CHAPTER 7

Biotherapeutic Agents for Clostridium difficile-Associated Disease

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1. Introduction

Clostridium difficile-associated disease is a classic example of the type of disease that may be most amenable to treatment with biotherapeutic agents (BTA). The gastrointestinal tract contains a complex milieu of interacting organisms whose populations may shift dramatically in response to antibiotics, medications, or medical procedures. The most common result of the disruption of colonic equilibrium is diarrhea. Opportunistic pathogens may establish a disease state when the host’s normal microbiologic flora has been disturbed, and although most cases may respond at first to antimicrobial therapy, a permanent cure relies on the re-establishment of the normal flora. Additional antibiotic treatment may actually be detrimental in that the continual disruption by different types of antibiotics slows the recovery of normal flora. In these types of diseases, BTA may prove to be most beneficial.

C. difficile is an opportunistic anaerobic Gram-negative spore-forming bacillus (Fig. 1). Infection with C. difficile may result in a variety of clinical manifestations. Most commonly, the target organ is the gastrointestinal tract, and the outcome of infection may range from asymptomatic carriage to diarrhea that may progress to colitis, toxic megacolon, or death. Extraintestinal C. difficile infections have been reported infrequently (1,2). C. difficile is currently the most frequent cause of hospital-acquired diarrhea reported for inpatients and a common etiology of chronic, recurrent diarrhea/colitis found in outpatients (2).
2. Impact of \textit{C. difficile} Infections

The impact of \textit{C. difficile} infections is reflected in an increasing reporting of nosocomial outbreaks in hospitals, increased medical costs associated with longer in-hospital stays, prolonged antibiotic therapy, and increased rates of comorbidity and mortality.

2.1. Increasing Frequency

Clinical concern has grown as the number of reported hospital outbreaks of \textit{C. difficile} increased. The number of outbreaks in US hospitals has increased from an average of 4/yr in 1980 to an average of 12/yr in 1994. \textit{C. difficile} infections have increased almost eightfold between 1990 and 1994 in England and Wales (3). Currently, nosocomial outbreaks have been reported in a wide variety of countries, including the United Kingdom, France, Germany, Spain, Japan, and Belgium (Fig. 2).

2.2. Costs

The costs associated with \textit{C. difficile} disease are not trivial, especially if the patient is hospitalized and develops complications. Several