ISSN 1466-2523

Animal Health Research Reviews **15**(2); 175–177
doi:10.1017/S1466252314000279

Will antimicrobial resistance of BRD pathogens impact BRD management in the future?

Gordon W. Brumbaugh

Caine Veterinary Teaching Center, University of Idaho, Caldwell, Idaho, USA

Received 20 May 2014; Accepted 17 September 2014; First published online 20 November 2014

Abstract

Resistance is a qualitative interpretation of antimicrobial activity *in vitro*. Critical to management of bovine respiratory disease (BRD) is the clinical response *in vivo*. Attempts to connect activity *in vitro* to response *in vivo* have been complicated by the complexity of BRD, interpretation of antimicrobial activity *in vitro*, and inconsistent measures of clinical success or failure. During recent history, the discovery, development, and commercialization of antimicrobials have decreased. In response to resistance, voluntary and imposed restrictions on use of antimicrobials have been implemented. Resistance can be reversed using technology and knowledge of mechanisms of resistance. Perhaps approaches that reverse resistance will be used in clinical management of BRD in the future. The short answer to the question posed in the title is, 'yes.' Since antimicrobial drugs were discovered, resistance has been a consideration for selection of treatment of any infectious disease and BRD is not unique. In the opinion of the author, the more important question is, '*How* will antimicrobial resistance of BRD pathogens impact BRD management in the future?'

Keywords: bovine respiratory disease, antimicrobial resistance, pathogens, clinical management

Resistance is one of three qualitative interpretative categories ('susceptible', 'intermediate' or 'resistant') based on measures of antimicrobial activity *in vitro*, and is defined in the USA by the Clinical and Laboratory Standard Institute (CLSI) as follows: 'This category implies that there will not be a favorable clinical outcome, because the achievable systemic concentrations of the agent will be lower than the minimum inhibitory concentration (MIC) of the causative organism with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms are likely (e.g. beta-lactamase), and clinical efficacy has not been reliable in treatment studies' (CLSI, 2002a, b; Silley, 2012). Break-points are semi-quantitative (arguably) measures (usually MIC, or diameter of the zone of inhibition) that distinguish among the three qualitative categories. There are no details about how data from 'treatment studies' are considered during the establishment of breakpoints (CLSI, 2002a, b).

Standard procedures described by the CLSI are designed to be optimal for the pathogen, and are used for identification of the pathogen as well as for assessment of antimicrobial activity *in vitro*.

Corresponding author. E-mail: gordonb@uidaho.edu

Confusion about how to interpret results *in vitro* is multifactorial, as is the nature of bovine respiratory disease (BRD) (Taylor *et al.*, 2010a, b). Many of the simple questions have not been answered. If more than one pathogen is isolated, what is the fractional contribution of each? What is the influence of resistance with one pathogen but not the other(s)? Are resistant organisms found in animals that do not have clinical signs? Do they remain in treated and recovered animals?

'Concerns' about antimicrobial resistance are not new. Before penicillin was commercially available, Dr Fleming raised awareness that bacteria could change after exposure to penicillin (Rosenblatt-Farrell, 2009). Surveillance/monitoring of *in vitro* activity of antimicrobials began in 1951 (Giles and Shuttleworth, 1958). Focus on antimicrobial activity *in vitro* has been intense, perhaps because it is the easiest to identify of the factors that contribute to clinical failure. However, clinical correlation of those data has not been evaluated effectively. Using non-standardized procedures for studies *in vivo* further confuses attempts to correlate *in vitro* activity and response *in vivo* (O'Connor *et al.*, 2010).

Resistance is not to blame for all clinical failures. Clinical response is the net effect of all factors that contribute to BRD – including antimicrobial resistance. Factors other than antimicrobial resistance play a role in the death of feedlot cattle with BRD (Lamm *et al.*, 2012). Is there a point (percent

resistance) at which medications should not be selected for clinical use? Should selection only include compounds for which susceptibility (what percent?) is identified? Patterns of practice for human patients with community acquired pneumonia (CAP) were 'shifting in response to the perception that current levels of drug resistance necessitate changes in treatment patterns. This is unfortunate because it severely limits one's ability to continue to monitor the effectiveness of available therapies in light of changing patterns of antibacterial drug resistance' (Metlay, 2004). Dr Metlay summarized, '. . .antibacterial drug resistance has not reduced substantially the effectiveness of first-line treatments for CAP. Whether levels of drug resistance will continue to increase or decline is unknown. Therefore, carefully designed outcomes studies likely will continue to be essential to help define optimal therapy for patients who have CAP.' Could those statements apply to BRD?

Antimicrobial resistance and clinical failure are not directly, quantitatively correlated (Lamm *et al.*, 2012; McPherson *et al.*, 2012). Likewise, clinical success is not inseparable from antimicrobial susceptibility. Basic definitions distinguish them; and, the labeling of antimicrobial products contains statements similar to the following: 'The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.' Treatment failures occurred when susceptible organisms were isolated; and, treatment successes occurred when resistant organisms were isolated (Apley, 2003; McClary *et al.*, 2011). Clinical failure, when BRD is associated with susceptible organisms, cannot be due to antimicrobial failure! The association of clinical response with antimicrobial activity *in vitro* is not the same for all BRD pathogens (McClary *et al.*, 2011). Virulence of the organism, the host's resistance to infection, and the host's tolerance to presence of pathogens are also distinct considerations deserving of greater attention (Beceiro *et al.*, 2013; Jamieson *et al.*, 2013). Antimicrobial medications are important; but, the entirety of clinical response is not the responsibility of the medication.

The strongest evidence for clinical decisions is derived from head-to-head, randomized, controlled clinical studies (Karriker, 2007). Techniques such as risk assessment and survival analysis could contribute greatly to evaluating clinical response and the relationship of antimicrobial activity *in vitro* with clinical response. Appropriate economic evaluation of treatments is also warranted (Simoens, 2010).

Driven by fear of resistance, pharmaceutical companies in the USA have re-labeled products to clarify indicated therapeutic uses and decreased research of new antimicrobial agents (Spellberg *et al.*, 2004; Silley, 2012; FDA GFI #213, 2013; Wright, 2013). Regulatory activities are directed toward reclassifying products so that they will be available only with 'veterinary oversight' and have the stated purpose of reducing resistance (FDA GFI #213, 2013).

Realistic considerations for the future should be to include management of fears of resistance, to utilize understanding of mechanisms of virulence and mechanisms of antimicrobial resistance, to improve designs of clinical studies, and to develop technologies or products that could reverse resistance (Spellberg *et al.*, 2004; Tillotson and Echols, 2008; Wright, 2013). Clinical studies with appropriate designs will require many animals and considerable financial investment.

Non-traditional methods of treating infectious diseases have included technologies that reverse resistance. The dogma that mutations only progress toward resistance is wrong. Genetic mutations can be induced to reverse resistance (Cirz and Romesberg, 2006; Ricci *et al.*, 2006; Katsuda *et al.*, 2009). Bacteriophages have been used to reduce bacterial contamination of food, change virulence of bacterial pathogens, alter damage created by bacterial pathogens or enhance the host's tolerance of the pathogen, or reverse antimicrobial resistance (Abuladze *et al.*, 2008; Rasko and Sperandio, 2010; Abedon *et al.*, 2011; Beceiro *et al.*, 2013; Wright, 2013; Hong *et al.*, 2014; Vale *et al.*, 2014). Might it be possible to administer a vaccine that targets BRD pathogens in the upper respiratory tract of cattle and cause those bacteria to become susceptible to treatment, or concurrently administer medications that reverse/prevent resistance while others inhibit or kill the pathogen? 'Concerns' and 'perceptions' are driving regulations, corporate decisions, public response, and therapeutic decisions. Are results of a scientifically based future of treatment of BRD worth the risks of taking that 'bull by the horns'?

References

Abedon ST, Kuhl SJ, Blasdel BG and Marin Kutter E (2011). Phage treatment of human infections. *Bacteriophage* **1**: 66–85.

Abuladze T, Li M, Menetrez MY, Dean T, Senecal A and Sulakvelidze A (2008). Bacteriophages reduce experimental contamination of hard surfaces, tomato, spinach, broccoli and ground beef by *Escherichia coli* O157:H7. *Applied Environmental Microbiology* **74**: 6230–6238.

Apley MD (2003). Susceptibility testing for bovine respiratory and enteric disease. *Veterinary Clinics of North America, Food Animal Practice* **19**: 625–646.

Beceiro A, Tomás M and Bou G (2013). Antimicrobial resistance and virulence: a successful or deleterious association in the bacterial world? *Clinical Microbiology Reviews* **26**: 185–230.

Cirz RT and Romesberg FE (2006). Induction and inhibition of ciprofloxacin resistance-conferring mutations in hypermutator bacteria. *Antimicrobial Agents and Chemotherapy* **50**: 220–225.

Clinical and Laboratory Standards Institute (CLSI) (2002a). *Development of in vitro Susceptibility Testing Criteria and Quality Control Parameters for Veterinary Antimicrobial Agents; Approved Guideline*, 3rd edn. CLSI document M37-A3.Wayne, Pennsylvania: CLSI.

Clinical and Laboratory Standards Institute (CLSI) (2002b). *Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard*, 3rd edn. CLSI document M31-A3.Wayne, Pennsylvania: CLSI.

FDA (2013). Guidance for industry #213: new animal drugs and new animal drug combination products administered in or on medicated feed or drinking water of food-producing animal: recommendations for drug sponsors for voluntarily aligning product use conditions with GFI#209. [Available online at http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm299624.pdf Last accessed May 20, 2014].

Giles C and Shuttleworth EM (1958). The sensitivity of various bacteria to antibiotics during the years 1951 to 1956. *Journal of Clinical Pathology* **11**: 185–189.

Hong Y, Pan Y, Ebner PD (2014). Meat science and muscle biology symposium: development of bacteriophage treatments to reduce

https://doi.org/10.1017/S1466252314000279 Published online by Cambridge University Press

Escherichia coli O157:H7 contamination of beef products and produce. *Journal of Animal Science* **92**: 1366–1377.

Jamieson AM, Pasman L, Yu S, Gamradt P, Homer RJ, Decker T and Medzhitov R (2013). Role of tissue protection in lethal respiratory viral-bacterial coinfection. *Science* **340**: 1230–1234.

Karriker L (2007). The contribution and utility of case studies to evidence based medicine. *Proceedings of the 38th Annual Meeting of the American Association of Swine Veterinarians*; Orlando, FL: 17–18.

Katsuda K, Kohmoto M, Mikami O and Uchida I (2009). Antimicrobial resistance and genetic characterization of fluoroquinolone-resistant *Mannheimia haemolytica* isolates from cattle with bovine pneumonia. *Veterinary Microbiology* **139**: 74–79.

Lamm CG, Love BC, Krehbiel CR, Johnson NJ and Step DL (2012). Comparison of antemortem antimicrobial treatment regimens to antimicrobial susceptibility patterns of postmortem lung isolates from feedlot cattle with bronchopneumonia. *Journal of Veterinary Diagnostic Investigation* **24**: 277–282.

Metlay JP (2004). Antibacterial drug resistance: implications for the treatment of patients with community-acquired pneumonia. *Infectious Disease Clinics of North America* **18**: 777–790.

McClary DG, Loneragan GH, Shryock TR, Carter BL, Guthrie CA, Corbin MJ and Mechor GD (2011). Relationship of in vitro minimum inhibitory concentrations of tilmicosin against *Mannheimia haemolytica* and *Pasteurella multocida* and in vivo tilmicosin treatment outcome among calves with signs of bovine respiratory disease. *Journal of the American Veterinary Medical Association* **239**: 129–135.

McPherson CJ, Aschenbrenner LM, Lacey BM, Fahnoe KC, Lemmon MM, Finegan SM, Tadakamalla B, O'Donnell JP, Mueller JP and Tomaras AP (2012). Clinically relevant Gram-negative resistance mechanisms have no effect on the efficacy of MC-1, a novel siderophore-conjugated monocarbam. *Antimicrobial Agents and Chemotherapy* **56**: 6334–6342.

O'Connor AM, Wellman NG, Rice M and Funk L (2010). Characteristics of clinical trials assessing antimicrobial treatment of bovine respiratory disease, 1970–2005. *Journal of the American Veterinary Medical Association* **237**: 701–705.

Rasko DA and Sperandio V (2010). Anti-virulence strategies to combat bacteria-mediated disease. *Nature Reviews Drug Discovery* **9**: 117–128. doi: 10.1038/nrd3013

Ricci V, Tzakas P, Buckley A, Coldham NC and Piddock LJV (2006). Ciprofloxacin-resistant *Salmonella enterica* serovar typhimurium strains are difficult to select in the absence of AcrB and TolC. *Antimicrobial Agents and Chemotherapy* **50**: 38–42.

Rosenblatt-Farrell N (2009). The landscape of antibiotic resistance. *Environmental Health Perspectives* **117**: A245–A250.

Silley P (2012). Susceptibility testing methods, resistance and breakpoints: what do these terms really mean? *Reviews in Science and Technology Office of International Epizootics* **31**: 33–41.

Simoens S (2010). Cost-effectiveness and antimicrobial resistance in community-acquired pneumonia. *Open Antimicrobial Agents Journal* **2**: 79–83.

Spellberg B, Powers JH, Brass EP, Miller LG and Edwards JE (2004). Trends in antimicrobial drug development: implications for the future. *Clinical Infectious Disease* **38**: 1279–1286.

Taylor JD, Fulton RW, Lehenbauer TW, Step DL and Confer AW (2010a). The epidemiology of bovine respiratory disease: what is the evidence for predisposing factors? *Canadian Veterinary Journal* **51**: 1095–1102.

Taylor JD, Fulton RW, Lehenbauer TW, Step DL and Confer AW (2010b). The epidemiology of bovine respiratory disease: what is the evidence for preventive measures? *Canadian Veterinary Journal* **51**: 1351–1359.

Tillotson GS and Echols RM (2008). Clinical trial design and consequences for drug development for community-acquired pneumonia: an industry perspective. *Clinical Infectious Disease* **47**: S237–S240.

Vale PF, Fenton A, Brown SP (2014). Limiting damage during infection: lessons from infection tolerance for novel therapeutics. *PLoS Biology* **12**: e1001769. doi: 10.1371/journal.pbio.1001769.

Wright GD (2013). Q&A: antibiotic resistance: what more do we know and what can we do? *BMC Biology* **11**: 51–54.