

Original Paper

Current Issues in Acute Diarrheal Disease

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REZUMAT

Aspecte actuale în boala diareică acută

Obiective: numărul relativ mare de pacienți diagnosticați cu boală diareică acută cu *Clostridium difficile* (CD) în Clinica II de Boli Infecțioase a Spitalului de Boli Infecțioase și Pneumoftiziologie Timișoara, în 2013, ne-a determinat să evaluăm care dintre următorii factori pot fi invocați în declanșarea acestui episod diareic endemic: stări patologice particulare sau context terapeutic; deficiențe ale personalului sau a măsurilor de igienă; o metamorfozare a bolii infecțioase.

Metode: Această lucrare conține un studiu retrospectiv, transversal-observațional, efectuat pe un număr de 72 de pacienți internați în Clinica noastră diagnosticați cu enterocolită cu *Clostridium difficile* (CD), în perioada ianuarie 2013- ianuarie 2014.

Rezultate: boala diareică acută cu CD reprezintă 3,8% din toate cazurile de adulți internați în 2013. Ca și factori de risc au fost consemnați următorii: pacienți internați sau antibiotic administrate anterior internării, vârsta peste 60 de ani, comorbidități multiple. S-a consemnat o corelație directă, semnificativă din punct de vedere statistic, între scorul ATLAS și evoluția pacienților.

Concluzii: datele prezentate ne permit să încadrăm CD în grupul agenților cauzali ai infecțiilor nosocomiale. Cazurile fără antecedente personale semnificative ne atrag atenția asupra procesului de metamorfozare a anumitor boli infecțioase.

Cuvinte cheie: *Clostridium difficile*, infecții nosocomiale, scor ATLAS

ABSTRACT

Objectives: the relatively high number of patients with *Clostridium difficile* (CD) acute diarrheal disease admitted in the 2nd Infectious Diseases Department of the Hospital for Infectious Diseases and Pneumophthisiology Timișoara in 2013 determined us to evaluate which of the following factors could be invoked in triggering this endemic diarrheal episode: particular pathologic conditions or therapeutic context; deficiencies in the personal or hygiene measures; a metamorphosis of the infectious disease.

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Methods: This paper contains a retrospective study, cross-observational, conducted on a number of 72 adults hospitalized in our Department diagnosed with enterocolitis with *Clostridium difficile* (CD), between January 2013 and January 2014.

Results and discussions: CD acute diarrheal disease represented 3.8% from all adult cases admitted in 2013. As risk factor there were noted the following: hospitalized patients and prior antibiotherapy, age over 60 years, multiple comorbidities. There was a direct statistically significant correlation between the ATLAS score and the outcome of the patients.

Conclusions: the data presented allow us to put CD in the group of nosocomial infections causative agents. The cases without any significant history bring to attention a process of metamorphosis of certain infectious disease.

Key words: *Clostridium difficile*, nosocomial infections, ATLAS score

INTRODUCTION

The intestinal microflora consists of micro-organisms (bacteria required for normal functioning of the digestive tract), which are interacting with the human body (commensalism), the digestive tract is the habitat required for the development of these bacteria, and these, in turn, produce the constituents necessary for the organism. Disruption of this balance makes some ordinary saprophytic species to become pathogenic.

Clostridium difficile (CD), gram positive bacillus, anaerobic, sporulated, enters into the structure of normal enteric resident flora in a proportion of 60-70% in newborns, 10 to 30% in hospitalized patients, and only 3% in healthy adults (1). If this flora is iatrogenic depressed by antibiotic therapy, chemotherapy, inhibitors of gastric acidity, CD wins "vital space"; by multiplying causes damage to the intestinal mucosa and subsequently, on the background of comorbidities, gives the lead of severity to the clinical evolution.

Recently a number of changes were noticed in the epidemiology, clinical manifestations and evolution of infection with CD (2):

- The number of diagnosed cases increased, especially in persons over 65 years of age;
- There was an increase in the share of severe illness, the number of patients with recurrences of infection and lethality caused by this infection;
- The appearance of 027/NAP1 ribotype in circulation, which has been shown to be involved in nosocomial outbreaks, in the illness of community origin or in the case of persons without other comorbidities.

Increased aggression of CD in the last decade: - the lethality rate tripled, recurrence in at least 20% of the cases that survive the initial episode - and the limits of current therapeutic solutions increased the pressure for the development of new therapeutic interventions effective in the acute episode and / or in prevention of relapses.

Exacerbation causes of this type of infection are due to (3):

- the existence of predisposing factors, represented by the administration of antibiotics active on the intestinal flora, but which do not act on CD (hence the label of antibiotic-associated diarrhoea);
- existing risks after surgery, administration of antibiotics, immunosuppressant's, gastric anti-secretive drugs- better demonstrated for proton pump inhibitors.

Therefore, through the clinical casuistic of the last years, CD gains a more visible place in literature. To the status of sporulating anaerobic bacillus, part of the intestinal saprophyte flora granted in the year 1935 it is added the quality of potentially pathogenic germ in 1978, and currently by ribotype 027/NAP1 a new involvement in the etiology of diarrheal syndrome is outlined (4).

MATERIAL AND METHODS

This paper contains a retrospective study, cross-observational, conducted on a number of 72 adults hospitalized in the II Clinic of Infectious Diseases of the Hospital for Infectious and Lung Diseases Timisoara diagnosed with enterocolitis with *Clostridium difficile* (CD), between January 2013 and January 2014.

The analysis was based on the following: age structure of cases of enterocolitis with CD; presenting features of terrain (comorbidities, surgery, etc.); where the disease started (at home or at the hospital); possible presence of favourable conditions, which may increase the bacteria's aggression in discussion; data on disease dynamics.

The observational nature of the study included both the descriptive side and the analytical one of the analysed phenomena. Evaluation of CD infection was followed by systematization of possible predisposing factors or triggers of this important public health problem, in the desire of finding potential solutions.

Statistical analysis was performed using the program SPSS version 10.0.

The correlation coefficient was applied to Spearman rank type variables. The statistical significance was considered to be ≤ 0.05 or ≤ 0.01 , based on the instructions of the statistical analysis program.

Results: In the descriptive part of the paper, there are presented some general variables: age, gender, origin, neoplastic pathology, comorbidities, and underserved areas. The age of the Patients included in the study ranged between 22 and 90 years averaging 64 - (fig. 1).

The distribution by genders showed a slightly

higher incidence of the female sex (51%). Urban-rural distribution recognizes the same incidence in urban areas (74% -53 patients).

Neoplastic pathology was present in 25% of patients (18); solid malignant tumors, localized within gastrointestinal tract, lungs, genital tract and skin at 16 patients and hematologic malignancies in 2 patients have been reported.

Comorbidity was well represented: 86%; dominated heart disease, diabetes, pulmonary tuberculosis.

The following risk factors were noted: 93% are generated in hospital environment; a percentage of 65% of the patients infected with the CD prior to the disease triggering had indications of antibiotic therapy

Analysing monthly incidence during epidemic evolution, it appears that the highest value was recorded in October 2013 (16%), triple the amount in March, September 2013 (fig. 2).

Clostridium etiology accounted for 20% (72 patients) of all cases with diarrheal disease (358 patients) and 3.8% of all adults (1878) admitted during the analysed interval (fig. 3).

The morbidity peak was noted in the group of patients aged over 60 years -66% (fig. 4).

The increased incidence of these infections in the

Figure 1. Patients age

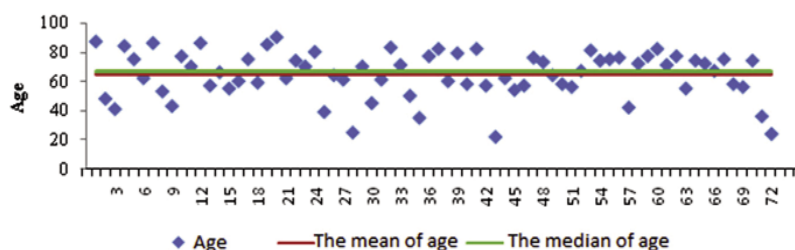


Figure 2. Monthly incidence

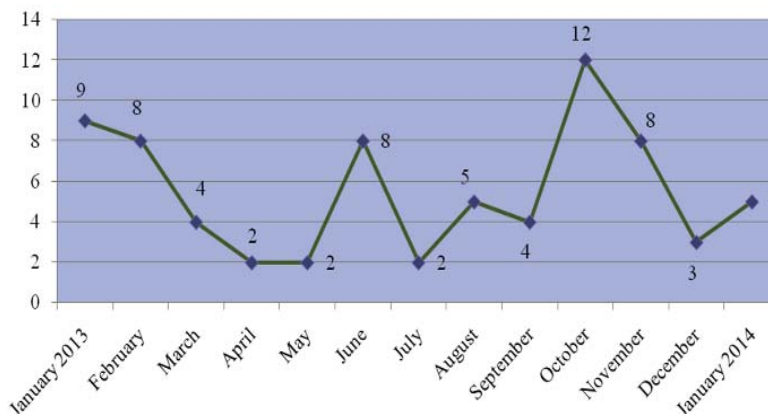
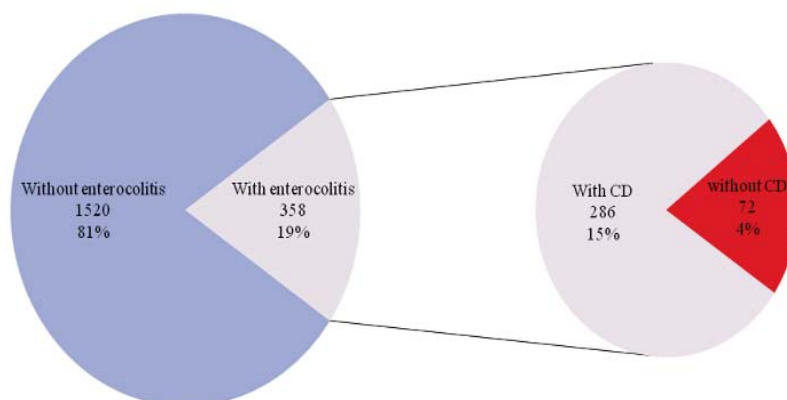


Figure 3. Prevalence of infections with CD

age group over 60 years, due to both physiological decreased immunity, and especially, the installing of secondary immunodeficiency associated comorbidities, explains the influenced overall condition of the majority of affected patients on admission to the clinic.

In immunocompromised individuals, at the severity of the underlying disease also was associated the prolonged evolution of the diarrheal disease, which caused a significant increase in the duration of hospitalization. Average duration of hospitalization was 11 days (fig. 5).

The treatment according to current guidelines consisted of vancomycin, metronidazole or Normix. Evolution was favourable in 72% of patients (52), 18% presented recurrence (13); the fatality rate was 10% (7).

The evolution of cases with the CD infection depends on the severity of the episode of colitis, as well as the patient's condition prior to disease. Older

age (over 65), the association of major chronic diseases, secondary immunosuppression, recent antibiotic treatment, orientate towards a diagnosis of severity.

These factors can be grouped as severity scores; true the predictive ability and its facility of assessment stands out the ATLAS score: Age, Temperature, Leukocytosis, the value of albumin (Albumin) and not least the use of simultaneous antibiotic therapy (Simultaneously associated antibiotics), the score is obtained by giving points between 0-2, and their sum will denote the value of the risk posed to the patient. Lethality varies according to the value score (5).

In a group of 20 patients the ATLAS score value was calculated. Further aim was to establish a statistical correlation (direct, indirect, significant or statistically insignificant) between its value and clinical evolution which was recorded of in the observation charts.

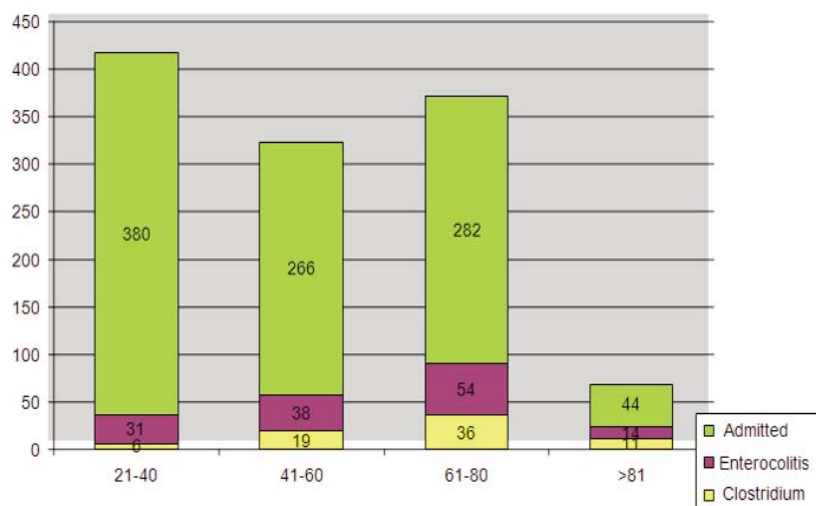
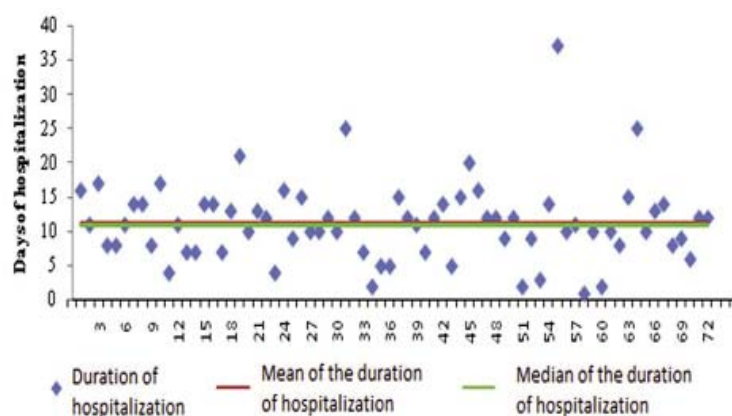
**Figure 4.** Distribution by age groups

Figure 5. Days of hospitalization



Statistical analysis was performed using the program SPSS version 10.0. The correlation coefficient was applied to Spearman rank type variables. The statistical significance was considered to be ≤ 0.05 or ≤ 0.01 , based on the instructions of the statistical analysis program.

A Spearman correlation coefficient of 0.833 was obtained, which indicates a strong direct correlation, statistically significant.

DISCUSSION

The data allow adding the CD bacteria to the large group of causative agents of nosocomial infections.

The incidence of this etiology was significantly higher in the age group over 61 years (65%: 47 patients), followed by the adult group (41-60 years: 19 patients). Although it turns out to be the prerogative of older ages, in the period of investigation there were recorded cases of younger people (6 cases). The median age was 64 years (min. 22, max. 90).

In the studied cases, the disimmune terrain emerged as secondary to solid tumours, hematologic malignancies and amid the multiple associated comorbidities; neoplastic pathology observed in 25% of patients (18 cases) had a urogenital localization in 10 patients, neurological in 3 patients, pulmonary in 1 patient, gastric in 2 patients. Haematological malignancy was represented by an acute leukaemia on a background of myelodysplasia (1 case) and bone marrow aplasia (1 case).

According to literature data, the prevalence of infections with CD among hospitalized patients is 1%, but can reach up to 20% when the duration of hospitalization is 7 days, and even up to 50% if it is more than 4 weeks.

Based on the studied cases, 67 patients (93%) met the requirements that define the notion of nosocomial infection. In 53 patients (74%) symptoms started in the hospital, and 14 patients (19%) during the 30 days following discharge.

The profile of the clinics in which the endemic character of this infection in 2013 was outlined, were the cardiology, pulmonology neurology, gastroenterology service respectively nephrology and intensive care service

Regarding surgical wards, they are represented, in descending order by the general surgery (20 cases, 51%), neurosurgery (5 cases, 13%), orthopaedic (5 cases, 13%), urology (4 cases-10%), vascular surgery (2 cases, 5%), cardiothoracic surgery (2 cases, 5%), gynaecology (1 case, 3%). Surgery consisted of cholecystectomies, appendectomies, neoplastic diseases; orthopaedic interventions were femoral neck fractures, due to osteoporosis account of the age. The neurosurgery interventions have been for various vascular and neoplastic diseases, and those of urology were all reserved for bladder neoplasm.

In the studied group, the proportion of sickening in people without a recorded past significant pathology (6%) supports the idea of enhancement of aggressiveness in terms of disruption of the existing balance of bacteria in the structure of the normal resident flora of the intestine.

Regarding these patients, we note that there are young people without comorbidities, but by the specific daily activity come in contact with hospitalized patients (a doctor, three nurses).

In the relation *Cl. difficile* - diarrheal disease, an important place was held by the presence of repeated courses of antibiotics, excessive use of antibiotics being responsible for the destruction of the normal intestinal microflora, selection and

development of resistant strains of pathogens. In the study group, 65% (47 patients) received antibiotics in the last 3 weeks. In the great majority was noted the use of broad spectrum antibiotics. Of these, the most common were: clindamycin, ciprofloxacin, ceftriaxone.

In 2013, in the II Clinic of Infectious Diseases were hospitalized a total of 1878 adults. In the hospital laboratory were processed a total of 358 stool samples of patients hospitalized for acute diarrheal disease representing 19% of the clinic's casuistic.

The etiology of infectious diarrhea is varied, involving numerous bacterial, viral, parasitic and fungal pathogens. Higher frequency of intestinal bacterial diseases represented in official statistics in our country is not the actual incidence of etiologies involved, but rather concerns the limitations of specialized laboratory work, especially for determining these bacterial etiologies.

Determination of A, B toxin of CD is performed using ELISA. Clostridium etiology (72 patients) represented 3.8% of all patients admitted to the clinic, and 20% of cases of diarrhea in adults.

Regarding age, we found the lowest incidence in younger patients: 31 cases of enterocolitis of the total of 380 hospitalized patients, of which 6 with Clostridium etiology. The prevalence increases with the age, and 66% of the cases of diarrheal illness occurred in the age group of 61-80 years.

Accumulation of risk factors resulted in a prolonged duration of hospitalization in 42 patients (58%) of the studied group. The length of stay was between 7 and 37 days with an average of 11 days. The average duration was over two times higher than those hospitalized for other conditions (about 5 days), which indirectly resulted in a significant increase of the hospitalization costs. The hospital stay was prolonged, especially in patients over 61 years. Patients with long-stay (37 days) had a poor outcome due overlapping comorbidities: lung cancer, hypertension, multiple radio-chemotherapy courses, repeated diarrheal episodes.

In the researched casuistic, the average clinical forms of severity prevailed, fatality rate was 10%. Relapses were observed in 18% of patients analyzed.

Correlation of ATLAS score with the evolution of the case, in a lot of 20 patients, yielded a correlation coefficient ρ (rho) = 0.833, p less than 0.01, that which indicates a direct link, strong, statistically significant. As the ATLAS score is higher, the risk of

poor outcome is higher. The correlation is excellent, because a perfect correlation would have rho 1. But the sample being small (under 30 people) reduces the statistical power of the data analysis. The high value of the mean / median ATLAS Score is associated with unfavourable evolution, while low values are associated with favourable evolution.

CONCLUSIONS

The emergence of *Clostridium difficile* infection means: the increase of the average length of hospitalization and inpatient care costs; increase in the number of deaths especially in elderly patients with recent hospitalization; compromising the effectiveness of advanced / aggressive medical interventions in hospitals in which evolve nosocomial outbreaks of diarrhoea.

In our study, CD infection was identified in 3.8% of adult patients hospitalized in II Clinic of Infectious diseases, being close to the data reported in Europe.

Endemic nature of this infection reported in the year 2013, cannot exclude the presence of deficiencies in the process of epidemiological surveillance of hospital units. In the presence of pathologies with have the potential to induce secondary immunodeficiency, the adequate therapeutic act for the disease in question must be accompanied by measures aimed to limit nosocomial infections, in our case CD infection.

Currently, for any nosocomial diarrhoea, the first hypothesis regarding the cause should be *Clostridium difficile* infection if there is no other obvious explanation.

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