

ANATOMY OF *C. DIFFICILE*

Clostridium difficile is a spore-forming, gram-positive bacterium that can cause disease when ingested. While stomach acids kill most of the bacteria, the spores can withstand the harsh gastric environment, passing through to the intestines where they germinate and latch onto the epithelial cells lining the gut. Once attached, the bacteria produce toxins that attack the colon lining, causing abdominal pain and diarrhea. A newly emerged hypervirulent strain of *C. difficile* produces robust amounts of toxins, and a greater percentage of the hypervirulent bacteria produce spores, increasing the bacterial load in the bowel of the patient as well as the number of spores that pass into the environment, where they can be spread to other individuals. The hypervirulent *C. difficile* strain also produces stickier surface-layer proteins, which enhance the bacterium's ability to attach to gut and environmental surfaces, making it more difficult to kill with traditional treatments.

ATTACK THE GUT

When *C. difficile* colonizes the large intestine, it releases toxins A and B, which directly damage the gut epithelium **1**. The host's immune system responds with an array of immunological agents such as antibodies, cytokines, and other immune-stimulatory molecules **2**. This inflammatory response results in the increased secretion of fluids across the gut barrier, causing diarrhea **3**. The immune battle also results in the generation of a pseudomembrane along the colon wall made up of dead epithelial, immune, and *C. difficile* cells, which blocks the transmission of antibodies and other protective host-generated molecules from the blood stream into the intestine **4**.

ALTERNATIVE THERAPIES

While traditional antibiotics target DNA synthesis and bacterial cell-wall development to kill the bacteria after they've invaded, alternative approaches aim to arm the immune system before *C. difficile* ever reaches the colon. ViroPharma Incorporated is developing a therapy to prevent *C. difficile* from latching on to the bowel gut-cell receptors by introducing competing nontoxic strains of *C. difficile* that bind to the same attachment sites on the colon wall. Such competitive binding makes colonization by pathogenic *C. difficile* strains less likely **A**. Sanofi-Pasteur and Merck & Co. are developing a vaccine and monoclonal antibody, respectively, which use neutralized forms of toxins A and B to boost antibody production against the toxins **B**.

