SWINE
TECHNICAL
ARTICLES

Clostridium difficile: General Pathogenesis Overview

Bailey Arruda[1] DVM, PhD; Paulo Arruda[1,2] DVM, MS, PhD
[1.] VRI/AMVC Audubon Manning Veterinary Clinic
[2.] Department of Veterinary Diagnostic and Production Animal Medicine, Iowa State University

Clostridioides difficile, previously *Clostridium difficile*, is a common bacterial cause of diarrhea in multiple species including suckling piglets. *C. difficile* is a spore-forming, obligate anaerobe; characteristics that are important in the pathogenesis of *C. difficile* associated disease (CDAD) in neonatal pigs. Once inside the gastrointestinal tract, particularly the colon, the pathogenesis of CDAD is connected to spore germination and toxin production that injure the colonic epithelium.

C. difficile colonization occurs by way of the fecal-oral route, primarily in the form of spores. The spores are able to navigate the acidic pH of the stomach and germinate in the small intestine in response to primary bile acids. The metabolically active vegetative cells colonize and infect the colon upon obliteration of a healthy microbiota. Without a healthy microbiota in the large intestine, there are increased primary bile acids and an overabundance of short-chain fatty acids and sialic acid resulting in the proliferation of *C. difficile* and toxin production. The ability of *C. difficile* to colonize and cause lesions in the colon depends on virulence factors, including toxins as well as adherence and motility factors.

Colonocytes die after toxin entry and activation in the cell. The two primary toxins are TcdA (also known as Toxin A) and TcdB (also known as Toxin B); both of which are large secreted proteins (Figure 1). When antibodies to these toxins are present, there is decreased severity of CDAD. In equines, immunization of mares with the binding domains of TcdA and TcdB elicited serum and colostral antibodies that blocked the cytopathic effect of these toxins in vitro. Some human strains of *C. difficile* also express a third toxin known as binary toxin which may enhance virulence through a series of events that increase the adherence of *C. difficile* to the epithelium. Both TcdA and TcdB attach to receptors of epithelial cells and cause disruption to the cytoskeletal architecture, which normally maintains the cell shape and attaches the cell to adjacent cells, leadings to cell death.

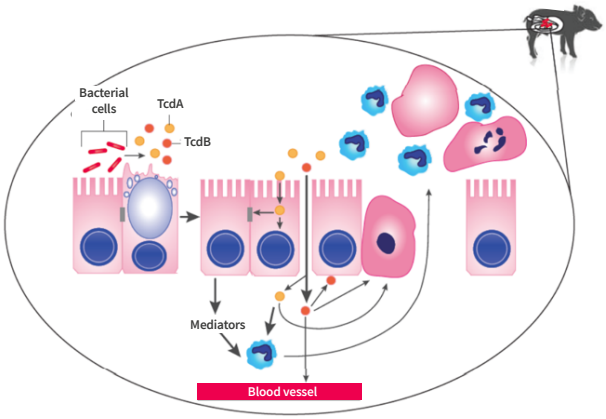

Figure 1. Pathogenesis overview: *C. difficile* colonizes the colonic epithelium and produces primarily toxins A (TcdA) and B (TcdB). Toxin A binds to receptors within the apical border of enterocyte and is internalized via receptor-mediated endocytosis. Disruption of tight junctions and cell rounding allows toxin B to bind to lateral and base border of affected cells. Toxin A and B are involved in cell signaling and actin cytoskeleton regulation. Toxins can reach the blood vessels within submucosa and in combination with cytokine(s) produced by enterocytes attract neutrophils.

Death of colonocytes results in the loss of mucosal barrier of the intestine exposing the underlying tissue to the intestinal microorganisms and activation of the piglet's inflammatory response. As a result, histologic evaluation of the large intestine reveals ulceration of the mucosa with luminal and subjacent accumulation of neutrophils (Figure 2). The role of the immune system is to limit damage to the cells lining the intestine and eventual dissemination of the intestinal bacteria into the blood stream. However, an excessively vigorous inflammatory response can contribute to additional intestinal damage.

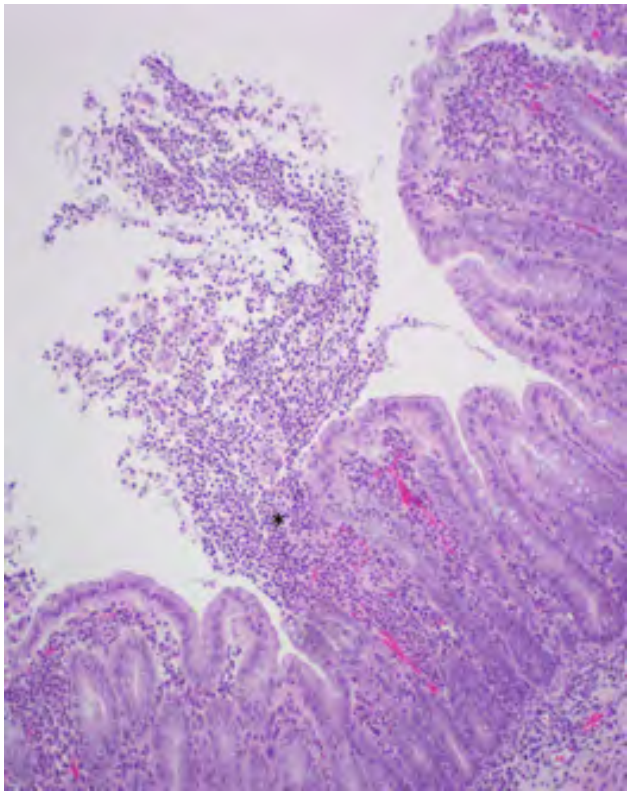

Figure 2. Histopathologic section of colon: * classic volcano-like lesion characterized by a focal ulceration and replacement by moderate to abundant amounts of cellular and karyorrhectic debris, degenerate neutrophils, and fibrin.

Our understanding of the biologic mechanisms of *C. difficile* infection has significantly increased during the past decade. Our current knowledge coupled with further advancements in microbiota and vaccinology, will likely lead to new approaches for treatment and interventions to thwart or ameliorate CDAD in piglets.

References:

1. Abt M, McKenney P, Pamer E. Clostridium difficile colitis: pathogenesis and host defense. Nat Rev Microbiol. 2016;609-620. doi:10.1038/nrmicro.2016.108.
2. Chandrasekaran R and Lacy D. The role of toxins in Clostridium difficile infection. FEMS Microbiology Reviews. 2017:723-750. doi: 10.1093/femsre/fux048.
3. Arruda, P. Clostridium difficile infection in neonatal piglets: Pathogenesis, risk factors, and prevention. 2014. PhD Thesis, Iowa State University.

   https://lib.dr.iastate.edu/cgi/viewcontent.cgi?article=5103&context=etd
4. Artiushin S, Timoney J, Fettinger M, Fallon L, Rathgeber R. Immunisation of mares with binding domains of toxins A and B of Clostridium difficile elicits serum and colostral antibodies that block toxin binding. Equine Veterinary Journal. 2013;476-480. doi: 10.1111/evj.12007.

HIPRA

Laboratorios Hipra, S.A. Avda. la Selva, 135 · 17170 Amer (Girona) · Spain
Tel. (34) 972 43 06 60 · Fax. (34) 972 43 06 61 · hipra@hipra.com · www.hipra.com