

RESPIRATORY DISEASE: PHARMACOLOGY



BASICS

OVERVIEW

- Respiratory diseases of cattle are usually referred to as “syndromes” involving one or more infectious organisms and environmental stressors in a compromised animal.
- Bovine respiratory disease complex (BRD) represents the syndrome in older beef calves and adult cattle, while enzootic pneumonia is the syndrome in young dairy calves. Similar respiratory syndromes occur in goats and sheep.
- Also known as shipping fever, BRD is the primary cause of illness and death in feedlot cattle.
- *Mannheimia hemolytica*, *Pasteurella multocida* and *Histophilus somni* are nasopharyngeal Gram-negative bacteria considered to be the primary causes of BRD. They are thought to be introduced into the lower airways during the course of a viral infection.
- *Trueperella pyogenes* (Gram-positive, facultative anaerobe), Gram-negative enteric bacteria, anaerobes, and *Mycoplasma* sp. are secondary pathogens involved in chronic cases.
- To be successful, empirical or definitive antimicrobial therapy must be initiated early in the course of pre-existing disease and should respectively target the suspected or known bacterial pathogen(s). Early treatment will reduce pathogen-associated lung injury. There are several short- and long-acting formulations of antibacterial drugs approved for BRD. However, some of these medications are not approved for use in lactating dairy cattle or veal calves.
- Many feedlots administer antibacterial drugs on a metaphylactic basis to calves at high risk for BRD and to a smaller proportion of older cattle upon arrival to prevent or mitigate BRD.
- Treatment with an approved NSAID may improve clinical signs and reduce lung injury.

INCIDENCE/PREVALENCE

- Antimicrobial therapy of undifferentiated respiratory bacterial infections in feedlot cattle is considered successful if a large majority of animals recover after one drug treatment, the case fatality rate is low (< 7%), and the number of animals with chronic infections does not exceed the number that died.

PATHOPHYSIOLOGY

- The pathogens represented in the BRD complex are ubiquitous in cattle and are often part of the normal flora (i.e. they are pathobionts) in the nasopharynx.
- When cattle are exposed to various stressors, such as long shipping distances, transit shrinkage, and co-mingling, they are at risk for developing BRD, particularly if their immune systems are naïve or impaired.
- During stressful events or respiratory viral infections, host immunocompetence is reduced. This allows pathobionts in the upper airway to flourish and produce infections in the lower respiratory tract.
- The primary bacterial pathogens can generate toxins, which contribute to severe signs of bronchopneumonia.



MEDICATIONS

DRUGS OF CHOICE IN BOVINE INFECTIOUS RESPIRATORY DISEASE

Antimicrobials

- Definitive antimicrobial drug therapy must be administered early in the course of BRD. An antimicrobial drug must attain an effective concentration at the site of infection for an adequate length of time to clear the microorganism(s).
- The approved antibacterial drugs for treatment of BRD vary in their pharmacokinetic and pharmacodynamic properties (Table 1). Drugs with a relatively high volume of distribution (V_d) may penetrate well into tissues and lung fluids, e.g. macrolide antibiotics. A drug's elimination half-life ($t_{1/2}$) is a measure of its persistence in plasma and is associated with drug withdrawal time. Tilmicosin, for example, has a high V_d and a long $t_{1/2}$ in comparison to ceftiofur sodium, which has a lower V_d and shorter $t_{1/2}$. The latter drug is preferred in cattle approaching market weight because of its shorter withdrawal time.
- Antimicrobial action is classified as either concentration-dependent or time-dependent. The antibacterial efficacy of **concentration-dependent drugs** depends upon achieving concentrations that are eight to ten times the minimal inhibitory concentration (MIC) for the targeted bacterial pathogen. For **time-dependent drugs**, antimicrobial efficacy is associated with maintaining drug concentrations above the bacterial pathogen's MIC value for at least 50% of the dosing interval.
- Older fluoroquinolones approved for BRD treatment, including enrofloxacin and danofloxacin, have **concentration-dependent** bactericidal effects on susceptible Gram-negative aerobes and *Mycoplasma* sp. (Table 2).
- Most other classes of antimicrobial drugs that are indicated for BRD have **time-dependent** activity. These include the bactericidal cephalosporins and florfenicol as well as oxytetracycline and the macrolides, which are bacteriostatic (Table 2).
- Metaphylaxis and first pull therapy should target the major Gram-negative BRD pathogens. All of the antimicrobials approved for BRD have good initial activity against *M. hemolytica*, *P. multocida* and *H. somni*. If therapeutic failure occurs, antimicrobial resistance of the primary pathogens and opportunistic infections with *T. pyogenes*, Gram-negative enteric bacteria, anaerobes, and *Mycoplasma* should be considered. Activity against these pathogens varies among the approved drugs.
- Appropriate therapy against opportunistic respiratory tract bacteria may fail because effective drug concentrations may not be achieved at the site of infection, especially in cases of advanced disease with lung injury. The susceptibility of *Mycoplasma* species to antimicrobial drugs determined *in vitro* poorly correlates with the clinical efficacy of these drugs *in vivo*.
- Approved drugs include fluoroquinolones (enrofloxacin, danofloxacin), florfenicol, macrolides and related drugs (gamithromycin, tildipirosin, tilmicosin, tulathromycin), a long-acting oxytetracycline, and a ceftiofur free acid formulation (Table 2). Single-dose therapy with long-acting antibacterial drugs decreases animal stress from handling and reduces labor costs.
- Although approved for BRD, other antimicrobial drugs such as penicillins, erythromycin and anti-folate drugs are less commonly used due to issues such as the requirement for repeated administration, a less desirable pharmacokinetic profile, lower efficacy, and carcass damage at injection sites.

Table 1. Basic Pharmacological Properties of Commonly Used Antibacterial Drugs Approved for BRD Treatment (CD = concentration-dependent; TD = time-dependent)

DRUG	Action	V _d	t _{1/2}	Route
Ceftiofur sodium or HCl	TD	Low	Short	IM, SC
Ceftiofur free acid	TD	Low	Long	SC in the ear
Danofloxacin	CD	High	Moderate	SC
Enrofloxacin	CD	High	Moderate	SC
Florfenicol	TD	Moderate	Long	IM, SC
Gamithromycin	TD	Very high	Very long	SC
Oxytetracycline (long-acting)	TD	Moderate	Long	SC, IM, IV
Tildipirosin	TD	Very high	Very long	SC
Tilmicosin	TD	Very high	Very long	SC
Tulathromycin	TD	High	Long	SC

Table 2. Relative Antibacterial Activities of Representative Antibacterial Drugs Approved for BRD Treatment (+++ = high activity to + = low activity on susceptible bacteria; - = no activity)

Bacteria	Ceftiofur	Danofloxacin or Enrofloxacin	Florfenicol	Oxy- tetracycline	Tilmicosin
Gram (-) respiratory	+++	+++	+++	++	+++
Gram (-) enteric	++	+++	+	+	—
Gram (+)	+++	+	+++	++	+++
Anaerobes	+++	—	+++	+++	+++
<i>Mycoplasma</i>	—	+++	+	+	++

Anti-inflammatory Drugs

- Corticosteroids may reduce inflammation in calves with necrotic laryngitis or tracheal edema syndrome. Single doses of a corticosteroid are unlikely to cause significant immunosuppression.
- Flunixin meglumine, a NSAID, is approved for cattle with BRD when administered by the IV route. It has antipyretic and anti-inflammatory actions, but its effects on long-term performance are not well established.
- A florfenicol-flunixin combination for SC injection in the neck has been recently approved by the FDA for treatment of BRD in beef cattle.

OTHER CONSIDERATIONS

- AMDUCA regulations and appropriate milk and meat withdrawal times must be followed for all compounds administered to food-producing animals.
- Fluoroquinolones, such as enrofloxacin, are not approved for extra-label use in the United States.
- Contact a U.S. (1-888-873-2723) or Canadian (1-866-243-2723) gFARAD office for withdrawal recommendations for extra-label drug use.
- Deep nasal swab cultures are predictive of bacterial isolates from the lungs of cattle with acute BRD.
- Avoid sampling from dead animals, as the *in vitro* susceptibility of the pathogens isolated from treatment failures will not represent the bacterial population as a whole.
- Treated cattle must be closely monitored for response to therapy. Typically, if clinical improvement and normalization of body temperature does not occur within three days of therapy, an alternative therapy is used.
- Avoid over-treating animals with chronic disease as their response is poor and treatment is uneconomical.
- Tilmicosin is an occupational safety hazard and should be handled carefully. Its accidental injection has resulted in human fatalities.



MISCELLANEOUS

SYNONYMS

- Bovine respiratory disease complex
- Enzootic pneumonia
- Shipping fever

ABBREVIATIONS

BRD = bovine respiratory disease

FDA = Food and Drug Administration (U.S.)

gFARAD = global Food Animal Residue Avoidance Databank

MIC = minimum inhibitory concentration

NSAID = non-steroidal anti-inflammatory drug

SEE ALSO

Respiratory Disease: Bovine

Suggested Reading

Apley, M.D., Treatment of calves with bovine respiratory disease: duration of therapy and posttreatment intervals. *Vet. Clin. North Am. Food Anim. Pract.* 2015; 31: 441-453.

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O'Connor, A.M., Coetzee, J.F., da Silva, N., Wang, C., A mixed treatment comparison meta-analysis of antibiotic treatments for bovine respiratory disease. *Prevent. Vet. Med.* 2013; 110: 77-87.

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