Nearly all antibiotics can cause some form of diarrhoea. Clostridium difficile infection has become an important area in our daily clinical practice and is known to cause a broad spectrum of conditions ranging from asymptomatic carriage to the life-threatening pseudomembranous colitis (PMC), with toxic megacolon and ileus. Patients most at risk are those who have been treated with broad spectrum antibiotics, those with serious underlying co-morbidities and the elderly. Over 80% of Clostridium difficile infection reported are in people aged over 65 years. Combination of rapid and accurate diagnosis will result in a better management of Clostridium difficile infection. Discontinuation of causative agents such as antibiotic treatment is often curative. In more serious cases, oral administration of metronidazole or vancomycin is the treatment of choice. Patients should be treated promptly when the diagnosis of Clostridium difficile colitis is made to avoid sepsis or bowel perforation. Relapses of Clostridium difficile infection have been reported in about 20-25% of cases, this may increase to 45–60% after the first recurrence. In some cases colectomy may improve the outcome of the patient with systemic infection or complicated Clostridium difficile colitis.

This article reviews the current literature regarding epidemiological picture, microbiology, histopathology and both medical and surgical managements.

Key words: antibiotics, Clostridium difficile, colitis

INTRODUCTION

Antibiotic associated diarrhoea occurs after the consumption of antibiotics as a result of disturbance of the balance in the normal bacteria flora of the individual. Most of the bacterial flora are commensals and keep in check the virulent bacteria in the same flora. Once the balance is disturbed then virulent bacteria may prevail and cause illness which is characterised by any one or combination of the following symptoms: watery diarrhoea, fever, mucus in stool, nausea, loss of appetite and in severe cases bloody diarrhoea and features of toxaeemia.

Nearly all antibiotics are liable to cause diarrhoea but most commonly are Cephalosporin, Clindamycin, Penicillins and Fluoroquinolones.

The most severe form of antibiotic associated diarrhoea is caused by Clostridium difficile (CD). CD is an anaerobic, gram positive, spore forming bacterium. It is the leading cause of hospital-associated diarrhoea in patients receiving antibiotic therapy and causes substantial morbidity and mortality. It has been estimated that a 1/3rd of hospital associated diarrhoea are due to CD infection. CD was described as part of the normal flora of the neonatal gastrointestinal tract in 1935. It colonises 40–60% of neonates and 1-3% of the lower gastrointestinal tracts of healthy, asymptomatic adults. Incidence of CD colonisation increases to 20-50% in hospitalised patients and those in long-term healthcare facilities.

It colonises 40–60% of neonates and 1-3% of the lower gastrointestinal tracts of healthy, asymptomatic adults. Incidence of CD colonisation increases to 20-50% in hospitalised patients and those in long-term healthcare facilities.

The critical factor in the pathogenesis of CD infection is disruption of the normal colonic microflora caused by broad spectrum antimicrobials and immunosuppressive therapy. Colonization of CD generally occurs through the ingestion of heat-resistant spores, which convert to vegetative forms in the colon. Risk factors for CD infection include age over 65 years, significant co-morbidities and immunodeficiency. One study shows the incidence of CD infection is rising in patients with Inflammatory Bowel Disease (IBD) with a higher incidence and case fatality rate in ulcerative colitis patients than in those with CD, and both significantly more than the general population.
Other factors contributing to increased risk of CD infection include recent gastrointestinal procedures and the presence of nasogastric tubes and gastric acid suppressants.

CD causes a broad spectrum of conditions ranging from asymptomatic carriage, through mild or moderately severe disease with watery diarrhoea, to the life-threatening pseudomembranous colitis (PMC), with toxic megacolon and ileus. It has been implicated as the causative organism in 10-25% of patients with antibiotic-associated diarrhoea, 50-75% of those with antibiotic-associated colitis, and 90-100% of those with antibiotic-associated PMC [8]. There is evidence to suggest that restricting the use of broad-spectrum antibiotics, specifically cephalosporins and clindamycin can reduce the incidence of CD infection. The incidence and severity of hospital CD infection in USA nearly doubled from 31 per 100,000 to 61 per 100,000 per year between 1996 and 2003 and CD infection is responsible for 1 in every 1000 hospital admissions in Europe.

A new hypervirulent strain of CD known as PCR ribotype 078 has emerged in the Netherlands. The human and pig isolates of this ribotype are highly genetically related. The incidence of this strain has increased from 3% to 13% between 2005 and 2008, whereas the proportion of infections due to the hypervirulent type 027 strain decreased from 27% to 1%. Ribotype 078 affects more community associated younger populations without any predisposing factors. 9

The cost to the UK health service in 1996 was estimated to be in excess of £4000 per case 10. At 2009 costs, a 10% reduction in infection with 55,000 cases could save 115,500 bed days and £22 million.

Investigation of Clostridium difficile Infection

**Microbiology**

The results from laboratory based diagnostic tests server only as a diagnostic aid and must be seen in conjunction with the clinical picture. There are many individuals exposed to CD who will not become ill 11.

CD does not generally cause infection in infants, as the cells of the colonic mucosa are too immature to bind the toxin.

The established guidelines for laboratory diagnosis of CD infection are either based on bacterial culture or demonstration of toxin A and B in a stool sample.

Direct stool detection assay can be performed either using cytotoxicity assay or enzyme immunoassay. Enzyme immunoassay (EIA), which allows direct detection of CD toxin, is the preferred diagnostic assay and widely used.
in the most clinical laboratories because the technique is relatively sensitive (60% to 95%), easy to perform and the result can be available in as little as 2 hours.

It is important to emphasise that a negative EIA result does not rule out a diagnosis of CD infection. EIA kits also suffer from poor positive predictive values as the prevalence within the population being tested falls below 10%.

Today, many laboratories rely on CD toxin A/B testing alone despite the limits of this approach and have abandoned bacterial culture. Detection of the CD specific enzyme glutamate dehydrogenase antigen (GDH) may in part replace culture techniques and therefore be an alternative to culture. The GDH is highly sensitive which allows reliable exclusion of CD without additional tests if the GDH screen is negative. The disadvantage of this test is that it will not determine the presence of toxin, therefore GDH screen-positive samples should be further processed by performing toxin A/B testing such as EIA and those samples that are GDH positive but toxin A/B EIA negative may be further tested by using Polymerase Chain Reaction (PCR).

**HISTOPATHOLOGY**

The affected colon may appear externally normal but the mucosa may show a variable degree of oedema, congestion and ulceration with pseudomembrane formation typical of CD infection. Sometimes the external appearance does not match the mucosal changes but sometimes it appears congested, dilated and up to the point of perforation.

Finney first described pseudomembranous lesions of the intestinal tract in 1893. In the early 1980’s it was implicated as factor in antibiotic-associated diarrhoea.

In PMC the colonic mucosa becomes necrotic with the formation of a fibrinous mushroom-like exudative membrane consisting of mucin, leucocytes and epithelial cells (summit lesions). This pseudomembrane is attached to the mucosa and is seen as multiple friable yellow and white plaques varying in size from a few millimetres up to approximately 2 centimetres. The plaques coalesce to form larger plaques as the disease progresses. The mucosa between the plaques may show slight hyperaemia and inflammation, or may appear normal; however, the submucosa generally shows an inflammatory reaction and necrosis. Ischemia may show features of PMC.

**Endoscopy**

Most cases with pseudomembranes found on endoscopy will have CD infection. Flexible sigmoidoscopy can provide an immediate diagnosis in fulminant cases of CD infection, but may fail to detect up to 10% of cases without visualisation of the proximal colon. Colonoscopy is therefore recommended in case pseudomembranes are limited to the proximal colon, which is inaccessible by sigmoidoscopy. Absence of pseudomembranes does not exclude CD infection, as they are usually not seen in mild cases or in patients with concomitant inflammatory bowel disease. In general, endoscopy should be avoided in patients with fulminant colitis due to the risk of toxic megacolon and colonic perforation.

**Other non-specific investigations**

Plain abdominal radiography and computed tomography (CT) may aid in the detection of colitis. Patients with toxic megacolon and paralytic ileus may be diagnosed quickly with the aid of a CT scan.

**Medical management**

Although CD is the major infectious cause of antibiotic-associated diarrhoea, it must be distinguished from other infectious and non-infectious causes of diarrhoea. Other potential pathogens include *Klebsiella oxytoca*, *Staphylococcus aureus*, *Clostridium perfringens*, *Candida* spp. and *Salmonella*. The treatment of CD infection depends on the clinical presentation and once the diagnosis of CD infection has been made, the disease should be managed as a disease entity on its own right.

The management of CDI can be divided into the following categories:

**Asymptomatic patients**

No CD infection treatment is required in asymptomatic patients.

**Mild to moderate disease**

Patients who are clinically stable and who have no criteria of severe disease may be managed conservatively by removal of the causing antibiotic and fluid resuscitation. Such patients should be closely monitored for signs of deterioration. Diarrhoea can be expected to resolve promptly in 15 to 23 percent of patients. Supportive care should be given, including hydration, electrolyte balance and nutrition. Anti-peristaltic agents should be avoided in acute infection. This is because of the theoretical risk of precipitating toxic megacolon by slowing the clearance of CD toxin from the intestine. If specific CD infection therapy is required then metronidazole 400mg-500mg orally three times a day for 10-14 days is suitable and as effective as oral vancomycin in mild to moderate CD infection.

**Severe disease**

The UK Department of Health Steering Group on Healthcare Associated Infection recommends using any of the following as an indication of severe CD infection: WBC >15 X 10/L, acutely rising blood creatinine (e.g. >50% increase above baseline), body temperature >38.5°C and evidence of severe colitis (abdominal signs, radiology)

They also recommend the use of oral vancomycin in preference to metronidazole in this group of patients.
For patients with severe or refractory cases of CD infection, there is evidence that oral vancomycin (125 mg four times per day for 10–14 days) is preferable to metronidazole as metronidazole has a relatively high rate of treatment failure and also a slower clinical response compared with oral Vancomycin [17]. The major pharmacological advantage of vancomycin over metronidazole is that vancomycin is not absorbed as readily by the gut so the maximal effect of the vancomycin can act intra-luminally on CD toxin producers.

A recent study by Zar et al [18] showed that the cure rate in patients treated for severe CD infection was significantly higher with vancomycin compared to metronidazole (97% versus 76%).

In severe cases not responding to oral vancomycin (125 mg four times per day), high dose oral Vancomycin (up to 500 mg four times per day if necessary administered via a nasogastric tube) plus intravenous (iv) Metronidazole (500 mg four times per day) are recommended [17]. The addition of oral rifampicin (300 mg twice daily) or iv immunoglobulin (400 mg/kg) may also be considered. Although there are no robust data to support these recommendations, the very poor prognosis may justify aggressive therapy [17].

Severely ill patients with CD infection may require immediate surgical attention, particularly if they fail to improve clinically or exhibit signs of abdominal complications. In life-threatening situation, toxic megacolon should be suspected if the patient develops abdominal distension with less frequent diarrhoea; this may reflect paralytic ileus resulting from loss of colonic muscular tone [17].

**Recurrent / relapsing CD infection**

Management of recurrent CD infection remains controversial, although most relapses respond to further courses of antibiotics that have been given previously.

20–25% of patients with CD infection will go on to develop relapsing CD infection even with appropriate treatment. This is usually due to germination of persistent CD spores in the colon after treatment, generally within 3 to 21 days, or to re-infection because of re-ingestion of the pathogen. One study showed that 50% of relapses were due to re-infection with a different strain rather than recurrence with the original strain. The risk of relapse or re-infection increases to 40–60% after the first recurrence, and up to 5% of patients can have more than six recurrences [17]. Recurrence due to antibiotic resistant organisms is uncommon.

The antibiotic therapy used in the first CD infection recurrence is usually the same antibiotic that had been initially used unless the infection is severe.

**Surgical management**

With the rapidly increasing incidence of CD infection over the past ten years, the early involvement and regular review of gastrointestinal surgeons is essential in the management of patients with severe fulminant colitis.

Even so, mortality rates following colectomy are in the region of 30-60% [17].

Antibiotic prophylaxis administered in the perioperative period has been shown to significantly decrease the rate of surgical site infection following colorectal surgery [19]. Although all antibiotics carry a risk of CD infection, research has shown that certain antibiotics such as third-generation cephalosporins and fluoroquinolones are associated with a significantly higher risk than others. High incidences of CD infection have also been described following other types of gastrointestinal and vascular surgery [17].

**Indications for surgery**

Although frequently developed during a hospitalization and often after a surgical procedure, CD infection may develop outside of a hospital setting. Diarrhoea may be absent and stool samples may be negative for CD toxin. There is evidence to suggest that abdominal computed tomography offers a higher degree of sensitivity in diagnosing PMC, although it is not effective at predicting the need for surgical intervention. Rapid immunoassays may allow for preoperative confirmation of the cause of severe colitis where surgery cannot wait until culture results are available.

To decrease morbidity and mortality in patients in particular in high risk groups such as the elderly or immunocompromised with acute severe colitis, an early surgical intervention should be considered after a joint decision between medical and surgical gastroenterologists.

Evidence from large-scale studies to assist in guiding surgical management of these patients is lacking. There are no published randomized controlled trials evaluating the role of surgery in managing PMC. In a small, retrospective study by Koss et al involving 14 patients, indications for surgery were given as systemic toxicity and peritonitis, radiological and clinical evidence of progressive toxic colonic dilatation and bowel perforation [20]. In a further report published by Synnott et al, indications for operation were systemic toxicity with pyrexia, marked leucocytosis and abdominal signs leading to progressive organ failure, despite appropriate anticyclostridial antibiotic therapy [21].

Basically, fulminant form of PMC is the only condition that candidates the patient for surgical treatment. This is the case in 3-8% of patients [22].

The real challenge in surgical treatment of PMC is the question when to operate, and when can we state that colectomy under such difficult circumstances actually reduces patient mortality or whether it does more damage in such severely ill patients.

All other outcome measures in such difficult patients are actually of no clinical importance. An excellent systemic review by Stewart et al all [23] presented results of colectomy in cases of fulminant PMC. Authors concluded that a patient with fulminant form of PMC, whose disease has progressed to the point of a life-threatening infection despite all available non surgical therapy,
colectomy provides a mortality benefit compared with ongoing medical therapy (Figure 1).

On the other hand, we should always be careful and shouldn’t offer surgical treatment to every patient, regardless of ones comorbidities. Also in mentioned systemic review not in all studies included, patient benefited from surgical treatment. Another very important issue that is still to be answered is timing for surgical treatment. Offered too early surgery can have very favorable results, and if we wait too long, operation can be deemed unnecessary, because fatal outcome is inevitable in every way.

Surgical procedures

In the study by Koss et al, the 9 patients who underwent total colectomy had a mortality rate of 11.1% compared with 100% in the 4 patients who underwent left hemicolectomy. One patient who underwent right hemicolectomy survived after a prolonged hospital stay20. In their study of 13 patients who underwent colectomy for PMC, Lipsett et al found that all 4 patients who underwent segmental colectomy died compared with 14% of the remainder who had a subtotal colectomy 25. The authors emphasise that the external appearance of the colon may be deceptively normal despite severe mucosal disease, and this should not influence the decision to resect the entire colon. In the largest reported series of 73 CD infection patients undergoing colectomy, the mortality rates of patients who underwent segmental (n=10) or subtotal (n=63) colectomy was (10% vs. 38%, respectively 24.

A less invasive yet equally effective solution has recently been suggested - a diverting loop ileostomy with colonic lavage as an alternative to colectomy. Neal et al. 26 published the results for 42 patients with fulminant PMC who underwent a diverting loop ileostomy, with polyethylene glycol and vancomycin colonic lavage through the efferent limb. Again, the question when to operate remained unanswered. Also in some patients colectomy was performed after diverting ileostomy. There is always the danger of recurrent colitis after ileostomy closure, as well as the case of resistant types of C. difficile, where lavage agents have no real effect.

Prognostic factors following surgical intervention

A retrospective study by Pepin et al of 130 patients undergoing surgery with similar indications to those described above concluded that 30-day mortality increased with increasing age (but not co-morbidity), and correlated with raised preoperative lactate, leucocytosis, reduced albumin and renal failure. On multivariate analysis, 75% of patients with a preoperative leucocytosis ≥ 50.0 x 10^9/L or lactate ≥ 5.0 mmol/L died 27.

One of reasons for very high mortality following surgery is delay in surgery.

It is interesting to note that the occasional case of CD infection affecting the ileum after subtotal colectomy 25, 28.

**SUMMARY**

**TRETMAN ODNOSA ANTIBIOTIKA I CLOSTRIDIUM DIFFICILE**

Skoro svi antibiotici mogu izazvati određeni stepen dijareje. Infekcija sa *Clostridium difficile* je postala značajni deo naša svakodnevnih kliničke prakse i uzročnik je mnogih problema, od asimptomatskih kliničkih sledaka do poživ opasnog pseudomembranoznog kolitisa sa tokušćim megakolonom i ileusom. Najzrijevijem su bolesnici lećeni antibioticima širokog spektra, sa ozbiljnim udruženim ko-morbidityom i starosti. Preko 80% infekcija sa *Cl. difficile* se javljaju kod osoba starijih od 65 godina.

Kombinacija brzog i tajnog dijagnoze rešenja boljim lečenjem infekcije sa *Cl. difficile*.

Izključenje uzročnika, kao što je antibiotika terapija, je često efikasno. U težim slučajevima metoda izbora je oralna primena Metronidazola ili Vancomicina.

Bolesnike sa kolitisom izazvano *Cl. difficile* treba urgentno tretirati da bi se izbegla sepsa ili perforacija creva.

Saopšteno je da se relaps infekcije zbog *Cl. difficile* javlja u oko 20-25% slučajeva a može da naraste i do 45-60% posle prvog recidiva bolesti.

U izvrsnim slučajevima kolostoma može poboljšati ishod lečenja bolesnika sa sistemskom infekcijom ili komplikacijama kolitisa izazvao *Cl. difficile*.

Ovaj članak predstavlja revizualni prikaz savремene literature koja se odnosi na epidemiološku sliku, mikrobiologiju, histopatologiju i medikamentno i hirurško lečenje.

Ključne reči: antibiotici, Clostridium difficile, kolitis

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