Treatment and Prevention of endemic pig diseases using the latest generation macrolide antibiotic.

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Identification and traceability of livestock and their products is extremely important for animal disease control and public health. Conventional identification is based on national databases of unique ear-tags, recognised internationally as extremely valuable for tracing animal movement, managing grants and subsidies, and providing assurance to the consumer and regulatory authorities. Costly and very prevalent endemic diseases threaten the health of pigs and reduce the economic returns of pig farmers in Northern Ireland. Two diseases, Ileitis and enzootic pneumonia in particular are discussed here. Recently an effective tool has been added to the range of options for successful treatment and prevention of these endemic diseases. Tylvalosin (Aivlosin®, Schering Plough Animal Health) is a newly approved antibiotic molecule, a member of the macrolide family, with all the useful pharmacological properties of the group that includes erythromycin, tulathromycin, tylosin and tilmicosin.

Ileitis or Porcine Proliferative Enteropathy (PPE) is an enteric infection associated with Lawsonia intracellularis that leads to diarrhea, weight loss and, in severe cases, mortality. Lawsonia intracellularis is frequently isolated from growing pigs with “colitis” or “grey scours”.

Enzootic pneumonia (EP) is a respiratory disease caused by Mycoplasma hyopneumoniae which leads to coughing, reduced growth rate and increased susceptibility to severe Porcine Respiratory and Reproductive Syndrome (PRRS) and Circovirus Associated Diseases. EP is a chronic respiratory disease with worldwide distribution.

The active ingredient in Aivlosin, acetyl isovaleryltylosin, has recently had a non proprietary name allocated by the WHO, tylvalosin. Tylvalosin is derived from the fermentation of tylosin, with Streptomyces thermotolerans. This fermentation results in the acetylation of the highly active 16 member lactone ring. These structural changes confer benefits such as: rapid absorption from the gut following administration in-feed or in-water, high bioavailability in the target tissues (see table 1) and increased antimicrobial properties due to the addition of the isovaleryl group. Tylvalosin is rapidly metabolized in the liver to 3 acetytylosin (3 AT), which also has antimicrobial properties, and excreted through the bile and into faeces. The mode and mechanism of action of all macrolides is related to interference with protein synthesis in bacteria and mycoplasma by reversibly binding to the 50S ribosome subunit of the 70 S ribosome. The molecule binds to the donor site and prevents the translocation of amino acids, therefore preventing the peptide chain growing. Tylvalosin has a higher level of antibacterial activity than tylosin, which may be due to stronger binding potential or possibly an extra binding site due to the additional side chains. Macrolides are generally considered bacteriostatic but at high concentrations can be bactericidal. Tylvalosin is mycoplasmacidal at concentrations at or close to the Minimum Inhibitory Concentration 90 (MIC90).

An additional property of tylvalosin is the ability to concentrate inside of various cell types in vitro. Tylvalosin has been shown to enter white blood cells, intestinal epithelial cell lines (CaCo2 cells, HRT 18 cells) and pig kidney epithelium cells in studies done in cooperation with the University of Cambridge. Furthermore, it was demonstrated that the intracellular concentration of tylvalosin was higher.

### Table 1. Bioavailability in the lung after oral dosing with 2.125 mg tylvalosin /kg daily for 7 days (From Aivlosin® Dossier)

<table>
<thead>
<tr>
<th>Withdrawal time</th>
<th>Lung tissue (ng/g)</th>
<th>Plasma (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hrs</td>
<td>65.5</td>
<td>&lt;12.5</td>
</tr>
<tr>
<td>12 hrs</td>
<td>60.2</td>
<td>&lt;12.5</td>
</tr>
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compared with other macrolides and in HRT 18 cells did not appear to become saturated.

Becoming intracellular is a critical property of antibiotics for the successful treatment of Lawsonia intracellularis, an obligate intracellular bacterium responsible for ileitis in pigs.

**Treatment and prevention of Enzootic Pneumonia**

Enzootic pneumonia (EP) is caused by Mycoplasma hyopneumoniae which colonises the endothelium of the respiratory tract, damaging ciliated cells and affecting the muco-ciliary system, leading to the classic purple consolidated lesions on the cranio-ventral lung lobes. Coughing is the most obvious clinical sign of EP. Typically, a dry hacking cough is seen in growing pigs from 8 weeks of age until slaughter. This is very obvious when pigs first get up in the morning. In naïve herds, pigs of all ages can be affected by a severe dry cough. Because Mycoplasma colonises the airways attaching to the hair-like cilia, it is very hard for the pig’s immune system to respond rapidly to the infection. Therefore pigs remain infected for a long time (chronic infection). The damage to the airway cilia, in charge of clearing dust and pathogens, can lead to more serious mixed infections with Pasteurella multocida, Actinobacillus pleuropneumoniae, PRRS virus and Porcine Circovirus (PCV2). In complicated infections the cough may become wet, with thumping respiration and pigs will be dyspnoeic, with high fevers and even mortality (commonly known as Porcine Respiratory Disease Complex- PRDC).

Mycoplasma hyopneumoniae can spread a few meters from infected pigs to other pigs by aerosol droplets produced during coughing. Piglets are often already infected at the time of weaning, presumably from the sow, despite the presence of elevated mycoplasma antibodies in colostrum.

M. hyopneumoniae is not believed to survive well outside the pig, so transmission from farm to farm is likely due to the introduction of infected livestock. Frequently, closed EP negative herds become
infected by lateral spread for unknown reasons, perhaps airborne in special weatherv circumstances, by people or mechanically with contaminated objects.

Economic Importance
Erzotitic pneumonia is present in most herds to some degree, except in Specific Pathogen Free farms or farms stocked from EP negative herds.

Affected herds will have depressed growth rate, poor feed conversion efficiency and increased weight variation within a batch at slaughter. The cost of the disease will vary depending on the severity of infection, herd management system, the cost of treatments, and the presence of other bacteria and viruses complicating the clinical presentation. EP can decrease average daily gain by over 40 g and lead to a 16 day increase in number of days to slaughter for every 10% of pig lung affected by pneumonia. In a recent slaughterhouse survey of pig lungs in Northern Ireland 87% of lungs were affected by typical EP lesions and 96% of herds inspected had lesions (Pig Producers Development Council sponsored slaughterhouse survey May 2006).

Treatment and Prevention of Ileitis
Ileitis or Porcine Proliferative Enteropathy (PPE) is caused by the obligate intracellular bacterium Lawsonia intracellularis. The classical disease described in the literature could be separated into 2 distinct presentations:

1. Porcine Intestinal Adenomatosis (PIA); this is characterised as a non haemorrhagic diarrhoea in pigs from 6 to 20 weeks of age. Stools are often soft but not liquid (cow pat appearance). Pigs appear gaunt with hollow abdomen, growth rate is reduced and groups have increased weight variation. Morbidity is variable with no mortality. Differential diagnosis should include: Nutritional Colitis, Enteric Salmonellosis, Brachyspira pilosicoli, Enteritis associated with Porcine Coccidiosis, Yersinia pseudotuberculosis and Trichuris suis.

2. Porcine Hemorrhagic Enteropathy (PHE). Hemorrhagic diarrhoea is often seen as a dark brown liquid or frank blood in the stool. Pigs often appear pale and mortality rate in affected pigs is high. Morbidity is variable but can be high (50%) in completely naïve pigs. Usually the disease affects pigs in the late finishing period or replacement gilts. Differential diagnosis should include: Swine Dysentery (Brachyspira hyodysenteriae), severe enteric Salmonellosis, and haemorrhaging gastric ulcers.

Lately a less clinically severe, endemic form of the disease is being diagnosed in pig herds with very mild diarrhoea and no other clinical signs. Diagnosis has become more complicated with the advent of Porcine Multisystemic Wasting Syndrome (PMWS), which often presents with mild diarrhoea in addition to more severe clinical signs and the presence of many mixed enteric

Management and Control of EP

Elimination of EP
a) Achieve and maintain EP free status by de-stocking and re-stocking with EP negative stock. This is expensive and unfortunately breakdowns are common. Not worth considering in highly pig dense areas.

b) EP eradication by closing the herd to new replacement gilts, partial depopulation of the growing pigs and medication of the breeding stock with antibiotics. Often less expensive than depopulation, but the success rate is reduced compared to depopulation. This method also has the risk of breakdowns. Tylosin, with its low MIC values against M. hyopneumoniae, which are very close to the Minimal Bactericidal Concentration, has been used successfully for these programs.

Control of EP
As many herds are chronically infected and located in pig dense areas, controlling the costly effects of the disease are essential. No single intervention will completely control the infection with M. hyopneumoniae. Three tools in the prevention of EP are available to practitioners:

1) Vaccines - Many vaccines protecting pigs against mycoplasma infection are available in the market. The farm veterinarian will be in the best position to determine the best program to use on a farm, as vaccination before weaning, single dose or 2 dose protocols are available. Each herd should apply a vaccination program based on the epidemiological profile of EP on the farm (severity, time of infection age of first clinical signs and cost of disease). Immunity after intramuscular vaccination with killed mycoplasma antigens does not completely prevent Mycoplasma hyopneumoniae infection, but will significantly reduce clinical signs and pneumonia damage. Protective immunity after vaccination may be delayed 3 to 6 weeks, thus allowing a window without protection for infections to occur.

2) Management - Many interventions like improved ventilation, reduced penned building density, moving pigs using all in all out principles and avoiding mixing of various ages or sources in the same building will reduce the severity of EP.

3) Antibiotics - Various antibiotics are effective against Mycoplasma. The key components of effective therapy and prevention are:
   a) Low MIC (minimum inhibitory concentration) against Mycoplasma hyopneumoniae.
   b) Rapid absorption into the lung
   c) High cell penetration to help kill the Mycoplasma after it has been cleared up by immune system cells
   d) Highly palatable when mixed with feed or water
   e) Well tolerated by the pigs
   f) Short duration of pre-slaughter antibiotic withdrawal.

Tylosin (Avlosol©, Schering-Plough Animal Health) meets all the above criteria. In challenge and field studies tylosin was fed for 7 days at a dose of 2.125 mg/kg, (25 ppm) was shown to very effectively treat and prevent EP with significant improvements in weight gain and lung lesion scores compared to controls. In fact, when compared with Valnemulin, the tylosin treated gilts grew faster, had an improved Feed Conversion Ratio and a lower % of lung affected by pneumonia. Antibiotics in combination with effective vaccines often give the best clinical and economic return in herds with complicated respiratory disease, severe Erzotitic pneumonia or PRDC problems.
infections in growing pigs. In particular combinations of *Lawsonia intracellularis* and *Brachyspira pilosicoli* or enteric *Salmonella* infections seem common in the field. Studies have found *Lawsonia intracellularis* to be ubiquitous and detected in 20 to 80% of herds worldwide with variation in the proportion of pigs showing clinical signs.

**Treatment of Ileitis**

Clinical cases of PPE respond well to antibiotics provided either in the drinking water, feed or in cases of PHE using injectable antibiotics to ensure sick pigs receive a full therapeutic dose. It is critical that infection with *Lawsonia intracellularis* has been confirmed with laboratory diagnosis. Antibiotics licensed for the treatment of ileitis include: lincomycin/spectinomycin combinations, tylosin, tiamulin and valnemulin. Recently, tyvalosin (Avlosin®, Schering Plough Animal Health) has been approved for treatment of ileitis in feed at a dose of 4.25 mg/kg daily for 10 days. Data collected for approval have shown tyvalosin to be highly effective against ileitis in induced disease (challenge) experiments and field challenge studies. Ideally, treatment would be initiated in the earliest stages of infection with *L. intracellularis* to avoid the pathological changes (thickening of the epithelium) and reduce the economical impact of the disease due to reduced nutrient absorption. Treatment using pulse dosing may allow for development of natural immunity to *L. intracellularis*.

**Prevention of Ileitis**

In the past only strategic medication with antibiotics, hygiene improvements and dietary changes were available to veterinarians for the prevention of ileitis. Recently, a live oral vaccine to prevent ileitis has become available (Enterisol Ileitis®, Boehringer Ingelheim). The vaccine is administered orally either by direct dosing as a drench or mixed in the drinking water and is administered to pigs at least 3 weeks before the onset of infection. The vaccine has been shown to be effective in reducing clinical signs and weight gain losses due to ileitis in field studies. The additional labour implications and the perceived cost per dose have hampered uptake by farmers. Once again due to the likelihood of mixed infections leading to “colitis” signs in growing pigs it is imperative that laboratory confirmation of the infection with *L. intracellularis* and correlation with lesions and clinical signs of PPE is carried out by veterinarians.

If mixed infections with *Lawsonia intracellularis* and *Brachyspira pilosicoli* are suspected it may be better to use a strategic medication program with antibiotics effective against both bacteria. Short pulses of medication at the correct therapeutic dose rather than continuous in-feed medication at low levels would better fulfil judicious antibiotic usage criteria.

In conclusion, veterinarian input is critical for the effective control of endemic pig diseases on farm. Thankfully new therapeutic and preventative options have become available to veterinarians that should lead to a reduced economic and animal welfare impact of diseases like Enzootic Pneumonia and Ileitis.

*To not extend the length of this article references have been omitted. References are available from the author upon request.*

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