Animal Health Research Reviews

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Pharmacological considerations of antibiotic failures in bovine respiratory disease cases

Brian V. Lubbers

Kansas State University, 1800 Denison Ave., Mosier Hall, Manhattan, KS 66506, USA

Abstract

Bovine respiratory disease (BRD) is one of the most common indications for antimicrobial therapy in beef cattle production and research trials demonstrate that antibiotic therapy greatly improves clinical outcome for BRD. These trials also show that BRD treatment success rates are less than 100% and that there are opportunities to optimize antimicrobial prescribing and improve clinical outcomes if the underlying cause(s) of BRD treatment failures can be identified and addressed. As the etiology of BRD in an individual animal is frequently multi-factorial in nature; it is likely that BRD treatment failures also result from complex interactions between the drug, drug administrator, animal host, pathogens, and the environment. This review will focus specifically on the pharmacological aspects, specifically the interactions between the host and the drug and the drug and the drug administrator, of BRD treatment failures and the actions that veterinary practitioners can take to investigate and mitigate therapeutic failures in future cases.

Review

Cite this article: Lubbers BV (2020). Pharmacological considerations of antibiotic failures in bovine respiratory disease cases. *Animal Health Research Reviews* **21**, 177–178. https://doi.org/10.1017/S1466252320000122

Received: 12 November 2019
Revised: 7 April 2020
Accepted: 21 May 2020
First published online: 2 December 2020

Key words:
Antimicrobials; bovine respiratory disease; pharmacology

Author for correspondence:
Brian V. Lubbers, Kansas State University, 1800 Denison Ave., Mosier Hall, Manhattan, KS 66506, USA.
E-mail: blubbers@vet.k-state.edu

Introduction

Clinical trials repeatedly demonstrate that antibiotic therapy greatly improves clinical outcome in bovine respiratory disease (BRD) cases. These trials also show that treatment success rates are less than 100%; in fact, results from 30 controlled studies submitted for FDA approval of eight different antimicrobials used to treat BRD demonstrate that average treatment success is 70% (range 51–92%). Treatment success rates for clinical cases of BRD in the feedyard setting are similar to those reported for drug approval (personal communication – Dr Robert Smith). These data suggest that veterinarians may be able to optimize antimicrobial prescribing and improve clinical outcomes if the underlying cause(s) of BRD treatment failures can be identified and addressed.

As the etiology of BRD in an individual animal is frequently multi-factorial in nature (Cusack *et al*., 2003), it is likely that BRD treatment failures also result from complex interactions between the drug, drug administrator, animal host, pathogens, and the environment. This review will highlight some of the pharmacological aspects of BRD treatment failures; namely, those interactions between the host and the drug and interactions between the drug and the drug administrator.

Host–drug factors that contribute to clinical failure

One of the central tenets of drug therapy is that antibiotics must achieve sufficient concentrations at the site of action (bacterial receptor) to be effective. In cases of severe disease, alterations in host physiology can influence the pharmacokinetics of antibiotics. In humans, the pathologic changes associated with sepsis can lead to loss of capillary integrity, alterations in protein binding, and changes in renal clearance that potentially lower the plasma concentrations of an antibiotic and result in treatment failures; while end-stage organ dysfunction may lead to increases in plasma concentrations of antibiotics (Shah *et al*., 2015). These same physiological changes likely occur to some extent in severe cases of BRD. Although not a consideration in human medicine due to intravenous administration of antibiotics to severely ill patients, the pharmacokinetics of an antibiotic in food animals are potentially altered due to changes in absorption of drug from intramuscular or subcutaneous injection sites caused by severe dehydration (and reduced blood flow to the superficial tissues). Alterations in the absorption of an antibiotic could result in lower plasma concentrations leading to reduced efficacy and/or increased concentration of drug at the injection site leading to violative drug residues.

Factors such as end-organ failure and endotoxemia may result in higher than expected plasma concentrations due to reduced clearance of drugs. These pharmacokinetic changes could result in drug toxicities, or potentially increase the likelihood of violative residues in food animals (Martinez and Modric, 2010). In reality, drug concentrations in patients with severe systemic disease, such as BRD, will be increased by some of the pathophysiologic

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changes that occur as a result of systemic disease, while other factors may decrease the concentrations of antimicrobials; thus making the sum effects on pharmacokinetics 'markedly unpredictable' for these patients (Goncalves-Pereira and Povoa, 2011).

Drug–drug administrator factors that contribute to clinical failure

In human medicine, the most common drug administrator factors associated with treatment failure are selection of an antimicrobial with inadequate spectrum or improper timing of drug administration (Houck *et al*., 2004; Garcia, 2009). While these factors also potentially contribute to BRD treatment failures, other drug–drug administrator factors should be considered when evaluating therapeutic failures in cattle treated for BRD. As antibiotics are chemical compounds subject to degradation, one of the factors that should be evaluated in cases of treatment failure is drug handling and storage. A study by Ondrak *et al*. showed that typical storage conditions (non-refrigerated truck bed box) in the summer months in Nebraska and Texas exceeded recommended manufacturer storage temperature for 32.5 and 61.8% of temperature readings, respectively (Ondrak *et al*., 2015). In addition to storage and handling issues, underdosing antimicrobials can lead to therapeutic failure. Underdosing may be intentional (for economic reasons) or unintentional due to poor estimation of body weights.

Adverse event report summaries published by the US Food and Drug Administration – Center for Veterinary Medicine also show that transcription errors on prescriptions, confusion between human and veterinary brand names (for prescriptions filled by human pharmacies), and drug packaging and labeling have all contributed to cases of therapeutic failure.

Learning from treatment failures

Most regulatory authorities consider treatment failure ('lack of efficacy') an adverse drug event and it should be reported whether the exact cause of failure can be determined or not (De Briyne *et al*., 2017). Clinicians or animal owners can report therapeutic failures to either the pharmaceutical company that markets the product or directly to the FDA by completing Form 1932 (https://safetycall.com/wp-content/uploads/dlm_uploads/2015/12/FDA-1932_50810.13.pdf – current as of 5 November 2020). Pharmaceutical companies are required by law to forward any adverse event reports to the FDA as part of their post-approval drug monitoring.

The initial step of investigating treatment failure should begin with treatment records. Treatment records can be used to determine the frequency of treatment failure, as well as the relative timing between antibiotic administration and drug failure. Accurate treatment records are also valuable in establishing associations between treatment failures and specific antibiotics (or a specific lot of antibiotic), certain pens or groups of animals, and/or particular drug administrators.

Any potential issues with product use, handling, and administration should be ruled out as part of a therapeutic failure investigation. Although seemingly obvious, medication errors are commonly documented in human medicine and also occur in veterinary medicine. Verifying that the *correct product* was dispensed and used is important to rule out these uncommon prescription errors. Confirming that the product was stored properly and used within the expiration date on the label are simple steps in ruling out product-specific issues. Additionally, treatment failure investigations should include some inquiry into the specific doses and the method for determining the dose (estimated weight, scale weight) used.

Finally, as a specific cause(s) for the treatment failure is determined, steps should be taken to revise treatment protocols and/or Standard Operating Procedures (SOPs) to mitigate these root causes in the future.

Summary

Antimicrobial product activity (or lack thereof) is but one of the factors that results in a BRD treatment failure. Product efficacy can be substantially impacted by both product handling and the BRD disease process. Certainly, other factors associated with the pathogen (antimicrobial resistance), host animal (immune status), environment (transport and nutrition), and animal caretakers (incorrect diagnosis) can, alone or in sum, lead to 'BRD treatment failures'. All of these factors may deserve consideration by veterinary practitioners seeking to optimize antimicrobial therapy of future BRD cases.

Conclusion

Treatment failures for BRD are relatively infrequent occurrences, in light of the number of treatments administered for BRD therapy. However, these events provide considerable opportunity to improve antimicrobial stewardship and enhance cattle health.

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https://doi.org/10.1017/S1466252320000122 Published online by Cambridge University Press