

## Better treatment option for bovine respiratory disease (BRD)

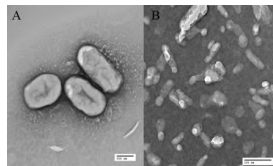
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## Bovine respiratory disease (BRD)

- Most prevalent infectious disease in dairy and beef cattle
- Most prevalent within the first weeks of arrival to the feedlot
  - Fever, breathing problems, nasal discharge, etc.
- Economic loss: \$US 600-750 millions (North America)
- Some feedlots: 65-80% of sickness and 45-75% deaths
- Major risk factors
  - Environmental factors such as weather and shipping
  - Bacteria
  - Viruses

## Major bacterial pathogens of BRD in Canada

- *Mannheimia haemolytica*
- *Pasteurella multocida*
- *Haemophilus somni*



S. Ayalew et al. (2013). Clinical and Vaccine Immunology, 20, 191-196.

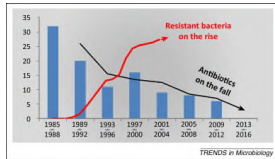
## Preconditioning and metaphylactic treatment

- Preconditioning
  - Vaccination
  - Weaning
  - Bunk feeding
- Metaphylactic (control) treatment
  - Tulathromycin (Draxxin)



### Concern of antibiotic usage

- New regulation in Canada: Veterinary prescription required to purchase any livestock antibiotic from December 2018



T.F. Schäberle and I.M. Hack (2014). Trends in Microbiology, 22, 165-167

### Future directions

- Alternative therapies
  - Vaccination
  - Probiotics
  - **Phytomedicine (prevention and control of BRD)**
- Combination therapies
  - **Reduce dosage of antibiotics (delay and/or eliminate drug resistance development)**
- Novel antibiotics
  - Drug repositioning
  - **Novel hybrid drugs**

### Phytomedicine

- Widely used in Asian countries such as China
- Concerns:
  - Does it work?
  - Active ingredients?
  - How to decide dose?
  - Is it safe?



Folium isatidis

### Phytochemicals against major bacterial pathogens of BRD and BM

| Name of the bacterium                               | MIC (µg/ml)          |                       |                     |             |             |           |              |
|---|----------------------|-----------------------|---------------------|-------------|-------------|-----------|--------------|
|   | allyl/isothiocyanate | benzyl isothiocyanate | chromone/strychnine | resveratrol | gallic acid | quercetin | ferulic acid |
| <i>Moraxella bovocanis</i><br>ATCC 29192            | 125                  | 62.5                  | 125                 | 250         | 500         | -         | 500          |
| <i>Streptococcus bovis</i><br>ATCC 49137            | 31.3                 | 15.6                  | 62.5                | 250         | -           | 12.5      | -            |
| <i>Mycoplasma bovis</i><br>(clinical isolate 112-2) | 500                  | 125                   | 250                 | 500         | -           | -         | 250          |
| <i>Mycoplasma bovis</i><br>(clinical isolate 112-2) | 125                  | 125                   | 125                 | 500         | 250         | -         | 250          |
| <i>Escherichia coli</i><br>ATCC 29424               | -                    | 1000                  | 500                 | 500         | -           | -         | -            |
| <i>Staphylococcus aureus</i><br>ATCC 29218          | -                    | -                     | 500                 | 1000        | -           | -         | -            |
| <i>Staphylococcus epidermidis</i><br>ATCC 12228     | 500                  | 250                   | 500                 | 1000        | -           | -         | -            |
| <i>Streptococcus pyogenes</i><br>ATCC 49619         | 125                  | 62.5                  | 125                 | 500         | -           | -         | -            |
| <i>Streptococcus uberis</i><br>ATCC 49619           | 1000                 | 250                   | 250                 | 1000        | -           | -         | -            |
| <i>Enterococcus faecium</i><br>ATCC 29212           | -                    | 500                   | 500                 | 1000        | -           | -         | -            |
| <i>Enterococcus faecalis</i><br>ATCC 29212          | -                    | 500                   | 500                 | 1000        | -           | -         | -            |
| <i>Enterococcus hirshii</i><br>ATCC 29212           | -                    | 1000                  | 500                 | -           | -           | -         | -            |

## Gallic acid and tulathromycin (MICs)

|                       | Gallic acid (µg/mL) | Tulathromycin (µg/mL) |
|-----------------------|---------------------|-----------------------|
| <i>M. haemolytica</i> | 250                 | 0.31                  |
| <i>P. multocida</i>   | 500                 | 0.31                  |

## Strong additive effect between tulathromycin and gallic acid (inhibition of growth)

|                       | Gallic acid (3.91 µg/mL) | Tulathromycin (0.16 µg/mL) | Gallic acid & Tulathromycin |
|-----------------------|--------------------------|----------------------------|-----------------------------|
| <i>M. haemolytica</i> | 8%                       | 37%                        | 81%                         |
| <i>P. multocida</i>   | 5%                       | 77%                        | 91%                         |

## Bacterial resistance generated from pre-exposure

|                       | Tulathromycin (µg/mL) |      |      |
|-----------------------|-----------------------|------|------|
|                       | 1G                    | 2G   | 3G   |
| <i>M. haemolytica</i> | 0.31                  | 0.62 | 1.25 |
| <i>P. multocida</i>   | 0.31                  | 0.31 | 0.31 |

|                       | Gallic acid (µg/mL) |     |     |
|-----------------------|---------------------|-----|-----|
|                       | 1G                  | 2G  | 3G  |
| <i>M. haemolytica</i> | 250                 | 250 | 250 |
| <i>P. multocida</i>   | 250                 | 250 | 500 |

Inhibition of mixture of *M. haemolytica* and *P. multocida*

|                             | MIC                    |
|-----------------------------|------------------------|
| Gallic acid                 | 500 µg/mL              |
| Tulathromycin               | 0.31 µg/mL             |
| Gallic acid & Tulathromycin | 500 µg/mL + 0.16 µg/mL |

### Future research in our laboratories

- Screen and database construction of phytochemicals against clinical BRD and BM bacterial strains in Saskatchewan
- Evaluate the toxicity of phytochemicals (safety profiles)
- Develop novel combination therapies
- Optimize hybrid drugs

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