Clostridium Difficile Colitis in Trauma Patients – a Global Step by Step Review

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ABSTRACT
Clostridium difficile associated disease is a well recognized nosocomial infection evolving as a severe diarrheal illness, associated with significantly higher rates of morbidity and mortality in critically ill patients. The incidence of Clostridium difficile infection is higher and its impact is more severe in trauma patients when compared with general inpatient population. There are several potential diagnosis tools for Clostridium difficile colitis, however choosing the right diagnostic approach is a difficult task, especially in trauma patients in whom a rapid and certain diagnosis is of paramount importance. Moreover, managing these patients may prove to be a very challenging task, considering the emergence of novel aggressive Clostridium difficile strains resulting in increased disease severity.

Keywords: Clostridium difficile, trauma, infection, diagnosis, therapy

SHORT HISTORICAL INSIGHTS INTO CLOSTRIDIUM DIFFICILE INFECTION
Clostridium difficile is a gram positive, anaerobic, enteric, spore-forming pathogen which was first discovered in healthy newborns’ stool specimens in 1935 by Hall and O’Toole (1). This newly discovered bacteria was named Bacillus Difficilis due to its slow rhythm of growth in culture medium. However, the first reported case of pseudomembranous intestinal tract tissue changes was published (after anatomic studies) by Finney in 1893 and was the one of a young 22-year-old female patient who was operated on for an antro-pyloric tumor. Postoperatively she developed severe diarrhea and consequently she succumbed in the 15th postoperative day (2). Until 1950’s (the preantibiotic era) the pseudomembranous enterocolitis was a rare event. Between 1950s and 1970s, due to the new emerging antibiotics, its incidence slowly grew, while the incriminated agent was considered to be Staphylococcus aureus. An important turning point was made in 1974 by Tedesco et al in Barnes Hospital in St Louis who demonstrated the presence of Clostridium difficile (C. diff.) toxin (3). From that point, the researches escalated, and during the following two decades,
new elements were brought into light such as the spectrum of disease, its epidemiological data and pathophysiological mechanisms (4).

The association between antibiotherapy and the occurrence of C. diff. was thus clearly established and was confirmed for almost all classes of antibiotics, but it was recognized that it has a greater chance of occurrence with Clindamycin and third-generation cephalosporins (5). Another class of drugs recognized to be involved in risk elevation of C. diff. infection development is the use of anti-secretory drugs. Several studies confirmed that the administration of H2-antagonists and proton-pump inhibitors increase this risk by lowering gastric acidity and consequently inducing an imbalance of gastrointestinal microflora, thus creating the needed conditions for pathogens colonization (6-8). One particular category of patients who has a special risk for developing C. diff. infection is the trauma population due to the fact they require large amounts of anti-secretory agents in order to avoid gastro-duodenal stress-induced ulcer, known as Curling’s ulcer.

C. diff. colitis (recognized today as a nosocomial infection) evolves, in most of the cases, as a severe diarrheal illness which can lead to dehydration, hemodynamic instability, malnutrition and electrolyte disturbances and is associated with significantly higher rates of morbidity and mortality in critically ill patients (such as the trauma patients). Moreover, this category of patients gather the majority of the well recognized risk factors for the development of C. diff. infection such as combination and long-term antibiotherapy, prolonged intensive care unit (ICU) and hospital stay, multiple nonsurgical and surgical procedures, low immune status and high trauma scores. Taking these into consideration, in order to improve their clinical status and overall survival, new studies were thus needed to determine the best strategies for these patients.

INTENSIVE CARE UNIT CLOSTRIDIUM DIFFICILE INFECTION CHALLENGES IN CRITICALLY ILL TRAUMA PATIENTS

Post-traumatic death can occur following a pattern of three possibilities: immediate and early (under 48 h) deaths due to massive, uncontrolled bleeding or severe head trauma, on one hand, and multiple organ dysfunction syndrome that can be triggered or not by infection, on the other. The latter group and those who finally survive encounter multiple clinical events while in the ICU. Among these, diarrhea represents a frequent symptom in these patients, encountered in up to 40% of ICU patients. Considering the overall incidence of C. diff. infection that is estimated to be 2% of the hospitalized patients, related to this value, in ICU, the incidence is at least twofold, and a fifth of these patients will progress to severe rapid progressive colitis with a frightening mortality of 60% (9).

The fact that the trauma population has a higher infection rate was demonstrated by Wallace et al., in a study, in which they evaluated trauma and surgical patients in the intensive care settings. The overall trauma patients C. diff. infection rate was twofold when compared with the rate of infection in the surgical patients group (10).

Moreover, a very large cohort study published in 2011 that included 155,891 trauma patients tried to highlight the cause-effect relationship between the hospital acquired infections (including C. diff. infection) and prognosis. The results were astonishing: the overall mortality rate for the group without nosocomial infections was 2%, comparing to 21.2% for the patients with sepsis - 10.6% for the ones with pneumonia, 7.9% for the patients with staphylococcus infections and 7.2% for those with C. diff. colitis (which is almost four times higher than for the control group)(11). Apart from that, the mortality rate determined by Clostridium difficile is high not only in trauma patients. In a large electronic data base analysis on articles published between January 2005 and April 2011, Brett G Mitchell and Anne Gardner showed that all cause mortality in patients with C. diff. infection at 30 days varied from 9% to 38% (12).

Concerning the impact of C. diff. infection on the neurosurgical trauma patients, Musa et al. found that the time frame from the admission until the emergence of the first symptoms of colitis was of 5 up to 7 days, with a mortality rate of 19%. The same author, but with another team, made an analysis in the cardiothoracic intensive care unit and showed that in this case the mean time frame was of 10 days in these patients and the mortality rate at 30 days from admission was 26% (13,14). The mortality rate is high also in orthopedic trauma patients, be-
the major drawback of being time-consuming (the incubation period in anaerobic conditions lasts 72-96 hours), besides requiring adequate culture medium. Moreover, the isolation of one Clostridium difficile strain is insufficient; in order to have a high level of diagnostic certainty it has to be combined with a method for detecting toxigenic Clostridium difficile because alone it cannot distinguish between toxin and non-toxin producing strains (21).

However, the most available instrument is detection of Clostridium difficile toxin B, or both toxin A and B, by enzyme immunoassay tests. They can be performed directly from the stool and provide the results within the same day. The inconvenience of the tests is that they cannot reach the target value of sensitivity of >90% because in order to have a positive result, a quantity of toxin A or B of 100-1000 pg is needed; as a result of this, its sensitivity ranges between 65-85% (21,24).

Molecular testing, such as PCR (polymerase chain reaction) are very rapid and sensitive methods and can identify tcdB (Clostridium difficile toxin B gene), one of the five major genes – tcdA, tcdB, tcdC, tcdD and tcdE found in the pathogenicity locus – PaLoc, which is responsible for encoding toxin B, but they are extremely expensive and most of the laboratories do not have the required facilities. And last but not least, for screening purposes, physicians can use the glutamate dehydrogenase test, this being able to detect the antigen but unable to identify toxin from non-toxin producing strains (21).

Thus, choosing the right diagnostic approach is a difficult task, especially in trauma patients who require a rapid and certain diagnosis in order to initiate the proper therapeutic measures.

Is There a Perfect Diagnosis Tool?

There are several potential diagnosis tools for C. diff. infection. One of the most recognized diagnosis instruments is the cell cytotoxicity test. According to Ticehurst et al. it is considered to be the most sensitive Clostridium difficile diagnostic test (20,21) and according to Turgeon et al. it is the reference method for toxin detection (gold standard) (22). Despite its sensitivity, however, the disadvantages of this method are its considerable costs, its prolonged duration, which is impractically high (24-48 hours), and the fact that it requires adequate lab equipment for cell culture (21).

Another detecting method is the toxigenic stool culture. It has a high sensitivity (94.7% - according to Fedorko et al.) (23) but it has also the major drawback of being time-consuming (the incubation period in anaerobic conditions lasts 72-96 hours), besides requiring adequate culture medium. Moreover, the isolation of one Clostridium difficile strain is insufficient; in order to have a high level of diagnostic certainty it has to be combined with a method for detecting toxigenic Clostridium difficile because alone it cannot distinguish between toxin and non-toxin producing strains (21).

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Modern Treatment Strategies for C. Diff. Infection

Currently, the etiologic connection between C. diff. infection and broad-spectrum antibiotics is clearly recognized (especially for clindamycin, cephalosporins, penicillins and fluoroquinolones) (25). General treatment principles include cessation, if possible, of contributing factors – antibiotic and anti-secretory agents and implementation of measurements for limiting infection transmission. Besides supportive treatment measures (as fluid replace-
symptoms resolution within 90 days of stool transplant, of 91% with stool transplant only and of 98% when vancomycin was administered, subsequent to faecal microbiota transplant. In fact the unexpected benefits of this therapy encouraged the researchers to expand the applicability of this method, not only for C. diff. infection, but also in other medical conditions.

As a matter a fact, Clostridium difficile can be found in two forms: as spores and as an active, vegetative form, which is responsible for producing virulence factors (TcdA and TcdB). However, besides these factors, it also secretes several surface layer proteins, called flagella (FliD, FLiC) and cell wall proteins (Cwp66, Cwp84, CwpV). Flagella appears to have an important role in intestinal mucus layer penetration and in increasing bacteria adherence to intestinal epithelial surface. Intense studies have been carried out to understand the organism’s flagella in order to develop C. diff. vaccines. Moreover, immunotherapy (active and passive immunization against C. diff. toxins, or vaccines targeting surface proteins) could be a target treatment strategy, and it is well known the fact that the immune status plays an important role in the occurrence of C. diff.

Given the fact that the mucus intestinal layer has a protective role against bacterial adherence and penetration, a new therapeutic agent has been proposed. Phosphatidylcoline is an important component of the colonic mucus and, as was supposed, its administration proved to have benefits in patients with ulcerative colitis (31). In a recent study, Olson et al. demonstrated in vitro the positive impact and results of this agent in C. diff. infection: important decrease of tumor necrosis factor, IL 6 levels and of toxin A uptake and reduction of intestinal epithelial cell necrosis with more than 50% (32). However, clinical applications are awaited.

Besides all the above, scientists are in search for future treatment strategies such as phage therapies and bacteriocins (small antimicrobial peptides) (33).
DIAGNOSIS AND TREATMENT ALGORITHM

![Diagnosis and Treatment Algorithm](image)


**FIGURE 2.** Inpatient treatment algorithm for the initial management of C. diff infection (adapted from Royal Devon and Exeter NHS Foundation Trust Clostridium difficile guidelines).

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All patients:
- Assess hydration;
- Baseline urea and electrolytes, albumin, C-reactive protein;
- Deep vein thrombosis prophylaxis unless contraindicated;
- Review medication and withhold needed (proton pump inhibitors, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, diuretics, laxatives);
- Ensure patient +/- family aware of diagnosis and received patient info leaflet;
- At discharge general practitioner sent appropriate information regarding relapses.

In sick patient other options include:
- IV metronidazole 500mg tds 10 days.
- Rectal vancomycin
  - (insert Foley catheter to rectum;
  - inflate balloon;
  - instill vancomycin 500mg in 100ml saline;
  - catheter clamped 60 minutes;
  - deflate and remove;
  - repeat 6 hourly).
- Intravenous immunoglobulin 400mg/kg (one dose)
CONCLUSIONS

Critically ill trauma patients are at high risk for acquiring Clostridium difficile infection, which can have serious consequences on their status. Algorithms of rapid diagnosis and rapidly instituted effective treatment strategies should be well established for this category of patients. Considering the important increase of morbidity and mortality in these patients, further studies and research are needed in order to discover new treatment modalities and we are confident that the future will bring the expected improvements in this respect.

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