Porcine Research

Edema disease of swine: a review of the pathogenesis

[1] Flaviu Tabaran, [2] Alexandra Tabaran

[1] Anatomic Pathology Department, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Faculty of Veterinary Medicine, Cluj-Napoca, Romania;
[2] Animal Breeding and Food Safety Department, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Romania. Corresponding author: F. Tabaran, flaviutabaran@gmail.com

Abstract. Edema disease (ED) is an often-fatal enterotoxemia produced by specific pathogenic strains of *Escherichia coli* in weaner and feeder pigs, with major importance in porcine production, management and health. ED is also used as a naturally occurring disease model for the severe systemic pathologies caused by Shiga toxin-producing Escherichia coli (STEC) in humans. Recently, porcine strains of STEC are also receiving attention from a food safety and public health perspective. In this review, we briefly discuss and outline the current knowledge regarding the pathogenesis of ED in pigs, with particular reference to the gross and microscopic features of the disease.
Key Words: *E. coli*, edema disease, enterotoxemic colibacillosis, pathogenesis.

Introduction. Edema disease/enterotoxemic colibacillosis (ED/EC) is a communicable, often fatal, naturally occurring, acute enterotoxemia with worldwide distribution, affecting the rapidly growing pigs during weaner and feeder production phases. Edema disease is produced by a pathogenically distinct strain of porcine adapted strains of *Escherichia coli*, collectively known as "Edema diseases *E. coli*" (EDEC), "Shiga toxin-producing producing *E. coli*" (STEC) or "Verotoxin producing *E. coli*" (VTEC), which are able to induce systemic vascular damage due to the exotoxin secretion. In the context of swine pathology, EDEC, STEC and VTEC are generally used as synonyms.

For a clear distinction from the close related enterotoxigenic strains (ETEC), the *E. coli* strains responsible for ED are described from the perspective of pathogenic factors as: Stx2e-producing, non-attaching and effacing (non A/E) and possessing fimbria colonization factor 18ab (F18ab-positive strains of *E. coli*). Most often, the *E. coli* serogroups involved in ED are O138, O139 and O141 (Bertschinger & Gyles 1994). Important for the pathogenesis, some virulence genes critical for STEC are coded by bacterial mobile genetic elements (MGEs), such as plasmids, pathogenicity islands, transposomes and insertion sequence elements, and therefore can be transmitted to other receptive *E. coli* strains (Dobrindt et al 2002).

In addition to the small intestinal colonization by STEC, which do not necessarily correlate with ED, several other factors mostly related to husbandry practices, age and individual susceptibility are typically required for ED to be clinically apparent. Thereby, the etiology of ED is multifactorial and requires complex interactions between the STEC, feed (including composition and changes in feeding practices), environmental and forage temperature and several critical predisposing factors, such as weaning (especially by loss of lactogenic passive protection and changes in intestinal microbiota) and genetics (Imberechts et al 1992). This important feature of ED is also highlighted by the fact that 68.3% of clinically healthy finishing pigs have their intestinal content positive for STEC (Cha et al 2018). Thus, for the accurate diagnosis of ED in pigs, the pathological findings should always be included in the diagnostic (Schneeberger et al 2017).

Infections with STEC or food contamination is also critical for the perspective of food safety and public health (Tseng et al 2014). In humans, several outbreaks of hemorrhagic colitis or systemic, clinical severe diseases, like idiopathic hemolytic uremic syndrome, had been associated, although infrequently, with consumption of pork meet or meet based products containing pork contaminated with STEC (Paton et al 1996; Conedera et al 2007). The role of pig Stx2e-producing *E. coli* is largely unknown in human health, since Stx2e-produced by *E. coli* isolates from humans and pigs differ in their virulence profiles (Sonntag et al 2005).

In addition to the importance in porcine industry and public health, porcine ED/EC has many similarities with diseases induced by enterohemorrhagic strains of *E. coli* in humans. Thus, ED is currently utilized as a naturally occurring model for systemic disease caused by Shiga toxin-producing *E. coli* in humans (Cornick et al 1999) along with other STEC models, like the murine, non-human primate (baboon model) and, to a lesser extent, rat, rabbit or bovine models (Jeong et al 2018).

In this review, we briefly discuss the current knowledge on the pathogenesis of ED, outlining the peculiar gross and microscopic features routinely used for the diagnosis of this disease in pigs.

The pathogenesis of the edema disease. The first identification and description of VTEC pathogenicity is attributed to Konowalchuk et al, in the late 70`s. They observed that certain toxigenic strains of *E. coli* ("Vero toxin") are able to induce an irreversible cytotoxic effect on Vero cell cultures, which are renal epithelial cells of African green monkey (*Chlorocebus* sp.*)*. This was not observed for CHO or Y-1 cells. Pig derived Stx2e has no cytotoxic effect on HeLa cell cultures due to variations in the B-subunit of the toxin (Paton & Paton 1998). In the early 80`s, O'Brien & Laveck further characterized the VTEC exotoxin responsible for the cytopathic effects on Vero cell lines, and classified them as "Shiga-like toxins" based on the large similarities in both structure and toxic effect to the bacterial exotoxin produced by *Shigella dysenteriae*, another *Enterobacteriaceae* which share several pathogenic feautures with *E. coli*. In brief, this is the initial source of the alternative nomenclature (VTEC/STEC) of these pathogenic strains of *E. coli.*

The pathogenesis of the edema disease can be divided in two successive phases:

1. Enteral colonization and initial alimentary enterotoxaemia, associated with changes in microbiota.

2. The systemic distribution of the Stx2e, related with diffuse, but mainly central-nervous and digestive fibrinoid vasculopathy.

The second pathogenic phase is responsible for the characteristic vascular damage (arteriolopathy/arteriopathy), increased vascular permeability, fluid loss and vasculogenic tissue edema (Imberechts et al 1992; Zachary & McGavin 2016).

Pathogenic factors. The key pathogenic factors in ED are those which ensure the digestive colonization, survival and STEC enteral multiplication (e.g. fimbriae and secretion factors), and those responsible for the systemic vascular damage following the toxin absorption (Zachary & McGavin 2016). Thus, the *E. coli* adhesins (e.g. fibrils as F18ab) and Shiga toxin 2e are two of the fundamental virulence factors produced by STEC (Zimmerman et al 2012).

Adhesins act as major pathogenic features in ED, being involved in the initial colonization of the intestine by the porcine STEC. The most important adhesion mediating virulence factors for STEC are F18 (F18ab or F18ac) and F4 (K88) (Zimmerman et al 2012). The bacterial AIDA (adhesin involved in diffuse adherence) are also involved in this initial pathogenic step (Niewerth et al 2001). The *E. coli* strains responsible for ED are typically not enteroinvasive and can be retrieved during the entire ED clinical course from the intestinal content.

Shiga toxins. Shiga toxin 2e, Stx2e, also known as verotoxin 2e or edema disease principle (Zachary & McGavin 2016) is the key pathogenic factor of STEC and responsible for the systemic vascular effects. Unlike other Shiga toxins, Stx2e does not act as an enterotoxin, but has a targeted effect towards endothelial cells (angiotoxin) (Melton-

Celsa 2014) mainly due to the B-subunit of the toxin. As Stx1 (the other Shiga toxin produced by *E. coli*), Stx2e is an AB_5 toxin and structurally consists in two subunits: an active "A-subunit" that joins noncovalently an enzymatically-inactive, receptor binding pentamer "B-subunit" (Tumer et al 2012; Melton-Celsa 2014). Although frequently produced together by the same STEC, Stx2 has only 56% identity with Stx and Stx1 (Jackson et al 1987).

The Toxic Mechanism of the Shiga toxin. Following its production within the intestinal lumen (few days following experimental inoculation of pigs with STEC), Stx2e is absorbed by the enteral mucosa, the toxin translocation across intestinal barrier being enhanced by neutrophil recruitment and transmigration (Hurley et al 2001) and distributed systemically, hematogenously, by a "cell carrier" represented by red blood cells (RBCs). This cellular transport (e.g. the binding capacity of RBCs for the toxin) can modulate the pathogenicity of Stx2e (Matise et al 2003). Stx2e action requires a step-by-step process of: receptor recognition, cell internalization and cell organelle (ribosomal) function disruption, which will lead to the inhibition of protein synthesis (O'Brien 1992) and finally to cell death (apoptosis, but mainly liquefactive and coagulative necrosis) (Matise et al 1999). The receptor density and repatriation are crucial in the development of ED and dictate the effects of systemic Stx2e toxemia. Thus Cornick et al (1999), in an experimental model of ED in pigs, identified subclinical individuals with Stx2e positive blood, highlighting the fact that in ED individual susceptibility plays an important role.

The specific cell receptors for the Shiga toxin family are surface plasmalemmal glycolipids, like globotriaosyl Ceramide/globotriaosylceramides (Gb3, Gal alpha 1-4Gal beta 1-4GlcCer). In addition to Gb3, Stx2e has the globotetraosylceramide (Gb4 GalNAc beta 1-3Gal alpha 1-4Gal beta 1-4GlcCer) as a cell membrane receptor, which is well expressed on RBCs, blood endothelial cells and small arterial/arteriolar myocytes, concentrated in the plasma membranes in lipid rafts (insoluble portions of cell membranes). Gb4 is considered to be the preferential binding site over the Gb3 (DeGrandis et al 1989; Paton & Paton 1998) for the Stx2e. It is also able to bind and use the Forssman antigen and isogloboside as receptors (DeGrandis et al 1989).

Following its binding with the receptor on targeted cells via binding moiety, Stx2e is actively internalized (receptor mediated endocytosis) by endosomes and, following the avoidance of lysosomal fusion, transported to rough endoplasmic reticulum (RER). The Golgi apparatus mediates this circuit through retrograde transport (Sandvig et al 2010; Obrig 2010). Instead of vesicular organelle delivery of toxins to RER, a fraction of the internalized Stx2e can be transported through a CD77 dependent retrograde transport to the nucleus (Khine et al 1998). However, the following biological processes in clinical cases are poorly understood. Within the RER, the Stx2e is enzimatically activated by furin (protease induced cleavage). Cleavage of the protease sensitive sites of Shiga toxin induces the formation of the enzymatically toxic, active "A1 chain" (Kurmanova et al 2007; Tumer et al 2012).

Stx2e induce cell damage, apoptosis or necrosis, as discussed below, by three main mechanisms (Obrig 2010):

1. Cell protein synthesis inhibition by ribosomal activity disruption. Within the cell cytosol, the enzymatically active A1 chain of the Stx2e acts as ribosome inactivating proteins (RIPs), irreversibly inhibiting ribosomal function by removing a specific adenine base from the large rRNA, and thus blocking the elongation step of protein synthesis (Endo et al 1988).

2. Induction of the "ribotoxic stress response" (Smith et al 2003), which is a cellular stress response typically associated with toxic disruption of the ribosomal function (Laskin et al 2002).

3. A less characterized mechanism mediated by Stx2e (entire toxin or its B-subunit) binding to the Gb receptors, related with cytoskeleton remodeling and redistribution of a number of cellular proteins from the cytosol (Takenouchi et al 2004).

Clinicopathological Findings of ED in pigs. Clinically, acute neurological signs consisting of depression, staggering gait and tremor represent the hallmarks of ED.

These are followed by lateral recumbence, with characteristic rhythmic limb paddling, dyspnea, extensor muscle rigidity, convulsions and finally flaccid paralysis, coma and death, in most cases within 24 h following the appearance of the clinical signs (MacLeod et al 1991; Zimmerman et al 2012). After clinical debut, the mortality is generally high (up to 90%), being influenced by both STEC strain pathogenicity and individual susceptibility. This neurological signs are associated with various degrees of eyelid, face (mainly forehead) and laryngeal edema (Zimmerman et al 2012; Zachary & McGavin 2016), although these clinical signs can be easily missed due to the mild severity of most cases and the peculiarities of swine husbandry systems. Subclinical cases of ED, in which the characteristic vascular lesions are histological present, but without the above described clinical signs, are reported (Kausche et al 1992). Diarrhea and hyperthermia may be present in some ED episodes, enterotoxins being also produced by some STEC (Imberechts et al 1992). Constipation can also occasionally be observed in ED affected pigs (Zimmerman et al 2012).

Postmortem findings in pig ED. During postmortem examination the typical diffuse, vasculogenic edema, occasionally accompanied with petechia (due to micro-thrombosis that follows the vascular endothelial disruption) can be present in most tissues. Most often, the edema affects the digestive system (gastric lamina propria and submucosa, spiral colon wall, meso-colon, small intestine mesentery and mesenteric lymph nodes and gallbladder) (Fig. 1.), skin and subcutis (palpebrae, frontal skin, submandibular, ventral abdomen) and adjacent lymph nodes, thoraco-abdominal and pericardial serosa (consisting of moderate to abundant effusions, often presented as protein rich/modified transudates).

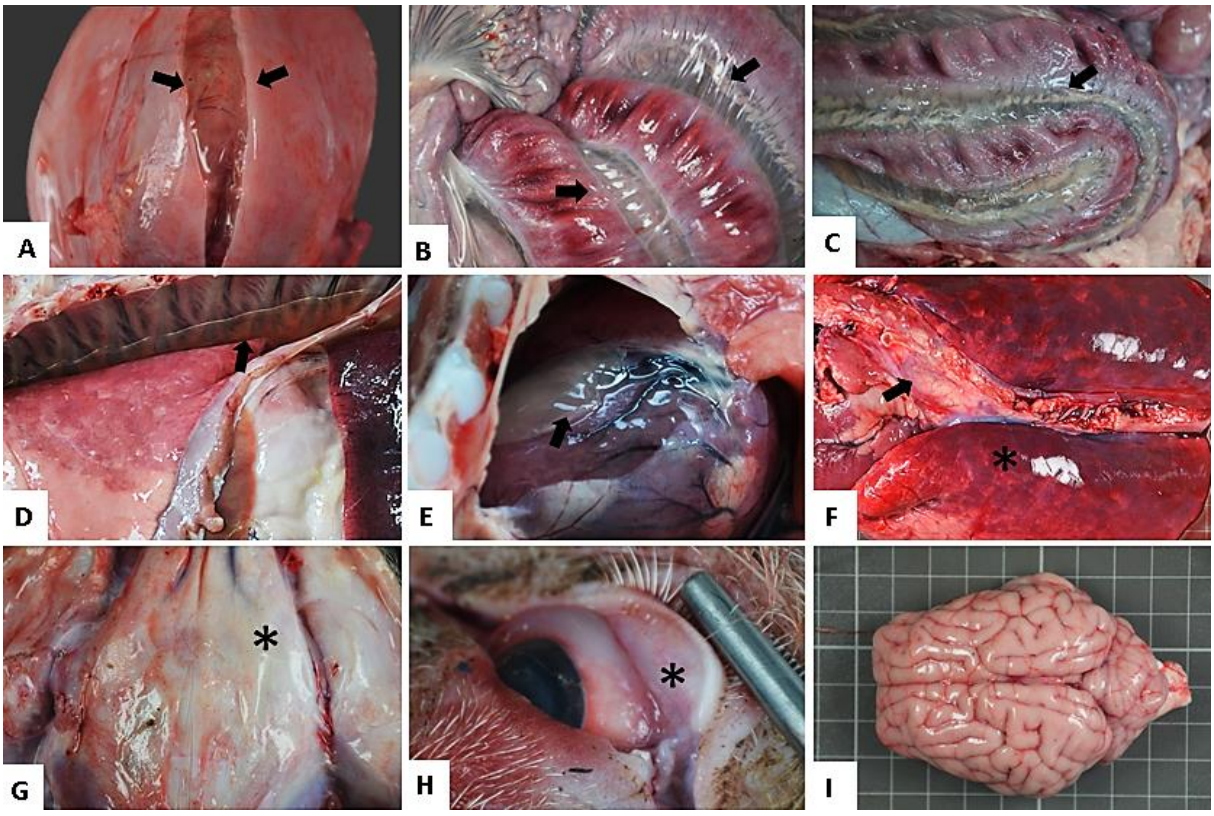

Figure 1. Typical gross lesions present during severe episodes of ED (original image). A - section of the large gastric curve; severe edema of the gastric wall (indicated by arrows), presented as a gelatinous material diffusely expanding the submucosa. B and C - diffuse "gelatinous" edema of the mesocolon (arrows), associated with segmental colonic-serosa reaction. D - pleural effusion (arrow) (hydrothorax) with secondary, mild pulmonary collapse. E - pericardial effusion rich in protein clots (arrow). F - diffuse, bilateral, mild, pulmonary congestion and edema (asterisk) accompanied with mediastinal edema

(arrow). G - the forehead subcutis is locally expanded by edema (asterisk), mainly in areas adjacent to the eyelids. H - eye and adnexa: edema of the eyelids and mild congestion of the bulbar conjunctiva. I - diffuse, minimal, cerebral congestion and edema.

Hemorrhagic gastroenteritis is also occasionally observed. The respiratory system (larynx, and lungs) and lower urinary tract are occasionally affected. The cerebrum is responsible for most of the dramatic and diagnostically suggestive clinical signs (cerebrospinal angiopathy/swine cerebral angiopathy) which accompany edema disease. However, macroscopically changes are often absent or minimal to mild and consist of meningeal congestion and petechias, brain edema (wide gyri and diffusely shallowed sulci) and occasionally symmetric neural cerebral malacia (focal symmetric encephalomalacia) (Zimmerman et al 2012; Zachary & McGavin 2016). The neuroanatomical distribution of the malacic lesions in ED are medulla oblongata, diencephalon (mainly thalamus), and basal nuclei (i.e. caudate nucleus, putamen, substantia nigra, globus pallidus, subthalamic nucleus, etc.). Mild cerebellar edema and hemorrhage are frequent findings in experimental ED (MacLeod et al 1991). Gastric ulceration of the esophageal (cardia) region is occasionally present in animals which survive the acute phase of ED (Clugston et al 1974). Most of the lesions described above are depicted in figure 1.

An interesting change is represented by the bilateral, acute renal cortical necrosis. However, it presents low specificity for ED since it was not experimentally reproduced by MacLeod et al (1991), following intravenous administration of purified Stx2e. This is due to a Shwartzman like reaction mimicking the massive renal glomerular damage observed in humans in the hemolytic uremic syndrome (HUS), induced by O157:H7, enterohemorrhagic *E. coli*.

All the above described changes are due to the systemic action of the Stx2e and reflect the distribution of the cellular membrane receptors for this toxin. The presence and distribution of these receptors dictate the pathological features (anatomical distribution of the arteriolar hyaline degeneration) and clinical signs and outcome of edema disease cases.

Histopathologic findings in ED. Histologically, the key lesions of ED are considered to be directly induced by Stx2e and consist of segmental (occasionally transmural) fibrinoid necrosis affecting the small arteries and arteriolar media (smooth muscle cells) ("arteriolar hyaline degeneration"), with endothelial disruption, and intraluminal mural (occluding or sub-occluding) fibrinous thrombi (Matise et al 1999; Zachary & McGavin 2016). The lesions described above are associated with secondary changes induced by vascular disruption (as vasculogenic, severe edema, congestion and hemorrhage), ischemia and infarction (especially important within the central nervous system). A leukocytic infiltrate (lympho-histiocytic and neutrophilic) can also be occasionally admixed with the fibrin and cell debris within the necrotic arteriolar walls (Matise et al 1999). Ocular lesions consisting of retinal edema and hemorrhages are reported by MacLeod et al (1991), in experimental cases of ED. Colonic and cecal microerosions with no associated inflammation are occasionally reported, (MacLeod et al 1991), being most likely the consequence of enteral focal ischemia secondary to endovascular microthrombosis.

Ultrastructurally, within the affected areas, endothelial cells are swelled and vacuolated, with subendothelial deposition of fibrin (electron dense material), discontinuous plasma membranes, with cytoplasmic condensation, reduced number of mitochondria and decreased endoplasmic reticulum, chromatin clumping and margination (Methiyapun et al 1984; Matise et al 1999). Endothelial proliferation is rarely observed and present as early as 3 days following STEC (O139: K12: H1) inoculation in gnotobiotic piglets (Methiyapun et al 1984). The arteriolar necrosis can be occasionally observed in the medial myocytes without significant disruption of the vascular endothelium (Matise et al 1999). Within the small intestine, the Stx2e-producing *E. coli* are occasionally present as rod shaped Gram negative ("coliform") bacteria adherent on the apical domain of the enterocytes (Methiyapun et al 1984).

Conclusions. In this review, we briefly discuss and outline the current information and knowledge on the pathogenesis of ED in pigs, with particular reference to the gross and microscopic features of the disease. Further research is especially needed for a better understanding of the contribution of pig strains of STEC to human diseases, notably the Stx2e pathogenesis and implication in food safety and public health.

References

Bertschinger H. U., Gyles C. L., 1994 Oedema disease of pigs. In: *Escherichia coli* in Domestic Animals and Humans. Gyles C. W. (ed), CAB International, Wallingford, pp. 193-220.

Cha W., Fratamico P. M., Ruth L. E., Bowman A. S., Nolting J. M., Manning S. D., Funk J. A., 2018 Prevalence and characteristics of Shiga toxin-producing *Escherichia coli* in finishing pigs: implications on public health. Int J Food Microbiol 264:8-15.

Clugston R. E., Nielsen N. O., Smith D. L. T., 1974 Experimental edema disease of swine (*E. coli* enterotoxemia) III. Pathology and pathogenesis. Can J Comp Med 38(1):34-43.

Conedera G., Mattiazzi E., Russo F., Chiesa E., Scorzato I., Grandesso S., Bessegato A., Fioravanti A., Caprioli A., 2007 A family outbreak of *Escherichia coli* O157 hemorrhagic colitis caused by pork meat salami. Epidemiol Infect 135(2):311-314.

Cornick N. A., Matise I., Samuel J. E., Bosworth B. T., Moon H. W., 1999 Edema disease as a model for systemic disease induced by Shiga toxin-producing *E. coli*. Adv Exp Med Biol 473:155-161.

DeGrandis S., Law H., Brunton J., Gyles C., Lingwood C. A., 1989 Globotetraosylceramide is recognized by the pig edema disease toxin. J Biol Chem 264(21):12520-12525.

Dobrindt U., Hentschel U., Kaper J. B., Hacker J., 2002 Genome plasticity in pathogenic and nonpathogenic enterobacteria. Curr Top Microbiol Immunol 264:157-175.

Endo Y., Tsurugi K., Yutsudo T., Takeda Y., Ogasawara T., Igarashi K., 1988 Site of action of a Vero toxin (VT2) from *Escherichia coli* O157: H7 and of Shiga toxin on eukaryotic ribosomes: RNA N-glycosidase activity of the toxins. Eur J Biochem 171(1-2):45-50.

Hurley B. P., Thorpe C. M., Acheson D. W., 2001 Shiga toxin translocation across intestinal epithelial cells is enhanced by neutrophil transmigration. Infect Immun 69(10):6148-6155.

Imberechts H., De Greve H., Lintermans P., 1992 The pathogenesis of edema disease in pigs. A review. Vet Microbiol 31(2-3):221-233.

Jackson M. P., Neill R. J., O'Brien A. D., Holmes R. K., Newland J. W., 1987 Nucleotide sequence analysis and comparison of the structural genes for Shiga-like toxin I and Shiga-like toxin II encoded by bacteriophages from *Escherichia coli* 933. FEMS Microbiol Lett 44(1):109-114.

Jeong Y. J., Park S. K., Yoon S. J., Park Y. J., Lee M. S., 2018 Experimental In Vivo Models of Bacterial Shiga Toxin-Associated Hemolytic Uremic Syndrome. J Microbiol Biotechnol 28(9):1413-1425.

Kausche F. M., Dean E. A., Arp L. H., Samuel J. E., Moon H. W., 1992 An experimental model for subclinical edema disease (*Escherichia coli* enterotoxemia) manifest as vascular necrosis in pigs. Am J Vet Res 53(3):281-287.

Khine A. A., Firtel M., Lingwood C. A., 1998 CD77-dependent retrograde transport of CD19 to the nuclear membrane: functional relationship between CD77 and CD19 during germinal center B-cell apoptosis. J Cell Physiol 176(2):281-292.

Konowalchuk J., Speirs J. I., Stavric S., 1977 Vero response to a cytotoxin of *Escherichia coli*. Infect Immun 18(3):775-779.

Kurmanova A., Llorente A., Polesskaya A., Garred Ø., Olsnes S., Kozlov J., Sandvig K., 2007 Structural requirements for furin-induced cleavage and activation of Shiga toxin. Biochem Biophys Res Commun 357(1):144-149.

Laskin J. D., Heck D. E., Laskin D. L., 2002 The ribotoxic stress response as a potential mechanism for MAP kinase activation in xenobiotic toxicity. Toxicol Sci 69(2):289-291.
MacLeod D. L., Gyles C. L., Wilcock B. P., 1991 Reproduction of edema disease of swine with purified Shiga-like toxin-II variant. Vet Pathol 28(1):66-73.
Matise I., Cornick N. A., Samuel J. E., Moon H. W., 2003 Binding of Shiga toxin 2e to porcine erythrocytes in vivo and in vitro. Infect Immun 71(9):5194-5201.
Matise I., Sirinarumitr T., Bosworth B. T., Moon H. W., 1999 Ultrastructure and DNA fragmentation analysis of arterioles in swine infected with Shiga toxin-producing *Escherichia coli*. Adv Exp Med Biol 473:163-171.
Melton-Celsa A. R., 2014 Shiga toxin (Stx) classification, structure, and function. Microbiol Spectr 2(2):1-21.
Methiyapun S., Pohlenz J. F. L., Bertschinger H. U., 1984 Ultrastructure of the intestinal mucosa in pigs experimentally inoculated with an edema disease-producing strain of *Escherichia coli* (0139: K12: H1). Vet Pathol 21(5):516-520.
Niewerth U., Frey A., Voss T., Le Bouguénec C., Baljer G., Franke S., Schmidt M. A., 2001 The AIDA autotransporter system is associated with F18 and stx2e in *Escherichia coli* isolates from pigs diagnosed with edema disease and postweaning diarrhea. Clin Diagn Lab Immunol 8(1):143-149.
O'Brien A. D., Tesh V. L., Donohue-Rolfe A., Jackson M. P., Olsnes S., Sandvig K., Lindberg A. A., Keusch G. T., 1992 Shiga toxin: biochemistry, genetics, mode of action, and role in pathogenesis. Curr Top Microbiol Immunol 180:65-94.
O'Brien A. D., LaVeck G. D., 1983 Purification and characterization of a *Shigella dysenteriae* 1-like toxin produced by *Escherichia coli*. Infect Immun 40(2):675-683.
Obrig T. G., 2010 *Escherichia coli* Shiga toxin mechanisms of action in renal disease. Toxins 2(12):2769-2794.
Paton A. W., Ratcliff R. M., Doyle R. M., Seymour-Murray J., Davos D., Lanser J. A., Paton J. C., 1996 Molecular microbiological investigation of an outbreak of hemolytic-uremic syndrome caused by dry fermented sausage contaminated with Shiga-like toxin-producing *Escherichia coli*. J Clin Microbiol 34(7):1622-1627.
Paton J. C., Paton A. W., 1998 Pathogenesis and diagnosis of Shiga toxin-producing *Escherichia coli* infections. Clin Microbiol Rev 11(3):450-479.
Sandvig K., Bergan J., Dyve A. B., Skotland T., Torgersen M. L., 2010 Endocytosis and retrograde transport of Shiga toxin. Toxicon 56(7):1181-1185.
Schneeberger M., Dietz O., Kirchgässner C., Schmitt S., 2017 Aetiologically Relevant Typing of *E. Coli* Isolates from Diseased Pigs in Switzerland during 2014 and 2015. AJAVS 3(1):1-7.
Smith W. E., Kane A. V., Campbell S. T., Acheson D. W., Cochran B. H., Thorpe C. M., 2003 Shiga toxin 1 triggers a ribotoxic stress response leading to p38 and JNK activation and induction of apoptosis in intestinal epithelial cells. Infect Immunity 71(3):1497-1504.
Sonntag A. K., Bielaszewska M., Mellmann A., Dierksen N., Schierack P., Wieler L. H., Schmidt M. A., Karch H., 2005 Shiga toxin 2e-producing *Escherichia coli* isolates from humans and pigs differ in their virulence profiles and interactions with intestinal epithelial cells. Appl Environ Microbiol 71(12):8855-8863.
Takenouchi H., Kiyokawa N., Taguchi T., Matsui J., Katagiri Y. U., Okita H., Okuda K., Fujimoto J., 2004 Shiga toxin binding to globotriaosyl ceramide induces intracellular signals that mediate cytoskeleton remodeling in human renal carcinoma-derived cells. J Cell Sci 117(17):3911-3922.
Tseng M., Fratamico P. M., Manning S. D., Funk J. A., 2014 Shiga toxin-producing *Escherichia coli* in swine: the public health perspective. Anim Health Res Rev 15(1): 63-75.
Tumer N. E., Li X. P., 2012 Interaction of ricin and Shiga toxins with ribosomes. Curr Top Microbiol Immunol 357:1-18.
Zachary J. F., McGavin M. D., 2016 Pathologic basis of veterinary disease expert consult. Elsevier, St. Louis, pp. 402-403, 607, 889-890.

Zimmerman J. J., Karriker L., Ramirez A., 2012 Diseases of Swine. 10th edition, John Wiley & Sons, New Jersey, pp.723-750.

Received: 24 April 2019. Accepted: 5 May 2019. Published online: 11 June 2019.
Authors:
Flaviu Tabaran, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Faculty of Veterinary Medicine, Anatomic Pathology Department, Romania, Cluj-Napoca 400372, 3-5 Mănăştur St., e-mail: flaviutabaran@gmail.com
Alexandra Tabaran, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Faculty of Veterinary Medicine, Animal Breeding and Food Safety Department, Romania, Cluj-Napoca 400372, 3-5 Mănăştur St., e-mail: lapusan_alexandra@yahoo.com

How to cite this article:
Tabaran F., Tabaran A., 2019 Edema disease of swine: a review of the pathogenesis. Porc Res 9(1):7-14.