

Are We Willing to Accept a Degree of Loose Stools in Piglets During the Post-Weaning Period in the Era of ZnO Ban and Reduction of Antimicrobial Use?

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ABSTRACT

Post-Weaning Diarrhea (PWD) due to Enterotoxigenic *E. coli* (ETEC) in pigs is a worldwide economically important disease associated with abnormal fecal consistency and higher use of antimicrobials. Currently, strategies for prevention and control of PWD due to ETEC are the in-feed use of ZnO and antimicrobials, e.g. colistin. However, new European regulations have been established resulting in the ban of ZnO by 2022, combined with more stringent advice on prudent use of antimicrobials and general reduction in the antimicrobial use. In the field, clinical fecal consistency is one of the most important evaluation criteria for efficacy of the currently used and novel alternative strategies to prevent and control PWD due to ETEC. Many of these alternative strategies reduce the number of pathogenic bacteria in the gut, resulting in a decreased clinical severity of PWD. This leads to an improved fecal clinical score, although a temporary deterioration in fecal consistency might still occur within the most critical period of PWD. In order to assure a long-lasting and sustainable reduction in antimicrobial use, a change in attitude towards evaluation of clinical efficacy of alternative strategies should be taken by both swine farmers and their field veterinarians.

Abbreviations: CVMP: Committee for Veterinary Medicinal Products; ETEC: Enterotoxigenic *Escherichia coli*; FCS: Fecal Clinical Score; IAV-S: Influenza A Virus – Swine; LT: Thermo-labile Toxin; Medium Chain Fatty Acids (MCFAs); PCV-2: Porcine Circo Virus-type 2; ppm: Parts Per Million; PRRSV: Porcine Reproductive and Respiratory Syndrome Virus; PWD: Post-Weaning Diarrhea; STa: Thermo-Stabile Toxin a; STb: Thermo-Stabile Toxin b; Stx2e: Shiga-Toxin 2e; ZnO: Zinc Oxide

Post-Weaning Diarrhea: The Disease

Post-Weaning Diarrhea (PWD) in pigs is a worldwide economically important disease [1], characterized by abnormal fecal consistency, increased mortality, weight loss, retarded growth, increased treatment costs, higher use of antimicrobials and larger batch-to-batch variation [2-8]. Enterotoxigenic *E. coli* (ETEC) is regarded the most important cause of PWD. The ETEC pathotype is typically characterized by the presence of fimbrial adhesins, which mediate attachment to porcine intestinal enterocytes, and enterotoxins, which disrupt fluid homeostasis in the small intestine. This results in mild to severe diarrhea within a few days post-weaning, associated with clinical signs of dehydration, loss of

body condition (= disappearance of muscle volume) and mortality [9]. The adhesive fimbriae most commonly occurring in ETEC from pigs with PWD are F4 (K88) and F18 [9]. Other fimbriae such as F5 (K99), F6 (987P) and F41 rarely occur in *E. coli* isolates from PWD [9-13]. The main enterotoxins associated with porcine ETEC are heat-labile Toxin (LT), heat-stable Toxin a (STa) and heat-stable Toxin b (STb). In some cases, both enterotoxins and a Shiga toxin (Stx2e) are produced by the pathogenic strains [9].

Current Approach to Tackle PWD

The disease is currently controlled using antimicrobials, although the emergence of antimicrobial resistance in *E. coli* strains


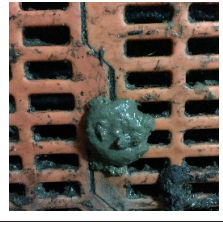



isolated from cases of PWD urges the need for alternative control measures [14-18]. From the late 1980's onwards, several studies on zinc supply to post-weaned piglets have been performed. Several nutritional studies demonstrated the effects of dietary zinc oxide (ZnO) in the prevention and healing of PWD [19]. Therefore, ZnO has been admitted in the prevention and control of PWD at levels up to 3,000 parts per million (ppm) through the feed for a maximum of 14 days post-weaning. However, the Committee for Veterinary Medicinal Products (CVMP) has recently decided that the use of ZnO in post-weaning diets should be phased out the latest by 2022 throughout the EU [20]. Several alternative strategies have been explored to increase intestinal health and decrease incidence of PWD due to *E. coli* in post-weaned piglets [21-23]. Overall, inclusion of additional dietary fiber and reduction of crude protein levels in post-weaning diets seemed to be an effective nutritional strategy that may counteract the negative effects of protein fermentation in the pig gut [22,24-26]. Although specific fermentable carbohydrates combined with reduced crude protein content altered the microflora and fermentation patterns in the gastrointestinal tract of post-weaned piglets, these favorable effects did not necessarily result in increased growth performance [27]. Other feeding strategies were more focused on feed consistency, thereby feeding more coarsely ground meal to the post-weaned piglets [28]. Coarsely ground feed meals change the physico-chemical conditions in the stomach, thereby increasing concentrations of organic acids which lower the pH. This promotes growth of anaerobic lactic acid bacteria and reduces survival of *E. coli* during passage through the stomach [28]. Fermentation of undigested dietary protein and endogenous proteins in the large intestines yield putative toxic metabolites that can impair epithelial integrity and promote enteric disorders such as PWD [29]. Incidence and severity of PWD may also be influenced by addition of probiotics to the diet, which may change the fermentation profile and thus promote gut health [30]. Furthermore, Medium Chain Fatty Acids (MCFAs) can neutralize bacterial metabolites in the small intestine [31]. However, efficacy of these alternative strategies is variable among different farms and over time, depending on multiple inferring factors such as specific feeding strategies and equipment, type of housing and climate control, number of piglets per pen or presence of other concurrent pathogens (e.g. PRRSV, PCV-2, IAV-S, ...)

Fecal Clinical Score: an Objective Look at PWD

In order to score fecal consistency during PWD, a Fecal Clinical Score (FCS) was developed with a fecal consistency score from 0 to 4 with and appropriate description [32,33] and applied under field conditions to objectively assess the fecal consistency during the post-weaning period (Table 1) throughout time and in the presence of multiple persons assessing the clinical fecal consistency [34-36]. The fecal clinical score is extensively described and illustrated in Table 1. Under field conditions, clear advantages have been observed in using the FCS to evaluate the effect of specific

preventive or prophylactic interventions during the post-weaning period [34-36].

Table 1: Fecal clinical score from 0 to 4 with a realistic picture and a generic description of the consistency and the ratio between the liquid and solid fraction within the fecal material.

Score	Picture	Description
0		Normal feces
1		Pasty feces
2		Mild diarrhea – fecal consistency with more solid components than fluids
3		Moderate diarrhea – fecal consistency with more fluid than solid components
4		Severe diarrhea – fluid fecal consistence

Future Challenges: Ban of ZnO and Prudent Use of Antimicrobials

As already mentioned above, CVMP has decided the use of ZnO in post-weaning diets is to be phased out the latest by 2022 throughout the EU [20]. This decision has mainly been taken in the light of increased environmental risk due to Zn residues via fecal excretion and risk for increased prevalence of bacteria with antimicrobial resistance [36]. In addition to the ZnO ban, more stringent measures towards the preventive and therapeutic use of antimicrobials, e.g. colistin, have been implemented by the

European Parliament and the European Council [37]. Briefly, antimicrobial therapy can not be applied in a systematic way, nor to promote growth in production animals. Moreover, prophylactic use is prohibited, except for exceptional individual treatment of affected animals. These new regulations should be applied from 28 January 2022 onwards. Since the post-weaning period is one of the most challenging moments in the life of a piglet, the ban of ZnO and the imposed reduction in antimicrobial use will have a serious impact on our perspectives towards prophylaxis, prevention and treatment of PWD due to ETEC. Using ZnO and antimicrobials, FCS can easily be kept under control and little abnormal fecal consistency is apparent during the post-weaning period. However, this might be a bigger challenge using alternative strategies to ZnO and antimicrobials in the near future.

Vaccination with an Oral Live Avirulent *E. Coli* Vaccine

Besides the aforementioned alternative strategies, focusing on feed changes and addition of pre- and probiotics to the feed, vaccination with an oral live avirulent *E. coli* vaccine (Coliprotec® F4/18; Elanco) might be a potential strategy to overcome the economic damage due to F4-ETEC or F18-ETEC. For an *E. coli* vaccination against PWD due to F4-ETEC and F18-ETEC, the prerequisite is that active mucosal immunity against F4 and F18 is mounted following application of the vaccine. This implies the local production of F4- and/or F18-specific secretory IgA antibodies, which prevent pathogenic F4-ETEC and F18-ETEC to attach to the intestinal F4- and F18-receptors and thus reduce clinical signs of PWD [38]. Recently, vaccination with a live non-pathogenic *E. coli* F4 or *E. coli* F4 and F18 vaccine has demonstrated efficacy against PWD due to F4-ETEC or F4-ETEC and F18-ETEC [32,33]. Immunization against the F4-ETEC and F18-ETEC pathogens resulted in decreased severity and duration of PWD clinical signs, as determined by FCS, and reduced fecal shedding of F4-ETEC and F18-ETEC [32,33]. The reduced clinical signs were based on the absence of fecal droppings with an FCS above 2, according to the previously described FCS (Table 1). This means that a temporary deviation of FCS from normal fecal consistency (FCS = 0) should be acceptable as long as the FCS does not increase to FCS levels of 3 or 4. These scores are characterized by a higher volume of liquid as compared to solid material in the fecal droppings. Moreover, these registration studies [32,33] have also shown that when FCS temporarily increasing up to 1 or 2, no negative effects on piglets' performances were present since an increased weight gain was demonstrated following vaccination with the *E. coli* F4 vaccine [32].

Conclusion

In conclusion, several novel strategies towards PWD due to ETEC have been applied or will be introduced in the field in the near future. Many of these strategies impact the reduction in the number of pathogenic bacteria that may induce or impact PWD due to ETEC. This reduction of pathogenic bacteria clearly impacts

the clinical signs of PWD, however, in many cases a temporary deterioration in fecal consistency may occur, although the impact on piglets' performance remains minimal. Therefore, a new attitude towards evaluation of the clinical efficacy of alternative strategies to prevent or control PWD due to ETEC should be taken by both swine farmers and their field veterinarians in the near future. Only through a drastic change in attitude, we will collectively be able to prevent or control PWD due to ETEC without a risk to increase the use of antimicrobials and thus compromise the current process towards prudent use of antimicrobials resulting in a long-lasting and sustainable reduction in antimicrobial use during this critical phase in swine production worldwide.

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