ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 14617
Title: The burden of Clostridium difficile infection between 2010 and 2013: trends and outcomes from an academic center in Eastern Europe
Reviewer's code: 02731212
Reviewer's country: United States
Science editor: Jing Yu
Date sent for review: 2014-10-18 11:46
Date reviewed: 2014-11-04 03:12

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	PubMed Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good		[ ] Duplicate publication	
[ ] Grade D: Fair	[ ] Grade C: A great deal of language polishing	[ ] Plagiarism	[ ] Rejection
[ ] Grade E: Poor		[Y] No	[ ] Minor revision
	[ ] Grade D: Rejected	BPG Search:	[Y] Major revision
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is a case-control study conducted from 2010-2013 among inpatients with community- or healthcare-acquired CDI who were admitted to a large, academic medical center in Budapest. The authors seek to evaluate the morbidity and mortality of patients with CDI as well as risk factors associated with CDI. They identified 247 cases of CDI and matched these 1:3 with control patients by age, sex, care period, and unit. They found that antibiotics and PPIs were associated with CDI, which confirms the results of previous studies. The epidemiology of CDI is important because CDI remains a major nosocomial infection in the western world and the epidemiology of CDI appears to be shifting more from healthcare- to community-acquired disease. However, there are important methodological questions that should be addressed in this study. Major: I would describe the study design as retrospective because it was conducted as a database review, however the authors describe it as a prospective in several places including the abstract. Unless case verification was done in real time (e.g., by going to the bedside to ascertain diarrhea) the study should be described as a retrospective study. The paper does not adequately distinguish between community-acquired

CDI and healthcare-acquired CDI, yet this is the major question in CDI epidemiology.   (Also, some risk factors such as unit type are only relevant for healthcare-acquired CDI since unit type could not possibly affect diagnoses that were already present at the time of admission.)   I suggest the authors stratify outcomes into community- and healthcare-acquired disease.   Alternatively, they may wish to exclude community-acquired disease since this is an inpatient study.   The Methods section should begin by clearly defining the outcome—including healthcare-acquired vs community-acquired CDI—and then the matching criteria.   For example, was age matched within the categories shown in Figure 2?   Or by quartile?   Then the Methods should clearly define all the exposure variables.   For example, what was the time window for antibiotics exposure?   Was this ascertained from admission notes only?   What if the patient could not give a history?   The Methods section should also state the criteria used to evaluate variables for the multivariable model.   Minor: Say "general medical inpatients" instead of 1st Department of Medicine.   Unless it conflicts with the journal's style, the p-values and ORs should be given with just 2 significant figures.   Table 1: Is this data skewed? Probably better to give the median and IQR rather than the mean and SD for continuous variables. Table 2: Include relevant definitions within the table.   For example, was PPI exposure any dose/duration of PPI?   Within one year?   Also, were these the only variables in the model?   The tables should describe the matching criteria and explicitly state which variables were in the model. Figure 1: List a p-value comparing the 2 survival curves.   Figure 2: Show the mortality of the control patients as a comparison, and the p-values for CDI cases vs controls within each age bracket.   Also: include a figure showing the flow of patients into the study.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 14617
Title: The burden of Clostridium difficile infection between 2010 and 2013: trends and outcomes from an academic center in Eastern Europe
Reviewer's code: 02458689
Reviewer's country: Germany
Science editor: Jing Yu
Date sent for review: 2014-10-18 11:46
Date reviewed: 2014-11-05 15:32

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	PubMed Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good		[ ] Duplicate publication	
[ ] Grade D: Fair	[ ] Grade C: A great deal of language polishing	[ ] Plagiarism	[ ] Rejection
[ ] Grade E: Poor		[Y] No	[ ] Minor revision
	[ ] Grade D: Rejected	BPG Search:	[Y] Major revision
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The authors present prospective data regarding incidence, risk factors, treatment and outcomes of Clostridium difficile infection. The paper covers an interesting topic and includes a considerable number of patients. However, I have some questions for these authors: Major points: 1. I have a question regarding the laboratory parameters given in table 1.: When were the samples taken? Are these mean values of all tests during hospitalization or during acute infection? 2. Methods: Please give more detailed information regarding your statistics: Six tests are mentioned, but it is not clear which test was used for which analysis. 3. Results: Risk factors for CDI and Table 2 In the text, you only give the results of the univariate analysis. What are the factors you adjusted for in the multivariate analysis in table 2?   Confidence interval of "Previous Clostridium difficile infection" is not reported in table 2. 4. Results, Outcome of CDI infection: In this section you describe duration of hospital stay, mortality and recurrence rates. Please address in a separate paragraph how many patients (with severe CDI) were admitted to emergency surgery, and what kind of surgery (ileostomy creation, colectomy, subtotal colectomy), and what was the outcome of these patients, because early

surgical intervention is critical in patients with severe CDI not responding to medical and ICU-treatment. Please also discuss these results. 5. Results, Outcome of CDI infection: As CDI was more severe in elderly patients (e.g. highest mortality rates) it is not clear to me why length of hospitalization was not different between age groups. These data should be shown or explained. Minor points: 1. Please check the manuscript for several mistakes in punctuation marks (e.g. Results, Treatment strategy, line 5: "vancomycin alone.)" and typographical mistakes. Maybe the manuscript should be corrected by a native English speaker. 2. Methods: Please describe your criteria for recovery after CDI. As Recovery after CDI is one of your three endpoints/outcomes, this should be addressed in your section "Outcome after CDI infection." 3. Results, Treatment strategy, line 4: SD for length of antibiotic treatment is not given. 4. Results, Treatment strategy, line 6: I don't understand what the authors mean with the sentence: "The length of the treatment was 13.6 days (SD: 5.9 days), and 12.6 days (SD: 7.1 days) in severe cases." Was this the length of treatment after change in the antibiotic therapy? 5. "CDI infection" in your manuscript is duplicate: The "I" already stands for "infection" 6. In the Results you say that mortality rate was 21.9%, but in the Discussion it is 20.2? What is correct?

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 14617
Title: The burden of Clostridium difficile infection between 2010 and 2013: trends and outcomes from an academic center in Eastern Europe
Reviewer's code: 02982286
Reviewer's country: Japan
Science editor: Jing Yu
Date sent for review: 2014-10-18 11:46
Date reviewed: 2014-10-23 10:10

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	PubMed Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language	[ ] The same title	[ ] High priority for
[Y] Grade C: Good	polishing	[ ] Duplicate publication	publication
[ ] Grade D: Fair	[Y] Grade C: A great deal of	[ ] Plagiarism	[ ] Rejection
[ ] Grade E: Poor	language polishing	[Y] No	[ ] Minor revision
	[ ] Grade D: Rejected	BPG Search:	[Y] Major revision
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is an epidemiological study regarding C. difficile infection in Eastern Europe where its incidence is unclear. The study data were mainly descriptive with some analysis, such as that of the risk factor associated with CDI. However, the risk factors noted in the study were already examined in multiple studies of CDI, and the paper noted no major new findings. However, the incidence data could be important if the global burden of CDI were considered.   Major/minor concerns are noted below. The manuscript requires major modifications to strengthen it.   1. Overall major comment   The manuscript requires editing by a native English speaker or editing service since there are many typographical and grammatical errors in the abstract.   The focus of the study is a current descriptive epidemiology of CDI and the risk factors associated with developing CDI in Eastern Europe. Since the burden of CDI in Eastern Europe is not well known, the findings in the study will heighten awareness of this issue. Although the data were prospectively obtained, because this is a single-center study, it may not represent the current state of CDI epidemiology in Eastern Europe. I felt that the discussion section of the manuscript could be more tightly written, especially the

paragraph regarding risk factors associated with CDI, given the lack of novel findings in this study. 2. Specific comments.   Methods: Page 4, first paragraph   The authors defined CDI as 'acute diarrheal disease' (more than three liquid stools per day based on reference 19. Do you have any data regarding the Bristol stool chart? Since 'liquid stool' is very subjective, objective parameters for liquid stool should be noted.   Page 4, first paragraph The authors stated that, "In our department we apply standardized medical protocols."   What does 'standardized medical protocol' mean?   Page 5 method section How did the authors track mortality information? The authors should describe this in the methods section.   Results: Page 5, paragraph 1 (incidence of CDI and severe CDI section)   The author stated that the "Community acquired infection rate was 45.3%." How do you define community-acquired CDI in this study? This is extremely important as the denominator in information for hospital onset CDI and community onset CDI is different and these incidence densities should be separately reported to help understand CDI epidemiology better. The definition of community-acquired CDI should be included in the methods section. The definition of the onset of CDI is available in the current US and European CDI guidelines.   Page 5,   Do you have the data for testing densities? Since the incidence is correlated with the frequency of testing in the previous European study (Bauer MP et al. Lancet 2011), the testing density (number of tested /10000 patient-days) is needed when evaluating CDI incidence.   Page 5 The authors should provide information regarding "time to CDI" for patients with hospital onset CDI.   Page 5 Regarding severe CDI, the author stated: "The incidence of severe CDI was 12.6% (2.63/1000 of all cause hospitalizations). In severe CDI patients were older (severe: 84.2% vs all: 69.6% of patients were >65 years, p<0.001) and duration of hospitalization was longer (18.4 (SD 11.7) vs 17.3 (SD 10.3) inpatient days, p<0.001). "   It is unclear which population(s) were compared with those with severe CDI (the control population?   Or non-severe CDI patients?). The author should clarify this.   If the authors compared severe CDI patients with non-severe CDI patients, they should explain what the difference in length of hospital stay was after diagnosis of CDI in each group.   Discussion   Page 8   Why was the incidence density of CDI in this institution extraordinarily high among European countries? The data in the manuscript reflected much higher values than even the data from Poland. Is this biologically plausible? The autho