Preventing the damaging effects of ileitis infections

by Dr Ulrich Klein, Novartis Animal Health Inc., Basel, Switzerland.

Ileitis, also known as proliferative enteropathy, is a disease that affects growing and finishing pigs. It is caused by the intracellular bacterium Lawsonia intracellularis and results in production losses from pigs with poor appetite, poor growth rates, poor batch uniformity and, often, scours. The acute form of ileitis is called proliferative haemorrhagic enteropathy, which usually strikes older pigs and can lead to acute intestinal haemorrhage and sudden death, within 48 hours of infection.

The worldwide presence of ileitis infection has been well monitored with 2008 data showing that, on average, only 4-5% of all farms tested were completely free of Lawsonia. These prevalence data (see Table 1) indicate that ileitis is not going away. In fact, in many countries, an increase has been observed. This increase may be due to tighter restrictions on the routine use of antibiotics in many countries.

On many breeding farms, managed by a variety of the major breeding companies, significant numbers of Lawsonia-positive sows and boars can be detected.

To date, no breeding company has been able to include ileitis as part of its 'high health' certificate status. So, while producers can sometimes buy breeding pigs that are certified free of swine dysentery and mycoplasma, no such guarantee exists for ileitis.

Attempts to eradicate ileitis from production farms have generally failed. Those few farms that have been proven negative for Lawsonia have tended to be isolated breeding farms without any finisher pigs.

Antimicrobial agent	US L intracellularis isolates (n=6)		European L intracellularis isolates (n=4)	
	Intracellular MIC (µg/ml)	Extracellular MIC (µg/ml)	Intracellular MIC (µg/ml)	Extracellular MIC (µg/ml)
Chlortetracycline	4-64	32-64	0.25-16	16-64
Lincomycin	16->128	>128	8-64	32->128
Tylosin	0.25-32	1->128	0.5-2	2-16
Tiamulin	0.125-0.5	1-32	0.125	1-4

Table 2. Intracellular and extracellular MIC ranges for L. intracellularis strains from the United States and Europe.

Table 1. Global prevalence of Lawsonia intracellularis infection.

Country	2000 % farms	2000 % pigs	2008 % farms	2008 % pigs
France	77	35	96	85
UK	95	62	93	64
Spain	73	38	98	71
Italy	67	31	100	100
Germany	73	31	96	83
Belgium	81	38	85	67
Netherlands	84	33	88	83
Denmark	94	30	100	95
Poland	65	23	100	83
Portugal	57	31	100	63
USA	96	60	96	55
Canada	95	60	93	55
Mexico	97	44	95	54
Argentina	68	20	85	35
Brazil	96	22	95	33
Venezuela	91	31	92	43
Japan	68	34	85	35
Korea	96	54	95	55
China	80	71	71	67
Thailand	99	38	100	43
Philippines	86	42	100	45

Effective treatment

In 2009, Dr S. Wattanaphansak and Dr C. Gebhart published their findings from an in vitro study designed to determine the relative sensitivity of this bacterium to leading antimicrobial drugs registered for enteric diseases of swine.

In this study, the minimum inhibitory concentration (MIC_{90}) for several antibiotics against 10 Lawsonia intracellularis strains from the United States (n=6) and Europe (n=4) was assessed. Each of the four antimicrobials was tested in a range of different concentrations (0.25 to 128µg/ml) making the titration of low and high MICs possible.

Intracellular and extracellular MIC assays were performed to mimic the real infectious situation in which Lawsonia intracellularis is exposed to antimicrobials both in the gut lumen and subsequently in the cytoplasm of the intestinal epithelial cells.

The MIC of each antimicrobial was identified as the lowest concentration that inhibited 99% of L. intracellularis growth, as compared to an antimicrobial-free control.

The results showed that of the four antimicrobials tested, L. intracellularis was most

Continued on page 29

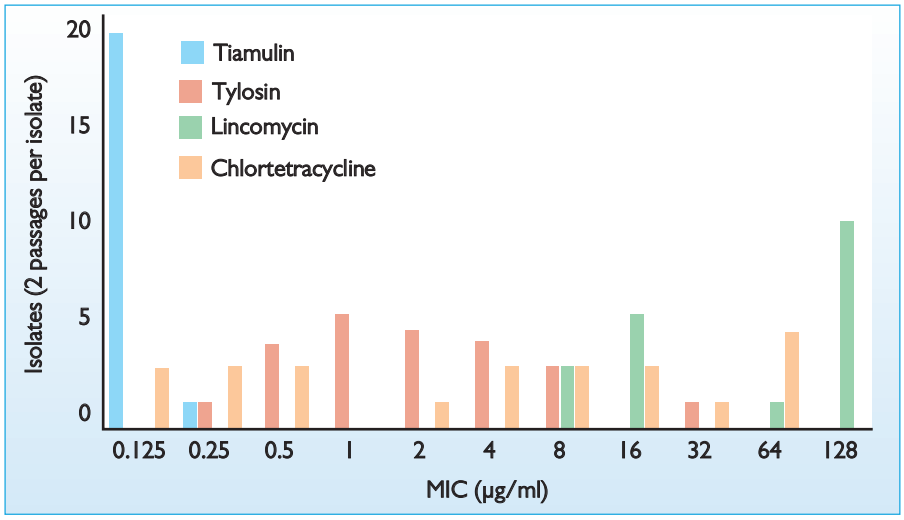

Fig. 1. Distribution of MIC of four antibiotics against L. intracellularis isolates from United States and Europe (10 isolates in total).

Continued from page 27
sensitive to tiamulin in both extra- and intracellular assays (Table 2).

Additionally, these L. intracellularis strains demonstrated a low and non-uniform sensitivity to tylosin, lincomycin and chlortetracycline. In contrast, the sensitivity of L. intracellularis to Denagard was very high and uniform (see Fig. 1).

These trial results provide a scientific basis for the clinical selection of tiamulin (Denagard, Novartis Animal Health Inc.) for the treatment of L. intracellularis infection (ileitis) provided the drug pharmacokinetics are such that therapeutic concentrations are achieved in both the ileum and colon.

PK and PD of tiamulin

The pharmacokinetic (PK) and pharmacodynamic (PD) relationships of tiamulin hydrogen fumarate (THF, Denagard Premix) correlate well with its clinical activity against ileitis.

A study conducted in 2008 describes the THF concentrations in the colon and ileum contents following in feed medication at 110ppm and 220ppm for 14 days.

THF concentrations were measured in the colon contents and a model of the relationship between the colon and ileal contents was used to estimate the concentrations of THF in the ileum. The results are shown in Fig. 2.

When the concentrations of THF established by the data described in Fig. 1 are correlated to the MIC sensitivity data described earlier in Table 2 it can be seen that the effective concentrations of Denagard in the ileum (where Lawsonia infections take place) are well above the MIC90 for L. intracellularis even when administered at relatively low dose rates.

However, it is necessary to compare this to clinical efficacy in field trial data to be sure that effective dose levels can be established for the treatment of ileitis infections.

In a challenge study, the effect of Denagard Premix as a treatment (150ppm, commencing seven days post infection) or as a preventive (50ppm, commencing two days pre-challenge and continuing for 21 days until the trial termination) has been established.

All pigs receiving Denagard Premix at 50 and 150ppm before and after challenge, remained clinically normal, were free from diarrhoea and had no PE lesions at post mortem. (see Table 3). These data prove Denagard administered, in feed, at 50ppm is sufficient to inhibit the development of ileitis, while an inclusion rate of 150ppm treats ileitis infections completely.

Treatment	Gross lesions	Micro lesions
Infected control	6/7	7/7
Denagard 50ppm (P)	0/6	0/6
Denagard 150ppm (T)	0/7	0/7

Table 3. Necropsy results (ileum) at prevention (50ppm) and treatment (150ppm) dosage.

A quick comparison of these effective treatment levels with the ileum and colon concentrations clearly establishes the extent to which these treatment levels exceed the MIC90 of Denagard against L. intracellularis

Summary

For the treatment of ileitis infections caused by Lawsonia intracellularis the substantial therapeutic effect of tiamulin (Denagard) is established and can be explained by the gut pharmacokinetics and the high sensitivity of L. intracellularis strains to Denagard.

Based on recent MIC data, tiamulin (Denagard) is considered as the most active antimicrobial inhibiting the intracellular activity of all L. intracellularis isolates at <0.5µg/ml. The extracellular activity results also confirm the highest sensitivity of L. intracellularis strains to tiamulin in comparison to other antimicrobials tested.

Finally, because Denagard in-feed medication given at recommended dose levels provides high THF concentrations in the ileum and colon – its proven efficacy can readily be explained by a combination of microbe's sensitivity to, and the PK/PD performance of, Denagard. ■

References are available from the author upon request

Fig. 2. Tiamulin colon and estimated ileum contents concentration.

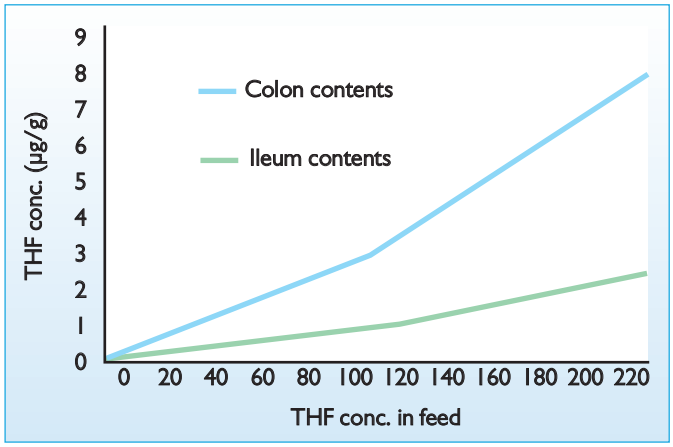

Fig. 3. PK/PD relationship of THF in the ileum contents and Li MIC90 of 0.125µg/ml.