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ALGORITHMS FOR THE TREATMENT OF CLOSTRIDIUM DIFFICILE IN THE INTENSIVE CARE UNIT

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Clostridium Difficile infection (CDI) remains the most important cause of healthcare associated diarrhea and it is associated with considerable morbidity and mortality. Ensuring the optimal treatment of CDI is vital given the multiple options that have been described for potential patient management and since data reporting decreased effectiveness of metronidazole in treatment of severe cases of infection have been published. Metronidazole is the drug for the initial episode of mild to moderate CDI. Vancomycin is the drug of choice for the initial episode of severe CDI (125 mg orally 4 times per day for 10-14 days, and per rectum if ileus is present). Vancomycin administration (orally/per rectum) with or without iv administered metronidazole is the choice in cases of severe, complicated CDI. Surgical treatment is considered for severely ill patients and a subtotal colectomy with rectum preservation is recommended. Monitoring the serum lactate levels, serum creatinine levels and white blood cells count are evaluated before surgery, being known that serum lactate levels of 5 mmol/L, leukocytosis rising to 50 000 cells/μL and serum creatinine over 3 mg/dl have been associated with greatly increased perioperative mortality.

Keywords Clostridium difficile; Metronidazole; Vancomycin; intensive care

INTRODUCTION

Clostridium difficile infection (CDI) is associated with considerable morbidity and risk of mortality. Ensuring the optimal treatment of CDI is important given the multiple options that have been described for potential patient management since data reporting decreased effectiveness of metronidazole in treatment of severe cases of infection have been published[1]. The aim of the study was to determine therapeutical options for the treatment of patients with confirmed CDI admitted in ICU.

MATERIAL AND METHODS

This is a prospective study of the CDI cases from *"C.C. Iliescu"* Institute for Cardiovascular Disease – ICU 1, Bucharest, in 2014. The case definition of CDI included the presence of clinical symptoms (usually diarrhea) and a stool test result positive for *C. difficile toxins* or *toxigenic C. difficile*, and colonoscopic findings demonstrating pseudomembranous colitis. From a total of 594 patients with length of stay >48h in ICU there were 7 confirmed CDI cases (all with 1st episode of CDI), with a median age of 53 years, with cardiac and vascular surgical interventions and antibiotic prophylaxis 1-3 days with Cerfuroxim and Gentamicin, prior to the onset of CDI. Age was not a risk factor and all patients were immunocompetent. There were 6 severe cases of CDI associated with fever and leucocytosis between 16.000-26.000 and 1 mild clinical presentation (no fever, leucocytosis 13.000). The incidence of CDI in ICU was 1.18%. We applied the following therapeutical algorithm for the severe cases: Vancomycin 125-500 mg PO/NG 6-hourly and Metronidazole 500 mg IV 8-hourly x 10-14 days, Antimicrobial Use Restrictions and ICU specific treatment that included: IV nutrition and fluids, standard ICU monitoring, central venous line, dialysis (1 case of septic shock associated with acute kidney failure with serum creatinine levels >6 mg/dl). For the mild case we administered oral metronidazole 500mg 8-hourly 10 days and standard ICU monitoring. During the treatment in all 7 cases, PPI's, antimotility agents and probiotics were withheld. None of the patients had undergone colectomy for toxic megacolon.

RESULTS AND DISCUSSION

6 patients had a favourable outcome and were discharged from ICU. 1 patient with a severe form of CDI and significant risk factors (onset leucocytosis of 25.200/ml, acute kidney failure with serum creatinine levels > 6 mg/dl) deceased in septic shock.

Metronidazole remains appropriate as the first-line therapy for mild to moderate disease. In recent studies, oral vancomycin used a single antibiotic agent in severe CDI appears to be associated with better clinical outcomes than metronidazole[2]. However, in cases of severe CDI with complications, reduced or absent bowel motility may prevent adequate amounts of orally administered vancomycin from reaching the site of infection. Several case reports have supported the intracolonic administration of vancomycin when oral therapy cannot be tolerated. Some experts will also use higher doses of oral vancomycin with the goal of improving the chance that adequate fecal concentrations will be reached although this practice has not been studied. Intravenous metronidazole may be added to either oral or intracolonic vancomycin in severely ill patients with ileus, although this approach has also not been adequately evaluated[3].

The main therapeutic goal consisted of optimization of cellular oxygenation by maintainig hemodynamic stability and fluid balance. Acid-base status of the patients as well as serum lactate, hourly urinary flow and creatinine levels acted as indirect tissue perfusion indicators.

Fidaxomicin (Dificid), has been approved to treat C. difficile and in one study, the recurrence rate of C. difficile in people who took fidaxomicin was lower than among those who took vancomycin. It may be considered in patients who cannot tolerate vancomycin, although more data is needed4. Fidaxomicin costs considerably more than metronidazole and vancomycin. For patients with severe CDI, suitable antibiotic regimens include vancomycin (125 mg 4 times daily for 10 days; may be increased to 500 mg 4 times daily) or fidaxomicin (200 mg twice daily for 10 days). The use of fidaxomicin is not supported in life-threatening CDI5.

In a 2014 CDC analysis of data regarding antibiotic prescribing in hospitalized patients, Fridkin and colleagues estimated that a 30% reduction in the use of broad-spectrum antibiotics would result in a 26% reduction in Clostridium difficile infections. In addition, improvement in physician's antibiotic prescribing habits from overuse and incorrect use would also help to reduce antibiotic resistance[3].

Patients with fulminant colitis and toxic megacolon may require operative intervention, such as colectomy with preservation of the rectum. These patients' serum lactate levels and peripheral leukocyte counts may aid in the decision to operate; there is a significant risk for perioperative mortality with elevated serum lactate levels (5 mmol/L) and leukocytosis (50,000 cells/µL).

CONCLUSION

The treatment was correlated to the severity of the infection. In the severe cases metronidazol and vancomycin were used in conjunction, monotherapy with metronidazol being reserved for the mild cases.

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