
Mladen M. Maksić¹, Andela Ž. Đokić¹, Nataša D. Zdravković¹², Biljana N. Milojković - Kicevska¹, Radiša H. Vojinović¹², Tijana B. Veljković¹, Svetlana S. Popović - Matović¹, Slobodan M. Janković¹²

¹ University Clinical Center Kragujevac, Kragujevac, Serbia
² Faculty of medical Sciences, University of Kragujevac, Kragujevac, Serbia

SUMMARY

Introduction: Optimal management of toxic megacolon as a consequence of Cl. difficile colitis is still matter of controversy, as well as timing of available therapeutic modalities. In this article we report a case of severe C. difficile colitis associated with toxic megacolon in a pregnant patient with Covid 19, who was successfully treated conservatively.

Case Report: A 33-years old pregnant woman contracted SARS-CoV-2 in the 32nd week of pregnancy. She was admitted to regional hospital and treated extensively by wide-spectrum antibiotics. After the delivery she developed severe form of Cl. difficile colitis with toxic megacolon. In spite of severe clinical picture, the patient was treated conservatively, with high initial oral doses of vancomycin, with subsequent tapering. The outcome of the treatment was complete recovery and colonic functions were regained completely.

Conclusion: In conclusion, our case shows that in younger patients, who were fit before occurrence of Cl. difficile colitis and toxic megacolon, conservative therapy should be tried as long as possible before turning to colectomy, since chances for cure without surgery are considerable.

Keywords: CCl. Difficile Colitis, Toxic Megacolon, Vancomycin

INTRODUCTION

Toxic megacolon is life-threatening disease and may be defined as a nonobstructive partial or pan colonic dilatation in excess of 6 cm with signs of systemic toxicity [1,2].

Leading cause of toxic megacolon is Inflammatory bowel disease, but it could be consequence of Clostridium difficile infection, too [3]. Incidence of toxic megacolon after colitis induced by Clostridium difficile is relatively low and ranges from 0.4% to 3%, but the mortality rate is very high, between 38% and 80%, mostly due to colonic perforation followed by peritonitis, septic shock and multiple organ dysfunction [4,5,6]. In hospital settings main reason for Cl. Difficile infection (CDI) is prolonged treatment of patients with broad-spectrum antibiotics. Current COVID 19 pandemics has contributed to this problem.
indirectly, through overzealous administration of antibiotics to patients with COVID 19 and pneumonia, since it is difficult in clinical practice to differentiate between viral and bacterial origin of pneumonia, especially in resource-poor settings [7].

Although clindamycin, cephalosporins and fluoroquinolones are antibiotics the most frequently associated with C. Difficile infection, other broad-spectrum antibiotic are followed by certain percentage of C. Difficile cases, too [8]. Toxins of C. difficile induce release of proinflammatory cytokines into the colon wall which further increase permeability of blood vessels and cell necrosis [9]. Mourelle et al showed induction of inducible nitric oxide (NO) synthetase in the muscularis propria of patients with toxic megacolon [10]. Increased production of NO leads to inhibition of smooth muscle tone and colon becomes dilated [11]. Sudden stopping of diarrhea due to ileus, rapid abdominal distension, abdominal pain and tenderness, tachycardia and hypotension in patients diagnosed with CDI are key signs pointing to emergence of toxic megacolon [12]. The diagnosis of toxic megacolon has to be radiologically confirmed. Computerized Tomography (CT) of abdomen may show at least 6 cm wide dilatation of colon, wall thickening, distortion of haustral folds, and ascites [13]. Optimal management of toxic megacolon is still matter of controversy, as well as timing of available therapeutic modalities [14]. We found only one case report with association toxic megacolon in Covid 19 patient and they tried with antibiotics but main therapy was a surgery,because patient had a perforation of colon [15].

In this article we report a case of severe C. Difficile colitis associated with toxic megacolon in a pregnant patient with Covid 19, who was successfully treated conservative.

**CASE REPORT**

The patient was a 33-year-old woman with hypothyroidism on tablets levothyroxine-natrium (Euthyrox®, Merck Healthcare KgaA) 100 mcg / daily, without allergy and previously operation, in well health condition, who in the 32nd week of pregnancy contracted SARS-CoV-2.

She was admitted to regional hospital and treated with broad spectrum antibiot-
omicin (Voxin®, Vianex S.A.-Plant C) 1 g at 24h administered both orally and by an enema, the ampules metronidazole (Orvagil®, Galenika AD Beograd) 500 mg at 8h was given intravenously, and the following drugs were also added intravenously: corticosteroids (metylprednisolon Lemod®-Solu Hemopharm AD Vršac 40 mg/ml intravenously at 24h), human albumin (Albutein 20% Instituto Grifols S.A. 200 g/L intravenously at 8h), diuretics (furosemid Lasix® Opella healthcare international sas 40 mg at 24h per os), neostigmin-metilsulphat (Neostigmine/Cooper, Cooper S.A. 2.5 mg/ml at 24h intramuscular) and packed red cells transfusions with 3 units (one unit 250 mL), haemoglobin (110-180 g/L) transfusion trigger was 80 g/L. She was not treated surgically due to low parameters of inflammation, C reactive protein dropped to 64 mg/l (0-5 mg/L), preserved peristalsis and the absence of abdominal pain. However, during this period, nearly 2 weeks of hospitalization the patient remained febrile with maximum 38 degrees Celsius (°C)/100.4 degrees Fahrenheit and never less from 37.3 °C/99.32 degrees Fahrenheit. After vital functions of the patient became stable, temperature was 37.5 °C, CRP dropped to 45 mg/l (0-5 mg/L), blood pressure was 100/60 mmHg, patient was transferred to the internal medicine department. The abdomen was extremely enlarged, with circumference of 111 cm at the level of umbilicus. The fever persisted, and the patient developed cellulitis of the lateral parts of anterior abdominal wall. The laboratory showed low haemoglobin (110-180 g/L) from 77 mg/l to 95 mg/l, D-dimer 2,87 µ/mL (0-0.5 µ/mL), albumin (41-51 g/L) from 26 g/l to 39 g/l, C reactive protein (0-5 mg/L), gradually dropped to 39 mg/l, and then to 6.9 mg/l, amylase (40-140 U/L) and procalcitonin (0-05 µg/L) became normal. The patient was treated additionally with parenteral vancomycin, while oral administration of vancomycin (Voxin®, Vianex S.A.-Plant C) and ampules metronidazole (Orvagil®, Galenika AD Beograd) 500 mg at 8h was continued. Serum levels of vancomycin (Voxin®, Vianex S.A.-Plant C) were monitored to prevent toxicity. The signs of cellulitis gradually abated, however repeated MDCT showed persistent signs of colonic inflammation: the wall of large intestine was up to 3 cm thick in some parts due to extensive edema, and several inclusions of gas were seen in submucosa. General condition of the patient was improved little by little, as well as her stools. Antibiotic therapy with

Figure 1. MDCT in sagittal plane, Multiplanar (MPR reconstruction-sagittal section) distension of the colon just below the anterior wall.

Figure 2. MDCT- axial section at the level of the transverse part of the colon which is extremely dilated.
intravenous vancomycin and oral metronida-
zole was discontinued after 3 weeks, and oral
vancomycin (Voxin®, Vianex S.A.-Plant C) 1 g
at 24h was continued with tapering doses for
further 5 weeks.

The patient was discharged after 46
days of hospitalization for further home treat-
ment when an additional MSCT showed signs
of mild intestinal distension. She continued
taking oral vancomycin (Voxin®, Vianex S.A.-
Plant C) at home with tapered doses until 8
weeks from the beginning of oral vancomycin
(Voxin®, Vianex S.A.-Plant C) ensued. After
1.5 months at home, the patient came for a
check-up in good health.

DISCUSSION

Diagnosis, and especially therapy of clostridial
infection is a problem at any level of the health
system organization.

The greatest effect in therapy would be
achieved by complete exclusion of antibi-
otic therapy in the patient, in order to allow
spontaneous recovery of the intestinal flora
and restoring the balance between patho-
genic and non-pathogenic strains. Such an
approach, usually is not possible in a practice,
because, often, these patients have multiple
associated infections, systemic infections or
are in a critical general health condition, and
therefore, treatment with antibiotics is neces-
sary.

According to the recommenda-
tions, metronidazole or vancomycin should
be administered orally as the first line drug
treatment, although, metronidazole may also
be administered intravenously, especially in
hospitalized patients, in critical condition. Ac-
cording to some authors, possible presence
of adynamic ileus in patients during the post-
operative course can significantly affect the
distribution and absorption of orally adminis-
tered drug, and therefore, vancomycin enema
is often given as an additional therapy [16].

Vancomycin should be included in
the treatment of the first relapse of CDI only if
there is a return of symptoms of the disease
associated with clinical parameters that indicate
a severe form of the disease (if the patient has
severe leukocytosis, or hypotension and renal
failure). Each relapse of the disease should be
treated primarily with vancomycin, with long-
term gradual dose tapering, or with the use of
pulse doses over a long period of time. Some
of the authors recommended the following ta-
pering regimen: during the first two weeks of
therapy, vancomycin should be administered
in a dose of 1 g daily, divided into 4 doses,
then 500 mg divided into two doses over the
next 7 days, then 125 mg in a single dose for
another 7 days. After that, the therapy should
be applied in a dose of 125 mg, but first on ev-
ey other day for a total of 8 days, and then on
every third day for another two weeks. In
general, there is a number of therapeutic ap-
proaches with gradual dose reduction, and
further research should confirm the superior-
ity of one of these approaches [17,18]. Howev-
er, If these treatment regimens do not lead to
a cure, treatment with oral rifaximin or some-
times suggested [19].

There is small number of studies ex-
amining the efficacy of ramoplanin and ni-
tazoxanide in relapsed CDI. A lower degree
of resistance was observed to ramoplanin
compared to vancomycin. On the other hand,
nitazoxanid has shown similar efficacy as the
drugs used so far for CDI but additional stud-
ies need to confirm the safety of its use [20,21].
However these two drugs do not have market-
ning authorization for treatment of Cl. Diffi-
cile colitis, yet. In the treatment of recurrent
forms, fidaxomicin can be used. Fidaxomicin
is more effective than vancomycin in terms of
the number of recurrent cases. It has similar
properties as vancomycin. Its absorption from
the digestive tract is minimal, so the possibil-
ity of side effects is low. It also has a minimal
bactericidal effect on the remaining microor-
ganisms that are part of the normal intestinal
flora [22,23].

Studies have shown that despite the
practice of excluding proton pump inhibitors
(PPIs) and H2 blockers - from CDI therapy,
relapse is only affected by infection-specific
drugs [24]. Also, using additional antibiotics
in order to control other and systemic infec-
tions that are concomitant with CDI, is associ-
ated with prolonged duration of diarrhea and
a greater number of recurrent forms of CDI
[25].

A vaccine that can prevent recurrent
forms of CDI has been developed. It is a toxoid
vaccine that allows the production of protec-
tive antibodies to the toxin Clostridium diffi-
cile: toxins A and B. Recent recommendations
include using of intravenous immunoglobu-
lins (IVIG) in CDI, which is mainly based on
neutralization mediated by antibodies to toxin
A, although antibodies to toxin B have an additive effect [26,27,28]. Up to date, it has not been proven that the use of probiotics can prevent the occurrence of recurrent forms of CDI. Fecal transplantation is one of newer methods used in patients with severe clinical picture and in those in whom all other treatment modalities were ineffective. It can also be used in patients with toxic megacolon within the CDI, who are candidates for surgical treatment. The stool of a healthy donor is inserted through a catheter into the lower or upper part of the digestive tract. In this way, it can stimulate the restoration of the normal flora of the patient’s digestive tract [29].

In patients with CDI-induced megacolon who did not develop additional complications, mortality is about 15%. This mortality increases if the patient develops more severe complications over time, such as ischemia and perforation of the intestinal wall [30].

The mortality of patients with CDI toxic megacolon who were subjected to total colectomy before occurrence of perforation, is significantly lower compared to those who were operated after the large bowel perforation [31,32]. Besides, surgery significantly reduces mortality if performed before development of septic shock [33].

Of course, it is necessary to think about the Oligvie syndrome as differential diagnosis, but Ogilvie syndrome usually does not present with signs of systemic toxicity, with similar CT finding as toxic megacolon [34].

In our patient we combined the use of metronidazole as the first treatment line and vancomycin in patients with severe infection, the main reason is better efficacy compared to the use of only one antibiotic and less chance for resistant on both antibiotics in similar time [34,35].

CONCLUSION

In conclusion, our case shows that in younger patients, who were fit before occurrence of Cl. difficile colitis and toxic megacolon, conservative therapy should be tried as long as possible before turning to colectomy, since chances for cure without surgery are considerable. Total colectomy bears significant morbidity by itself, therefore any chances to avoid it without endangering the patient’s life should be taken.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES


34. Lahue B, Davidson DM. Metronidazole and vancomycin outcome for Clostridium difficile-associated diarrhea in a US hospital database [Internet]; Abstract presented at: 17th Annual Meeting of the European Congress of Clinical Microbiology and Infectious Disease; 2007 Mar 31 - Apr 04;

Toksični megakolon posle iracionalne primene antibiotika u lečenju trudnice sa Covid-om 19: prikaz slučaja

Mladen M. Maksić¹, Andela Ž. Đokić¹, Nataša D. Zdravković¹,², Biljana N. Milojković - Kicevska¹, Radiša H. Vojinović¹,², Tijana B. Veljković¹, Svetlana S. Popović - Matović¹, Slobodan M. Janković¹,²
¹ Univerzitetski klinički centar Kragujevac, Kragujevac, Srbija
² Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Kragujevac, Srbija

KRATAK SADRŽAJ

Uvod: Optimalno upravljanje toksičnim megakolonom kao posledicom Cl. difficile kolitis je još uvek predmet kontroverzi, kao i vreme kada su dostupni terapijski modaliteti. U ovom članku izveštavamo o slučaju teškog kolitisa C. difficile povezanog sa toksičnim megakolonom kod trudnice sa Covid-om 19, koja je uspešno lečena konzervativno.

Prikaz slučaja: Trudnica stara 33 godine zarazila se SARS-CoV-2 u 32. nedelji trudnoće. Primljena je u regionalnu bolnicu i intenzivno lečena antibioticima širokog spektra. Nakon porođaja razvila je teški oblik Cl. difficile kolitis sa toksičnim megakolonom. I pored teške kliničke slike, pacijent je lečen konzervativno, visokim početnim oralnim dozama vankomicina, uz naknadno smanjivanje. Ishod lečenja je bio potpun oporavak i potpuno su vraćene funkcije debelog creva.

Zaključak: U zaključku, naš slučaj pokazuje da kod mlađih pacijenata, koji su bili u formi pre pojave Cl. difficile kolitis i toksičnog megakolona, konzervativnu terapiju treba pokušavati što je duže moguće pre nego što se pređe na kolektomiju, pošto su šanse za izlečenje bez operacije znatne.

Ključne reči: Cl. difficile kolitis, toksični megakolon, vankomicin

Received: May 16, 2022
Accepted: June 29, 2022