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# Different ideas on the pathogenesis and treatment of swine edema-disease

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***SUMMARY***

*Although literature data associate the reason of swine edema-disease with certain serotypes of Escherichia coli bacteria, the authors assume that the primary cause of edema is more different. Susceptible agents and factors, mostly of feed compound are involved. During the digestion of some feed-origin protein opiate-like metabolites, exorphins arise, simultaneously arrest the release of acetylcholine. Consequences of acetylcholine shortage are spasm of sphincters (mostly pylorus), intestine-dilatation, contraction of bladder-sphincter, and urine retention. The endorphins and exorphins intensify the insulin release from the pancreas, hypoglycemia evolves, which is associated with loss of balance. According to the authors in edema-disease piglet dies because of hypoglycemia.*

***Keywords:*** *E.coli , hypoglycemia, exorphins, pig stress*

## *INTRODUCTION*

Edema disease was first described in Ireland in 1938 as an "unusual condition affecting the digestive organs of the pig." (Moxley, 2000). Studies in 1955 were the first to identify an association between hemolytic *Escherichia coli (E.coli*) and edema disease (Gregory, 1955; Schofield and Davis, 1955). Pig-edema disease (ED) is mainly observed in recently weaned piglets, although it can also appear in the growing and finishing phases. ED appearance 1 to 4 weeks after weaning is associated with fast growth (Nabuurs et al., 2001), about 70% of affected pigs die, and surviving pigs may grow slowly. The clinical history of per acute death: healthy, well-conditioned, recently weaned pigs, along with visual observation of periocular edema and extensive edema of the stomach and mesocolon, are helpful in diagnosis. There may be a characteristic squeal due to edema of the larynx. Diarrhea may precede the signs of edema disease if the *E.Coli* responsible also possesses genes for enterotoxins. Enterotoxins are extracellular proteins or peptides (exotoxins) which are able to exert their actions on the intestinal epithelium (Nagy and Fekete, 1999). These toxins damage the walls of small blood vessels including those in the brain and cause fluid or oedema to accumulate in the tissues of the stomach and the large bowel. Characteristically, the stomach is full of dry feed. Diagnosis is easy to make in an outbreak in which the full range of clinical signs and pathologic features are likely to occur. It is more difficult when only a few animals are affected or when the disease occurs in an atypical age group. *E.coli* isolation and characterization are necessary for a definitive diagnosis. Culture of the small intestine and colon typically yields a heavy growth of hemolytic *E.coli*, but in some cases, the organism may no longer be present in the intestine at the time of death (The Merck Vet.Man., 2010). This disease is attributed to a heat-labile toxin from the Shiga toxin family (also called verotoxins or Shiga-like toxins) produced by certain serotypes of *E.coli* (Alexa et al., 2004; Nabuurs, 2001; Souza et al., 2001). *E.coli* colonizing the small intestine and produce verotoxin 2e. This toxin absorbs from the intestine into the bloodstream, damages the endothelial cells in target tissues. The endothelial cell damage induces an increase in vascular endothelium permeability resulting in edema (Perozo and Mallorqui, 2019). The same *E.coli* strains were also found in non-afflicted pigs at lower or at comparable frequencies. It suggested that the weaned pig is a reservoir for pathogenic bacteria (Imberechts et al., 1992). It is unclear how the enterotoxins can pass the intestinal barrier. Nabuurs et al. (2001) found pigs with acute edema disease show acidosis of the gut wall and metabolic acidosis. The intestinal pH 7.0 causes mucosal hyper-permeability, corresponds with a three-fold increase in macromolecular (e.g. toxins) permeability. Probable the endotoxin produced by *Coli* bacteria causes opioid secretion (Carr et al., 1982). The etiology of the disease is complex since changes in food composition and temperature, loss of passive protection from the sow, and genetic susceptibility of the pigs are involved in the pathogenesis (Imberechts et al., 1992). Responsiveness of pigs is different and seems to be transmitted hereditarily since some herds seem to be naturally resistant to edema disease (Souza et al., 2001).

Control of bacterial proliferation in ED is difficult as the toxin has already been absorbed into the circulation and bound to receptors when clinical is clear. Antimicrobial therapy often used to protect unaffected animals, may increase antibiotic-resistant isolates of healthy pigs or with clinical signs non-compatible with diarrhea. Moreover, due to the rapid course of the illness, treatment comes too late for piglets with clinical symptoms (Casanova et al., 2018). Misuse and overuse of antimicrobials are the main drivers in the development of drug-resistant pathogens. Antimicrobial resistance is a global health and development threat. It requires urgent multisectoral action in order to achieve the Sustainable Development Goals (WHO, 2021).

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## *MATERIALS AND METHODS*

### Own observations, experiences, and raising questions

The practical observations were in the 1980s and 1990s, on small-scale pig farms, in Hungary (Szabolcs-Szatmár county). Typical clinical signs of pigs suffered from edema disease in our practice: Sudden appearance of disease after weaning, the voice of the ill animal was raucous, there was an abnormal high pitched squeak, puffy eyelids, the under-skin connective tissue of head edema-like puffed-up. Incoordination, lameness, staggering in the later stages, became partially paralyzed and went off their legs. There were breathing difficulties. The pig stopped eating, cannot vomit (even cannot make him vomit), and didn't urinate. The temperature was right, in general. Post-mortem examinations showed edema (fluid in tissues) of the greater curvature of the stomach wall, coiled colon, and eyelids. The stomach was markedly tight and stretched at, the content of which is drier than in general. The stomach wall sometimes was wide and infiltrated, the mucosa gelatinous on some areas. The small gut was unstrung, distended, and full of diluted matter. The mesenteric lymph nodes swollen, sometimes were dark-red. The urinary bladder was full. The colonic mesentery was edematous and gelatinous too.

According to the practical observations, large white-type piglets in good condition died. The medical treatment of sick animals was rarely successful. Recovery of those pigs which did not die took up to 2 to 3 weeks. Certain breeds of pigs might be associated with disease, suggesting a genetic predisposition.

Based on our observations and experiences we assume, that edema-disease primarily is not caused by *Coli* bacteria, but different susceptible agents and factors, mostly of feed-compound, among others.

The practical observations showed that the edema disease developed mainly after some stress, for example, change of food, vaccination, emasculation, transport, weaning, overfeeding, trooping, etc. We assume that edema disease happened in the case of receptive pigs. Some sow litters were more endangered than others, the problem applied in these sow litters one after the other. Presumably, these pigs were stress-sensitive, so we assume that edema-disease is genetically determined, connect with stress sensitivity.

Based on our practical experience edema disease more often evolved when rye and pumpkin seeds were in the feed. Mainly the crude - not completely matured-rye was dangerous in this regard.

The gluten of cereal seeds is particularly rich in glutamic acid. Glutamic acid was separated first from the sugar beet exudates and to pumpkin seed-germ.

– The question arises: is there any role of glutamic acid in the development of edema-disease? The danger of these feeds is in their high glutamic-acid concentration?

Once, a farmer mowed poppy seed (*Papaver rhoeas*), and his pigs eat from this. The next day, one of the gilts' moved uncertainly, swaying. Later the animal recovered. Probably, there are opium-like substances in the plant wild poppy, which could result in movement disorders.

– The question arises: is it possible that the pathogenesis of this disease is due to the actual role of opioids, opioid peptides?

In the case of the human acute morphine-poisoning, small pupil, slow pulse, disturbance of consciousness observed. Glandular secretion ceases, the bowel movements are stopped, and in the end, respiration paralysis occurs. The pylorus spasms prevent stomach content's movement. The stomach of piglets that died in edema disease is full and strained too. The side effects of opiates are the urethral sphincter (sphincter vesicae) contraction, urinary retention, and swollen eyelids. The edematous piglets were characterized by swollen eyelids, heavy fullness of the bladder, and urinary retention.

– The question arises: whether the edema disease can be an acute morphine-poison or similar to, or whether it is possible pathogenesis of this disease the actual role of opioids, opioid peptides, respectively?

Peptides, which functions are similar to morphine or other opioids, were isolated from the brain and other sources as the pituitary. Peptides with opioid activity can be points out in pepsin hydrolysates of wheat gluten and α-casein. These peptides are called exorphins because of their exogenous origin and morphine-like activities. Some stomach-produced exorphines are resistant to the intestinal proteinases. They absorb from the gastrointestinal tract into the bloodstream (Zioudrou et al., 1979).

However, peptic digestion some food proteins, such as casein and wheat gluten same materials so formed, which have opiate-like activity. So the feed, which contains these proteins, produces opiate-like materials during their digestion. These metabolites could include rye, pumpkin seeds, and gluten.

Assuming the effect of edema disease caused by exorphines, the primary cause is that kind of foods (for example rye) which digestion release gluten, consequently opioid-like effect exorphins.

As mentioned above, the stress-sensitivity is a causing effect in pig edema pathogenesis. In stressful circumstances, the animal produces more acid in the stomach. During the digestive process, feeds rich in gluten (e.g. rye grains) release exorphins. Exorphins reach the synaptical vesiculums preventing the release of acetylcholine neurotransmitters, acetylcholine deficit occurs. Acetylcholine affects intestine motion. Consequences of acetylcholine shortage are spasm of sphincters (mostly pylorus), intestine-dilatation, contraction of bladder-sphincter, and urine retention. Because of these phenomenon's the ill animal is not urinate and cannot vomit.

This physiological effect is traceable as the stomach of dead pigs in edema disease was always full and cannot make them vomit.

The exorphins and endorphins enhance the insulin release from the pancreas, so insulin surplus and hypoglycemia formed, respectively (Schusdziarra et al., 1981). The hypoglycemia manifested first in movement disorders after then complete paralysis

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occurs results in tetraplegia. At the same time, a coma develops, which in turn causes the death of the animal. The pig dies because of hypoglycaemic coma in edema disease, consequently. The cause of death is respiratory-center depression.

## *CONCLUSIONS*

Literature data assign the reason of post-weaning diarrhea and swine edema-disease caused by certain serotypes of *Escherichia coli* bacteria (Frydendahl, 2002; Luppi et al., 2016). No product has been developed that is currently effective to treat edema disease (Moxley, 2000). One antimicrobial agent that may be effective is enrofloxacin (Kyriakis, 1997). Although antibacterial agents may be useful, there are two serious problems with their use. One is that they may interfere with active immunization, thereby allowing clinical signs and mortality to develop after withdrawal of the antimicrobial drugs from the feed. The second is that selection of strains with antimicrobial resistance may occur. Increasing antimicrobial resistance can easily become a problem in herds with enzootic edema disease (Moxley, 2000).

Based on author's observations and experiences edema-disease primarily is not caused by *Coli* bacteria, but different susceptible agents and factors. The practical observations showed that the edema disease developed mainly after some stress and happened in the case of receptive pigs. Presumably, the disease is genetically determined, connect with stress sensitivity.

Other issues that arose: is there any role of glutamic acid in the development of edema-disease and is it possible pathogenesis of this disease the actual role of opioids, opioid peptides. Peptides with opioid activity can be points out in pepsin hydrolysates of wheat gluten and α-casein. Assuming the effect of edema disease caused by exorphines, the primary cause is that kind of foods (for example rye) which digestion release gluten, consequently opioid-like effect exorphins. In stressful circumstances, the animal produces more acid in the stomach. During the digestive process, feeds rich in gluten release exorphins which block the synaptical vesiculums preventing the release of acetylcholine neurotransmitters. Acetylcholine deficit affects intestine motion. The exorphins and endorphins enhance the insulin release from the pancreas, so insulin surplus and hypoglycemia formed, respectively.

Based on the author's observations, transferring of glucose was efficient, symptoms disappeared. Most appropriate was the 40% glucose solution intravenous administration. Oral administration of honey was effective too, 2–3 times per day, 2–3 teaspoons to the sick animals. Healing began with the slow normalization of movement disorders. Firstly, the patient steps on hind legs slowly stood up, collapsed sometimes, and then took a few steps. It was striking that the animals at the beginning of healing urinated a lot, then defecated thickened faces. A few days later, they were fed alone and then recovered spontaneously with almost no symptoms.

After all, the authors hope that these ideas will serve as a basis for further research on various aspects of swine edema disease.

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### *REFERENCES*

Alexa, P.–Hamrik, J.–Stouracova, K.–Konstantinova, L.–Salajka, E. (2004): Passive immunoprophylaxis of edema disease in weaned piglets. Vet. Med. Czeh 49. (12) 447–452.

Carr, D.B.–Bergland, R.–Hamilton, A.–Blume, H.–Kasting, N.–Arnold, M.–Martin, J.B.–Rosenblatt, M. (1982): Endotoxin-stimulated opioid secretion: Two secretory pools and feedback control in vivo. Science. Vol. 217. 27. 845–848.

Casanova, N.A.–Redondo, L.M.–Dailoff, G.C.–Arenas, D.–Miyakawa, M.E.F. (2018): Overview of the role of shagia toxin sin porcine 1 edema disease pathogenesis. Toxicon 148: 149–154. doi: 10.1016/j.toxicon.2018.04.019.

Frydendahl, K. (2002): Prevalence of serogroups and virulence genes in *Escherichia coli* associated with postweaning diarrhea and edema disease in pigs and comparison of diagnostic approaches. Veterinary Microbiology 85. 169–182.

Gregory, D. (1955): Role of beta hemolytic coliform organisms in edema disease of swine. Vet Med 50:609.

Imberechts, H.–DeGreve, H.–Lintermans, P. (1992): The pathogenesis of edema disease in pigs. A review Veterinary Microbiology, 31. 221–233.

Kyriakis, S.–Tsiloyiannis, V.–Vlemmas, J.–Lekkas, S.–Petridou, E.–Sarris, K. (1997): The efficacy of enrofloxacin in-feed medication by applying different programmes for the control of post weaning oedema disease in weaned piglets. Zentralbl Veterinarmed [B] 44:523.

Luppi, A.–Gibellin, M.–Gin, T.–Vangroenweghe, F.–Vandenbroucke, V.–Bauerfeind, R.–Bonilauri, P.–Labarque, G.–Álvaro Hidalgo, Á. (2016): Prevalence of virulence factors in enterotoxigenic *Escherichia coli* isolated from pigs with post-weaning diarrhoea in Europe. Porcine Health Management 2:20 DOI 10.1186/s40813-016-0039-9

Moxley, R.A. (2000): Edema Disease. Diagnosis of disease of the digestive tract. Vol. 16. Nr.1 March.

Nabuurs, M.J.A.–Van de Weijgert, E.J.H.M.–Grootendorst, A.F.–Niewold, T.A. (2001): Edema disease s associated with metabolic acidosis and small intestinal acidosis. Research in Vet. Sci. 70. 247–253.

Nagy, B.–Fekete, P.Zs. (1999): Enterotoxigenic *Escherichia coli* (ETEC) in farm animals. Veterinary Research, BioMed Central, 30 (2–3), pp.259–284.

Perozo E.–Mallorqui, J. (2019): Field trial proves vaccine against edema disease is safe and efficacious. https://thepigsite.com/articles/field-trial-proves-vaccine-against-edema-disease-is-safe-and-efficacious

DOI: 10.34101/ACTAAGRAR/2/10038

Schofield, F.–Davis, D. (1955): Oedema disease (entero-toxaemia) in swine. II. Experiments conducted in a susceptible herd. Canadian Journal of Comparative Medicine 19:242

Schusdziarra, V.–Henrichs, I.–Holland, A.–Klier, M.–Pfiffer, F. (1981): Evidence for an effect of exorphins on plasma insulin and glucagon levels in dog. Diabetes Vol.30. April. 362–364.

Souza da Silva, A.–Valadares, G.F.–Penatti, M.P.A.–Brito, B.G.–da Silva Leite, D. (2001): *Escherichia coli* strains from edema disease: O serogroups and genes for Shiga toxin, enterotoxins, and F18 fimbriae. Veterinary Microbiol. 80. 227–233.

The Merck Veterinary Manual (2010) X.th edition. ISBN: 978-0911910-93-3.

Zioudrou, C.–Streaty, R.A.–Werner, A.K. (1979): Opioid peptides derived from food proteins. The exorphines. The Journal of Biological Chemistry Vol. 254. No.7, Issue of April 10, pp. 2446–2449.

WHO: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance / 2021. August/