How to manage mycoplasma-induced arthritis

Mycoplasmal arthritis means inflammation of the intra-articular tissue of one or more pig joints and is caused by mycoplasmal bacterial infection. The condition is an important cause of lameness and can occur in pigs of all ages. Young piglets (3-10 weeks of age), fattening pigs (50-90kg) and also adults (gilts, sows, boars) can develop mycoplasma-based arthritis.

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Increasing prevalence, based on increased reporting of arthritis cases and improvements in diagnosis, indicate the emerging problem of mycoplasmal arthritis infections in pig farms worldwide.

Mycoplasma-associated clinical arthritis is a concern to pig producers and can impact both animal well-being and performance during all stages of swine production.

The disease is associated with increased production costs and often one of the main reasons for culling and non-selection of pre-breeding gilts and sows.

In addition to the economic losses, there is the issue of decreased animal welfare due to reduced locomotion, pain and general discomfort.

Pathogens and epidemiology

The aetiologic agents are Mycoplasma hyorhinis and M. hyosynoviae. Mycoplasma hyorhinis-associated arthritis is reported in nursery pigs, especially between 4-10 weeks of age. M. hyosynoviae is mostly identified as the causative agent of arthritis in finishing or adult pigs.

M. hyorhinis is prevalent in most farms and commonly detected in tonsils, nasal cavities and lungs. M. hyosynoviae can also be found in the tonsils, nasal cavities and the pharynx of piglets.

The mechanisms of the systemic spread of both pathogens and the final disease development are still unknown.

Colonisation often takes place as a 'sleeping pathogen' without causing clinical disease. The following factors which predispose to and trigger systemic spreading and disease should be taken into account:

- Stress due to transfer or movement of animals.
- Overcrowding.
- Poorly adjusted ventilation.
- Concurrent infection with other respiratory bacteria (P. multocida, A. pleuropneumoniae).
- Viruses (PRRSV) causing respiratory problems.
- Claw lesions/cartilage pre-damage.

Providing a stress-free environment and avoiding factors that contribute to systemic spread are the best prevention methods. It is known that joint infections with Mycoplasma spp. can be clinically asymptomatic since the pathogens have been diagnosed in synovial fluid of non-lame pigs.

Mycoplasmal infection takes place after colostral immunity has worn off. Infection is by the oronasal route.

The presence of maternally derived antibodies until approximately seven weeks (M. hyorhinis) and 11 weeks (M. hyosynoviae) of age is responsible for different colonisation and infection timelines of both pathogens. Low level colonisation takes place during lactation. Rapid spread is observed early after weaning with an incubation time of 3-10 days. M. hyosynoviae spreads slowly in the nursery and colonises over very long periods of time.

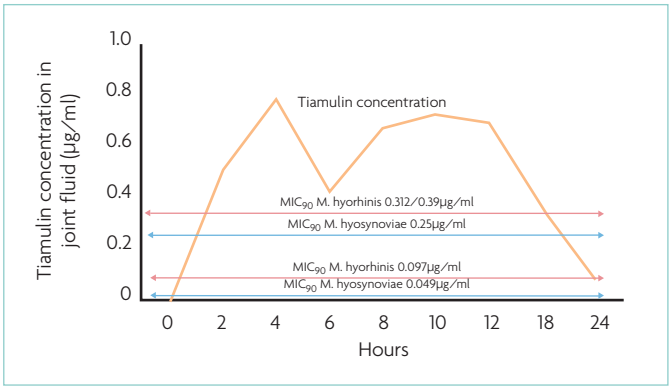

Fig. 1. PK/PD relationships of Vetmulin (tiamulin) Injection (dose: 18mg THF/kg bw) on globally generated M. hyorhinis and M. hyosynoviae strains (arthritis synovial fluid samples).

Clinical signs

Joint swelling and lameness are the most obvious and persistent clinical signs of infectious mycoplasmal arthritis. More than one limb is usually affected, meaning that the pig will be reluctant to rise and walk. Piglets can be infected with both mycoplasma pathogens either directly from the sow, by the pen mates and/or via the environment.

M. hyorhinis arthritis is characterised by polyserositis and lameness.

Typical lesions based on pleuritis, pericarditis and peritonitis are seen and infected pigs show swollen joints and are unwilling to move (stiff movement).

Synovial fluid is viscous, coagulates rapidly and is not clear and transparent.

M. hyosynoviae arthritis is characterised by sudden lameness (one or more limbs affected) and stiff movement. Swollen, soft and fluctuating joints are found. The synovial fluid volume is increased, sero-fibrinous, cloudy and brownish in colour.

Animals do not want to move, which finally results in growth retardation over time.

Table 1. Diagnostics used for M. hyorhinis/M. hyosynoviae detection.

Method/Test	Feasibility/Notes
Clinical diagnosis	Include G. parasuis, S. suis in differentials
Bacterial culture and isolation	Do-able, slow, only certain laboratories
Genetic material detection (PCR)	Rapid results, high accuracy
Antibody detection	ELISA, not commercially available
Antibiotic susceptibility	Rarely performed, as isolates are needed

Diagnosis

Mycoplasmal arthritis must be suspected when lame animals are observed. In most cases, heat and swelling in a joint is sufficient to suggest mycoplasmal arthritis.

During post-mortem examinations, when arthritic joints are cut, synovial fluid in the joint cavity is yellowish-brown in colour and may contain flakes of fibrin. The change in colour from its normal clear and transparent form and consistency indicate an arthritis infection.

Arthritis presence in affected pigs is confirmed by further analysis of the synovial fluid. Final proof of M. hyorhinis or M. hyosynoviae infection is based on PCR testing and culture.

This is done in specialised laboratories able to conduct mycoplasma bacterial culturing in specific mycoplasma media and strain isolation.

Clinical diagnosis include Glaeserella parasuis, Streptococcus suis and Erysipelothrix rhusiopathiae

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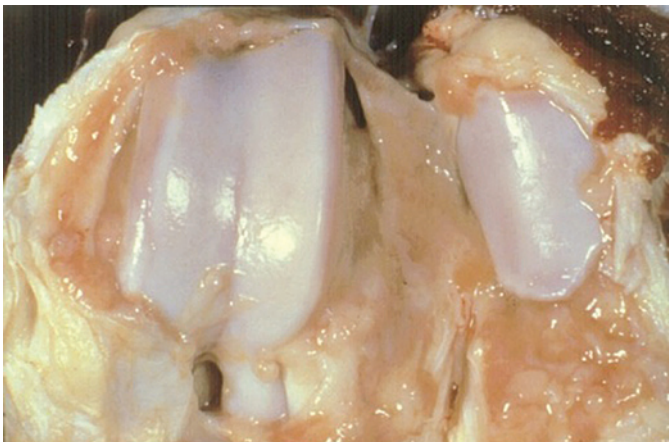
Bacterial swab testing.



Yellowish brown synovial fluid (M. hyosynoviae infection).

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differential diagnosis by bacterial culture, strain isolation and genetic material detection (PCR).

Commercial tests for antibody detection are not available for M. hyorhinis/M. hyosynoviae.

Mycoplasmal arthritis diagnosis options:

- Bacterial culture from tonsil tissue and synovial fluids.
- Serum testing by ELISA.
- Joint and nasal swab by real-time PCR.

Accurate diagnosis is critical for the selection of effective interventions and setting expectations for the likelihood of treatment success.

This includes careful clinical examination, proper sampling and confirming the cause(s) with appropriate diagnostic testing.

Vaccination and control

There is no known cross-immunity between M. hyorhinis and M. hyosynoviae. No vaccine for disease prevention has been registered or is commercially available for either pathogen. Autogenous vaccines are used to develop immunity in affected farms but ambiguous efficacy is reported from the field.

Susceptibility testing

Prudent use of antibiotics requires antibiotic susceptibility testing. Susceptibility profiles of EU M. hyorhinis strains are shown in Table 2. Low and narrow Minimum Inhibitory Concentration (MIC) ranges were found for tiamulin, independent of the country of origin, which indicate a high sensitivity of the tested M. hyorhinis strains. In Table 4, the MICs of several antibiotics tested against M. hyosynoviae strains from Europe and Thailand are summarised. High sensitivity of these strains with the lowest MIC_{90} and MIC ranges were determined for tiamulin.

Treatment of mycoplasmal arthritis

Curative intervention with antibiotics is the standard measure for mycoplasmal arthritis treatment. The timing of treatment is especially important to achieve a full recovery. Treatment is most effective if given early in the course of the disease before chronic lesions have formed.

Successful treatment of M. hyorhinis and M. hyosynoviae arthritis infections can only be achieved by the administration of an antibiotic that reaches therapeutic concentrations at the joint infection site where both pathogens are present.

Antimicrobial susceptibility of M. hyorhinis and M. hyosynoviae strains is fundamental to combat the emergence and expansion of antimicrobial resistance.

For the treatment of M. hyorhinis and M. hyosynoviae arthritis, antibiotics with the lowest MIC need to be used. MICs indicate the lowest antibiotic concentration which inhibits the growth of Mycoplasma spp. and other bacteria species.

The selection of the best antibiotic is ideally based on pharmacokinetic (PK) and pharmaco-dynamic (PD) knowledge.

A favourable pharmacodynamic (PD) activity measured as MIC and pharmacokinetic (PD) behaviour with sustained activity at the joint infections site are the key criteria for successful treatment. Arthritis treatment requires effective distribution of the antibiotic into the joint fluid. For an inhibitory or killing effect, the concentration of the antibiotic used for treatment should exceed the determined MICs during the dosing interval.

Consistent tiamulin concentration (average 0.6µg Tiamulin Hydrogen Fumarate/ml) and concentration maintenance in the joint fluid for about 24 hours are achieved after a single parenteral administration of Vetmulin Injection when used at the treatment dosage (see Fig. 1).

The data summarised in Fig. 1 indicate that, over 24 hours after one parenteral administration of Vetmulin, the tiamulin concentration in the joint fluid exceeds the MIC_{90} values for M. hyorhinis and M. hyosynoviae strains generated globally.

Considering the achieved joint fluid concentrations at the treatment dosage over 24 hours and the tiamulin MIC_{90} values determined globally, an excellent therapeutic effect can be expected from Vetmulin injection against

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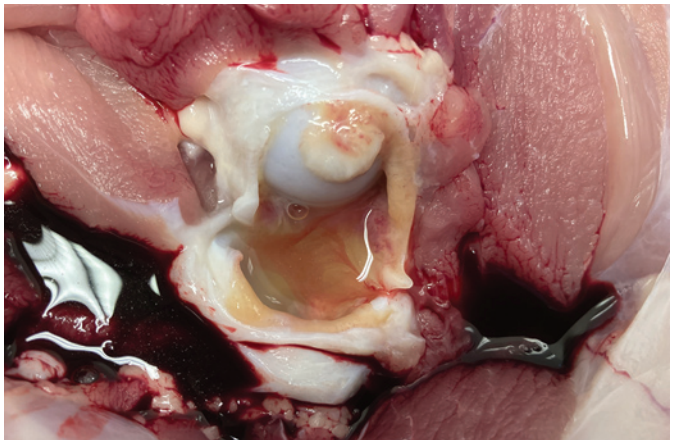
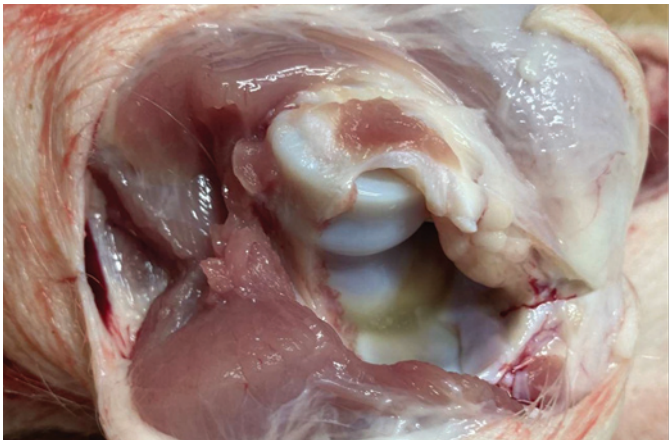
Table 2. Antibiotic susceptibility profiles (MICs in µg/ml) of European M. hyorhinis isolates.

	Hungary (n=20)		Italy (n=20)		Poland (n=19)		Germany (n=15)	
	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range	MIC_{90}	MIC range
Vetmulin (Tiamulin)	0.156	≤0.039-0.312	0.312	0.078-0.312	0.625	≤0.039-0.625	0.312	0.078-0.312
HydroDoxx (Doxycycline)	0.156	≤0.039-0.156	0.156	≤0.039-0.625	0.078	≤0.039-0.156	0.078	≤0.039-0.156
Oxytetracycline	0.25	≤0.125-0.5	0.25	≤0.125-0.5	0.5	≤0.125-0.5	≤0.125	≤0.125-0.25
Enrofloxacin	0.625	0.078-10	0.625	0.625-1.25	1.25	0.312-2.5	1.25	0.312-1.25
Amphen (Florfenicol)	2.0	0.25-4.0	2.0	≤0.125-4.0	2.0	≤0.125-2.0	2.0	1.0-2.0
Tylvalosin	5.0	≤0.039-5.0	5.0	≤0.039->10	5.0	≤0.039-10	10.0	≤0.039->10
Tilmovet (Tilmicosin)	>64	1.0->64	>64	2.0->64	>64	1.0->64	>64	1.0->64
Huvemycin (Tulathromycin)	>64	4.0->64	>64	2.0->64	>64	4.0->64	>64	2.0->64
Lincoral (Lincomycin)	>64	≤0.25->64	>64	≤0.25->64	>64	≤0.25->64	>64	≤0.25->64





Synovial fluid fibrino-suppurative exudate of M. hyorhinis infection (Courtesy of Dr Miklos Gyuranecz).

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arthritis. In several efficacy field studies in pigs affected by significant lameness problems based on M. hyorhinis and M. hyosynoviae infection, the pronounced therapeutic activity of Vetmulin parenteral treatment (1.5ml/20kg bodyweight daily/three consecutive days) was confirmed.

Conclusions

Mycoplasma-associated clinical arthritis is an emerging problem worldwide. Pigs at different ages are affected from nursery to adult pigs. Diagnosis is based on PCR testing and bacterial culture. Antibiotic drugs are used for treatment and control.

No commercial vaccines are available for arthritis disease prevention.

Pharmacokinetic and pharmacodynamic data for Vetmulin Injection administration indicate high tiamulin joint fluid concentrations which exceed the tiamulin MIC values determined for M. hyorhinis and M. hyosynoviae isolates from clinical arthritis cases.

Vetmulin injection (1.5ml/20kg bodyweight daily/three consecutive days) is the antibiotic product of choice for mycoplasmal arthritis treatment based on its excellent PK/PD profile. ■

References are available from the author on request

Table 3. Tiamulin MICs (in µg/ml) against M. hyorhinis isolates from different countries and regions.

Author	Country/Region (n = number of strains tested)	Vetmulin (Tiamulin) MIC_{90}
Beko et al., 2019	Hungary (n=38)	0.312
Rosales et al., 2020	Spain (n=48)	0.25
Makhanon et al., 2012	Thailand (n=104)	0.39
Thongkamkoon et al., 2011	Thailand (n=9)	0.097
Jang et al., 2016	Korea (n=12)	0.25
Klein et al., 2022	EU (n=76)	0.312

Table 4. Antibiotic susceptibility profiles (MICs in µg/ml) of EU and Thailand M. hyosynoviae isolates (n.t. = not tested).

	EU (n=38)		Thailand (n=8)	
	MIC_{90}	MIC range	MIC_{90}	MIC range
Vetmulin (Tiamulin)	0.25	0.039-0.25	0.049	≤0.006-0.049
HydroDoxx (Doxycycline)	2.0	0.25-4.0	100	3.12-100
Oxytetracycline	n.t.	n.t.	0.25	≤0.125-0.5
Enrofloxacin	n.t.	n.t.	6.25	0.78-6.25
Lincoral (Lincomycin)	4.0	0.5-8.0	1.56	0.049-1.56
Pharmasin Tylovet (Tylosin)	16.0	2-32	3.12	0.78-3.12