Vetrimoxin® L.A.

LONG ACTING AMOXICILLIN

Your **first-line treatment** for responsible antibiotic use

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Vetrimoxin® L.A. is the 1st choice in the treatment and control of *Streptococcus suis* infections

Arthritis

Meningitis

Streptococcus suis, an important pathogen in swine production

- *Streptococcus suis* represents one of the major threats in swine as regards to bacterial infections in industrial farms.
- It is a very early coloniser, the first contaminations can occur already during parturition when piglets are colonised by sows.
- Disease is prevalent in all types of production, including SPF (specific pathogen free) and conventional farms.
- Infection by *S. suis* is classical example of systemic disease characterised by septicaemia, meningitis and localised infections of joints (arthritis) and endocarditis.
- Infection is difficult to control by vaccination as there are currently 35 serotypes of *S. suis* described, based on capsular polysaccharides.
- Successful treatment of septicaemia and meningitis depends mainly on the proper selection of antibiotics and early individual treatment at the first clinical signs.

Comparison of the efficacy of amoxicillin with other antimicrobials against *Streptococcus suis*

Comparison of tested antimicrobials, % of sensitive isolates according currently available MIC breakpoints[1]

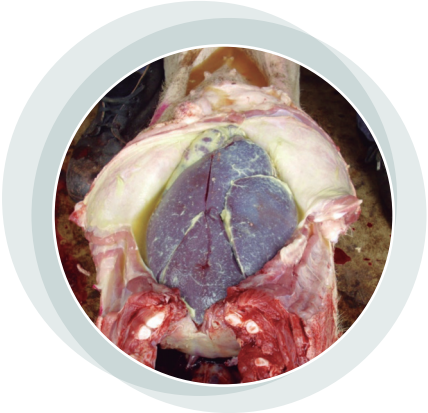
Atb	MIC_{50}	% of sensitive isolates	Range of MIC	MIC breakpoint for resistance (µg/ml)
Amoxicillin	**< 0,125**	**100**	**≤ 0.125- 0,5**	**≥ 2.0**
Tulathromycin*	8	ND	< 4,0- > 256	unavailable
Ceftiofur	< 0,25	100	< 0,25- 1,0	≥ 8.0
Enrofloxacin	0,5	100	< 0,125- 1,0	≥ 2.0
Tetracyklin	> 8,0	36	0,5- > 8,0	≥ 2.0

* The commercial injectable tulathromycin product does not include efficacy against *Streptococcus suis* in its summary of product characteristics.

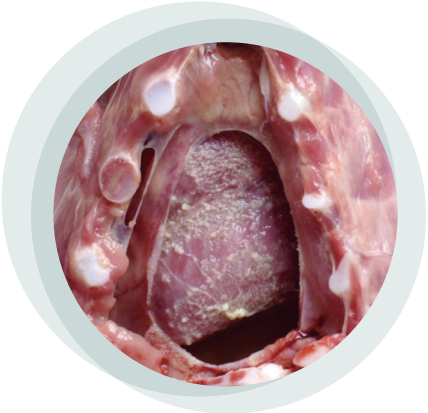
Conclusions

- Amoxicillin is the best optimal choice for the treatment and control of *Streptococcus suis.*
- Considering the PK/PD parameters of amoxicillin, **Vetrimoxin® L.A.** can be considered as the best treatment of choice for the streptococcal infections of swine.

Vetrimoxin® L.A. is the 1st choice in the treatment and control of *Haemophilus parasuis* infections



Peritonitis



Pericarditis

Haemophillus parasuis, important bacteria to control in swine production

- Glässer's disease caused by *H. parasuis* (Hps) is present in all major swine-raising countries.
- *H. parasuis* difficult to eradicate by different methods and systems and still consider important pathogen in farms with high health status (SPF).
- As typical example of "early coloniser" *H. parasuis* may result in systemic disease of high morbidity and mortality affecting swine at any stage of production.
- Classical manifestation of disease is the development of septicaemia, arthritis, fibrinous polyserositis and in some cases pneumonia.
- The appropriate and rational use of antimicrobials is considered to be an important component in managing of *H. parasuis* infection.

Comparison of the efficacy of amoxicillin with other antimicrobials against *H. parasuis*

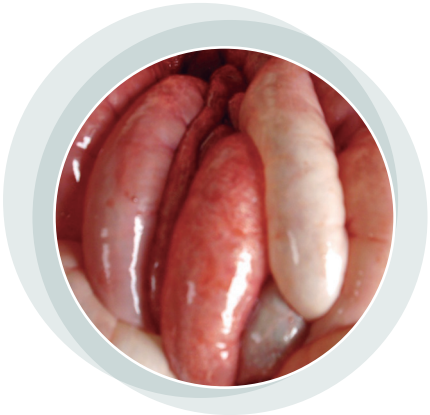
Comparison of MIC_{50} and MIC_{90} for selected antibiotics and range of MIC concentrations obtained for *H. parasuis*[2]

	MIC_{50} (mg/l)	MIC_{90} (mg/l)	Range of concentration (mg/l)
Amoxicillin	**0,06**	**0,25**	**≤ 0,03- 4**
Ceftiofur	< 0,125	0,5	≤ 0,125-1
Tulathromycin	2	64	0,5-64
Penicillin	0,25	4	≤ 0,06- 8
Tetracyclin	2	64	1-64

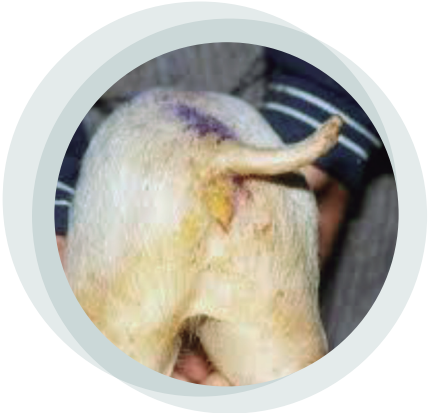
Conclusions

- Based on *in vitro* data generated, Czech isolates of Hps are highly susceptible to amoxicillin (highest).
- Taking into consideration the rational use of antimicrobials and the ban on 3rd and 4rd generation cephalosporins in some important swine producing countries, amoxicillin is considered the first line treatment.
- Tulathromycin seems to be clinically ineffective for the treatment of systemic infection because of its PK/PD characteristics (low plasma concentration and generally high MIC_{50} and MIC_{90}).

Vetrimoxin® L.A. is the 1st choice in the treatment and control of clostridiosis (caused by *Cl. perfringens*) in piglets



Hemorrhagic intestines



Clostridial diarrhea

Clostridiosis in piglets

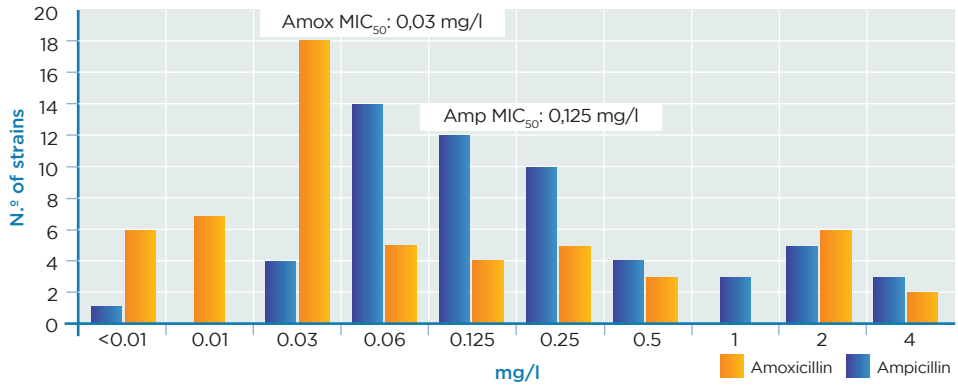
- Clostridial diseases of swine are worldwide present and characteristic almost exclusively for a neonatal period of life of piglets.
- Affected animals cannot develop real growing potential and are predisposed to other enteric pathogens.
- Antibiotic therapy remains an important tool for the control of clinical infection and outbreaks in farrowing houses.

Amoxicillin is considered an excellent drug according its antimicrobial activity to treat clostridiosis in piglets[3]

Comparison of MIC_{50}, MIC_{90} and concentration ranges

	MIC_{50} (mg/l)	MIC_{90} (mg/l)	Range of MIC
Ampicillin	0,125	2	< 0,01-4
Amoxicillin	**0,03**	**2**	**< 0,01-4**

Distribution of MIC for amoxicillin and ampicillin with interpretation of results



Conclusions

- Amoxicillin is the best option for the treatment of *Cl. perfringens* type A infection of piglets.
- Study concluded that no isolates resistant to aminopenicillins were found.
- According to the rational use of antimicrobials amoxicillin is considered to be an optimal choice for treating clinical cases of diarrhoea in farrowing houses.

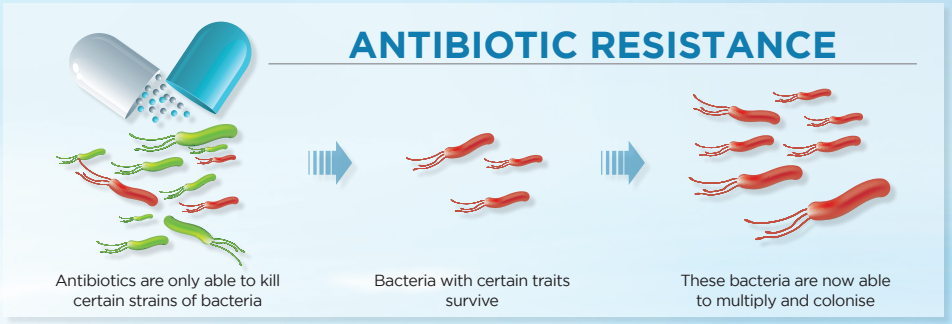
Vetrimoxin® L.A.

LONG ACTING AMOXICILLIN

Detection of ESBL production by *E. coli* in laboratory

Vetrimoxin®LA (amoxicillin) instead of 3rd and 4th generation cephalosporins for 1st choice treatment

- Beta-lactams are the most widely used family of antibiotics because of their extended spectrum of activity and low toxicity.
- Currently, the global rule is to limit the prescription of cephalosporins to avoid the selection for extended-spectrum betalactamase producing enterobacteria (ESBL). In addition, production of ESBLs is associated with resistance to other classes of non-beta-lactam antibiotics, (multidrug-resistance bacteria).
- However, aminopenicillins remain a mainstay first line therapy in the treatment of a large variety of infections.



In-vitro study:

Rapid development of high level resistance to cephalosporins after serial exposures of clinical enterobacteriaceae isolates to sub-inhibitory concentrations of cefalexin and ceftiofur.[4]

- In this study, four species of Enterobacteriaceae group used to generate *in vitro* resistance to amoxicillin, cefalexin and ceftiofur. Resistant mutants were generated by exposure to serial passages on sub-inhibitory concentrations of the three tested antibiotics.

Susceptibility of the mutants selected on amoxicillin, cephalexin & ceftiofur

E. coli Ref-strain (ATCC)	MIC of parental strain	Mutant MIC after 12 passages on amoxicillin	Mutant MIC after 12 passages on cefalexin	Mutant MIC after 12 passages on ceftiofur
Amoxicillin mg/l	2	16	64	8
Cefalexin mg/l	4	8	> 512	64
Ceftiofur mg/l	0.125	0.25	1	1
Resistance mechanisms	–	IP	*AmpC* hyperproduction + EFX	IP

E. coli (TEM 1)	MIC of parental strain	Mutant MIC after 12 passages on cefalexin	Mutant MIC after 12 passages on ceftiofur
Amoxicillin mg/l	> 512	> 512	> 512
Cefalexin mg/l	8	> 512	256
Ceftiofur mg/l	0.25	8	16
Resistance mechanism	–	*AmpC* hyperproduction	EFX + IP

S. typhi	MIC of parental strain	Mutant MIC after 12 passages on amoxicillin	Mutant MIC after 12 passages on cefalexin	Mutant MIC after 12 passages on ceftiofur
Amoxicillin mg/l	2	16	16	8
Cefalexin mg/l	4	16	128	64
Ceftiofur mg/l	0.38	0.5	1	1
Resistance mechanism	–	EFX + IP	IP	IP

K. pneumoniae (SHV-1)	MIC of parental strain	Mutant MIC after 12 passages on cefalexin	Mutant MIC after 12 passages on ceftiofur
Amoxicillin mg/l	> 512	> 512	> 512
Cefalexin mg/l	6	> 512	256
Ceftiofur mg/l	0.5	2	4
Resistance mechanism	–	EFX + IP	IP

EFX: MIC decreases with PAßN; **IP:** impermeability.

Results and discussion

- Amoxicillin selects for mutants which have low-level resistance to amoxicillin and cefalexin, and are susceptible to ceftiofur (MICs X 2).
- Ceftiofur selects for mutants which have low-level susceptibility or resistance to ceftiofur (MICs X 2-64), low-level resistance to amoxicillin and high-level resistance to cephalexin, in particular for penicillinase-producing strains. Thus, cephalosporins tend to select for mutants with crossresistance to cephalosporins and aminopenicillins, while aminopenicillins essentially select for their own resistance.

Conclusions

- Aminopenicillins can continue to be used on an empirical basis and in documented infections due to susceptible strains, without any significant risk of selection for cephalosporin resistant mutants.
- In contrast, cephalosporins should be used in the One Health context with parsimony as a second line therapy in veterinary and human medicine only for cases where amoxicillin is proven inactive.

Vetrimoxin® L.A. is more efficacious against septicaemic infections in piglets (*S. suis* and *H. parasuis*) than tulathromycin*

Tulathromycin shows typical pharmacokinetics for a macrolides: extensive distribution to the tissues, relatively slow elimination, and high and sustained lung concentration. **Besides this fact, the concentration in the plasma and extracellular fluids is rather low. Plasma (serum) concentration of free antibiotic is the most important parameter for predicting the effect on septicaemic bacteria (pathogens penetrating to the blood circulation) and factor influencing treatment outcomes. For this reason, antibiotics which are characterised by high plasma concentrations and more hydrophilic character (Vetrimoxin® L.A.) are much more effective.**

C_{max} (maximal concentration of ATB after injection of recommended dose):

	C_{max} mg/l
Tulathromycin	0,6
Amoxicillin	5,1

Comparison of MIC_{50} and MIC_{90} for amoxicillin and tulathromycin for *H. parasuis*

	MIC_{50}	MIC_{90}	Range of concentration
Amoxicillin	0,06	0,25	≤ 0,03- 4
Tulathromycin	2	64	0,5-64

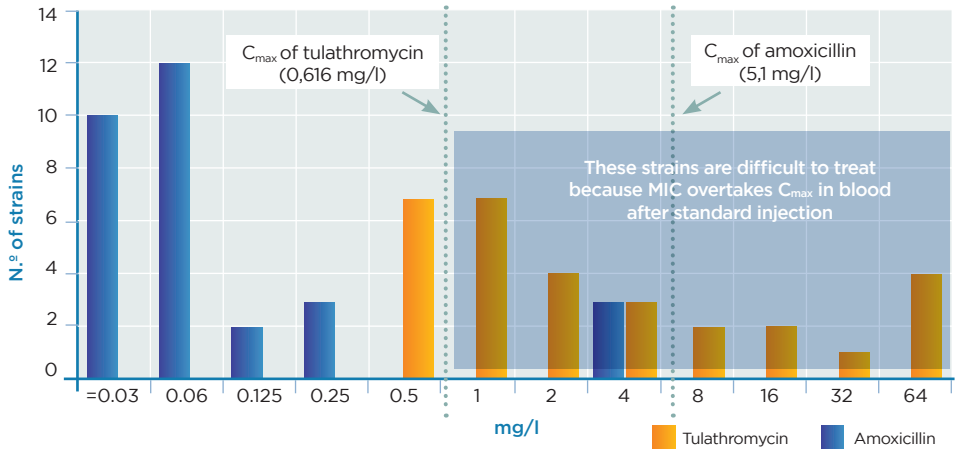
Taking in to consideration the results of published studies[1,2] (MIC for *S. suis* and *H. parasuis*) and pharmacokinetics parameters of tulathromycin (C_{max} and plasma concentration) **we consider tulathromycin as a not very effective treatment option for metaphylaxis and treatment of the infections mentioned.**

Comparison of MIC_{50} values for amox and tulathromicyn for *S. suis*[1]

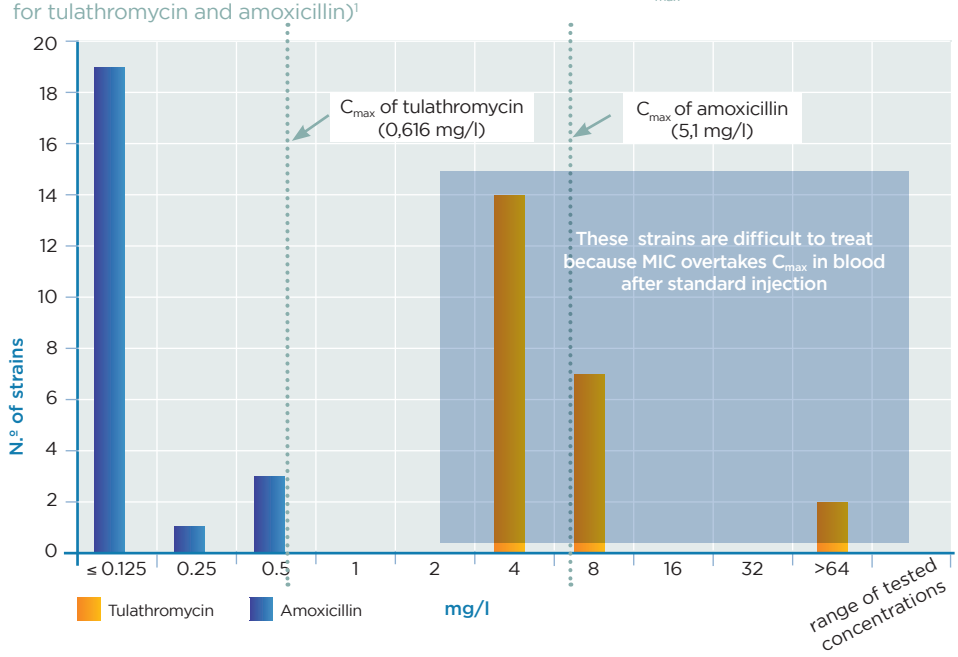
Atb	MIC_{50}	% of sensitive isolates	Range of MIC
Amoxicillin	< 0,125	100	≤ 0.125 - 0,5
Tulathromycin	8	ND	< 4,0- >256

*The commercial injectable tulathromycin product does not include efficacy against *Streptococcus suis* in its summary of product characteristics

H. parasuis MIC comparison of amoxicillin and tulathromycin (with C_{max} indication for thulatromycin and amoxicillin)[2]



S. suis MIC comparison of amoxicillin and tulathromycin (with C_{max} indication for tulathromycin and amoxicillin)[1]



Vetrimoxin® L.A. is more efficacious against septicaemic infections in piglets (*S. suis* and *H. parasuis*) than injectable tulathromycin

Vetrimoxin® L.A. is the 1st choice treatment against *S. suis, H. parasuis* and *Cl. perfringens* infections

Vetrimoxin® L.A. (amoxicillin) is the 1st choice treatment instead of 3rd and 4th generation cephalosporins

Bibliography

1. Comparison of the efficacy of amoxicillin with other antimicrobials against streptococcus suis. D. Sperling *et al.* APVS 2015.
2. The determination of minimum inhibitory concentrations of selected antimicrobials for porcine *Haemophilus parasuis* isolates from the Czech Republic. K. Nedbalcova *et al.* IPVS 2016.
3. In vitro susceptibility of Czech porcine isolates of C. perfringens Type A cpb2+ to amoxicillin, ampicillin and amoxicillin-clavulanic acid. M. Masarikova *et al.* IPVS 2016.
4. Rapid development of high level resistance to cephalosporins after serial exposures of clinical isolates of enterobacteriacae to sub-inhibitory concentrations of cefalexin and ceftiofur. F. M'Zali. ARAE 2015.

Vetrimoxin® L.A.

LONG ACTING AMOXICILLIN

VETRIMOXIN® L.A. (amoxicillin) - Injectable suspension. **Composition:** amoxicillin (as trihydrate salt) 15 g - Excipient q.s. 100 mL. **Properties:** the long-acting formulation allows the antibiotic to reach and maintain effective levels of amoxicillin for 48 hours. I**ndications:** cattle, sheep, goat, pig: treatment of diseases due to germs sensitive to amoxicillin. **Contraindications:** do not administer to animals sensitive to penicillins. Do not administer to rabbits and rodents. **Dosage and administration:** intramuscular route. Usual dosage is: 15 mg of amoxicillin/kg body weight, as 1 ml of VETRIMOXIN® L.A. per 10 kg body weight. This dose can be repeated 48 hours later if necessary. **Withdrawal period:** meat and offal: see local registration - **Milk:** see local registration.

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