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Author for correspondence:
T. L. Ollivett, University of Wisconsin-Madison School of Veterinary Medicine, 2015 Linden Drive, Madison, WI 53706, USA.
E-mail: theresa.ollivett@wisc.edu

BRD treatment failure: clinical and pathologic considerations

T. L. Ollivett

University of Wisconsin-Madison School of Veterinary Medicine, 2015 Linden Drive, Madison, WI 53706, USA

Abstract

In cattle treated for respiratory disease, resolution of clinical signs has been the mainstay of determining treatment response and treatment efficacy. Through the use of calf lung ultrasound, we have found that pneumonia can persist or recur in the face of antibiotic therapy, despite improved clinical signs, leading to greater risk of clinical disease and more antibiotic use in the future. This review will discuss the pros and cons of using clinical signs to define resolution of disease and discuss how to implement lung ultrasound to improve our ability to accurately measure the impact of antibiotic therapy in cattle with respiratory disease.

In young cattle, respiratory disease is treated primarily by the administration of long acting, injectable antimicrobials intended for single-dose administration. Interestingly, less than 60% of dairy producers consult their veterinarian for specific details about antibiotic usage and 85% use antibiotics in an extra label manner (USDA, 2018). High levels of disease, potential misuse, and retreatment rates contribute to the overall volume of antibiotics administered to dairy calves. This is costly and contributes to the selection pressure for antimicrobial resistance in both pathogenic and commensal bacteria. This is especially concerning because the three classes of antibiotics known for promoting antimicrobial resistance by selecting for multi-drug resistant bacteria in animals and people (third-generation cephalosporins, fluoroquinolones, and macrolides; Guardabassi *et al.*, 2018) are administered to nearly 50% of calves treated for respiratory diseases (USDA 2018).

In the field setting, treatment response is either not measured at all, or is assessed indirectly at the herd level by looking at producer treatment records (e.g. retreatment rate and average number of treatments per calf). In the research setting, response is often gaged by clinical cure rate, clinical relapse rate, mortality rate, average daily gain, and severity of lung lesions at necropsy. Using criteria based largely on the resolution of clinical signs, most reports suggest that 20–35% of treated calves require multiple antibiotic treatments for relapse or recurrence of their respiratory disease (van Donkersgoed *et al.*, 1993; Windeyer *et al.*, 2012; Heins *et al.*, 2014).

In dairy animals less than 6 months of age, lung ultrasound can rapidly and easily detect the non-aerated or consolidated lung lesions associated with bacterial pneumonia (Ollivett and Buczinski, 2016). Depending on the study and regardless of the clinical state of the calf, the sensitivity and specificity of lung ultrasound ranges from 79 to 94% and 94 to 100%, respectively (Rabeling *et al.*, 1998; Buczinski *et al.*, 2015; Ollivett *et al.*, 2015). In addition, there is a high correlation ($r = 0.92$) between the amount of consolidated lung identified on lung ultrasound and gross post-mortem examination (Ollivett *et al.*, 2013) which means we can use this tool to measure the severity of pneumonia in the live calf. Ultrasonographic lung lesions in dairy calves are associated with reduced preweaning ADG (Cramer and Ollivett, 2019), increased mortality (Buczinski *et al.*, 2014), and less milk production during the first lactation (Dunn *et al.*, 2018).

Three BRD subtypes (Ollivett and Buczinski, 2016; Cramer and Ollivett, 2019) can be defined when a systematic clinical scoring system, such as the Wisconsin Respiratory Score (McGuirk and Peek, 2014) is incorporated alongside lung ultrasound: (1) upper respiratory tract infections, (2) clinical pneumonia, and (3) subclinical pneumonia. Although the distributions of BRD subtypes will vary from farm to farm, we have found that at least 1/3 of new cases are subclinical and that for every case of existing clinical respiratory disease, we can expect to find two to four cases of subclinical disease (Ollivett and Buczinski, 2016; Binversie *et al.*, 2020).

For these reasons, lung ultrasound combined with clinical respiratory scoring has become the primary way that we monitor the presence of disease, the competency of farm staff for detecting sick calves, and the treatment response on local commercial dairies as well as research projects (Ollivett and Buczinski, 2016; Holschbach *et al.*, 2019; Binversie *et al.*, 2020). With regard to measuring the treatment response, once treatment has been initiated, the numbers of live bacteria within the lung are significantly reduced and the draw for new neutrophils into the airway slows down. Neutrophils within the airways will undergo apoptosis within 1–2 days of arrival, and that fibrin and cellular debris will be expelled from the airway through coughing and other cellular mechanisms within 7–10 days (Caswell and Williams, 2016). This phenomenon can be observed ultrasonographically through sequential examinations and lung lesion regression visualized as the airways become aerated again (Holschbach *et al.*, 2019; Binversie *et al.*, 2020).

Unfortunately, data from recent studies suggest that retreatment rates can be two to three times higher than those reported in the literature (Binversie *et al.*, 2020); ultrasonographic lung lesions associated with pneumonia initially respond to antibiotic therapy but often recur or worsen shortly after treatment (Holschbach *et al.*, 2019; Binversie *et al.*, 2020), and that antibiotic treatment does not always result in a bacteriologic cure within the lung despite early treatment and resolution of clinical disease (Holschbach *et al.*, 2019).

More specifically, the common definition for treatment success (rectal temperature < 104°F, normal respiratory pattern, normal attitude; as reviewed by DeDonder and Apley (2015)) used by many manufacturers when establishing efficacy of an antibiotic product, would incorrectly classify 100% of the calves with severe lung disease 5 days after a *Mannheimia haemolytica* challenge study and 14 days after a *Pasteurella multocida* challenge (Ollivett *et al.*, 2013; Holschbach *et al.*, 2019). These findings indicate that despite early recognition of disease, and judicious antibiotic use, bacterial infection has not resolved at the lung level using on-label treatment regimens. We hypothesize that incomplete bacterial killing along with ineffective innate immune function sets the stage for bacterial replication and relapse or recurrence of consolidation once the antibiotic pressure has been removed. Poor treatment response coupled with misleading clinical criteria for treatment success puts calves at risk for future clinical disease (Binversie *et al.*, 2020) and prolonged periods of slow growth (Cramer and Ollivett, 2019).

In summary, individual and herd level factors may contribute to treatment failures and ultrasound-guided treatment protocols could re-shape how we measure response to treatment, how we validate dosage regimens for currently approved antimicrobial drugs as well as those drugs undergoing the approval process. Implementing ultrasound-guided treatment protocols on farm should improve calf-level response, result in fewer relapses, decrease duration of disease, thereby improving calf welfare and decreasing cost of disease, ameliorate effect of disease, and ensure that administered antibiotics are effective at establishing a bacteriological cure within the lungs.

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