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Mini Review

Targeting *Clostridioides difficile* Infection-Induced Inflammation to Improve Treatment Outcome

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Abstract

Clostridioides difficile infection (CDI) is a worldwide concern. The increase in cases numbers and disease severity and mortality combined with the scarcity of effective antibiotics warrant intensive research for alternative strategies to combat this disease. Although CDI is inflammatory disease in nature, antiinflammatory agents are not recommended for the management of the symptoms. Further, some antiinflammatory drugs are considered predisposing factors for severe CDI and poor prognosis. On the other hand, several studies have demonstrated the benefit of curbing the inflammation in the management of CDI in both humans and experimental animals. Since CDI is a multifactorial disease that depends on host immunity, gut microbiota and bacterial virulence, a thorough investigation is required to assess the value of using antiinflammatory agents in the treatment of the infection. The current article highlights the conflicting evidence of using antiinflammatory agents during CDI and calls for in-depth research to evaluate their use in controlling CDI.

Keywords: *Clostridiodes difficile* Infection (CDI); Inflammation; Anti inflammatory; NSAIDs, Corticosteroids

Abbreviations: CDI: *Clostridioides difficile* infection; *C. difficile*: *Clostridioides difficile*; TNF: Tumor necrosis factor; IL-8: Interleukin-8; NF-κB: nuclear factor-κB; AP-1: activator protein-1; NSAIDs: non-steroidal antiinflammatory drugs; TcdA: *C. difficile* toxin A; TcdB: *C. difficile* toxin B

Introduction

Clostridioides difficile infection (CDI, previously known as *Clostridium difficile* infection) is the most concerning nosocomial infection. As per the US Centers for Disease Control and Prevention (CDC), immediate action is required to mitigate the threat imposed by CDI to the public in the US and around the world [1]. In 2017, CDI was the cause of 223,900 hospitalizations, 12,800 deaths and over $1 billion in health care cost within the United States alone [1]. CDI can be asymptomatic, cause mild to moderate diarrhea, or can result in a devastating disease with severe diarrhea, pseudomembranous fulminant colitis, toxic megacolon and death [2].

C. difficile colonizes the colon of patients with imbalanced bacterial flora, usually following antibiotic therapy. *C. difficile* then releases several toxins and mediators which initiate the inflammatory disease. Both the host and the pathogen participate in the development and progression of CDI thorough inflammation which is an important contributor of CDI. Toxin-mediated modulation of substance P and induction of cytokines (interleukin-8 (IL-8), nuclear factor-κB (NF-κB) and activator protein-1 (AP-1)) contribute to *C. difficile*-induced inflammation [3,4]. Recently, *C. difficile* was found to benefit from the inflammatory process of the bowel by using breakdown products of the extracellular matrix as Stickland reaction substrates to sustain its metabolic activity [5,6]. This was proposed as a potential reason why patients with underlying intestinal inflammation are more susceptible to CDI than the normal population [7-10]. In addition, a beneficial outcome was reported after using corticosteroids in the management of severe and unresponsive CDI in human patients [11,12]. On the

other hand, inflammation was found to play an important role in the primary protection against CDI and hence suppressing the inflammation through the use of antiinflammatory drugs has been considered a risk factor for CDI [13-15]. Therefore, several non-steroidal antiinflammatory drugs (NSAIDs), antihistamines and corticosteroids were associated with higher risk of CDI [15-19]. Experimentally, NSAID- (indomethacin-) pretreated mice had an exaggerated CDI [20]. Also, the use of proinflammatory prostaglandin analogue, misoprostol, protected mice against CDI and accelerated the recovery of intestinal flora after antibiotic disruption [21]. In spite of these conflicting reports, the effect of using antiinflammatory medications either as primary or add-on treatment to antibiotic therapy for the management of CDI has never been experimentally evaluated.

Discussion

Clostridioides difficile inflammation

Clostridioides difficile is a Gram-positive bacterial pathogen that causes life-threatening diarrhea primarily in hospital settings. Since the beginning of the millennium, *C. difficile* infection (CDI) has been considered as one of the most dangerous nosocomial infections. The problem is further complicated by the difficulty to treat the infection and the high recurrence rate after clinical resolution [22]. Virulent strains of *C. difficile* produce two major enterotoxins, TcdA and TcdB, in addition to a binary toxin, CDT [23,24]. Both TcdA and TcdB have a glucosyltransferase domain (GTD) that synergistically inactivate cellular small GTPases after entry to host cells. This results in disruption of the actin cytoskeleton, loss of epithelial tight junctions, increased mucosal permeability and cell death (cytopathic effect). In addition to the direct epithelial injury, *C. difficile* toxins trigger the inflammasome and activate NF-κB pathway. This induces the release of proinflammatory cytokines which leads to inflammatory state and recruitment of neutrophils through different pathways (cytotoxic/enterotoxic effect) [23,24]. Neutrophil infiltration, a hallmark of CDI, increases fluid secretion and mucosal inflammation and damage. *C. difficile*-induced inflammation has a nebulous role in CDI progression, it is not clear whether it has beneficial or damaging effects to the host. Certain immune pathways are thought to be associated with beneficial effects to the host e.g. fractalkine (CX3C) pathway, innate immune sensors (TLR4, TLR5 and NOD1) and neutralizing antibodies. On the other hand, immune reactions like neutrophil infiltration and IFN-γ, TNF-α, leptin, IL-8 and substance P signaling are believed to be harmful to the host [13, 23-25].

Studies supporting the benefit of using antiinflammatory agents

Recently, it was found that *C. difficile* benefits from the inflammatory state of the host. Fletcher *et al*. demonstrated the metabolic activity of *C. difficile* to be different in case of intestinal inflammation when compared to normal conditions. Intestinal inflammation was found to upregulate matrix metalloproteinase (MMP) encoding genes in mice. This in turn breaks down the collagen in the extracellular matrix releasing proline and other amino acids that can be directly utilized by *C. difficile* via Stickland reaction. In addition, the inflammatory state of the host excluded protective members of the normal bacterial flora [6]. In different studies, inhibiting inflammation had a positive outcome clinically in human medicine and in experimental animals. Cardoso *et al*. reported that administration of antiinflammatory medications was beneficial in controlling the symptoms of CDI and reducing the febrile response to TcdB in rats [14]. Additionally, the TNF inhibitor, pentoxifylline, significantly reduced paw edema and neutrophil influx after Sub-plantar injection of either TcdA or TcdB [26]. In human medicine, Skyes *et al*. reported three cases in which the addition corticosteroids to the treatment regimen helped managing severe CDI cases that was refractory to treatment with standard anticlostridial antibiotics [11]. Additionally, Cavagnaro *et al*. reported the benefit of corticosteroid in a child with severe refractory CDI [12]. Moreover, most patients with CDI and inflammatory bowel disease (IBD) responded well to combined therapy of vancomycin and steroids [27]. Also, anti-TNF therapy is reported to have a beneficial effect in patient with concurrent CDI and IBD [28].

Studies supporting the risk of using antiinflammatory agents

The usage of antiinflammatory drugs has been considered a risk factor for developing severe CDI in several human and animal studies. These drugs include corticosteroids, non-steroidal antiinflammatory drugs (NSAIDs), anti-TNF-α monoclonal antibodies (mAbs) and histamine H2-receptor blockers. In this vein, pretreating mice with indomethacin (an NSAID/prostaglandin inhibitor) before infecting with *C. difficile* resulted in more severe CDI [20,29]. On the other hand, misoprostol (a prostaglandin analogue) protected *C. difficile*-infected mice against severe CDI and had a positive outcome on their survival [21]. Pretreating mice with anti-TNF-α monoclonal antibodies was associated with more severe histopathology of the colon relative to untreated mice [30]. In addition, NSAIDs, H2-receptor blockers and steroids have all been associated with higher risk of CDI in several retrospective studies [16-19, 30-34]. Notably, several other studies demonstrated no correlation between the aforementioned drugs and the development of CDI [35-37].

Conclusion

Although the above reports are contradictory, we noticed a pattern that can apply to most of them. In most cases, initiation of the antiinflammatory medication before the exposure to *C. difficile* increased incidence and severity of CDI. However, administration

of an antiinflammatory drug in conjunction with an antibiotic after exposure to *C. difficile* was beneficial and, in some cases, superior to antibiotic administration alone. Accordingly, some studies recommended to postpone escalated steroid therapy in IBD patients with concurrent CDI till the initiation of anticlostridial antibiotics [32]. In conclusion, the use of antiinflammatory agents to control *C. difficile*-induced inflammation of the intestine has been debatable. Contradicting studies have been reported either encouraging or dispiriting the use of different classes of antiinflammatory medications to reduce disease severity and improve treatment outcome. With the current demand for improved anticlostridial agents, there is a need for a systematic research to investigate the benefit of suppressing the inflammation in CDI management [38-48]. This research should account for several factors including; disease severity, time course of the disease, class of the antiinflammatory agent and when to introduce it, patient conditions and infecting strain.

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Conflict of Interest

Authors declare no conflict of interest.

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