Introduction: Infection with Clostridium difficile (CDI) is the most frequent cause of nosocomial diarrhoea. Most cases are successfully treated by antibiotic therapy, but nearly 10% may progress to the fulminative form of this condition. The objective of the work is retrospective evaluation of the results of surgical treatment in patients with the fulminative form of Clostridium colitis with revealing of risk factors leading to serious post-operative morbidity and mortality. Patients and methodology: Retrospective evaluation of the results of surgical treatment in patients with the fulminative form of Clostridium colitis between 2008 and 4/2012. Results: Between 2008 and 4/2012 Clostridium toxins were positively detected in 1,088 patients in total, 21 of whom underwent operations due to the fulminative form of Clostridium colitis. The operations included 4 total colectomies with terminal ileostomy, 15 subtotal colectomies with terminal ileostomy, 1 caecostomy and 1 axial ileostomy. The 30-day mortality was 23.8%, and morbidity reached 66.6%. High leukocytosis is a statistically significant predictor of post-operative mortality and morbidity (p = 0.008). Conclusion: Early indication for a colectomy operation with terminal ileostomy in patients with the fulminative form of Clostridium colitis leads to lower morbidity and mortality.

Key words: Clostridium difficile, colectomy, colitis, pseudomembranous colitis

INTRODUCTION

Infection with Clostridium difficile (CDI) is the most frequent cause of nosocomial diarrhoeas with significant morbidity and mortality worldwide. C. Difficile is a sporulating, grampositive anaerobic bacteria that produces exotoxins that are toxic to the colon mucosa and may activate local as well as systemic inflammatory reactions.

Although first described in 1935, as the causative agent of post-antibiotic colitis it was recognised only in 1970. Clostridium difficile may infect up to 8% of hospitalised patients, most of whom remain symptom-free carriers and symptoms with diarrhoea occur only in 25% of these patients.

The increased incidence and significance of CDI is currently being connected with the presence of hypervirulent strains and other factors, but mainly with frequent administration and overuse of antibiotic therapy.

15-25% of all the post-antibiotic diarrhoea cases are caused by CDI. The probability that Clostridium difficile is the cause of post-antibiotic diarrhoeas increases with the severity of the disease and reaches 95-100% in patients with proven post-antibiotic pseudomembranous colitis.

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.

As already mentioned antibiotic therapy is considered the main risk factor of CDI development as it causes changes in the intestinal microflora and allows for multiplication of pathogenic strains. Many antibiotics are currently being related to the potential development of CDI, with clindamycin and cephalosporins being the most risky, followed by chemotherapeutics from the fluorochinolon group, especially if the infection is caused by epidemic strains.
Other risky antibiotics include macrolids, β-lactam antibiotics and antibiotics potentiated by β lactamase inhibitors. The risk grows further when antibiotics are combined with increased duration of therapy.

Other risk factors include age over 65, polymorbidity, long-term establishment of a nasogastric tube and long hospitalisation. Higher CDI occurrence was also noted in patients with non-specific intestinal inflammations (IBD) and in immunocompromised patients.

The possibility of Clostridium colitis should be considered in cases of diarrhoeas during, but also after already ended antibiotic therapy. In such cases, diarrhoeas may appear several days after the beginning, but up to 8 weeks after the end of antibiotic therapy. Diagnosis is confirmed by the detection of antigen or toxins A or B, most commonly through immunoanalysis with a sensitivity ranging between 98 and 99% with results available within 24 hours.

Colitis diagnosis may be subsequently confirmed by the presence of characteristic pseudomembranes during colonoscopy. 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 sigmoidoscopy, 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 the terrain of acute colitis. CT therefore represents a valuable tool in diagnosing Clostridium colitis. Typical findings include thickened wall of the colon with surrounding infiltration and loose liquid in the abdominal cavity.

The medicament of choice in symptomatic patients with mild or medium severity of disease is usually Metronidazole. Patients with severe course with heavy diarrhoea, leukotytosis, pseudomembranous colitis, toxic megacolon or systemic toxicity symptoms are usually given Vancomycin. At the same time, if complaints do not seem to retreat after 72 hours of Metronidazole therapy, a therapy change to Vancomycin is recommended. This antibiotic therapy is effective in more than 90% of patients.

In the case of conservative treatment CDI may reappear in 15-30% of cases. The idea of restoring the normal intestinal microflora by transplanting stool from healthy donors was first published in 1958. A number of transplantation methods were described from the application of stool dilution into the duodenum through a nasogastric tube, through douches to colonoscopic application of stool dilution into caecum. The method is used in patients with recurring CDI and according to published texts it represents an effective treatment method in this indication.

Progression of CDI with development into a fulminative state (FCDC) following the failure of conservative therapy, which is characterised by progressing abdominal pains with signs of peritoneal disturbance, distension of the colon, signs of dehydration, hypotension, oliguria to anuria with increasing azotemia, fevers, and significant leukocytosis with proven infection with Clostridium difficile is described in 1-3% cases, but may reach up to 10%. Development of the disease to the fulminative state is an indication for acute operative revision, but this carries a risk of 35-80% morbidity.

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>A (I-IIIA) N=12</th>
<th>B (IIIB-V) n=9</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M=3</td>
<td>M=3</td>
<td>P=1</td>
</tr>
<tr>
<td></td>
<td>F=9</td>
<td>F=6</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>69.6</td>
<td>70.7</td>
<td>p=0.87</td>
</tr>
<tr>
<td>Comorbidity score</td>
<td>1.33</td>
<td>1.55</td>
<td>p=0.63</td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total colectomy</td>
<td>4 (33.3%)</td>
<td>0</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Sutotal colectomy</td>
<td>6 (50%)</td>
<td>9 (100%)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Stoma</td>
<td>2 (16.7%)</td>
<td>0</td>
<td>p=0.48</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>83.6</td>
<td>170.9</td>
<td>p=0.09</td>
</tr>
<tr>
<td>Procalcitonin (ug/l)</td>
<td>1.42</td>
<td>1.03</td>
<td>p=0.56</td>
</tr>
<tr>
<td>Leukocytes (10⁹/l)</td>
<td>21.1</td>
<td>42.6</td>
<td>p=0.008</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>18.1</td>
<td>17.8</td>
<td>p=0.92</td>
</tr>
<tr>
<td>Total protein (g/l)</td>
<td>44.4</td>
<td>39</td>
<td>p=0.32</td>
</tr>
<tr>
<td>Circulatory instability</td>
<td>3 (25%)</td>
<td>4 (44.4%)</td>
<td>p=0.64</td>
</tr>
</tbody>
</table>
Indications for operative revision in patients with FCDC are not exactly defined. Signs of systemic toxicity with signs of sepsis not reacting to antibiotic therapy, toxic megacolon, symptoms of peritoneal disturbance, perforation, bleeding, shock from signs of deteriorating clinical condition despite established conservative therapy, are indications for acute operative revision according to the published works.\(^1,2,13\)

Colectomy with terminal ileostomy is currently the preferred operation, but it is linked with high morbidity and mortality reaching up to 35-80%, with the ileostomy remaining permanent in many cases. 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.\(^1\)

The surgeon’s task is the correct timing of the operative revision. Delayed operative solution, in case of progression into the fulminative state, leads to increased morbidity and mortality. On the other hand, performing the operation too early during the course of the disease leads to the loss of a substantial part of the large intestine and establishment of temporary or permanent ileostomy.\(^14\)

**MATERIALS AND METHODS**

In our work we retrospectively evaluated the operative treatment of patients with the fulminative form of Clostridium colitis at the Surgical Clinic of University Hospital Brno and Faculty of Medicine of Masaryk University Brno since 2008.

Data were sourced upon assessment of documentation. The following data were considered: demographic data, laboratory parameters, results of examinations using imaging methods, type of operation performed, including indications to operation, type and indication of previous antibiotic therapy, comorbidity, post-operative complications, histopathologic findings, as well as post-operative 30-day mortality and morbidity. In order to define the predictors of morbidity and mortality we divided our patient set into two groups. Group A consisted of patients with post-operative complications of I-IIIA Dindo/Clavien severity, while group B consisted of patients with IIIB -V severity.\(^15\)

Both groups were compared.

Used statistic methods: 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 2011 positive Clostridium toxins A or B were found in a total of 1,088 patients hospitalised at University Hospital Brno. Of these 85 patients were hospitalised at surgical departments and 1,003 at departments with a specialisation in internal medicine. 21 patients in total were operated on for present Clostridium colitis dur-
In 14 patients the disease developed during their stay at the University Hospital Brno, 7 patients were transferred to the Clinic of Infectious Diseases of University Hospital Brno from other medical facilities.

All the patients with positive stool cultivation findings and confirmed colitis upon CT, and ultrasound examinations or colonoscopy started conservative treatment with Metronidazole, 13 patients combined with Vancomycin; Metronidazole was administered intravenously, vancomycin perorally, and 3 patients received douches. 2 patients after chemotherapy for hematological malignancy received Metronidazole and Vancomycin combined with meropenem. 4 patients received only Metronidazole and 2 patients with recurrent Clostridium colitis received only Vancomycin in monotherapy. Surgical solution was indicated in case of failure of this therapy with progression of the disease.

A total of 21 patients were operated on for the fulminative form of Clostridium colitis at the University Hospital Brno and the Faculty of Medicine of Masaryk University Brno between 1/2008 and 4/2012; six of them were men with median age 62.5 years and 15 women with median age 76 years. 18 patients were treated for their first attack of the disease, 2 patients the second attack, and one patient for the third attack of this disease.

Performed operations included 4 (19%) total colectomies with terminal ileostomy, 15 (71.4%) 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 the resection had the pseudomembranous colitis diagnosis confirmed through histology, 2 cases included also an ischemic factor. Both patients had the Clostridium toxin in their stool, which was positive in 19 patients (90.5%). One female patient with negative toxin had positive colonoscopy of typical pseudomembranes.

As part of diagnostics, 14 patients had pre-operative CT with 93.3% 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 14 patients with 85.7% specificity. Sigmoidoscopy was performed in 4 patients, 3 of them had the typical pseudomembranes and one patient only had the dilated colon with paralysis.

20 patients (95.2%) received antibiotic treatment prior to the development of Clostridium colitis. Five (23.8%) (3 x Ciprofloxacin, 1x Norfloxacin, 1x Ofloxacin) received chinolon chemotherapeutics, 7 (33.3%) potentiated penicillins (6x Amoxicillin/clavulanic acid, 1x Ampicillin/sulbactam), 6 (28.6%) antibiotics from 2nd and 3rd generation of cephalosporins (5x Cefuroxim, 1x Cefotaxim) and 2 (9.5%) macrolids (2x Clarithromycin); 3 patients received 2 or more antibiotics at the same time or consecutively. The most frequent indication for these drugs was a urinary infection (52.4%), followed by bronchopneumonia (19%), antibiotic coverage of osteosynthetic operations (9.5%), vascular operations (4.8%), burns (4.8%) and chemotherapy (4.8%).

Diarrhoea was present in 90% of the patients. The average value of CRP 121 mg/l (min. 11; max. 32; med. 84) leukocytes 30.3x109/l (min. 5; max. 65; med. 23) trombocytes 276.6x109/l (min. 63.8; max. 799; med. 228) procalcitonin 1.28 ug/l (min. 0.11; max. 3.67; med. 0.38), albumin 17.9 g/l (min. 11.1; max. 27.8; med. 20.8) and total proteins 42.1 g/l (min. 23.2; max. 60.7; med. 55.9).

Coagulopathy with INR > 1.5 was present in 8 patients (38.1%), one patient even developed disseminated intravascular coagulation. Prior to operation, circulatory instability was present in 9 patients, of whom 8 (38.1%) had to have circulation support by katecholamins. The quality of conscious state was changed in 3 patients; one needed intubation prior to operation and artificial pulmonary ventilation due to signs of septic shock.

An operation was indicated in 10 patients for signs of sepsis to septic shock, of whom 4 patients progressed to multi-organ failure. 3 patients were indicated for surgical solution for signs of peritoneal disturbance, 4 for symptoms of toxic megacolon, and 4 for progressive affection of the colon despite maximum conservative therapy and profuse diarrhoea.

30-day mortality of our set was 23.8% (3x renal failure, 1x cardiac failure, 1x bronchopneumonia). Morbidity reached 66.6% (bronchopneumonia 3x, urinary infection 5x, eventration 3x, infection in wound 2x, coagulopathy with haemoperitoneum 2x, FISI + cardiac insufficiency 4x, renal insufficiency 3x, delirium 1x, intestinal bleeding1x).

A comparison of the patients divided in two groups upon the severity of post-operative complications did not show any statistically significant difference in the age composition, representation of sexes, as well as the presence of comorbidity. Group B received statistically more subtotal colectomies (p=0.01). Strong leukocytosis proves to be a significantly important predictor of post-operative mortality and morbidity (p= 0.008).(Tab. 1)

**DISCUSSION**

Increased incidence as well as severity of CDI has recently been recorded due to increasing administration of antibiotic therapy and the presence of hypervirulent strains is also linked to this condition. Clostridium colitis is often demonstrates through mild to medium diarrhoeas and is mostly successfully treated with Metronidazole or Vancomycin with a positive effect of these drugs after 3-4 days of therapy. However, in a small group of patients the symptoms remain even after the end of this therapy. Factors linked with response to treatment and incidence of recurring Clostridium colitis were prospectively studied by Nair, in whose work the frequency of recurrence reached 20%. Low levels of serum albumin and continued systemic therapies were the factors leading to the reduction of treatment effect. On the other hand, age, sex and health condition or the type of causative antibiotic had no
influence on the effect of the established therapy and frequency of colitis recurrence. Development of the colitis into the fulminative state occurred in less than 5% of the cases.16

There are typically two key factors necessary for development of Clostridium colitis: recently ended or currently running antibiotic therapy and colonisation by Clostridium difficile. However, in most patients the colonisation by these bacteria is asymptomatic or leads only to mild diarrhoeas. Progression of colitis into the fulminative state depends on other factors such as impaired immunity, the virulence of the Clostridium difficile strain, as well as type and timing of the causative antibiotic therapy.2

Factors potentially increasing the risk of occurrence of diarrhoeas caused by Clostridium difficile include advanced age, comorbidity, length of hospitalisation, stay at an intensive care unit, anti-ulcerous medication, laxatives, tube feeding, low immune response to toxin A, surgical operation and non-surgical operations on the digestive tract.8

Our set included 7 patients after surgical operations; 71% patients were aged over 65, 2 patients were treated for hematooncologic malignity, 7 patients had corticoids in their medication, and 90% of the patients were polymorbid.

In patients with fulminative 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.17

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.1

In most of the published works, the mortality of this operation ranges between 30 and 40%, but may reach up to 80%.18,19

In some of the papers authors strove to find the factors that could predict higher mortality of patients after colectomy for Clostridium colitis.

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 catecholamins.20

Byrn’s work assessed the pre-operative presence of circulatory instability with necessary vasopressor support, necessary intubation and qualitative changes of consciousness as significant factors predicting increased mortality. The group of patients who died also had a higher lactate and longer time of conservative pharmacological therapy.21

In our set, 30-day mortality reached 23.8%. All the patients who died were over 75 years old, 3 patients had circulatory instability with vasopressor support prior to the operation, 2 had quantitative change of consciousness and one required intubation. The average Leu value was 33.2. 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.

With increasing experience in treating patients with Clostridium colitis and their surgical treatment, subtotal colectomy with terminal ileostomy is currently the operation of choice, preferred to segmental resections of the colon.22,23,24

Many studies demonstrate significantly better results with colectomy than with segmental resections. Work published by Koss showed 11% mortality after colectomy for the fulminative form of Clostridium colitis while 100% of patients who underwent only segmental resection died.18

Another study performed by Ali on a large group of patients confirms the results of Koss. According to this work, 42% of patients who underwent segmental resection worsened and died despite follow-up with total colectomy.25

In our set of patients we performed 4 total colectomies and 15 subtotal colectomies with terminal ileostomy, and no segmental resections were performed.

Morbidity and mortality of the performed colectomy for fulminative colitis is still high. A further disadvantage of this operation is the loss of the colon and permanent ileostomy in many patients. In this relation an interesting work was published by Neal. In his set, patients with the fulminative form of Clostridium colitis underwent the establishment of axial ileostomy, of which 83% was done laparoscopically with perioperative lavage of the colon by 8 litres of polyethylene glycol solution or electrolyte solution followed by Vancomycinouches in the ileostomy 3 times a day for 10 days together with intravenous application of Metronidazole for 10 days. In this work, mortality was just 19% and the colon was saved in 93% of the patients. Continuity of the digestive tract was restored in 79% of the patients.1

In our work we performed one axial ileostomy in a female patient after repeated operative revisions where it was impossible 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 4 surviving patients out of 9 (44%) with a monitoring time of 6 months.

CONCLUSION

LITERATURA