

Development of Antimicrobial Resistance: Mechanisms

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Dr. David Satcher, director of the Centers for Disease Control and Prevention, stated at the September 1995 convocation address at George Washington University School of Medicine, that **“Probably more than anything else, emerging antibiotic resistance threatens to reverse many of the hard fought gains made in the control of infectious diseases in the last century.”** Antibiotic resistance has undergone an explosive development following the introduction of antibiotics in medical practice and in agriculture. To safeguard the efficacy of antibiotic therapy in veterinary medicine and to minimize possible public health risks, it is necessary to identify emerging antimicrobial resistance profiles and limit the spread of these resistant bacterial strains.

Antimicrobials have revolutionized veterinary medicine and improved animal health and productivity since their introduction some 45 years ago (1,3,6,7,9). Despite extensive use, and some misuse, many antimicrobials continue to remain useful. However, loss of efficacy through emergence of bacterial antibiotic resistance is always an ever present threat (1,2,4,5,9).

Gram negative bacteria, in particular *E. coli*, have been slowly acquiring multiple antibiotic resistance phenotypes, to a point where in the near future, therapeutic choices could become very limited (9,11,12). In the past few years, strains of *Escherichia coli* (animal and human origin) have become increasingly resistant to most frontline antibiotics, including third generation cephalosporins, aminoglycosides, and even quinolones. Infections caused by drug-resistant bacteria are a major and costly animal health problem; these infections prolong illness and if not treated in time with more expensive, alternative antimicrobial agents, can lead to increased morbidity and mortality.

Wild-type *E. coli*, unexposed to antibiotic pressures tend to be fully sensitive to all antibiotics and other antimicrobial therapeutics, but exposure to such agents will cause the development of resistance. This resistance development in *E. coli* has been observed from the earliest times of the use of these antimicrobial agents. Bacterial resistance to antibiotics usually develops by means of chromosomal mutations, or by the acquisition of large, transferable, extrachromosomal DNA elements, called plasmids, on which may be other mobile elements, termed transposons and integrons. These mobile elements have been shown to possess genetic determinants for several different mechanisms of resistance (2,8,9,11,12

Extensive use of antimicrobial agents favors the resistant bacterial strains by eliminating more susceptible competitors. If these resistant strains also happen to be more pathogenic than others, than more virulent bacteria could become established at the expense of less pathogenic commensal *E. coli* strains (12).

The term "Antimicrobial resistance" can be interpreted in many different ways. There is intrinsic versus acquired, chromosomal versus extrachromosomal, and microbiological versus clinical. Antibiotic resistance usually operates through one of four general mechanisms: reduced cellular uptake and or increased efflux; antibiotic inactivation; alteration of target enzyme; and alteration of target binding site. The majority of antibiotics used in veterinary medicine can be inactivated or rendered useless by one or more of these mechanisms. For instance, β -lactam antibiotics can be inactivated by the presence of bacterial enzymes called β -lactamases which cleaves the β -lactam ring. Fluoroquinolone resistance has been linked to chromosomal mutations mediating changes in the A subunit of bacterial DNA gyrase (*gyrA*), or to decreased levels of drug accumulation, or both (4,6,11).

The focus of my research at NDSU is to collect data concerning the occurrence of multiple antibiotic resistance among *E. coli* strains incriminated in bovine calf scours and avian colisepticemia. These strains were also screened for several virulence factors that have recently been identified in pathogenic *E. coli* strains. Bacterial antibiotic sensitivities were carried out using standard antibiotic disk diffusion assays and agar dilution methods (10).

For 1997 submissions, antimicrobial resistance percentages ranged from 93% for Tetracycline to less than 1% for Amikacin. Seventy-seven percent of strains were resistant to Ampicillin whereas only 23% were resistant to gentamicin. Eleven percent of strains were resistant to Ceftriaxone and 5% were resistant to Enrofloxacin, even though this drug is not approved for large animal use.

In conclusion, we have shown that resistance to front line antimicrobials is emerging in an alarming fashion among *E. coli* strains incriminated in bovine calf scours and avian colisepticemia. Many of these also possess several virulence factors that enable these strains to produce disease. This combination of virulence coupled with multi-drug resistance is an increasing threat to successful treatment of *E. coli* related diseases.

The issue of bacterial antimicrobial resistance is rapidly moving to the forefront among public health concerns. If veterinary scientists do not investigate the emergence of various antimicrobial resistances, specific antimicrobials are most assuredly going to be removed from the veterinary antibiotic arsenal. The removal of any antimicrobial class could have potential dire consequences in treating future infectious bacterial diseases encountered in veterinary medicine.

REFERENCES

1. Bazile-Pham-Khac, S. Q.C. Truong, J.P. Lafont, L. Gutmann, X.Y. Zhou, M. Osman, and N.J. Moreau. Resistance to fluoroquinolones in *Escherichia coli* isolated from poultry. *Antimicrob. Agents Chemother.* 40:1504-1507.
2. Blanco, J.E., M. Blanco, A. Mora, and J. Blanco. 1997. Prevalence of bacterial resistance to quinolones and other antimicrobials among avian *Escherichia coli* strains isolated from septicemic and healthy chickens in Spain. *J. Clin. Microbiol.* 35:2184-2185;
3. Brown, S.A.. 1996. Fluoroquinolones in animal health. *J. Vet. Pharmacol. Ther.* 19:1-14.
4. Everett, M.J., Y.F. Jin, V. Ricci, and L.J.V. Piddock. 1996. Contributions of individual mechanisms to fluoroquinolone resistance in 36 *Escherichia coli* strains isolated from humans and animals. *Antimicrob. Agents Chemother.* 40:2380-2386.
5. Gold, H.S., and R.C. Moellering, Jr. 1996. Antimicrobial drug resistance. *N. Eng. J. Med.* 335:1445-1453.
6. Griggs, D.J., M.C. Hall, Y.F. Jin, and L.J.V. Piddock. 1994. Quinolone resistance in veterinary isolates of salmonella. *J. Antimicrob. Chemother.* 33:1173-1189.
7. Irwin, R.J., S.A. McEwen, R.C. Clarke, and A.H. Meek. 1989. Prevalence of verocytotoxin producing *Escherichia coli* and antimicrobial resistance patterns of nonverocytotoxin producing *Escherichia coli* and Salmonella in Ontario broiler chickens. *Can. J. Vet. Res.* 53:411-418.
8. Kruse, H., and H. Sorum. 1994. Transfer of multiple drug resistance plasmids between bacteria of diverse origins in natural environments. *Appl. Environ. Microbiol.* 60:4015-4021.
9. Levy, S.B. 1992. *The Antibiotic paradox.* Plenum Publishing
10. National Committee for Clinical Laboratory Standards. 1997. (NCCLS Document M-31 Proposed Standard). Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals. National Committee for Clinical Laboratory Standards, Villanova, PA.
11. Piddock, L.J.V. 1995. Mechanisms of resistance to fluoroquinolones: state of the art 1992-1994. *Drugs.* 49 Suppl. 2:29-35.
12. Salyers, A.A., and C.F. Amiable-Cuevas. 1997. Why are antibiotic resistance genes so resistant to elimination? *Antimicrob. Agents Chemother.* 41:2321-2325.