

Toxin Production by *Campylobacter* spp.

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INTRODUCTION

The identification and characterization of virulence factors is a major activity of microbiological research. Knowledge on the nature, regulation, and mechanism of action of virulence factors is indispensable for prevention and treatment of infectious diseases. *Campylobacter jejuni* is the most common bacterial cause of acute infective diarrhea in humans in many developed countries, and is isolated at a high frequency from young children, both healthy and diseased, in developing countries. Two types of diarrhea are observed with *C. jejuni* infections: inflammatory diarrhea, with fever and slimy, often bloody stools containing leukocytes; and noninflammatory diarrhea, with watery stools and the absence of leukocytes and blood. Much effort has been invested to elucidate the pathogenic mechanisms of *C. jejuni* and the closely related, less common *C. coli*. By analogy to other enteropathogens and considering the typical motility of *C. jejuni* and *C. coli*, four major virulence properties were recognized: motility, adherence, invasion, and toxin production (117).

The role of motility in the pathogenesis of *C. jejuni* is now well established (1, 13, 83, 85, 117). Motility is not only required for the bacteria to reach the attachment sites but is also required for their penetration into intestinal cells, although the exact role of flagella in this process has not been defined. Adherence of bacteria to the epithelial surface is probably an important determinant for colonization and may increase the local concentration of secreted bacterial products. Adhesion has been studied extensively in vitro, but specific adhesins, on

the flagella or on the bacterial body, have not been identified. The presence or absence of the recently discovered fimbrial structures on the surface of the bacteria did not influence adherence as measured in vitro, but was significant for colonization in rabbit ileal loops (26). Invasion, i.e., adherence followed by penetration, has been shown in vivo and in vitro (14, 24, 37, 61, 62), and putative factors required for invasion have been identified (24, 31, 60, 77, 118; see also reference 51 for a general review of the pathogenesis of *Campylobacter* spp.). However, invasion levels as detected in vitro are normally low: less than 1% of the applied bacteria invade a monolayer of cells in culture (14, 118), and efficient intracellular killing of bacteria takes place (23). Therefore, toxins have been considered important factors for the pathogenesis of *Campylobacter* enteritis.

The characterization of toxin production by *Campylobacter* spp. has been a slow process. Although the production of several toxins has been reported, their mechanism of action and their importance in disease remains unclear. Some groups have failed to detect any toxins produced by *Campylobacter* spp. This has led to a confusing discussion regarding the very existence of *Campylobacter* exotoxins and the relevance thereof.

This review attempts to summarize current knowledge of proteinaceous toxins produced by *Campylobacter* spp. An attempt has been made to classify the described toxins. The possible relevance to virulence will be discussed. The few cases where toxin production by *Campylobacter* species other than *C. jejuni* and *C. coli* has been described are included. Since several published studies compare *Campylobacter* toxins with known toxins from pathogenic enterobacteria, the major modes of action of the latter are briefly summarized here. Proteinaceous toxins that are relevant in the context of enteropathogenicity

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