

1 **Running head: Clinical treatment modeling for minimizing drug resistance**  
2 **development: neonatal piglet diarrhea**

3 **Impact of antibiotic, probiotic and NSAID treatments on the expression of the *tra* genes**  
4 **of an R plasmid and on the host innate immune activity during colibacillosis in piglets**

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22 **Abstract**

23 **Background:** Although no animal model is perfectly mimicking the human condition, over the years  
24 the pig has used as an experimental animal model because of its much closer resemblance to humans.  
25 In clinical practice a wide range of antibiotics is used to control the infections and antibiotic resistance  
26 in individual microbiom is increasing, perhaps due to indiscriminate use of antibiotics. The purpose  
27 was to study the mobility genes of an *IncU* multidrug-resistance plasmid under various mono and  
28 combination therapy conditions using an *in vivo* newborn piglets infection-and-treatment model. A  
29 classical Enterotoxigenic *Escherichia coli* (ETEC) strain, drug resistant with a known R-plasmid (Tc<sup>R</sup>,  
30 Tm<sup>R</sup>, Su<sup>R</sup>), was used to orally infect newborn piglets. We measured the effect of various treatment  
31 alternatives; i) tetracycline (Terramycin<sup>®</sup>), ii) enrofloxacin (Baytril<sup>®</sup>), iii) NSAID (Meloxicam<sup>®</sup>) and  
32 iv) probiotics (Zoolac<sup>®</sup>) or v) combinations of them , on the clinical symptoms, the transfer capacity  
33 of the R-plasmid to other bacteria in the gut microbiota, the histopathological changes in the jejunal  
34 wall, and the blood parameters related to physiology and immunity.

35 **Results:** Certain treatments with Terramycin<sup>®</sup>, ineffective concentration of Baytril<sup>®</sup> strongly increased  
36 expression of the plasmid mobility genes, whereas effective dosage of Baytril<sup>®</sup> resulted in lower  
37 number of mRNA copies of these *tra* genes. Treatment with Zoolac<sup>®</sup> or Zoolac<sup>®</sup>+Metacam<sup>®</sup> caused  
38 slightly increased expression of the *tra* genes. Following effective treatment with Baytril<sup>®</sup> and its  
39 combinations with Zoolac<sup>®</sup> or Metacam<sup>®</sup>, and even after subinhibitory Baytril<sup>®</sup> dosage, the level of  
40 CRP were significantly increased compared to placebo-treated animals.

41 **Conclusions:** Our findings point to the importance of correct antibiotic choice together with  
42 supportive medicaments (probiotics or NSAID) and its combined effect on complex host-bacteria  
43 relations which may play an essential role in control of antibiotic resistance transfer at individualized  
44 infection therapy.

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