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

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Introduction:

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

Methods:

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

Results:

106 patients were diagnosed with CDI, mean age 76.3. Mean CCI was 5 and 2.3 and hospital onset CDI was 70.4% and 67.4% in VAMC and HUM, respectively. There was higher baseline functional debility in cases compared to controls (84% vs. 69%, p=0.014). Cases were more likely to be admitted from nursing home (NH) or longterm

care facility (LTCF) (22% vs. 8% of controls, p=0.006). Severity of CDI was significantly associated with age 80+ years and admission for CDI.

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

Discussion

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

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

The delayed effect on mortality by CDI following hospital discharge indicates that CDI may contribute to a decline in patient function and health over time, ultimately leading to death in many, an observation previously noted by others [2]. Unique to our study is the association of dementia with functional decline and mortality, suggesting the interaction of cognitive impairment and CDI impacts later outcomes. These observations highlight the importance of CDI sequelae long after acute disease, especially in older people with cognitive impairment. Non-independent baseline status was previously shown to be a risk factor for long-term mortality in very old patients with CDI [6]. In our study, high functional dependence - observed over 2 times as frequently in cases - did not predict short or long-term mortality.

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

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

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Author's Contributions:

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

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

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

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

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

	Cases n/total (%)	Controls n/total (%)	p
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 30 days 90 days 180 days	 12/106 (11) 14/106 (13) 24/106 (23) 35/103 (34)	 2/106 (2) 6/106 (6) 8/105 (8) 20/104 (19)	 0.013 NS 0.004 0.011
Readmission: 30 days 90 days 180 days	 28/104 (27) 48/105 (46) 64/103 (62)	 19/106 (18) 37/105 (35) 53/105 (50)	 NS NS NS

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

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

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

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