

## Particularities of Clostridium Difficile Infection in Patients with Psychiatric Pathology

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**Abstract:** *Clostridium difficile* infection (CDI) is a new pathology, but increasingly common in the elderly patient, with multiple comorbidities that often alter his quality of life and aggravate his vital prognosis. **Material and method:** The study is a prospective, observational, controlled active study, performed on 706 patients admitted to the Hospital “St. Parascheva Galați Infectious Diseases Clinical Hospital ” between 1.01.2017 ÷ 31.12.2018 with the diagnosis of CDI, of which 69 patients were associated with psychiatric disorders (PD).

**Results:** The demographic, clinical and paraclinical characters that differentiated the group with CDI and PD from the group with CDI and various comorbidities, statistically significant, were: female sex, predominant in the group with PD, older age in the group with PD, Charlson score with values higher in the PD group, Atlas score with higher values in the PD group, the number of deaths that occurred in the first 30 days after the CDI episode, as well as the number of deaths that occurred in the first 6 months after the CDI, higher in the group with CDI and PD compared to the group with CDI and various comorbidities.

**Keywords:** *Clostridium difficile*; comorbidities; dementia; prognosis.

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## Introduction

*Clostridium difficile* Infection (CDI) is an important public health problem in Romania. In 2018, a number of 10241 confirmed cases entered in the CDI surveillance system, with 2% more cases than 2017 (10080). The elderly were mainly affected, the median age of confirmed cases was 68 years (0-101 years), 51% being female.

Risk factors for triggering the episode of CDI are: antibiotic therapy, age over 65 years, contact with medical care units, cancer chemotherapy (Bilgrami et al., 1999; Gorschluter et al., 2001), gastrointestinal surgery (Sartelli et al., 2019; Thibault, Miller & Gaese, 1991), feeding on the nasogastric tube, upper or lower digestive endoscopy (Bliss et al., 1998), patient's comorbidities (chronic or disabling diseases accompanied by immunosuppression).

Risk factors for mortality from CDI are considered: age, comorbidities, hypoalbuminemia, leukocytosis, acute renal failure and ribotype 027 infection (Abou Chakra et al., 2014).

Psychiatric pathology is not usually accompanied by CDI, but there are studies that have observed high rates of CDI in patients with dementia in long-term care facilities (LTCF). In the United States, the rate of CDI in LTCF is 1.85 / 100 LTCF admissions with a 3-month mortality rate higher than those without CDI (Ziakas et al., 2016). The risk of CDI among LTCF residents is seven times higher compared to individuals in the community (Karanika et al., 2017). This increased risk is due to multiple risk factors for CDI in this patient population, including age, frequent antimicrobial exposure, multiple comorbidities, and recurrent hospitalizations (Karanika et al., 2017; Ziakas et al., 2015; Ziakas et al., 2016).

These conditions of patients are associated with changes in the structure of the microbiome (Lewis & Pamer, 2017). The study of the microbiome in patients with advanced dementia, living in a long-term care unit, showed a reduced diversity of commensal species. Thus, the diversity of the microbiome, as measured by the Shannon index, was substantially reduced in these patients, with a value of 3.2, than the reported values of 4.5 among the general population (Antharam et al., 2013).

Reconstruction of the microbiome could reduce the risk of CDI onset and recurrence. The identification of disturbances of the microbiome could identify patients with high risk of CDI and allow the formulation of preventive and therapeutic strategies targeted for CDI (Araos et al., 2018,

Manges et al., 2010, May, 2018; Theriot & Young, 2015; Vincent & Manges, 2015; Vincent et al., 2013).

Also, patients colonized with Clostridium difficile toxigenic strains have an increased risk of CDI. The structure of the microbiome in patients with dementia from long-term care facilities, who are colonized with Clostridium difficile toxigenic strains differs from non-colonized patients by the predominance of: Akkermansia spp., Dermabacter spp., Romboutsia spp., Meiothermus spp., Peptoclostridium spp., and Ruminococcaceae UGC 009 (Araos et al., 2018). Also, colonization with C. difficile is associated with a six-fold increased risk of CDI (Zacharioudakis et al., 2015). Specific microbiome disturbance indices may be able to identify subjects at high risk of C. difficile colonization and may help formulate targeted prevention and therapeutic strategies within LTCF (Anghel et al., 2019; Baroiu et al., 2018; Baroiu et al. 2019; Berbinschi et al., 2014; Zacharioudakis et al., 2015).

Other clinical studies have observed a higher incidence of CDI in elderly Americans with depression than in those without depression (282.9 / 100,000 person-years (95% CI 226.3 - 339.5) compared to 197.1 / 100,000 person-years (95% CI 168.0 - 226.1)). In this study, the rate of CDI was 36%, higher in patients with major depression (95% CI 1.06 ÷ 1.74). The conclusion of the study was that adults with depression who use antidepressant medication have a higher risk of CDI than the general population, with the highest risk being present in elderly widowed adults and those living alone (Rogers et al., 2013).

A United States study of 362 patients with CDI found that delirium, Charlson score, total leukocyte count, serum urea, intensive care hospitalization were predictive factors for 30-day mortality from the episode of CDI. Of these factors - patients who were admitted from a long-term care facility, diagnosed in the intensive care unit, and who developed delirium were at highest risk for dying within 30 days of CDI diagnosis (Archbald-Pannone et al., 2016).

This paper aims to identify the specific features of CDI in patients with psychiatric disorders from an epidemiological, clinical and therapeutic point of view.

## Methodology

A prospective, observational, actively controlled study was performed on 706 patients admitted to the “St. Parascheva Clinic Hospital of Infectious Diseases Galati” between 1.01.2017 ÷ 31.12.2018 with the diagnosis of Clostridium difficile Infection. 69 of them had psychiatric

comorbidities. Criteria for inclusion in the study were: adults with unformed stools, over 3 in the last 24 hours, with a consistency of 6-7 on the Bristol scale and toxins of *Clostridium difficile* A or B or A and B positive; patients who have written informed consent for participation in the study, staff in full knowledge.

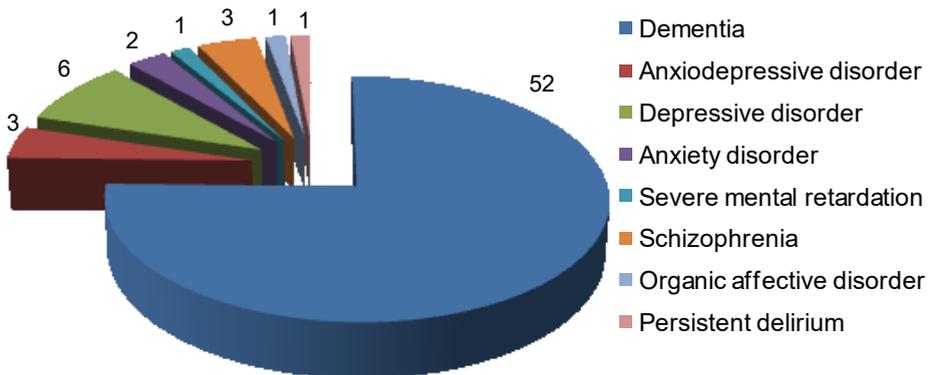
Exclusion criteria from the study were: unconscious patients or inability to sign informed consent; patients who refused to participate in the study; pregnant or breastfeeding women; patients under 18 years; patients who had extreme values ("outliers") in the usual laboratory tests (leukocytes, hemoglobin, serum albumin, ionogram, serum creatinine).

Patients were monitored during the hospitalization period and at one month, 2 months and 6 months after discharge, they were evaluated by telephone or in hospital.

For statistical analysis we used Med Calc program, version 15.8. Statistical analysis of the demographic data was performed on the group of patients with CDI and psychic diseases (group A) compared to the one with CDI and various comorbidities (group B). The presentation is in Mean, S.D. (standard deviation), minimum and maximum value for continuous variables and in absolute frequency for categorical variables, the test used in the inferential analysis being specified for each variable.

## Results

The diagnoses of patients with psychiatric disorders were: dementia-75.36% of cases, depressive disorder-8.69%, anxiodepressive disorder-4.34%, schizophrenia-4.34%, anxiety disorder-2.89%, severe mental retardation-1.44%, organic affective disorder-1.44%, persistent delirium-1.44%, Fig.1.



**Fig 1.** Profile of psychiatric pathology

The origin of the cases in the group with patients with CDI and various comorbidities was: 553 (78.32%) patients with infection associated with healthcare, and 153 (21.67%) patients with infection with indefinite and community source, and in the group of patients with CDI and **psychiatric disorders** (PD) was: 61 (88.40%) patients with healthcare associated infection, and 8 (11.59%) patients with indefinite and community source infection. The percentage of nosocomial infections was higher in the PD group with 10.08% (95% CI -0.33% -17.29%,  $p = 0.0697$ ) without being statistically significant. The characteristics of the group with CDI and PD and the group with CDI and various comorbidities and their statistical correlation are presented in Table 1 and 2.

**Table 1.** Numeric correlations of the characteristics of the group with CDI and psychiatric disorders versus CDI and various comorbidities

	CDI+PD+ (N=69)			CDI+ (N=706)			T-t p	95% CI
	Av.	SDev	Max; Min	Av.	SDev	Max; Min		
Age(years old)	75.71	13.29	91;21	66.23	15.37	95;19	<b>&lt;0.0001</b>	- 13.24; -5.71
Hospitalization length (days)	8.88	4.68	28; 1	8.08	3.57	28;1	0.0853	-1.71; 0.11
Treatment duration (days)	9.76	3.25	21; 1	10.19	3.27	35;1	0.2972	-0.37; 1.23

Legend: Av=Average; SDev=Standard Deviation; Max=Maximum Value; Min= Minimum value; T-t= Student Test (t) for differences between means; CI= confidence interval

**Table 2.** Statistic analysis of the characteristics of categorical variables of the patients with CDI and psychiatric disorders versus CDI and various comorbidities

		CDI+PD+ N=69		CDI+ N=706		OR 95%CI	X2 Test p
		n	%	n	%		
Sex	Female	41	59.42	314	44.47	1.89- 27.19	<b>0.0243</b>
	Male	28	40.57	392	55.52		
Living Area	Urban	52	75.36	477	67.56	-4.54- 18.03	0.2329
	Rural	17	24.63	229	32.43		
Charlson Score	0-3	8	11.59	301	4.39	0.50- 17.27 -7.23- 18.21	<b>0.0202</b> 0.4704 <b>&lt;0.0001</b>
	4-6	30	43.47	270	38.24		
	7-14	31	59.42	135	19.12		

						27.42- 52.30	
Antibiotics before CDI onset	Yes No	50 19	72.46 27.53	465 241	65.86 34.13	-5.97- 17.30	0.3297
PPI before CDI onset	Yes No	24 45	34.78 65.21	197 509	27.90 72.09	-4.72- 19.73	0.2853
Endoscopy before CDI onset	Yes No	2 67	2.89 97.10	29 677	4.10 95.89	-6.09-4.28	0.8667
Abdominal Surgery	Yes No	3 66	4.34 95.65	69 637	9.77 90.22	-2.67-9.64	0.2055
ATLAS Score	0-3 4-9	37 32	53.62 46.37	586 120	83.00 16.99	16.92- 42.08	<b>&lt;0.0001</b>
Recurrence	Yes No	13 56	18.84 81.15	124 582	17.56 82.43	-7.65- 12.82	0.9198
Deaths 0-30 days	Yes No	19 50	27.53 72.46	74 632	10.48 89.51	6.67- 29.32	<b>0.0001</b>
Deaths 0-6 months	Yes No	63 6	91.30 8.69	128 578	18.13 81.86	63.40- 79.27	<b>&lt;0.0001</b>

*Demographic characters.* In the group with CDI and PD, the female sex predominated as opposed to the one with CDI and various comorbidities in which the male predominated (statistically significant differences). In both lots the urban environment of origin predominates.

*Analysis of risk factors.* Patients with PD are older when they develop the episode of CDI than those with other pathologies associated. The mean age of the group with PD falls in the second degree of severity of the Atlas score (70-79 years) and the average age of the group with CDI and various comorbidities fall into the first degree of severity of the Atlas score (60-70 years), the difference of these means being statistically significant. The median age of both groups (79 years, group A, 68 years, group B) is in the risk zone for CDI (over 65 years).

The consumption of antibiotics and the chronic consumption of proton pump inhibitors (PPIs), before the onset of CDI, had not statistically significant differences between the two groups. Abdominal surgery and diagnostic or therapeutic endoscopies during the last 8 weeks before the onset of CDI, had similar proportion in the two groups.

The comorbidities of patients with CDI, as measured by the Charlson score, revealed statistically significant differences in the profile with various comorbidities and with PD. The patients with PD accumulated a proportion of value for Charlson Score 7-14 significantly higher than those with CDI and various comorbidities.

*Analysis of the severity of the episode and the prognosis of CDI.* The severity of the CDI episode, as quantified by the ATLAS Score, reveals statistically significant differences on the episodes of high severity disease, that is, the patients with PD experienced significantly more episodes of CDI with Atlas severity index 4-9 more than those with CDI and various comorbidities.

The length of hospitalization and the number of days of specific antibiotic treatment were comparable in the two study groups.

The number of recurrences, defined as the recurrence of symptoms with more than 3 stools, consistency 6-7 on the Bristol Scale, in the last 24 hours and toxins A and / or B positive for CD, in the first 8 weeks after the clinical resolution of the studied episode by CDI, was comparable in the two study groups.

The number of deaths occurring during the first 30 days after the CDI episode, as well as the number of deaths occurring during the first 6 months after the CDI, were statistically significantly higher in the group with CDI and PD compared with the group with CDI and various comorbidities, in direct correlation with the fact that these patients were older and with a profile of comorbidities, with a higher risk of death, and they experienced episodes of disease with higher severity (quantified by the Atlas score) (Perju-Dumbravă et al., 2013).

## **Discussions**

The study of patients with CDI and PD compared with those with various comorbidities identifies risk factors with significant importance in this group, such as older age and more complex profile of comorbidities, with higher risk of death (as measured by the Charlson score). Disorders of diversity and quantity of the microbiome described in literature in patients with dementia, who predominate in our group with PD, could also explain the high severity of the episode of CDI and the severe prognosis of CDI in these patients.

The higher severity of CDI episodes in PD patients, the older age, the complex comorbidity profile and the dysbiosis encountered in these patients had a statistic significant impact on the prognostic of these patients,

quantified by the death rate at 1 month and 6 months from the CDI episode (Perju-Dumbravă et al., 2010).

## Conclusion

Prevention measures for CDI should be carefully and rigorously implemented in patients with PD, especially in patients living in long-term care centers but also in those living at home because their risk profile predisposes to the onset of CDI and to the development of episodes of severe disease with reserved prognosis. The correction of microflora imbalances in the colon in psychiatric patients should be considered when designing their chronic treatment schemes, prophylactic and curative therapies with PPIs and antibiotics should be well reviewed and performed only when are strictly necessary. Further studies will evaluate the usefulness of screening healthy *Clostridium difficile* carriers when hospitalized in a psychiatric ward or in a long-term care unit.

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