CLOSTRIDIUM DIFFICILE EPIDEMIC OUTBREAK IN AN ONCOLOGY UNIT

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CLOSTRIDIUM DIFFICILE EPIDEMIC OUTBREAK IN AN ONCOLOGY UNIT (Abstract): Aims: Contributions to the knowledge of some peculiarities of C. difficile involvement in human pathology, nosocomial infections (NI) included. Material and methods: This clinico-epidemiological and laboratory study included 14 patients admitted to the Medical Clinic of the Iasi Regional Cancer Institute with the diagnosis of C. difficile NI based on detection of toxins A and B in stool samples. The data were assessed and interpreted using an algorithm which revealed the peculiarities of C. difficile NI outbreak occurrence and evolution. Results: Of the 14 cases included in the study, 5 (35.8 %) had community-onset infections and 9 (64.3 %) oncology unit-onset infections. The average hospital stay was 22 days. Immunocompromised condition and the use of antibiotics in the ciprofloxacin, colistin and cefotaxime group for 4 - 10 days were the main risk factors. Conclusions: This epidemic C. difficile NI outbreak which affected immunocompromised patients with high susceptibility to infection, common finding in oncology care was brought under control by active preventive measures associated with concomitant antimicrobial therapy effective in C. difficile infections. Keywords: CLOSTRIDIUM DIFFICILE, NOSOCOMIAL INFECTION, ONCOLOGY, EPIDEMIC OUTBREAK.

Similar to other species of the 200 described, Clostridium difficile can induce invasive phenomena and toxigenic processes through the mediation of some histotoxins (enterotoxins, haemolysins, proteases) that destroy the soft tissues, especially in immunocompromised patients treated with antibiotics who may develop colitis, sometimes severe, and invasive infections, such as bacteraemia (1, 2).

Although the role of clostridia in human pathology was reported before 1870, in the era of antibiotics C. difficile is still an important causative agent of human diseases, and the most common cause of nosocomial infections (IN), producing toxin-mediated diarrhea, pseudo membranous enterocolitis and toxic mega colon (3, 4, 5).

Recent clinico-epidemiological observations have demonstrated the involvement of highly virulent C. difficile strains in the occurrence of epidemic outbreaks in various health care units, requiring effective diagnostic, treatment and prevention interventions (6, 7).

The possible involvement of C. difficile
in intestinal infections has been suggested ever since 1935, but, in the absence of accessible methods of investigation, these infections were thought to be caused by *Staphylococcus aureus*, recognized as the main causative agent of NI at the onset of antibiotic era (6, 7, 8).

The identification in 1978 of *Clostridium difficile* as a Gram positive sporulated bacillus allowed its inclusion among the etiologic agents of antibiotic-associated diarrhea, proving its widely emerging tendency with various clinico-epidemiological manifestations (9, 10, 11).

The spread and aggressiveness of *C. difficile* strains may be favored by: the use of antibiotics (even in a single dose) and cytostatics, digestive tract surgery, severe chronic diseases, administration of proton pump inhibitors, immunosuppression from various causes; frequent hospitalizations, age over 65 years (12, 13, 14).

The risk of *C. difficile* infections is maintained by the healthy carriers in the general population, with a prevalence of 2-5%, with the possible involvement of other risk groups including children, women after delivery, and tissue and organ recipients, stem cells included.

**MATERIAL AND METHODS**

The clinico-epidemiological study was conducted in the interval January-October, 2013, using the data in the observation sheets and laboratory results.

The study group included 14 patients with a mean age of 56.4 years, admitted to the Medical Clinic of the Regional Cancer Institute for *C. difficile* NI diagnosed by the presence of toxins A and B in stool samples.

The data were assessed and interpreted by using an algorithm which revealed the peculiarities of *C. difficile* NI outbreak occurrence and evolution (fig. 1).

**Diagnosis of *C. difficile* infection (CDI)**

1. The patient had another CDI during the past 12 months
   - Yes → Recurrence
   - No → New case

2. Onset at over 2 days after admission
   - NI – Community-onset CDI (CCDI)
   - Discharged from another unit in the past 4 weeks

**Fig. 1** The scheme of the structural algorithm for *C. difficile* infection outbreak
RESULTS

Community-onset C. difficile NI (CCDI). The assessments, based on the clinico-epidemiologic algorithm, showed that of the 14 cases included in the study, 5 (35.8%) were considered community-onset NI. The 5 patients were aged between 30 and 72 years, 4 were females and 4 from urban areas, with onset on average 72 hours before admission, multiple previous hospitalizations, no surgeries, and clinical symptoms started on average 2 days after admission (tab. I).

Clinical symptoms occurred 3 to 9 days after prior hospitalization (mean: 2 - 6.4 days) with fever state, abdominal pain and accelerated intestinal transit (3-20 stools/day).

TABLE I
Some characteristics of the patients with community-onset C. difficile infection and clinical onset during hospital stay

<table>
<thead>
<tr>
<th>No. case</th>
<th>Age</th>
<th>Sex</th>
<th>Area</th>
<th>Diagnosis upon admission</th>
<th>Co morbidities</th>
<th>Antibiotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>72</td>
<td>M</td>
<td>urban</td>
<td>Acute myeloid leukemia Pseudo membranous colitis</td>
<td>Renal failure Heart failure Viral hepatitis C</td>
<td>Cefotaxime Ciprinol</td>
</tr>
<tr>
<td>2.</td>
<td>61</td>
<td>F</td>
<td>urban</td>
<td>Multiple myeloma Secondary immune deficit</td>
<td>Respiratory failure Cardiac failure</td>
<td>Ciprinol</td>
</tr>
<tr>
<td>3.</td>
<td>52</td>
<td>F</td>
<td>rural</td>
<td>Myeloproliferative syndrome</td>
<td>Myocardial infarction Breast cancer</td>
<td>Cefotaxime Ciprinol</td>
</tr>
<tr>
<td>4.</td>
<td>39</td>
<td>F</td>
<td>urban</td>
<td>Myeloproliferative syndrome Prolonged febrile syndrome</td>
<td>No</td>
<td>Augmentin</td>
</tr>
<tr>
<td>5.</td>
<td>30</td>
<td>F</td>
<td>urban</td>
<td>Diffuse non-Hodgkin’s lymphoma</td>
<td>No</td>
<td>Vancomycin Metronidazole</td>
</tr>
</tbody>
</table>

Despite cancer-induced immunosuppression, of the 5 patients with CCDI only 1 case (20%) presented a severe evolution.

Oncology unit-onset C. difficile NI: 9 cases (64.3%), mean age of 60.5 years, onset 9-35 days (average 22 days) after admission, characterized by abdominal pain (50%) accelerated intestinal transit (> 5 stools/day) (100%), fever (> 38.5 °C) (66.6%), and a mild clinical course (77.7%).

In these patients, the clinico-epidemiological investigation showed that the risk factors involved in the occurrence of CDNI were the use of antibiotics in the ciprofloxacin, colistin, cefotaxime group for 4-10 days in 4 cases (44, 4%); cefotax-
ime and a dose of cytostatics in 2 patients (22.2%), chemotherapy and radiotherapy alone in 3 patients (33.3%).

The most commonly recorded co morbidities were: hepatitis C virus, arterial hypertension and anemia (tab. II).

### TABLE II

<table>
<thead>
<tr>
<th>No. case</th>
<th>Age</th>
<th>Sex</th>
<th>Area</th>
<th>Diagnosis upon admission</th>
<th>Co morbidities</th>
<th>Surgery</th>
<th>Antibiotic therapy</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. days</td>
</tr>
<tr>
<td>1.</td>
<td>67</td>
<td>F</td>
<td>urban</td>
<td>Malignant biliary tract tumor</td>
<td>Anemia Malnutrition AHT</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>2.</td>
<td>68</td>
<td>F</td>
<td>urban</td>
<td>Lymphoid leukemia</td>
<td>AHT</td>
<td>no</td>
<td>Vancomycin 3</td>
</tr>
<tr>
<td>3.</td>
<td>67</td>
<td>M</td>
<td>urban</td>
<td>Malignant rectal tumor</td>
<td>Viral hepatitis C</td>
<td>yes</td>
<td>Cefuroxime 3</td>
</tr>
<tr>
<td>4.</td>
<td>70</td>
<td>M</td>
<td>urban</td>
<td>Malignant rectal tumor</td>
<td>AHT</td>
<td>yes</td>
<td>Cefotaxime 3</td>
</tr>
<tr>
<td>5.</td>
<td>76</td>
<td>F</td>
<td>urban</td>
<td>Malignant sigmoid colon tumor</td>
<td>Viral hepatitis C</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>6.</td>
<td>30</td>
<td>F</td>
<td>urban</td>
<td>Diffuse non-Hodgkin’s lymphoma</td>
<td>-</td>
<td>no</td>
<td>Vancomycin Metronidazole 3</td>
</tr>
<tr>
<td>7.</td>
<td>73</td>
<td>F</td>
<td>rural</td>
<td>Diffuse non-Hodgkin’s lymphoma</td>
<td>Anemia Osteoporosis AHT</td>
<td>no</td>
<td>Vancomycin Metronidazole 3</td>
</tr>
<tr>
<td>8.</td>
<td>78</td>
<td>F</td>
<td>urban</td>
<td>Malignant ovarian tumor</td>
<td>-</td>
<td>yes</td>
<td>Cefotaxime Cytostatics 3</td>
</tr>
<tr>
<td>9.</td>
<td>67</td>
<td>M</td>
<td>urban</td>
<td>Malignant rectal tumor</td>
<td>AHT Nephropathy</td>
<td>yes</td>
<td>Cefotaxime 3</td>
</tr>
</tbody>
</table>

**DISCUSSION**

*C. difficile* - associated diseases cause polymorphic clinical manifestations dominated by diarrhea of varying severity and possible severe course in the case of pseudo membranous enterocolitis or toxic mega colon.

Both isolated cases, as well as those involved in nosocomial outbreaks have as characteristic feature the association of antibiotic and immunocompromised status.

The use of the classes of antibiotics, including penicillins, cephalosporins, macrolides, aminoglycosides, and lincosamides, can be associated with the induction of human *C. difficile* infections.

The onset of *C. difficile* infection is associated with the use of antibiotics that disrupt the equilibrium of intestinal flora. The virulence of the pathogenic agent strains is dependent, in principle, on the production of two enteric cytotoxins (Ted A and Ted B), and the outbreaks of *C. difficile* infection, particularly those with
severe symptoms, are related to the presence of ribotype O27/NAP1 (1, 2, 5, 6, 9).

The clinico-epidemiological diagnosis may benefit from laboratory investigations, which include detection of toxins in the stool samples of patients with suspected C. difficile infection.

The use of culture media for the isolation of this pathogen is not recommended as approximately 2-5% of the general adult population may be intestinal carriers.

Cell cultures are exposed to stool filtrate for 24-48 and a specific cytopathic effect is observed followed by a confirmation test with neutralizing antibodies, the results being available in 48-72 hours.

Rapid and highly specific results for both C. difficile toxins can be obtained using some variants of the immunoenzymatic test (12, 13, 14).

C. difficile selective agar is a medium that allows the isolation of C. difficile strains from stool samples, and colony characteristics allow the differentiation from other clostridia possible causes of antibiotic-associated diarrhea.

As to the cultures grown on blood agar media the colonies can be easily identified by the odor due to the production of cresol (12, 13, 16).

Roberts et al. (17) and Byrne et al. (18) analyzing the results of clinicoepidemiological researches on the incidence of C. difficile infections in various geographical areas have concluded that due to the emerging trend, the medical and socioeconomic implications these infections are a major population health issue.

Redelings et al. (11) reported that in the USA, in 2005-2006, hospitalizations for C. difficile infections increased by 117% with a corresponding increase in hospital costs and death compared to a decade earlier.

Wysowski (15) showed that in the USA C. difficile-related mortality rate increased by 35%, from 5.7 per million population in 1999 to 23.7 per million population in 2004, the same being true for England.

Since 1990, the first-line therapy of non-severe C. difficile infections is metronidazole while vancomycin is recommended in severe infections, given the fact that there is a relatively low level of persisting spores at risk to germinate after reducing the concentration of antibiotics (5, 6).

Onderdonk and Garrett (5), and Vonberg (10) found that the spread of C. difficile NI can be controlled by consistently applied common hygiene-sanitary and epidemiological measures, directed to patients, suspects, health care workers and ambient environment. It is envisaged that C. difficile spores can live for long periods on surfaces, objects, food, and can be spread through aerosols especially in rural hospital without being destroyed by the usual methods of decontamination, which are effective only for the strains in vegetative form.

CONCLUSIONS

The nosocomial infection outbreak presented in this study although occurring in a group of immunocompromised patients and thus high susceptibility to infection, common situation in an oncology unit was brought under control by active preventive measures including daily screening, patient isolation, disinfection chemicals, including sporicidal agents, and the standard precautions of the health care professionals and support staff. Concomitantly, the antimicrobial therapy effective in Clostridium difficile infections was initiated, monitored by laboratory tests and customized in patients with certain co-morbidities.
REFERENCES