

# Characterizing the influence of various antimicrobials used for metaphylaxis against bovine respiratory disease on host transcriptome responses

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## Introduction

Bovine respiratory disease (BRD) is a multifactorial disease complex resulting from interactions among host immunological response, environmental conditions and polymicrobial components. Metaphylaxis, or the mass administration of an antimicrobial upon arrival to a stocker or feedlot facility, is the primary method of control for BRD. Our objective was to determine the influence of 6 different antimicrobials used metaphylactically on the whole blood host transcriptome in healthy steers upon and following arrival to the feedlot.

## Materials and methods

One hundred and five steers were stratified by arrival body weight (BW = 247 ± 28 kg) and randomly and equally allocated to 1 of 7 treatments: negative control (NC), ceftiofur (CEFT), enrofloxacin (ENRO), florfenicol (FLOR), oxytetracycline (OXYT), til-dipirosin (TILD) or tulathromycin (TULA). For each pen, 10 cattle received their designated treatment, and 5 cattle served as sentinel controls. On day 0, whole blood samples and BW were collected prior to a one-time administration of the assigned antimicrobial. Blood samples were collected again on days 3, 7, 14, 21 and 56. A subset of cattle (n = 6) per treatment group (excluding sentinels) were selected randomly for RNA sequencing across all time points. Isolated RNA was sequenced (NovaSeq 6000; ~30M paired-end reads/sample), where sequenced reads were processed with ARS-UCD1.3 reference-guided assembly (HISAT2/StringTie2). Differential expression analysis comparing treatment groups to NC was performed with glmmSeq (FDR < 0.05) and edgeR (FDR < 0.1). Functional enrichment was performed with KOBAS (FDR < 0.05).

## Results

When compared to NC, unique differentially expressed genes (DEGs) were identified for CEFT (n = 526), ENRO (n = 340), FLOR (n = 56), OXYT (n = 111), TILD (n = 3,001) and TULA (n = 87). At day 3, CEFT, TILD, and OXYT shared multiple functional enrichment pathways related to T-cell receptor signaling and FCERI-mediated NF-κB activation that were down-regulated in treatments compared to NC. By day 21, more functionally enriched pathways were identified for FLOR and TILD, with a down-regulation for cytokine signaling.

## Significance

Our research demonstrates immunomodulation and potential secondary therapeutic mechanisms induced by antimicrobials commonly used for metaphylaxis. Our results provide insight to the maintenance of efficacy despite the rise of antimicrobial resistance. These findings provide new concepts related to therapeutic success against BRD.

