

## Acute Clostridium Difficile Infection in two Polish Pregnant Women with Premature Rupture of Membranes

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### Abstract

We present two cases of acute *Clostridium difficile* infection (CDI) during pregnancy in Poland. Both patients were hospitalized due to premature rupture of membranes at 15 and 28 weeks of gestation and had antibiotic prophylaxis and therapy. The first patient was discharged on day 18 after the start of the infection but the second patient died after 4 days of hospitalization. Our data and a literature review show that extensive antibiotic usage in such patients may predispose to CDI despite a current lack of detailed studies. BV and health state will provide the depth insight in the etiology of BV.

### Introduction

*Clostridium difficile* are Gram-positive, anaerobic, spore-forming and motile rods. The bacterium was discovered in 1935 but no related diseases were reported in humans until the 70s of the previous century [1]. *C. difficile* can be found in the intestines of approximately 2-5% of adults, 50-60% of infants and 20-40% of hospitalized patients. A rapid increase in *C. difficile* infection (CDI) incidence has been observed in recent years. A growing number of acute infections, associated with elevated complication and mortality rates (even up to 25%, especially among the elderly and seriously ill), has been reported [2,3]. *C. difficile* produces various virulence factors including toxin A, an enterotoxin, and toxin B, a potent cytotoxin. During invasion, these toxins damage the intestinal mucosa with consequent necrosis, ulceration, fluid secretion and inflammation. In 2005, an even more virulent strain, i.e. *C. difficile*-NAP1/BI/027/III (North American PFGE type I/ restriction endonuclease analysis BI/PCR-ribotype 027, toxin type III), was described. It showed fluoroquinolone resistance, produced an additional binary toxin, and was associated with more severe disease and higher mortality [4-8].

CDI is characterized by diarrhea or toxic megacolon without a clear cause, coexisting with at least one of the following criteria: i) presence of toxin A and/or B in stool or culture-positive stool, ii) pseudo-membranous enterocolitis diagnosed by endoscopy or alternative invasive procedures and/or iii) histopathology [9,10]. Acute CDI is diagnosed if over the course of 30 days since symptom manifestation the following occurred in a patient with the above mentioned symptoms: i) admission to hospital due to community-acquired CDI, ii) admission to ICU due to CDI-related complications, iii) colectomy, iv) death. Treatment is based on cessation of the inciting antibiotics which may suffice in mild infections. Metronidazole or vancomycin (per os) are the two primary antibiotics in the treatment of CDI [11-13].

CDI has been estimated to be the cause of antibiotic-associated diarrhea (AAD) in 15-25% of the affected individuals [9,10]. CDI incidence among hospitalized patients depends on antibiotic use and ranges between 1-10/1000 cases. A significant increase in CDI incidence among hospitalized patients was noted between 1999-2005 in Europe and the USA. In the USA, the incidence increased by 100% as compared to earlier years [14]. Data from 14 European countries indicate growing

CDI mortality rates, from 2% in France to 42% in Great Britain. In 2007, the trend persisted in all countries but England, where a slight decrease in the mortality was observed [15]. The mean incidence of CDI in 27 Polish hospitals was 8.2 per 10,000 patients days as reported in the EUCLID study in 2012. Epidemic spread of fluoroquinolone-resistant *C. difficile* strains and the role of hospital settings in the development of infections have been documented [11,16,17].

CDI in pregnancy remains rare. According to the Morbidity and Mortality Weekly Report on CDI, pregnant women and parturients are believed to be low-risk populations [18]. The incidence based on data from 1998-2006 was estimated at 0.4-0.7 in 10,000 parturients, mainly including women after cesarean section [19]. Epidemiologic studies estimate the incidence at 7.5 in 1,000 women among parturients [20].

The first description of CDI in pregnancy dated 1985. The literature reports only single cases of the infection, mostly due to broad-spectrum antibiotic therapy, for example prophylactic measures during a cesarean section, premature rupture of membranes and amniotic fluid leak, or group B streptococcus (GBS) infections [21]. Secondary prevention in case of an infection is limited to maintaining proper hygiene.

### Case 1

A 32-year-old woman (para 3, 15 g.w.) presented to the hospital at 12 weeks of gestation due to cervical incompetence. The McDonald's cerclage was performed. No concomitant diseases were reported. Obstetric history revealed the following: first pregnancy - in 2010,

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cesarean section performed at 39 weeks of gestation due to a threat of fetal asphyxia (live newborn - female, birth weight: 2660 grams); second pregnancy - in 2012, cesarean section performed at 26 weeks of gestation due to premature amniotic fluid leak (live newborn - female, birth weight: 850 grams, survived 16 days).

The current third pregnancy required hospitalization at 12 weeks of gestation due to cervical incompetence and at 15 weeks of gestation due to amniotic fluid leak. Vaginal culture was negative. Antibiotic therapy (Cefuroximum 1.5 g, i.v.) was initiated. Diarrhea started on day 9 since amniotic fluid leak (>6 loose stools per day). Stool culture was performed and EIA revealed the presence of glutamate dehydrogenase, after which the presence of toxins was confirmed (BioMerieux VIDAS: *C. difficile*, toxin A and B: 5.04). Metronidazole (3 × 500 mg) and Lacidofil (*Lactobacillus acidophilus*, *Lactobacillus rhamnosus*) (3 × 2 per os) were initiated. Fetal demise and spontaneous abortion occurred on day 14 since the amniotic fluid leak. The cervical cerclage was removed and a dead male fetus (weight 580 grams), with signs of infection, was instrumentally evacuated. In the afternoon of the same day, the patient was febrile. On the next day the patient was transferred to ICU due to symptoms of anaphylactic shock: pressure 70/40, tachycardia 130 bpm, anuria, hypoalbuminemia (1 g/dL). Antibiotic therapy was initiated: Metronidazole (3 × 500 mg i.v.), Vancomycin (3 × 500 mg i.v.), Cefazidimim (3 × 1 g iv), Lacidofil (*Lactobacillus helveticus*, *Lactobacillus rhamnosus*) (3 × 1 g pre os), and catecholamine infusion. Central venous pressure (CVP) was used to guide fluid therapy. Additional tests revealed indicators of a septic shock (heart rate >120 u/min; leukocytosis 29.4, 19.1 × 10<sup>3</sup>/ul). Diarrhea persists during the course of hospitalization but the second test was negative for *C. difficile*. The patient became stable and symptom-free. Levonor was discontinued. Ultrasound was performed due to persistent generalized edema and revealed accumulating fluid in the abdominal and pleural cavity (laboratory findings confirmed hypoalbuminemia <2.5 g/dL). On day 7 of ICU stay, single loose stools were observed but the toxin test result was doubtful. The patient became febrile twice (39.0°C). On day 12, the blood test came back positive for methicillin-resistant coagulase-negative *Staphylococcus hemolyticus* (MRCNS) and Ciprofloxacin was initiated (2 × 400 mg iv). Additionally, albumin infusion and parenteral nutrition were administered. Significant amounts of fluid were evacuated from both pleural cavities on several occasions but the culture results remained negative. Stool tests for *C. difficile* on day 16 of the ICU stay were negative and the patient was transferred to a gastroenterology unit while in a satisfactory condition. Antibiotic therapy was stopped but Lacidofil was continued (3 × 1 g per os). Furosemidum was administered due to fluid in the pleural cavity, followed by thoracentesis - 1000 ml of pleural fluid were evacuated. The patient was discharged on day 6 of hospitalization at the gastroenterology unit in good overall condition.

## Case 2

A 34-year-old primipara was admitted to the hospital at 28 weeks of gestation due to premature amniotic fluid leak for 5 days. Medical history revealed endometriosis, pituitary microadenoma, and infertility treatment. The patient was transferred from the community hospital where she had received tocolytics, steroid therapy, and antibiotic treatment: Cefuroxim (2 × 1.5 g i.v.) and Clindamycin (2 × 300 mg i.v.).

In the referral hospital, the patient was put on bed rest, received tocolytics, anticoagulants and antibiotic therapy: Cefuroxim (3 × 1.5 g i.v.). Additional tests revealed a urinary tract infection and anemia; conservative treatment was initiated. Genital tract culture

was performed on day 7 of hospitalization and revealed *Ureaplasma urealyticum* infection of the cervix. Owing to amniotic fluid leak, broad-spectrum antibiotic was discontinued and narrow-spectrum antibiotic (Azithromycine 1 × 0.5 g per os) was administered to target the genital tract pathogen. After 3 days and a neonatologist's consultation, Azithromycine was changed to another target-antibiotic (Clarithromycin 2 × 0.5 g i.v.) due to diarrhea onset and a lower number of loose stools was documented. Fetal status upon ultrasound was normal. Additional tests revealed normal C-reactive protein (CRP) and normal urine values. The patient was afebrile.

On day 12 of hospitalization diarrhea intensified and uterine contractility, only temporarily responsive to intensive pharmacological treatment, was observed. On day 13 of hospitalization, emergency cesarean section was performed due to regular uterine contractions and a threat of intrauterine fetal asphyxia. A live preterm female (birth weight 1240 g, height 40 cm, Apgar score of 6/7/7/8 points in 1/3/5/10 minutes of life) was delivered. The neonate was discharged home in good overall condition on day 62 of life.

Approximately 1000 ml of colorless fluid was found in the abdominal cavity during cesarean section. In the postoperative course the following were observed: persistent diarrhea, elevated temperature on the day of surgery and the postoperative day 1, elevated leukocytosis and CRP, low albumin values, as well as positive stool culture for *C. difficile* toxin A and B. Albumin, fresh frozen plasma (FFP), colloid and electrolyte infusions and parenteral nutrition were used. Antibiotic therapy was discontinued and Metronidazole treatment (3 × 500 mg) was started but lowering the number of loose stools was impossible. On postoperative day 2, arterial blood pressure values decreased to undetectable levels and tachycardia (135 bpm) was observed. These values normalized after transfusion of 100 ml of colloids and 3 ampoules of sodium bicarbonate.

Owing to the steadily deteriorating condition of the patient, she was transferred on postoperative day 3 to a higher-referential hospital with ICU, where the presence of *C. difficile* toxin A and B was confirmed and Vancomycin therapy was initiated.

Exploratory laparotomy due to suspected intra-abdominal bleeding and fluid evacuation from the pleural cavity were conducted. Catecholamine infusions (Xigris) were used but no improvement was achieved and the patient died on day 4 after transfer due to septic shock and multi-organ failure.

## Discussion

The two presented cases are severe CDI in pregnancy. According to the European Society of Clinical Microbiology and Infectious Diseases classification, the necessity to transfer a patient to the ICU due to CDI classifies as severe complication [12,13]. Rouphele et al., report similar cases - data from the USA between 2005-2006, where 10 CDI cases in pregnancy or postpartum (up to 4 weeks after delivery) were registered. Only 3 cases had a mild course, whereas the remaining cases were complicated by toxic megacolon colectomy [6], sepsis [3], and disseminated intravascular coagulation - DCI [4]. Maternal and fetal demise were noted in 3 cases (1 twin pregnancy). CDI was diagnosed on the basis of stool testing for *C. difficile* using immune-enzymatic methods, verified by PCR. All of the patients had previously received antibiotic therapy and diarrhea was the main disease manifestation, between 3-60 days after treatment discontinuation. Mean time of hospitalization was 15 days (range: 2-80 days) and all patients were transferred to ICU [22].

The above mentioned case reports are consistent with data reported by Garey et al., who identified 24 cases of CDI in pregnancy (between 1966-2007), despite the fact that in 10 cases data were incomplete. They found that 91% of the affected women had received prophylactic or therapeutic (50%) antibiotic therapy. Diarrhea manifested in all patients and stool testing was positive for *C. difficile* and A and/or B toxins (ELISA). Pseudomembranous colitis was confirmed by colonoscopy in 4 women [23].

Venugopal et al., in their retrospective analysis demonstrated CDI incidence during the perinatal period to be 0.7/1,000 gravidas between 2003-2007. In these cases, additional REA type analysis (polymorphic restriction sites) was performed apart from standard immunoenzymatic diagnostic tests (Meridian Bioscience). Different variants of toxins were isolated in 7 patients. These authors concluded that cesarean section may constitute a significant risk factor for CDI in the postpartum period (RR: 11.6%, CI 95%). Their findings are consistent with ours, as in both cases Metronidazole therapy, with additional Vancomycin in 1 case, was initiated [21].

The analysis of 20 cases of CDI, whose outbreak was noted among pregnant women in Washington within a course of one year, generated interesting results. CDI incidence was estimated at 7.5/1,000 parturients. CDI-related factors included: cesarean section, antibiotic therapy, and PROM. Combination antibiotic therapy was demonstrated to be an independent risk factor for CDI in the multivariate analysis. According to these authors, pregnant women and parturients appear to be another population susceptible to CDI [20].

Their theory has been confirmed by Candiottto et al., who reported a case of a 39-year-old gravida at 29 weeks of gestation, with a competent immune system, classified as 'low-risk for CDI' with no history of hospitalization or antibiotic therapy in the course of 2 years before the study. CDI, confirmed by ELISA, manifested as diarrhea and led to the development of toxic megacolon and sepsis. Metronidazole treatment (3 × 500 mg) was initiated. CDI-related complications resulted in transfer to an ICU and, as in case of our patients, hydrothorax which appeared in the patient treated with thoracentesis. The patient made full recovery in the course of three weeks [24].

## Conclusions

Prolonged prophylactic or therapeutic antibiotic therapy in pregnant women with premature rupture of membranes may be associated with the risk of drug-induced CDI.

CDI manifests as diarrhea and in each such case toxin detection and *C. difficile*-specific stool culture ought to be performed immediately. If the test is positive, Metronidazole treatment should be initiated without delay.

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