

This is a post-peer-review, pre-copyedit version of an article published in Journal of General Internal Medicine. The final authenticated version is available online at: <http://dx.doi.org/10.1007/s11606-019-04935-6>.

**MS #25503**

## **TITLE PAGE**

### **Functional and cognitive status in *Clostridium difficile* infection in the hospitalized elderly: A Retrospective Study of Two Sites**

Maria-Jose Fernandez-Cotarelo MD, PhD<sup>1</sup>; Stephanie E. Nagy-Agren MD<sup>2</sup>; Mark E. Smolkin MS<sup>3</sup>; Leticia Jimenez-Diez-Canseco MD<sup>4</sup>; Maria-Teresa Perez-Pomata MD<sup>5</sup>; Brian V. Shenal PhD<sup>6</sup>; Cirle A. Warren MD<sup>7</sup>

1. Department of Internal Medicine, Hospital Universitario de Mostoles. Faculty of Health Sciences, Universidad Rey Juan Carlos. Madrid (Spain)
2. Department of Infectious Disease, Salem Veterans Affairs Medical Center. Virginia Tech Carilion School of Medicine and Research Institute. Roanoke, VA (US)
3. University of Virginia School of Medicine. Charlottesville, VA (US)
4. Department of Internal Medicine, Hospital Universitario de Mostoles. Madrid (Spain)
5. Department of Microbiology, Hospital Universitario de Mostoles. Madrid (Spain)
6. Center for Neurocognitive Services, Salem Veterans Affairs Medical Center. Roanoke, VA (US)
7. Division of Infectious Disease and International Health, University of Virginia. Charlottesville, VA (US)

Key words: *Clostridium difficile* infection; elderly; functional debility; cognitive impairment; gut microbiota.

**\* MJ Fernandez-Cotarelo and SE Nagy-Agren contributed equally to this work.**

#### **Corresponding author:**

Maria-Jose Fernandez-Cotarelo, MD, PhD

Department of Internal Medicine, Hospital Universitario de Mostoles.

Calle Doctor Luis Montes s/n 28935 Mostoles, Madrid (Spain)

Phone number: +34 91 664 8600 / 8040

Email: [mfcotarelo@salud.madrid.org](mailto:mfcotarelo@salud.madrid.org)

## **Functional and cognitive status in *Clostridium difficile* infection in the hospitalized elderly: A Retrospective Study of Two Sites**

### **Introduction:**

2           Advanced age is a risk factor for *Clostridium difficile* infection (CDI), and older  
3 patients have more severe CDI and worse outcome [1-3]. We investigated whether CDI  
4 in the elderly is associated with functional and cognitive decline, and mortality.

### **Methods:**

6           This is an IRB-approved 2-center case-control study, with retrospective review of  
7 the EMR in Salem Veterans Affairs Medical Center (VAMC) in Virginia, and Hospital  
8 Universitario de Mostoles (HUM) in Madrid (Spain). Cases were patients aged 60+ years  
9 old diagnosed with CDI during 2013 and 2014 using Cepheid GeneXpert at VAMC, and  
10 C.Diff Quick Check Complete (TechLab, Blacksburg, VA, USA) (2013) and Portrait  
11 Toxigenic *C. difficile* Assay (Great Basin Corp, UT, USA) (2014) at HUM. Controls were  
12 randomly selected from patients without a diagnosis of CDI, matched to cases by age, sex  
13 and Charlson comorbidity index (CCI). Other variables recorded were pre-hospitalization  
14 dwelling, cognitive conditions, functional status, development of delirium, length of stay,  
15 readmissions and mortality; and for cases: case-definition and severity. Cases and  
16 controls were tracked up to 180 days after diagnosis and discharge, respectively.

### **Results:**

18           106 patients were diagnosed with CDI, mean age 76.3. Mean CCI was 5 and 2.3  
19 and hospital onset CDI was 70.4% and 67.4% in VAMC and HUM, respectively. There  
20 was higher baseline functional debility in cases compared to controls (84% vs. 69%,  
21  $p=0.014$ ). Cases were more likely to be admitted from nursing home (NH) or longterm  
22 care facility (LTCF) (22% vs. 8% of controls,  $p=0.006$ ). Severity of CDI was significantly  
23 associated with age 80+ years and admission for CDI.

24 Six cases died during admission at each site. CDI cases with dementia had higher  
25 in-hospital mortality (24%) compared to those without dementia (8%,  $p=0.044$ ).  
26 Mortality was higher for cases during hospitalization and at 90 and 180 days (Table 1).  
27 CDI cases experienced delirium during hospitalization two times more than controls.  
28 Discharge to NH/LTCF, functional decline or death during admission was significantly  
29 worse for cases. Readmission (after correction for mortality) was not significantly  
30 different. Within the case group (Table 2), dementia was also significantly associated  
31 with functional decline or death, as was delirium. Analysis of mortality at later timepoints  
32 revealed dementia to be significantly associated with death at 90 and 180 days (Table 2).

### 33 **Discussion**

34 The association of CDI with cognitive impairment, functional decline and delayed  
35 mortality in the elderly shown by this study indicates that CDI may have consequences  
36 beyond acute intestinal infection.

37 Debility and cognitive impairment were previously reported to be associated with  
38 prolonged symptoms and severity of CDI [3,4]. In our study, functional decline or death  
39 during hospitalization was more common in cases than matched controls suggesting that  
40 given the same degree of comorbidities, elderly patients who develop CDI are sicker and  
41 at risk of poor outcomes. We found that those with diagnosis of either dementia or  
42 delirium among cases were particularly more likely to deteriorate or die during admission.  
43 Consistent with our findings, in a model to predict short-term mortality in patients  
44 hospitalized with CDI, delirium contributed the most points on the scale of weighted risk  
45 [5].

46 The delayed effect on mortality by CDI following hospital discharge indicates that  
47 CDI may contribute to a decline in patient function and health over time, ultimately  
48 leading to death in many, an observation previously noted by others [2]. Unique to our

49 study is the association of dementia with functional decline and mortality, suggesting the  
50 interaction of cognitive impairment and CDI impacts later outcomes. These observations  
51 highlight the importance of CDI sequelae long after acute disease, especially in older  
52 people with cognitive impairment. Non-independent baseline status was previously  
53 shown to be a risk factor for long-term mortality in very old patients with CDI [6]. In our  
54 study, high functional dependence - observed over 2 times as frequently in cases - did not  
55 predict short or long-term mortality.

56 The study was performed in two different settings and CCI varied between them  
57 related to population and care differences in Europe versus the U.S; nonetheless both in  
58 each site and combined, CCI did not predict disease severity nor mortality.

59 The interrelationships of cognitive and functional changes in older people affected  
60 by CDI with disease severity, mortality, and requirement for assisted living are complex  
61 and warrant larger, prospective studies.

## 62 **Acknowledgements**

63 This material is the result of work supported with resources and the use of facilities  
64 at the VAMC Salem Virginia. The contents do not represent the views of the U.S.  
65 Department of Veterans Affairs or the United States Government.

66 M.J.F.C. received a grant from the Instituto de Salud Carlos III (M-BAE 2015,  
67 Health Research and Development Strategy, Spain), the Spanish Foundation of Internal  
68 Medicine (FEMI) and the Madrid-Castilla la Mancha Society of Internal Medicine  
69 (SOMIMACA).

70 The authors thank Dr. Jorge Sanchez Redondo for his help with data collection.

71 Conflict of Interest: The authors have no conflict of interest.

72 Author's Contributions:

73 M.J.F.C: conception and design, acquisition of data, analysis and interpretation of  
74 data; drafting the article and revising it critically for important intellectual content; and  
75 final approval of the version to be published.

76 S.E.N: conception and design, acquisition of data, analysis and interpretation of  
77 data; drafting the article and revising it critically for important intellectual content; and  
78 final approval of the version to be published.

79 M.E.S: analysis and interpretation of data; revising the article critically for  
80 important intellectual content; and final approval of the version to be published.

81 L.J.D: acquisition and interpretation of data; revising the article critically for  
82 important intellectual content; and final approval of the version to be published.

83 M.T.P.P: acquisition and interpretation of data; revising the article critically for  
84 important intellectual content; and final approval of the version to be published.

85 B.V.S: analysis and interpretation of data; revising the article critically for  
86 important intellectual content; and final approval of the version to be published.

87 C.A.W: conception and design, analysis and interpretation of data; drafting the  
88 article and revising it critically for important intellectual content; and final approval of  
89 the version to be published.

90

91   **REFERENCES**

- 92       1. Abou Chakra CN, Pepin J, Sirad S, et al. Risk factors for recurrence,  
93            complications and mortality in *Clostridium difficile* infection: a systematic  
94            review. PLoS One 2014; 9:e98400. [PubMed: 24897375]
- 95       2. Dubberke ER, Butler AM, Reske KA, et al. Attributable outcomes of endemic  
96            *Clostridium difficile*- associated Disease in Nonsurgical Patients. Emerg Infect  
97            Dis 2008; 14:1031-1038. [PubMed: 18598621]
- 98       3. Kyne L, Merry C, O’Connell B, et al. Factors associated with prolonged  
99            symptoms and severe disease due to *Clostridium difficile*. Age Ageing  
100            1999;28:109-113. [PubMed: 10350405]
- 101       4. Rao K, Micic D, Chenoweth E, et al. Poor functional status as a risk factor for  
102            severe *Clostridium difficile* infection in hospitalized older adults. J Am Geriatr  
103            Soc 2013;61:1738-1742. [PubMed: 24083842]
- 104       5. Archbald-Pannone L, McMurry T, Guerrant RL, et al. Delirium and other clinical  
105            factors with *Clostridium difficile* infection that predict mortality in hospitalized  
106            patients. Am J Infect Control 2015; 43: 690–693. [PubMed: 4490980]
- 107       6. Leibovici-Weissman Y, Atamna A, Schlesinger A, et al. (2016) Risk factors for  
108            short- and long-term mortality in very old patients with *Clostridium difficile*  
109            infection: A retrospective study. Geriatr Gerontol Int, doi: 10.1111/ggi.12866.  
110            [PubMed: 27647625]

111

112

113 **Table 1.** Outcomes of cases and controls.

	<b>Cases n/total (%)</b>	<b>Controls n/total (%)</b>	<b>P</b>
Delirium during admission	30/106 (28)	15/106 (14)	0.028
Discharged alive within 7 days	29/106 (27)	81/106 (76)	<0.001
Decreased dwelling *	34/106 (32)	13/106 (12)	<0.001
Functional decline or death	41/106 (39)	15/105 (14)	<0.001
Mortality:			
In-hospital	12/106 (11)	2/106 (2)	0.013
30 days	14/106 (13)	6/106 (6)	NS
90 days	24/106 (23)	8/105 (8)	0.004
180 days	35/103 (34)	20/104 (19)	0.011
Readmission:			
30 days	28/104 (27)	19/106 (18)	NS
90 days	48/105 (46)	37/105 (35)	NS
180 days	64/103 (62)	53/105 (50)	NS

114 **Note:** \*Patients admitted from home and discharged to a NH or LTCF, or deceased.

115 **Table 2.** Analysis of factors associated with late mortality in CDI.

	Dementia			Delirium		
	Yes	No	p	Yes	No	p
<b>Functional decline or death</b>	14/21 (67%)	27/85 (32%)	0.003	17/30 (57%)	24/76 (32%)	0.017
<b>90-day Mortality</b>	9/21 (43%)	15/85 (18%)	0.013	7/30 (23%)	17/76 (22%)	NS
<b>180-day Mortality</b>	14/21 (67%)	21/85 (25%)	<0.001	11/30 (37%)	24/76 (32%)	NS

116