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CLOSTRIDIUM DIFFICILE COLITIS - A ROLE OF SURGERY

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Clostridium difficile infection (CDI) is the most frequent cause of nococomial diarrhoea. Most cases are succesfully treated by antibiotic therapy, but nearly 10% may progress to the fulminant form. The aim of this work is a retrospective evaluation of the results of surgical treatment of patients with the severe *Costridium colitis*, in the period 2008-2014.

Clostridium toxins were detected in patients in Bohunice University Hospital in 1956. Thirty seven of them underwent surgery due to toxic colitis. There were 6 total colectomies with terminal ileostomy, 29 subtotal colectomies with terminal ileostomy, 1 coecostomy and 1 axial ileostomy. The 30-day mortality was nearly 35 %, 90- day mortality 54% and morbidity 89%.

Early and precise indication for surgery could save about 65% of patients with fulminant course of *Clostridium difficile colitis*. *Acta Medica Medianae 2015;54(1):75-80.*

***Key words**: Clostridium difficile colitis, toxic colitis, surgery*

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Introduction

In recent years, *C. difficile* infections (CDI) have become more frequent, more severe and more diffucult to treat. CDI has become the leading cause of death caused by the healthcare-associated infections. C.difficile is a gram-positive sporulating anaerobic bacillus (spors can survive up to 5 months). It produces toxins A and B causing mucosal destruction and pseudomembrane formation (1-5). The prevalence of CDI-associated colitis has been increasing and there is a growing number of recurrent infections, refractory to standard therapy. We can find positive toxins in faeces of 3-5% of adult population and in 10-25% of hospitalised patients; it becomes more often up to 25% after therapy with antibiotics (ATB). Similar numbers were found in patients who received one dose of prophylactic antibiotics before surgical procedure (6).

Ethiology

C.Difficile most commonly affects older adults in hospitals, patients with different comorbidities, patients who stayed in ICU or underwent prolonged hospitalisation or long-term care facilities. Typically, it occures after course of ATB medications or after chemotherapy. CDI may affect up to 8% of hospitalized patients, most of whom remain symptom-free carriers, and symptoms with diarrhoea occur only in 25% of these patients. Twenty–five percent of human *C. difficile* isolates are nontoxigenic. Colonisation and infection with toxin-producing strains may lead to a wide array of diseases from asymptomatic through mild diarrhoeas, pseudomembranous colitis, toxic megacolon, intestinal perforation, sepsis, to death of the patient (7). CDI usually developes during or short after a course of ATB therapy. There is group of risk ATBs for *Clostridium difficile*-associated diarrhea: Chinolons, Cefalosporines, PNC, Linkosamides (8).

The first symptoms typically appear at 3-9th day of ATB therapy; however, they may not appear for weeks or even months afterward. Moderate watery diarhoea, 3-5 times a day and mild abdominal cramping can proceed to sepsis with systemic toxicity, peritonits or toxic megacolon and MODS. These are the signs of pseudomembranous colitis an acute inflammatory disease of the colon. Endoscopic examination can show minimal inflammation or edema of the colonic mucosa. In more severe cases, the mucosa is covered with adherent nodular or diffuse

exudates, with patches of row tissue that can bleed or produce pus. Typical endoscopic presentation of yellowish pseudomembranes lining over the colonic mucosa can be seen in the picture below (Figure 1.).

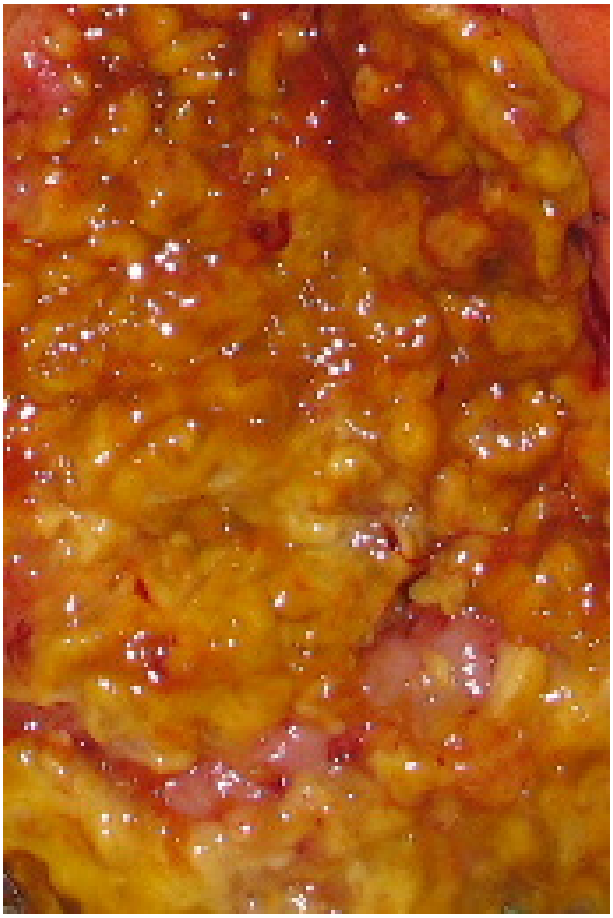

Figure 1. Typical endoscopic presentation of yellowish pseudomembranes lining the colonic mucosa

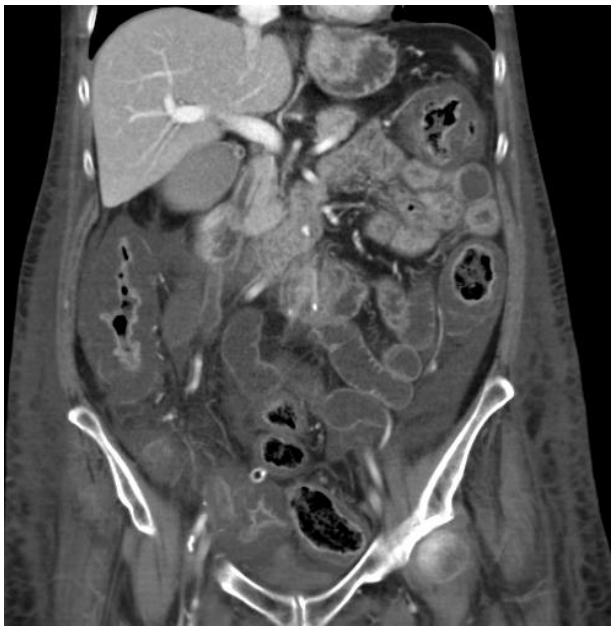

Fig 2. CT scan of Clostridium difficile associated colitis

A severe complication of *C.Difficile colitis* is toxic megacolon, the incidence of which varies from 0,4% to 3% of cases (9,10). There are defined risk factors for toxic megacolon: severe inflamatory condition, IBD, ischemic colitis, any infectious colitis, concurrent malignancy, COPD, immunosupression and renal failure. The mortality rate of toxic megacolon associated with *C.Difficile* is substantial and varies from 38 to 80% (5-10).

Diagnosis is based on clinical symptoms and history of ATB treatment. There are typical laboratory changes: leukocytosis 10-50.000/mm³, CRP elevation. We can find a typical image of an X-ray – mucosal oedema, abnormal haustra, colon dilatatation, paralytic ileus in 28% of patients. Ultrasound and CT scan finding: dilatation of the colon, wall thickening, edema, picture of pancolitis, pneumatosis of the colon wall and free fluid in the peritoneal cavity (Figure 2). Diagnosis is confirmed by the detection of antigen or toxins A or B, most commonly through immunoanalysis with a sensitivity ranking between 98 and 99% with results available within 24 hours.

Colitis diagnosis may be subsequently confirmed by the presence of characteristic pseudomembranes during colonoscopy. It is recommended under the specific conditions: 1.when there is a high level of clinical suspicion for *C.Difficile* despite repeated negative laboratory assays; 2. when a prompt diagnosis is needed before laboratory results could be obtained; 3. when *C.Difficile* infection fails to respond to antibiotic therapy, or 4. for atypical presentation of *C.Difficile colitis* (11). Due to the fact that in up to 1/3 of the patients the right part of the colon is affected primarily, colonoscopy is preferred to sigmoideoscopy, during which this part of the colon would not be examined. However, the characteristic pseudomembranes may not always be present, which is why the sensitivity of colonoscopy is around 51%. Moreover, colonoscopy bears the risk of perforation in terms of acute colitis and is seldom used to confirm the diagnosis.

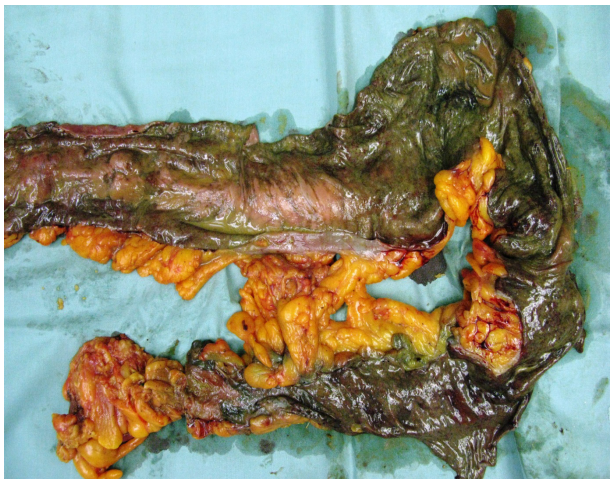

Figure 3. The specimen of the colon with Clostridium difficile colitis

Recommended treatment of CDC depends on the severity of symptoms. Antibiotics should be discontinued or changed, aggressive medical therapy may help prevent surgical intervention in up to 50% of cases (10). Antiperistaltic agents and opiates should be avoided. If oral therapy is possible, 500mg metronidazole every eight hours orally for 10-days, in severe colitis Vancomycin 125mg every six hours orally for 10 days. If oral therapy is impossible, metronidazol 500mg every eight hours intravenously for 10 days, in severe colitis metronidazole intravenously + intracolonic vancomycin 500mg in 100ml of normal saline every 4-12 hours or vancomycin 500mg every 6 hours by nasogastric tube. Patients with severe course with heavy diarrhoea, leucocytosis, pseudomembranous colitis, toxic megacolon or systemic toxicity symptoms are usually given vancomycin enemas to reach adequate intra-colonic concentrations. Vancomycin could be administered intravenously. This antibiotic therapy is effective in more than 90% of patients. Although patients with an initial episode of *C.Difficile colitis* usually responds to antibiotic therapy, 20-35% of patients will develop recurrent disease (12). Bowel rest, supportive infusion therapy, parenteral nutrition are as important as antibiotic treatment.

The idea of restoring the normal intestinal microflora by transplanting stool from healthy donors was first published in 1958. This procedure is currently known as: "Fecal Microbiota Trans-plantation (FMT)" (13). Until 1989, retention enemas had been the most common technique for FMT. In 1991 it was used as alternative stool infusion via duodenal tube, in 1994 via rectal tube and in 1998 via colonoscope. The method is used in patients with recurring CDI, it represents an effective treatment method in this indication (14). Efficiency of this procedure varies according to the site of infusion of a liquid suspension of stool. In a recent study it was 81% in the stomach; 86% in the duodenum/jejunum; 93% in the cecum/ ascending colon; and 84% in the distal colon (15).

The failure of conservative treatment leads to the development of fulminant CD colitis (FCDC). It is the most serious form of CDI colitis characte-rised by acute severe colitis with signs of systemic toxicity. Increasing abdominal pain with signs of peritoneal disturbances, colon distension, dehydration, hypotension, oliguria or anuria with increasing azotemia, fever, and significant leuko-cytosis with proven *C. Difficile* infection are descri-bed in 1–3% cases, but may reach up to 10% (16,17).

Mortality rate in patients with FCDC is critically high, and it is still the problem to decide about the right time for surgery. Urgent indications to surgery are signs of peritonitis, systemic toxicity, not reacting to antibiotic therapy, progressive colonic dilatation because of risk of perforation, toxic megacolon, mucous necrosis and bleeding. In fact, the decision to perform an emergency colectomy remains primarily empirical (18). Early

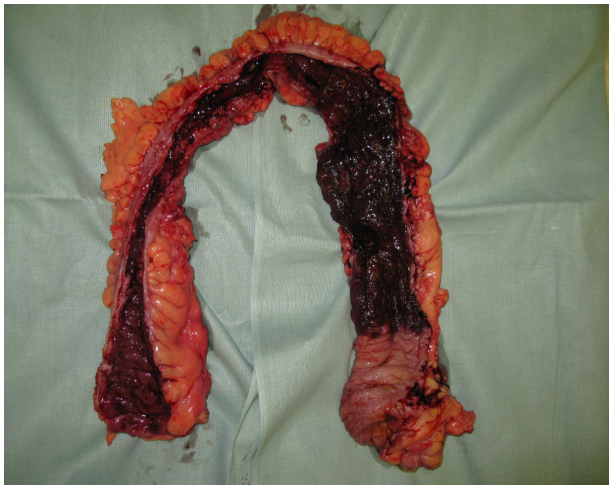

Figure 4. The specimen of the colon with Clostridium difficile colitis

surgery has been advocated for the treatment of FCDC by many authors (15,16,19).

Performed surgical procedures include total colectomy with end ileostomy, segmental or partial colectomy, and diversion stomy. Colectomy with terminal ileostomy is currently advocated, but it entails high morbidity and mortality reaching up to 35-80%. Ileostomy remain permanent in more than a half of patients. An alternative solution, during which axial ileostomy is established through laparoscopy with perioperative performance of colon lavage with polyethylene glycol solution or electrolyte solution followed by Vancomycin lavages, was published by Neal. Mortality decreased to 19% and the colon was preserved in 93% of the patients (16). There is a big deal with correct timing of surgery. Early surgical inter-vention is crucial in reducing the mortality of FCDC in selected cases. On the other hand, performing the operation too early leads to the loss of a substantial part of the large intestine and there is a high potential for permanent ileostomy.

Materials and methods

In this retrospective study we evaluated the operative treatment of patients with the fulminant form of *Clostridium difficile colitis* at the Surgical department of University Hospital Brno and Faculty of Medicine of Masaryk University Brno, in the period from January 2008 to December 2014.

Data were sourced upon assessment of documentation. The following data were conside-red: demographic data, laboratory parameters, results of examinations using imaging methods, type of operation performed, including indications for operation, type and indication of previous antibiotic therapy, comorbidity, postoperative complications, histopathologic findings, as well as postoperative 30-day and 90-day mortality and morbidity. In order to define the predictors of morbidity and mortality we divided our patient into two groups. Group A consisted of patients with postoperative complications of I-IIIA Dindo/Clavien

severity, while group B consisted of patients with IIIB –V severity (20).

Both groups were compared. Statistic methods used: count, arithmetic average, minimum, maximum, median. To assess significant difference, we used the Fisher exact test and Student T-test. We defined a two-tailed P value lower than 0.05 as significant.

Results

Between 2008 and 2014, positive Clostridium toxins A or B were found in a total of 1.956 patients hospitalised at the University Hospital Brno. Of these, 175 patients were hospitalized at surgical departments and 1.781 at departments with a specialisation in internal medicine. Thirty-seven patients in underwent surgery for present *Clostridium colitis* during that period, which accounts for 1.89 % of all the patients with positive Clostridium toxin.

In 24 patients the disease developed during their stay at the University Hospital Brno, 13 patients were transferred to the Department of Infectious Diseases at the University Hospital Brno from other medical facilities.

All the patients with proven *C.Difficile* infection and confirmed colitis upon CT, and ultrasound examinations or colonoscopy started conservative treatment with Metronidazole, 18 patients combined with Vancomycin; Metronidazole was administered intravenously, Vancomycin perorally, and 3 patients received douches. Two patients after chemotherapy for hematooncological malignity received Metronidazole and Vancomycin combined with Meronem. Four patients received only Metronidazole and 2 patients with recurrent Clostridium colitis received only Vancomycin in monotherapy. Surgery was indicated in case of antibiotic treatment failure with clinical deteriorating and progression of the disease.

A total of 37 patients underwent surgery for the FCDC at the University Hospital Brno between 1/2008 and 12/2014; 9 of them were men with median age 71 years and 28 women with median age 75 years. Thirty-three patients were treated for their first attack of the disease, 3 patients for the second attack, and one patient for the third attack of this disease. Before the attack of colitis, 11 patients underwent appendectomy.

Performed operations included 6 (16.2%) total colectomies with terminal ileostomy, 29 (78.4%) subtotal colectomies with terminal ileostomy, 1 caecostomy and 1 axial ileostomy. All the operations were performed in acute conditions, primary anastomosis was not performed.

All the patients who underwent surgery had the pseudomembranous colitis diagnosis confirmed through histology; two cases included also an ischemic factor. Both of them had the Clostridium toxin in their stool, which was positive in 35 patients (94.6%). One female patient with negative toxin had positive colonoscopy of typical pseudomembranes.

As part of diagnostics, 29 patients had preoperative CT with 96.5% specificity for colitis evidence, thickened wall of the colon was found in one patient during the first examination, toxic megacolon was found in 2 patients, and the rest had a proven pancolitis with loose liquid in the abdominal cavity. Ultrasound examination was performed in 21 patients with 85.7% specificity. Sigmoidoscopy was performed in 5 patients, 3 of them had the typical pseudomembranes and two patients had the colon dilatation with paralysis.

Thirty-four patients (91.9%) received antibiotic treatment prior to the development of Clostridium colitis. Nine (24.3%) (7 x Ciprofloxacin, 1x Norfloxacin, 1x Ofloxacin) patients received chinolon chemotherapeutics, 14 (37.8%) potentiated penicillins (13x Amoxicilin/clavulanic acid, 1x Ampicilin/sulbactam), 10 (27.0%) antibiotics from 2nd and 3rd generation of cephalosporins (7x Cefuroxim, 3x Cefotaxin) and 3 (8.1%) macrolids (2x Clarithromycin); 12 patients received two or more antibiotics at the same time or consecutively. The most frequent indication for these drugs was a bronchopneumonia in eleven cases (29.7%), followed by urinary infection (27.0%), antibiotic coverage of osteosynthetic operations (13.5%), vascular operations (5.4%), neurosurgical operations (5,4%) and chemotherapy (5.4%).

Diarrhoea was present in 91.9% of the patients. The average value of CRP 149 mg/l (min. 11; max.332; med.139) leukocytes 32.4x109/l (min.0,76; max.65; med.32) trombocytes 280.9 x109/l (min.63.8; max.799; med.278) procalcitonin 3.53ug/l (min.0.11; max.26; me d4.34), albumin 17.9g/l (min.10.9; max.27.8; med.17.9) and total proteins 43.9 g/l (min.23.2; max.64.8; med.43.3).

Coagulopathy with INR>1.5 was present in 13 patients (35.13%). One patient even developed disseminated intravascular coagulation. Prior to operation, circulatory instability was present in 18 patients, of whom 12 had to have circulation support by katecholamins. The quality of conscious state was changed in 8 patients; six needed intubation prior to operation and artificial pulmonary ventilation due to signs of septic shock.

An operation was indicated in 14 patients for signs of sepsis to septic shock, of whom 6 patients progressed to multi-organ failure. Seven patients were indicated for surgical solution for signs of peritoneal disturbance, 6 for symptoms of toxic megacolon, and 7 for progressive affection of the colon despite maximum conservative therapy and profuse diarrhoea.

30-day mortality in our group of patients was 35.1% (2x renal failure, 2x cardiac failure, 3x bronchopneumonia, 6x Multiple system organ failure, septic shock). Morbidity reached 89% (bronchopneumonia 4x, urinary infection 6x, wound dehiscence 13x, coagulopathy with haemoperitoneum 3x, atrial fibrillation + cardiac insufficiency 4x, renal insufficiency 5x, delirium 1x, intestinal

bleeding 2x. 12 patients had two or more complications in the postoperative period.

A comparison of the patients divided in two groups upon the severity of post-operative complications did not show any statistically significant difference regarding age, sex and comorbidity. Strong leukocytosis proves to be a significantly important predictor of post-operative mortality and morbidity (p=0.02) (Table.1).

Table 1.

	A (I-IIIA) n=11	B (IIIB-V) n= 15	P
Sex M/F	4/7	3/12	0,4
Age	66,7	73,9	0,222
Total colectomy	3 (27,3%)	3 (20%)	1
Subtotal colectomy	7 (63,6%)	11 (73,3%)	0,68
Stoma	1 (9,1%)	1 (6,7%)	1
CRP	110	137,9	0,47
PCT	1,42	1,44	0,97
LEU	**23,5**	**38,9**	**0,02**
ALB	19,7	15,9	0,1
TP	43,15	42,2	0,86
Circulatory instability	3 (27,3%)	7 (46,7%)	0,42

Discussion

The role of surgery in the management of *C. difficile* asosiated colitis is becoming more and more important. It is because of increased incidence and severity of CDI. The percentage of serious form of CDI rose from 7.1% in 1991 to 18.2% in recent years, and the number of patients who died within 30 days after severe *C.Difficile* associated diarrhea rose from 4.7% in 1991 to 13.8% in recent years (11). The increased incidence and significance of CDI is currently being connected with the presence of hypervirulent strains. It also became more likely to relapse.

Fluminant *C.Difficile* (FCDC) colitis was defined as acute severe colitis with signs of systemic toxicity (21). There are still no clear criteria for unified classification of this severe disease. Mortality rate in patients with FCDC stayed unsatisfactory. There remains the question if patients receive appropriate and timely treatment. The timing of the surgical intervention is the crucial point for survival of patients with FCDC. Colectomy for FCDC is connected with high morbidity and mortality, especially of delayed, but surgery is usually the last solution for the patient with clinical signs of peritonitis with septic shock.

In patients with fulminant colitis the currently most frequent operation is colectomy with terminal ileostomy. According to the published papers 1-3.8% of patients with *Clostridium difficile* infection undergo this operation (22).

In the first phase, Clostridium toxin causes a local inflammatory reaction in the colon mucosa and surrounding tissues, very often without damaging the vitality of the intestinal wall. Pathogenesis of the consequent systemic reaction has not been exactly explained, but a key role in it is played by toxins occurring in the large intestine with follow-up systemic inflammatory reaction. This is why colectomy is generally accepted as the last resort in the therapy of life-threatening disease not reacting to Vancomycin or Metronidazole treatment.

In most of the published works, the mortality of this operation ranges between 30 and 40%, but may reach up to 80% (3,23).

Some authors try to determine the factors that could predict higher mortality of patients after colectomy for Clostridium colitis (3,18).

Lamontage compared patients hospitalised at an intensive care unit (ICU) after colectomy for Clostridium colitis with patients hospitalised at an ICU for other conditions. He found the following factors that predicted increased 30-day mortality: leukocytosis >50, lactate >5, age >75 and shock with circulatory instability with the necessity to support with katecholamins (18).

In our group of patients, 30-day mortality reached 30.7%. Six patients who died were over 75 years old, 4 patients had circulatory instability with vasopressor support prior to the operation, 3 had quantitative change of consciousness and two required intubation. The average Leu value was 39.87. Leukocyte level was also confirmed as a statistically significant predictor for serious post-operative morbidity and mortality according to Dindo's classification of surgical complications. The operation of choise had become colectomy with end ileostomy. There are references confirming better result with this kind of operation than with segmental resctions. Work published by Koss showed 11% mortality after colectomy for the fulminant form of Clostridium colitis while 100% of patients who underwent only segmental resection died (23).

These results were confirmed by Ali on a large group of patients (24).

In our set of patients we performed 6 total colectomies and 18 subtotal colectomies with terminal ileostomy, and no segmental resections were performed.

One axial ileostomy was done in a female patient who underwent repeated laparotomies before where it was not possible to release and remove the colon due to many adhesions. One caecostomy was performed in a female patient with minimum macroscopic affection of the colon and mucosa from the performed colostomy. Both patients then continued with intravenous application of Vancomycin and Metronidazole. Both, however, had a recurrence of Clostridium enterocolitis after the treatment. The patient after ileostomy died 40 days after the first operation. Patient with caecostomy had a history of already 2 recurring Clostridium enterocolitides, always successfully treated with antibiotics. Continuity of the digestive system was restored in 5 surviving patients out of 12 (46%). The average duration of ileostomy was 10.8 months (7-26M).

Conclusion

Clostridium difficile associated colitis is potentially life-threatening disease. Fulminant form of CDI often requires early surgical intervention, delay in indication causes an increase in both morbidity and mortality. Colectomy with terminal ileostomy is currently the method of the first-choice.

References

1. Aslam S, Hamill RJ, Musher DM. Treatment of Clostridium difficile-associated disease: old therapies and new strategies. Lancet Infect Dis 2005;5:549-57. [CrossRef] [PubMed]
2. Barbut F, Gariazzo B, Bonné L, Lalande V, Burghoffer B, PetitJC. Clinical features of *Clostridium difficile* associated infections and molecular characterization of strains: results of retrospective study, 2000-2004. Infect Control Hosp Epidemiol 2007;28:131-9. [CrossRef] [PubMed]
3. Cleary RK. *Clostridium difficile*-associated diarrhea and colitis – Clinical manifestations, diagnosis and treatment. Dis Colon Rectum 1998; 41:1435-49. [CrossRef] [PubMed]
4. Wilmanns C, Schoffel U, Farthmann EH. Surgery as the Final Treatment of Clostridium-difficile-Associated pseudomembranous Colitis. Dig Surg 1997;14:222-8. [CrossRef]
5. Hall JF, Berger D. Outcome of colectomy for C.difficile colitis: a plea for early surgical management. Am J Surg 2008;196:384-8. [CrossRef] [PubMed]
6. Chan S, Kelly M, Helme S, Gossage J, Modarai B, Forshaw M. Clostridium difficile colitis. Int J Sur 2009;7:78-81. [CrossRef] [PubMed]
7. Mitas L, Svaton R, Skricka T, Kala Z, Penka I, Hanslianova M. Surgical Treatment fo *Clostridium Colitis.* Acta chirurgica iugoslavica 2012;59(2):63-9. [CrossRef] [PubMed]
8. Pépin J, Saheb N, Coulombe MA, Alary ME, Corriveau MP, Authier S, et al. Emergency of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: Acohort study during an epidemic in Quebec. Clin Infect Dis 2005; 41(9): 1254-60. [CrossRef] [PubMed]
9. Berman L, Carling T, Fitzgerald TN, Bell RL, Duffy AJ, Longo WE, et al. Defining surgical therapy for pseudomembranous colitis with toxic megacolon. J Clin Gastroenterology 2008;42:476-80. [CrossRef] [PubMed]
10. Earhart MM. The identification and treatment of toxic megacolon secondary to pseudomembranous colitis. Dimens Crit Care Nurs 2008;27:249-54. [CrossRef] [PubMed]
11. Sayedy L, Kothari D, Richards RJ. Toxic Megacolon associated Clostridium diffifile colitis. World J Gatrointest Endosc 2010;2(8):293-7. [CrossRef] [PubMed]
12. Barbut F, Richard A, Hamadi K, Chomette V, Burghoffer B, Petit JC. Epimiology of recurrences or reinfections of Clostridium difficile-associated diarrhea. J Clin Microbiol 2000;38:2386-8. [PubMed]
13. Bakken JS, Borody T, Brandt LJ, Brill JV, Demarco DC, Franzos MA, et al. Treating *Clostridium difficile* infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol 2011;9(12):1044-9. [CrossRef] [PubMed]
14. Jaber MR, Olafsson S, Fung WL, Reeves ME. Clinical review of management of fulminant *Clostridium difficile* infection. Am J Gastroenterol 2008;103:3195-203. [CrossRef] [PubMed]
15. Cammarota G, Ianiro G,Gasbarrini A. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection: a systematic review. J Clin Gastroenterol 2014;48(8):693-702. [CrossRef] [PubMed]
16. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage. An alternative to total abdominal colectomy for treatment of severe complicated *Clostridium difficile* associated disease. Ann Surg 2011;254: 423-9. [CrossRef] [PubMed]
17. Girotra M, Kumar V, Khan JM, Damisse P, Abraham RR, Aggarwal V, et al. Clinical predictors of fulminant colitis in patients with *Clostridium difficile* infection. Saudi J Gastroenterol 2012;18:133-9. [CrossRef] [PubMed]
18. Lamontagne F, Labbé AC, Haeck O, Lesur O, Patino C, Lalancette M, et al. Impact of emergency colectomy on survival pf patients with fulminant *C. Difficile* colitis during an epidemic caused by a hypervirulent strain. Ann Surg 2007; 245:267-72. [CrossRef] [PubMed]
19. Longo WE, Mazuski JE, Virgo KS, Lee P, Bahadursingh AN, Johnson FE. Outcome after colectomy for *Clostridium difficile* colitis. Dis Colon Rectum 2004;47:1620-6. [CrossRef] [PubMed]
20. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240:205–13. [CrossRef] [PubMed]
21. Jiang C. Current role of surgery for the treatment of fulminant *Clostridium difficile* colitis. Chinese Medical Journal 2013;126:949-56.
22. Chan S, Kelly M, Helme S, Gossage J, Modarai B, Forshaw M. Outcomes following colectomy for *Clostridium difficile* colitis. Int J Sur 2009;7:78-81. [CrossRef] [PubMed]
23. Koss K, Clark MA, Sanders DSA, Morton D, Keighley MRB, Goh J. The outcome of surgery in fulminant *Clostridium difficile colitis*. Colorectal Dis 2006;8:149-54. [CrossRef] [PubMed]
24. Ali SO, Welch JP, Dring RJ. Early surgical intervention for fulminant pseudomebranous colitis. Am Surg 2008;74:20-6. [PubMed]