therapeutics, prophylactics and growth promotion is a cause of concern for environmental contamination. In the United States,around 13,60,800 kg antimicrobials are consumed annually by human beings, while the estimates in animal use are 10-fold higher. The estimates of antimicrobial use are much higher for developing nations.

Any therapeutic usage of antibiotic is compromised by the potential development of resistance. As a result, antimicrobial resistance against major bacterial pathogens is emerging as one of the most serious and rapidly spreading problems across the globe. In United States, at least 2 million people acquire serious antibiotic resistance infections, and at least 23,000 people die annually as a direct result of these antibiotic-resistant infections. A recent database enlists the existence of more than 20,000 potential resistance genes of nearly 400 different types, predicted from available bacterial genome sequences though the number existing as functional resistance determinants in pathogens is much smaller. A relationship has been demonstrated between the high use of antimicrobials and the increased occurrence of resistant bacterial strains in the digestive tracts of man and animals.

Mastitis is the single greatest cause of antibacterial use on dairy farms, and appearance of antibiotic-resistant staphylococci is due to an inevitable genetic response to the selective antimicrobial pressure. The presence of AMR in the commensal microbiota of animals can have a serious impact on human health as these bacteria are likely to be transferred to humans through direct or indirect contact; via food chain or through transfer of genetic resistance determinants to zoonotic pathogens. It is also reported that more than 60% of human pathogens are animal in origin. Foods of animal origin such as meat, milk, and eggs are the important reservoir of antibiotic resistant organisms.

Emergence of antibiotic resistance

Antibiotic resistance is a natural phenomenon that occurs when microorganisms are exposed to antibiotic drugs. Under the selective pressure of antibiotics, susceptible bacteria are killed or inhibited, while bacteria that are naturally (or intrinsically) resistant or that have acquired antibiotic-resistant traits have a greater chance to survive and multiply. The over and/or indiscriminate use of antibiotics also contributes to the increase of antibiotic resistance. The importance of the environment in the spread of antibiotic resistance has been widely recognized in the recent years. The soil is regarded as a reservoir of antibiotic resistance genes, as contaminated water used on food crops may disseminate drug-resistant bacteria. The occurrence of resistant strains in animal products is regarded as a potential risk for public health. Another concern is the transmission of resistant bacteria via non-pasteurized milk and also the exchange of antibiotic determinants between pathogenic bacteria via horizontal gene transfer.

Drug Resistance in Bacteria

It is widely believed that any new commercialized antibiotic become ineffective within a decade due to emergence of resistance. Emergence of extensive and pan drug resistant bacteria has made treatment even more difficult particularly multidrug-resistant tuberculosis (MDR-TB). Similarly, emergence of methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Staphylococcus aureus* (VRSA) have led to nosocomial infections. It is alarming

that even *E. coli* and other commensal intestinal bacteria are demonstrating resistance to fluoroquinolone and carbapenem.

Staphylococcus

In last few decades, a dramatic increase in staphylococcal isolates exhibiting resistance against penicillin, oxacillin, ciprofloxacin, clindamycin, erythromycin, and gentamicin have been reported. Antibiotics are major component of mastitis therapy to cure clinical mastitis as well as a preventive measure in form dry-cow intra-mammary antibiotic infusion. Staphylococci as opportunistic pathogens have got extraordinary capacity to adapt to changing environmental conditions a seven coagulase-negative staphylococci (CoNS) are exhibiting high antimicrobial resistance. Selective pressure has proved an important factor in the development of resistance in Staphylococci that is reflected from high correlation with the resistance patterns of Staphylococci isolated from IMIs in the affected animals of various herds as compared to organic herds. *Staphylococcus* species isolated from multiparous cows that were treated with dry cow therapy showed higher odds of being resistant than isolates from primiparous cows that were not exposed to antimicrobials and could be a reason of failure of dry-cow therapy to eliminate staphyococcal IMI in cows that were prior exposed to antibiotics.

The resistance to penicillins in staphylococci has been attributed to penicillinases, a plasmid-mediated β–lactamase encoded by the *blaZ* gene and causing inactivation of the β-lactam ring. Resistance to ampicillin, tetracycline, erythromycin and lincomycin has also been reported in bovine CoNS isolates. Bovine *S. epidermidis* isolates have exhibited high penicillin resistance as compared to other CoNS species and has also been reported to exhibit higher MDR than other CoNS species. Moreover only less than 10% penicillin-susceptible *S. epidermidis* and *S. haemolyticus* strain could be isolated from hospitalized patients.

Resistance to β-lactams by expression of an additional penicillin-binding protein (PBP2a) encoded by the *mecA* gene (part of a mobile genetic element SCC*mec*) has been an important resistance mechanism in staphylococci. It leads to complete β-lactam resistance conferring multi-resistance to all classes of penicillin including cephalosporins, carbapenems, and monobactams except ceftobiprole and ceftaroline. Staphylococci acquire methicillin resistance through mobile genetic element SCC*mec* that contains *mecA* gene complex and *ccr* gene complex. Till date eleven main types of SCC*mec* (type I-XI) along with many subtypes have been distinguished among MRSA strains. Studies have found that health care associated MRSA (HA-MRSA) strains contain mainly type I, type II and type III SCC*mec* cassettes while CA-MRSA strains contain type IV and type V cassettes.

Non-typhoidal Salmonella (NTS)

Salmonellosis is one of the most common and widely distributed food borne diseases and is caused by bacteria of the genus Salmonella. There are over 1500 NTS serotypes, the most common being *S. Enteritidis*, *S. Typhimurium* and *S. Heidelberg*, that can be found worldwide in domestic and wild animals including birds and amphibians. Incidence of NTS infections has increased considerably in the recent years and every year 94 million cases of NTS gastroenteritis result in 1,55,000 deaths globally; the majority of the disease burden being in the Asian region. Multi drug resistance to commonly used antimicrobial agents (ampicillin, chloramphenicol, sulphonamides and tetracycline) is frequent in NTS. Antibiogram revealed 100% resistance towards cloxacillin, metronidazole and chloramphenicol followed by ceftriaxone sulbactum, ceftriaxone tazobactum, gemifloxacin and least towards amikacin, ampicillin, amoxicillin and gatifloxacin in *Salmonella* isolates from faecal samples of animal origin, including livestock, primates and birds.

Tuberculosis

The emergence and spread of multi drug-resistant strains of *Mycobacterium tuberculosis* (MDR-TB) represents one of the most daunting challenges to disease control worldwide. Incorrect treatment, low patient compliance, and poor quality of drugs, is contributing the development of resistant TB. For instance, extensively drug-resistant tuberculosis (XDRTB) has been recognized in 92 countries with about 4,50,000 new cases of multi drug-resistant tuberculosis (MDR-TB) worldwide in the year 2012. MDR-TB is defined as TB caused by a multi drug-resistant strain that is strain resistant to rifampicin and isoniazid. In

MDR-TB,the number of drugs necessary for treatment is higher than in non-MDR-TB. It is estimated that 9.6% of MDR-TB cases are indeed XDR-TB.

Alternatives to antibiotics

The risk of developing cross-resistance and multiple-antibiotic resistance in pathogenic bacteria both in human and farm animals, is strongly linked to the therapeutic, metaphylactic or prophylactic antibiotics use in human and veterinary medicine. Thus, to combat the global burden of AMR, there is a dire need to develop alternatives to antibiotics; and non-antibiotic additives for prophylactic use as well as growth promoters hold considerable promise. Herbal drugs have been used by clinicians for hundreds of years as indigenous systems of medicine but less than 10% of these plants have been scientifically investigated.

India, the largest producer of medicinal herbs, is appropriately referred to as the botanical garden of the world. The past decade has seen a significant increase in the use of herbal products due to their minimal side effects. This sudden increase in demand for natural products is due to advances in phytochemistry and identification of active compounds in the plants. Synergistic effect of their active ingredients and presence of minerals and salts in plants make them more beneficial in the treatment of diseases. Some substances such as polyphenols have antioxidant, anti-mutagenic, anti-carcinogenic, anti-inflammatory and antimicrobial properties that might potentially be beneficial in preventing diseases. The medicinal plants show great potential to be used as antibacterial agents that can effectively control microbes without any adverse reactions.

At present, the treatment of bovine mastitis is only carried out by antibiotic therapy. But, its overuse and/or indiscriminate use has caused havoc by producing resistance in the pathogens. Attention has also been focused on excretion of antibiotics in milk from untreated quarters after treatment of infected quarters and their administration by parenteral injection or by insertion into the uterus. The relative risk of drug residues in milk increases to 7.1 fold for SCC > 700, 000 cells/ml, and 60% of violations with respect to drug residues in milk occur due to mastitis therapy. For this reason, nowadays, the concept of using non-antibiotic strategies for controlling mastitis is gaining more attention.

One possible approach to control mastitis involves enhancement of host defense mechanism. One such approach is based on enhancement of the animal's natural defense mechanism using non-specific immune-modulators like herbs. Even World Health Organization (WHO) has emphasized on the use of medicinal plants, as they are safer and effective than the synthetic drugs. Many essential oils are relatively easy to extract, have low mammalian cell toxicity, and degrade quickly in water and soil, making them relatively easy to use and environment friendly antibiotic alternatives. Many studies have been conducted across the globe to prove or find the antimicrobial efficiency and / or properties of herbal drugs. For example, *Achillea millifolium* (yarrow), *Caryophyllus aromaticus* (clove), *Melissa officinalis* (lemon-balm), *Ocimum basilucum* (basil), *Psidium guajava* (guava), *Punica granatum* (pomegranate), *Rosmarinus officinalis* (rosemary), *Salvia officinalis* (sage), *Thymus vulgaris* (thyme) and phytochemicals such as benzoic acid, carvacrol, cinnamic acid, eugenol and farnesol were found to contain antimicrobial properties. Among all the oils, the essential oil of cinnamon has been found to be the most effective, followed by the essential oil of oregano and thyme (the active ingredient in latter two plants is carvacrol).

Herbal Drug Resistance

Resistance to herbal drugs in various clinical and/ or non-clinical isolates of pathogenic organisms is also being reported more recently from veterinary clinical isolates but this resistance or sensitivity is comparative and results vary with the concentration of drug used. For example, studies on resistance to herbal drugs showed varying degree of MIC depending upon species of microbes tested or within same species among different strains suggesting that microbes has mechanism to overcome the bactericidal concentration of herbal drugs also. Most herbal products in the market today have not been subjected to drug approval process to demonstrate their safety and effectiveness. Though the guidelines for the assessment of herbal medicine are developed by WHO, but it has not been systematically evaluated. This may lead to indiscriminate or overuse of these drugs which could cause herbal drug resistance in future.

Conclusions

Globally, AMR has become a matter of concern for the scientific community, the society and policy-makers. The WHO global report on surveillance of AMR reveals the lack of adequate surveillance in many parts of the world and large gaps in information on microbes of major public health importance. Attention should also be paid to the emergence of MDR, XDR and PDR pathogens. The advent of new vaccines may help in reducing the need for antibiotics. However, overall, the steps should be taken to reduce antibiotic misuse and inappropriate antibiotic prescriptions. Multidisciplinary and One-Health approach should be followed to prevent emergence and transmission of antimicrobial-resistant microorganisms. Also, the antimicrobial efficacy of herbs can be explored in the field of human as well as veterinary medicine.

References

Aarestrup, F.M., Wegener, H.C. and Collignon, P. 2008. Resistance in bacteria of the food chain: epidemiology and control strategies. *Expert Rev. Anti-inf.*: 6: 733-750.

Bansal, B., Gupta, D.K., Sharma, S., Shafi, T., and Filia, G. 2019. Phenotypic Antibiotic Resistance Pattern and Presence of mecA in Staphylococcus aureus Isolated from Bovine Mastitis. *Int. J. Livest. Res*.: 9(9), 65-79.

Bansal, B.K., Gupta, D.K., Shafi, T.A. and Sharma, S. 2015. Comparative anti-biogram of coagulase-negative staphylococci associated with subclinical and clinical mastitis in dairy cows, *Vet. World.:* 8(3): 421-426.

Bouki, C., Venieri, D. and Diamadopoulos, E. 2013. Detection and fate of antibiotic resistant bacteria in waste water treatment plants: a review. *Ecotoxicol. Environ. Saf.* : 91:1–9.

Carlet, J., Jarlier, V., Harbarth, S., Voss, A., Goossens, H. and Pittet, D. 2012. Ready for a world without antibiotics? The pensie`res antibiotic resistance call to action. *Antimicrob. Resist. Infect. Control.* : 1(1):1–13.

Chandra, H., Bishnoi P., Yadav, A., Patni, B, Mishra A. P. and Nautiyal, A. R. 2017. Antimicrobial Resistance and the Alternative Resources with Special Emphasis on Plant-Based Antimicrobials—A Review. *Plants*: 6, 16-25.

Diekema, D.J., Pfaller M. A., Schmitz F. J., Smayevsky J., Bell J, Jones R. N. and Beach M. 2001. Survey of infections due to Staphylococcus species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. *Clin. Infect. Dis.:* 32(Suppl. 2):S114–S132.

Francesca, P., Patrizio, P. and Annalisa, P. 2015. Antimicrobial resistance: a global multifaceted phenomenon. *Pathog. Glob. Health:* 109 (7): 309-318.

Gupta, R., Thakur, B., Singh, P., Singh, H.B., Sharma, V.D., Katoch, V.M. and Chauhan, S.V.S. Anti-tuberculosis activity of selected medicinal plants against multi drug resistant Mycobacterium tuberculosis isolates. *Ind. J. Med. Res.:* 131, 809–813.

Hiramatsu, K., Hanaki H., Ino, T., Yabuta, K., Oguri, T. and Tenover, F.C. 1997. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *J. Antimicrob. Chemother.:* 40:135–136.

Howard, S.J., Catchpole, M., Watson, J. and Davies, S.C. 2013. Antibiotic resistance: global response needed. *Lancet Infect. Dis.*: 13(12):1001–03.

Kalra, L., Camacho, F., Whitener, C.J., Du P, Miller, M. and Zalonis, C. 2013. Risk of methicillin-resistant Staphylococcus aureus surgical site infection in patients with nasal MRSA colonization. *Am. J. Infect. Control*: 41(12):1253–7.

Kaneene, J. B. and Miller. R. 1992. Description and evaluation of the influence of veterinary presence on the use of antibiotics and sulfonamides in dairy herds. *J. Am. Vet. Med. Assoc.* : 201:68-76.

Khan, R., Islam, B., Akram, M., Shakil, S. and Ahmad, A. 2009. Antimicrobial activity of five herbal extracts against multi drug resistant (MDR) strains of bacteria and fungus of clinical origin. *Molecules* : 14: 586-597.

Kock, R., Schaumburg, F., Mellmann, A., Koksal, M., Jurke, A., Becker, K. and Friedrich, A W. 2013. Livestock-Associated Methicillin-Resistant Staphylococcus aureus (MRSA) as Causes of Human Infection and Colonization in Germany. *PLoS ONE:* 8(2): e55040

Ling, L.L., Schneider, T., Peoples, A.J., Spoering, A.L., Engels, I. and Conlon, B.P. 2015. A new antibiotic kills pathogens without detectable resistance. *Nature*: 517(7535):455–9.

Lowy, F.D. 2003. Antimicrobial resistance: the example of Staphylococcus aureus. *J. Clin. Invest.*: 111:1265–1273

Malathi, V., Revathi, K. and Devaraj, S. N. 2014. Antimicrobial resistance an interface between animal and human diseases. *Indian J. Vet. Anim. Sci. Res.*: 43(2):113–4.

Ogunshe, A. A. and Kolajo, T.T. 2006. In vitro phenotypic antibiotic resistance in bacterial flora of some indigenous orally consumed herbal medications in Nigeria. *J. Rural Trop. Publ. Hlth.*: 5: 9-15.

Oliver, S.P., Murinda, S.E. and Jayarao, B. M. 2011. Impact of antibiotic use in adult dairy cows on antimicrobial resistance of veterinary and human pathogens: a comprehensive review. *Foodborne Pathog. Dis.*: 8(3):337–55.

Prasanna, V., Singh, B.R., Bharadwaj, M. and Singh, S.V. 2015. Emergence of Herbal Antimicrobial Drug Resistance in

Clinical Bacterial Isolates. *Pharmaceutica Analytica Acta.:* 6(10): 1-7.

Revathi, K., Kumar, C.A. and Thamizhavahan, K. 2012. Combined antimicrobial activity of lemon grass oil and Tulasi oil. *Int. J. Preclinical. Pharm. Res.*: 3: 79-81.

Seymour, E.H., Jones, G.M., McGilliard, M.L. 1988. Persistence of residues in milk following antibiotic treatment of dairy cattle. *J. Dairy Sci.*: 71 (8): 2292-2296.

Singh, B. R., Agrawal, R.K., Dubey S., Bhardwaj, M., and Vadhana, P. 2015. Antimicrobial activity of rose geranium (Pelargonium roseum) essential oil on bacteria of veterinary clinical origin. *Asian J. Pharmaceut. Technol. Inno.*: 3: 1-5.

Singh, B.R., Singh, V., Singh, R.K. and Ebibeni, N. 2011. Antimicrobial activity of lemongrass (*Cymbopogon citratus*) oil against microbes of environmental, clinical and food origin. *Int. Res. J. Pharmacy Pharmacol.* : 1: 228-236.

Verma, S. and Singh S.P. 2008. Current and future status of herbal medicines. *Vet. World*: 1: 347-350.

World Health Organization. 2001. WHO global strategy for containment of antimicrobial resistance. Geneva: WHO.

World Health Organization. 2012. The evolving threat of antimicrobial resistance. Options for action. Geneva: WHO Library Cataloguing-in-Publication Data.

World Health Organization. 2014. Antimicrobial resistance: global report on surveillance 2014. Geneva, Switzerland: WHO.