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Case Report

# A Difficile Endeavour - Pitfalls of Medical Treatment for Critically Ill Patients with Clostridium difficile Colitis

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## Abstract

We present the case of a 66 year old patient with several comorbidities attended at the emergency room because of acute emphysematous pyelonephritis grade IV with right ureterolithiasis, about 8 mm in diameter, and associated ureteral dilation. After a complicated urosepsis clinical course he suffered *Clostridium difficile* infection of fatal outcome besides combined oral vancomycin and intravenous metronidazole and finally colectomy. We discuss the difficulties of diagnosing and treating critically ill patients who suffer this severe complication because they present, very often, another infection not being possible to withdraw other antibiotics. We analyze new therapeutic approaches such as colonic lavages through either an ileostomy or naso-jejunal tube (NJT) trying to avoid colectomy. In conclusion, diagnosing and treating critically ill patients with *Clostridium difficile* colitis is a challenging endeavor because some scores like ATLAS or UMPC might be interfered by concomitant infections. On the other hand, stopping antibiotics as recommended is sometimes impossible when the other infection has not been controlled. In this scenario giving high doses of Vancomycin p.o. and through enema, and Metronidazole e.v. does not guarantee to achieve high colonic concentrations to control the colitis making colectomy inevitable when the patient deteriorates. Exploring alternative routes of administering either Vancomycin or Fidaxomicin such as either through NJT or an ileostomy deserves to be considered.

***Keywords:*** *Clostridium difficile; Critically Ill; Treatment; Colonic Lavage; Naso-Jejunal Tube*

## Abbreviations

CDI: *Clostridium difficile* Infection; CT: Computed Tomography; COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit; Naso-jejunal tube (NJT); NIMV: Non-Invasive Mechanical Ventilation; PCT: Procalcitonin

## Introduction

The incidence of *Clostridium difficile* colitis has significantly increased over the last three decades. The risk of progression to fulminant colitis is infrequent (1 - 3%) but mortality in this group of patients remains high due to a series of associated complications like megacolon, intestinal perforation and septic shock with development of multi-organ failure [1]. Considering the high mortality of those presentations, early detection of patients with high risk of developing fulminant curses is essential, as well as optimizing antibiotic treatment from the beginning [2]. Several studies have been published within the last few years defining risk factors and eventually developing different

prognostic scores [3]. Additionally, alternative treatments have been proposed trying to improve intra-luminal antibiotic concentration in order to achieve source control as well as to prevent progression to fulminant colitis and total colectomy [4].

Prompt recognition of risk factors for adverse clinical outcomes and optimal septic source control is even more important in critically ill patients, as they frequently associate concomitant sepsis from other foci and altered intestinal transit.

Thus, these are the patients who might benefit most from a novel approach in order to enhance intra-luminal antibiotic concentration.

Herein, we present a case report of severe *Clostridium difficile* colitis with a fulminant course in a patient with several risk factors and concomitant difficult-to-control urosepsis.

We discuss the suitability of considering multiple strategies in order to optimize intra-luminal antibiotic concentration in critically ill patients, such as high-dose Vancomycin p.o. in combination with Metronidazole e.v, concomitant early enema administration and systematic placement of a naso-jejunal tube (NJT) if the patient shows ileus or his frailty does not assure the oral route.

## Case Report

We present a 66 year old patient with arterial hypertension, history of smoking and COPD, as well as morbid obesity, who underwent bariatric surgery 20 years ago (Scopinaro's technique) with a present body-mass-index of 29.

He underwent a transurethral resection of a prostatic urethral and vesical neck papilar tumor, for which he also received Mitomycin-C as induction and maintenance treatment. Incidentally, our patient was diagnosed of *ren arcuatus* (horseshoe kidney), with a normal renal function.

The patient was admitted to the conventional ward diagnosed of acute emphysematous pyelonephritis grade IV with right ureterolithiasis, about 8 mm in diameter, and associated ureteral dilation. Concomitantly, both right perirenal and right posterior pararenal fluid collections were identified (Table 1).

| | **Hospital admission** | **ICU admission due to urosepsis** | **Ward** | **ICU readmission due to shock and respiratory failure** | **Ward** | **ICU readmission** | **Outcome: Death** |
|---|---|---|---|---|---|---|---|
| Number of Days of hospitalization (77) | **5** | **5** | **8** | **21** | **6** | **32** | |
| WBC (cels/µL) | 24.700 | 37.300 | 14.000 | 15.100 | 13.700 | 38.300 | 14.400 |
| Creatinine (mg/dL) | 1 | 0.7 | 0.62 | 1.10 | 0.91 | HFVVC | HFVVC |
| Albumin (g/dL) | 1.6 | 1.8 | 1.8 | 2.2 | 1.7 | 2 | 1.8 |
| Lactate (mmol/L) | 3 | 1.6 | 1 | 1 | 1 | 2.8 | 15 |
| PCT (ng/mL) | 4.3 | 11.8 | 6 | 40 | 0.6 | 0.6 | 4.3 |
| Tª (°C) | 38 | 35.4 | 36.2 | 35.9 | 36.2 | 36.5 | 35.5 |
| Intestinal symptoms | No | Diarrhea | Diarrhea | No | Diarrhea | Ileus | Gastric distension |
| Urinary culture | Negative | Negative | *Pseudomonas aeruginosa*<br>*C. glabrata* | Candida spp | *Pseudomonas aeruginosa*<br>*C. glabrata* | *Pseudomonas aeruginosa*<br>*C. glabrata* | |
| Blood cultures | Negative | Negative | Negative | Negative | Negative | Negative | |
| Toxin C. difficile | - | Negative | Positive | Not tested | Not tested | Positive | - |
| Clinical diagnosis | Urosepsis | Urosepsis<br>(perirenal abscess) | Urosepsis and<br>Colitis due to *C. difficile* | Urosepsis and<br>Colitis due to C. *difficile* | | Urosepsis and Relapsed severe Colitis due to C. *difficile* | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Meropenem (IV) | 5 | 5 | | | | | |
| Linezolid (IV) | 5 | 5 | 8 | | | | |
| Ceftazidime (IV) | - | - | 8 | 18 | 6 | | |
| Vancomycin (PO) | - | - | 1 | 9 | - | | |
| Metronidazole (IV) | - | - | - | 9 | - | 8 | |
| Fluconazole (IV) | - | - | 8 | - | | - | |
| Caspofungin (IV) | - | - | - | 21 | - | 15 | |
| Trimethoprim/ Sulfamethoxazole (IV) | - | - | - | - | - | 10 | |
| Levofloxacin (IV) | | | | | | 10 | |
| Fidaxomicin (PO) | | | | | | 8 | |
| Vancomycin (Rectal) | | | | | | 8 | |
| Ureteral catheter | Yes | | | | | | |
| Percutaneous drainage | | Yes | Yes | Yes | | | |
| Vasopressor required | No | Yes | No | Yes | No | Yes | Yes |
| Heminephrectomy | | | | 10 days after this ICU attendance | | | |
| Mechanical ventilation | No | No | No | 4 days NIMV | No | 11 days intubated 3 days extubated 18 days intubated | Yes |
| CVVHF | No | No | No | No | No | 8 days after this ICU attendance | Yes |
| Colonoscopy | | | | | | 8 days after this ICU attendance | |
| Colectomy | | | | | | 8 days after this ICU attendance | |
| Gastroscopy | | | | | | 8 days after this ICU attendance | |
| ATLAS score | - | - | 4 | 4 | 4 | 6 | 4 |
| UPMC score | | | 2 | 17 | 2 | 20 | 19 |

***Table 1:*** *Clinical course and procedures.*

*White Blood Cells (WBC), Creatinine, Lactate and Procalcitonin (PCT) values are the highest within each period of time. For Temperature (T$^{a}$) the values shown are the most out of normality (either the lowest or the highest) within each period of time. For Albumin the lowest values are given. For antibiotic treatment (in green) the number of days receiving the particular antibiotic and route of administration within each period of time is given. Intravenous (IV), Oral (PO). CVVHF = Continuous veno-venous hemofiltration.*

Empiric broad-spectrum antibiotic therapy with Meropenem and Linezolid was initiated and an urgent JJ-catheter for internal urinary diversion was placed. During this procedure, vesical tumor recurrence was noted. During his stay in the conventional ward, the patient was initially stable, but after 5 days leukocytosis and deterioration of his general status with arterial hypotension required admission in the Intensive Care Unit (ICU). Septic shock was attributed to an abscessed right urinoma, which was further addressed by percutaneous CT-guided drainage with general improvement in the following days. Cultures obtained from urine and drainage were reported negative. The patient developed diarrhea during his ICU stay, although abdominal examination remained unremarkable and *C. difficile* toxin determination in stool was negative.

After 5 days the patient was discharged from the ICU after resolution of his septic process with his right perirenal drainage and the ureteral catheter waiting for a definitive treatment.

In the following eight days, the patient remained stable, but diarrhea developed again and new stool sample was obtained, yielding a positive result for *C. difficile* toxin; treatment with Vancomycin 250 mg q8h p.o. was started. Persistence of the right perirenal collection was observed during a routine renal ultrasonography, therefore another drainage was placed, with isolation of *Candida glabrata* and *Pseudomonas aeruginosa*. Treatment was modified to Ceftazidime and Fluconazole, according to antibiogram. Nevertheless, the patient had to be re-admitted to the ICU because of global respiratory insufficiency, needing non-invasive mechanical ventilation (NIMV), and septic shock with renal dysfunction. Laboratory tests showed leukocytosis and raise in acute phase reactants, as well as hypoalbuminemia. At this point, the patient presented neither diarrhea nor abdominal discomfort or changes in abdominal examination, but Metronidazole 500 mg q8h e.v. was associated and oral Vancomycin was maintained due to high suspicion of progression of his colitis.

A new CT scan was performed to rule out intraabdominal complications, showing a persistent perirenal urinoma with urinary leak from the horseshoe kidney, but no signs of colitis. Over the following days the respiratory insufficiency improved, but the patient remained dependent on vasopressor therapy with persistent leukocytosis and occasional fever around 38ºC. Due to the bad control of the right perirenal septic source, the patient underwent heminephrectomy and perirenal fluid collection evacuation at day 10 of this second ICU admission with a prompt subsequent stabilization in the following days, allowing discharge from the ICU to the conventional ward. However, six days later the patient was re-admitted to the ICU because of shock and acute kidney injury, encephalopathy, leukocytosis and hypoalbuminemia secondary to colitis and persistent *Clostridium difficile* toxin positivity in stool. Intubation and mechanical ventilation was required. Due to suspicion of recurrence of colitis antibiotic treatment was shifted to Fidaxomicin p.o. and rectal Vancomycin enema administration plus Metronidazole e.v. A new CT scan was carried out showing colitis with no signs of complication and a transverse colon measuring 6 cm at maximum diameter, as well as no signs of complication secondary to the heminephrectomy. Urine cultures remained positive for *Candida glabrata* and *Pseudomonas aeruginosa*, leading to antibiotic shift towards Trimethoprim/Sulfamethoxazole, Levofloxacin and Caspofungin according to antibiogram. After 8 days of the new antibiotic regime, multiorgan dysfunction persisted without diarrhea. A colonoscopy was performed showing submucous vascular pattern unstructured, granular pattern with pseudomembranes, ischemic mucosa and ulcers. The surgery team was consulted and a total colectomy was performed, leaving an ileostomy and rectal stump.

After the surgical intervention the patient´s general condition discretely improved, although ileus and gastroparesis persisted. An episode of massive vomiting and aspiration required orotracheal intubation and mechanical ventilation, with new development of septic shock. The patient underwent a gastroscopy showing great gastric distention with ischemia of the alimentary loop of the previous bariatric surgery and abundant gastric residue. The patient finally died after 77 days of hospitalization.

## Discussion

The latest IDSA (The Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America) clinical guidelines [5] define severe *Clostridium difficile* infection (CDI) as presence of leukocytosis with a white blood cell count of ≥ 15000 cells/mL or a serum creatinine level > 50% above basal values. The same guidelines propose the term 'fulminant' to those cases who develop hypotension, shock, ileus or toxic megacolon.

According to a prospective Spanish study, around 12% of patients diagnosed of CDI show the aforementioned severity criteria [6].

Other groups describe absence of diarrhea as a remarkable signal of progression towards fulminant colitis [7].

However, such a definition is highly non-specific, especially among critically-ill patients, in whom the presence of ileus, arterial hypotension or shock are relatively common despite not being caused by the colitis itself, as in the current case report, where a persistent urosepsis in relation to the anatomic anomaly of a horseshoe kidney required prolonged course of antibiotics and eventually perform a heminephrectomy.

Hence, one of the most greatest challenges regarding these patients is trying to identify parameters which could help us predict severity [8-11].

Several systematic reviews have been published in the last years as an attempt to identify these risk factors and try to predict treatment response, without achieving international consensus [12-14].

Different published severity scores have been applied to patients with CDI, with a wide range of sensibility (63.2 - 84.2%) and specificity (59.4 - 93.9%) [3].

Except for leukocytosis, age and hypoalbuminemia, heterogeneity in the results is vast and the majority of the studies are limited by small sample size [12]. Others identify leukocytosis and acute kidney injury as predictors of developing a severe course [15].

The ATLAS score classified *Clostridium difficile* colitis in different severity groups, establishing a prognostic scale [16]. A combination of five variables commonly measured in patient´s follow-up and recorded at the moment of diagnosis of colitis were used. The ATLAS score includes (Table 2): age, treatment with systemic antibiotics, leukocyte count, serum albumin and serum creatinine. Patients with severe presentation are those with a leukocyte count > 15000/µL, serum creatinine > 1.5 times basal values, temperature > 38.5ºC and hypoalbuminemia < 2.5 g/dl. Nonetheless, it is still a fairly non-specific scale in which any critically ill patients can show many items without them being secondary to colitis.

| ATLAS Score System | | | |
|---|---|---|---|
| | **0 Points** | **1 Point** | **2 Points** |
| Age (years) | < 60 | 60 - 79 | ≥ 80 |
| Treatment with systemic antibiotics during CDI therapy (≥ 1 day) | No | - | Yes |
| Temperature (°C) | ≤ 37.5 | 37.6 - 38.5 | ≥ 38.6 |
| Leukocyte count (total) | < 16,000 | 16,000 - 25,000 | > 25,000 |
| Serum Albumin (g/L) | > 35 | 26 - 35 | ≤ 25 |
| Serum Creatinine (µmol/L) | ≤ 120 | 121 - 179 | ≥ 180 |

***Table 2:*** *ATLAS score system [16].*

As patients with fulminant colitis with systemic involvement require an urgent surgical intervention, the University of Pittsburgh Medical Center (UPMC) developed a score [17] for severe complicated cases so as to detect the need for an early surgical intervention [18]. This score assesses the presence of organ dysfunction such as haemodynamic or respiratory failure, altered mental status and laboratory parameters like leukocytosis, renal dysfunction and hypoalbuminemia, as well as clinical findings (fever, abdominal pain, ICU-admission) and CT results (Table 3). They define a severe-complicated infection as ≥ 7 points and patients with ≥ 15 points would have a high likelihood (75%) of presenting failure of medical treatment and thus requiring further surgery.

| UPMC Score | |
|---|---|
| **Criteria** | **Points** |
| Immunosuppression and/or chronic medical condition | 1 |
| Abdominal pain and/or distention | 1 |
| Hypoalbuminemia (<3 g/dL) | 1 |
| Fever > 38.5°C | 1 |
| Intensive care unit admission | 1 |
| CT scan with nonspecific findings of pancolitis, ascites, and/or bowel wall thickening | 2 |
| While blood cell count >15,000 or < 1500 and/or band count >10% | 2 |
| Creatinine 1.5 fold > baseline | 2 |
| Abdominal peritoneal signs | 3 |
| Vasopressors required | 5 |
| Mechanical ventilation required attributed to CDAD | 5 |
| Disorientation, confusion, or decreased consciousness | 5 |
| 1 - 3 points: mild-moderate disease<br>4 - 6 points: severe disease<br>7 or more points: severe complicated disease<br>≥ 15 points: high probability (75%) of treatment failure and need for surgery | |

***Table 3:*** *University of Pittsburgh Medical Center (UPMC) Severity Score System [17].*

Despite being able to detect major alarm signs through organ dysfunction assessment, in critically ill patients those can be interfered by concomitant active infections, severe malnutrition, non-infectious fever and multi-factorial acute kidney injury, which complicates attributing those findings to colitis.

Therefore, despite the published scores, it is still difficult to determine whether colitis or other septic foci are responsible for the adverse course of a patient.

The reported patient showed pronounced hypoalbuminemia from the beginning of his hospital stay and he required three ICU-admissions, two of which after the detection of *Clostridium* toxin in stool, because of septic shock secondary to an urinary origin with associated variable renal dysfunction. At the moment of diagnosis of CDI, he scored 4 in the ATLAS model, which would be associated to a cure rate of 81% [16]. However, if we apply the UPMC score, the patient had very high scores in each of the ICU-admissions which could represent a high risk of medical treatment failure for CDI, but the patient´s worsening during his second ICU stay was particularly due to the perirenal abscess which improved with heminephrectomy and allowed his discharge from the ICU shortly afterwards.

Recently, several studies have been published in which Procalcitonin (PCT) values were related to severity in CDI [19]. Some of small sample size suggest PCT > 0.5 ng/dl as a severity marker [20]. However, it is easy to conclude that PCT is not easily assessable as a specific predictor of severity in CDI in the event of a concomitant infection. Particularly, in the case described, the patient showed much higher PCT values during his second ICU stay, when septic shock was highly probable secondary to the urinary source, than in the third ICU admission where colitis relapse played a major role.

Neither endoscopic procedures seem to be a reliable test in order to guide the clinical course and responsiveness to treatment. The distinctive image of confluent membranes is observed in less than 50% of *Clostridium difficile* associated diarrhea and its frequency of presentation varies greatly depending on severity, from 20% in mild cases up to over 90% in the most severe cases [21].

Persistence of positive *C. difficile* toxin in stool samples does not ease clinical decisions at all, because in up to 60% of patients the toxin can be positive despite successful treatment and good clinical course [5].

Since the fatal outcome of the reported case, despite adapting antibiotic treatment to the disease stages and choosing combined treatment strategies and high doses, we would like to highlight our doubts regarding the oral route of administration for antibiotics in critically ill patients with hypercatabolism, high antibiotic pressure and intestinal motility disorders. Adequate treatment may be even more difficult in patients with a history of bariatric surgery and intestinal diversion, as in the reported case, where intestinal motility might be impaired or in which ileal involvement is likely [22].

New strategies have been proposed over the last years, intended to optimize intra-luminal antibiotic concentrations, such as combined Vancomycin p.o (500 mg q6h) plus Metronidazole e.v. (500 mg q8h) during 10 - 14 days [4,5]. In those patients who do not tolerate the oral route, Vancomycin enema application is an effective strategy [23,24], eventually achieving complete remission and thus preventing total colectomy. Therapeutic failure in this setting has been associated with advanced age and severe hypoalbuminemia (< 2,5 g/dl) [23]. While there has been no specific research regarding the subgroup of critically-ill patients, during the third ICU admission we associated Fidaxomicin p.o, Metronidazole e.v. and Vancomycin enema application; despite all of this, the patient eventually required colectomy. It would have been desirable to discontinue any other antibiotic treatment, but this was not possible due to the persistence of urinary infection.

Delay of surgical treatment in fulminant colitis has been associated with poor outcome [25]. Surgery should be considered before reaching hyperlactacidemia > 5 mmol/l [4,5]. However, some authors suggest short-term optimization of medical treatment in order to improve outcomes after colectomy. Unfortunately, yet no clinical or laboratory findings have been identified to predict response to medical treatment or the need for surgical management [26].

Less aggressive surgical treatment for severe CDI has been introduced recently [27]. Such protocols include ileostomy plus colonic lavage with Vancomycin-solution in order to increase local drug concentration, with good results regarding 30-days mortality compared to a control group [17].

Even a case of ileostomy and anterograde administration of Fidaxomicin has been reported with promising results [28]. Those positive results might be produced by cessation of intestinal transit and delivery of nutrients, limiting consequently bacterial growth and toxic load [17].

Colonic lavage is performed during ileostomy surgery following the Pittsburgh Protocol, which includes laparoscopic surgery, intraoperative polyethylene glycol colonic lavage (at least 8 L) and further Vancomycin flushes (500 mg q8h in 500 cc Ringer's lactate plus Metronidazole 500 mg q8h e.v. for ten days).

In view of the promising results of this pilot study, other authors have suggested applying the Pittsburgh lavage protocol to non-surgical patients through a NJT. A small retrospective study, with a small simple size, compared in-hospital mortality between patients who received lavages through a NJT, ileostomy and those who underwent total colectomy, finding a mortality reduction in patients who received NJT-based treatment.

Due to high bias risk in the previous studies, a prospective, multi-centric clinical trial (ERASE *C. difficile*) has been started [27], at the present time in recruitment phase. The aim of the study is to compare 30-day mortality in patients with severe CDI and with risk factors

for developing complicated colitis, albeit without urgent surgery criteria. An intervention group will be receiving high-dose Vancomycin p.o. + Metronidazole e.v. + lavages trough a NJT, and will be compared to a control group receiving conventional antibiotic treatment with a duration of 14 days in both groups. No results have been published so far.

Besides this interesting approach to prevent total colectomy in patients who evolve towards fulminant colitis, this strategy could be of interest when applied routinely to critically-ill patients, in whom intra-luminal antibiotic availability might not be optimal.

## Conclusion

Diagnosing and treating critically ill patients with *Clostridium difficile* colitis is a challenging endeavor because some scores like ATLAS or UMPC might be interfered by concomitant infections. On the other hand, stopping antibiotics as recommended is sometimes impossible when the other infection has not been controlled. In this scenario giving high doses of Vancomycin p.o. and through enema, and Metronidazole e.v. does not guarantee to achieve high colonic concentrations to control the colitis making colectomy inevitable when the patient deteriorates. Exploring alternative routes of administering either Vancomycin or Fidaxomicin such as either through NJT or an ileostomy deserves to be considered.

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