November 22, 2011

Author's Response to Decision Letter for Manuscript ID JHM-11-0216

Dear Editor:

Thank you for your comments and suggestions as well as the comments made by the reviewers. We have reviewed each comment and addressed the concerns and suggestions offered. Below you will find detailed responses to each individual reviewer's comments. We are excited about the potential to have this manuscript published in the *Journal of Hospital Medicine* and welcome any further suggestions and/or comments. We look forward to your decision on the resubmission of our manuscript.

Best regards,

Ciarán P. Kelly, MD

Reviewing: 1

The authors have written a clear and brief review about the management of C. difficile infections. A case approach based presentation is interesting. Although it is a well-written paper it doesn't have significant differences when compared to recent reviews about this item (except the part about the use of fidaxomicin). Some additions can make this paper more interesting:

Repeat stool sample with EIA? Is it really necessary? Please see Deshpande A, et al. Potential value of repeat stool testing for Clostridium difficile stool toxin using enzyme immunoassay? Curr Med Res Opin. 2010;26(11):2635-41.

Thank you for your suggestions.

Yes, you and Dr. Deshpande are correct that a repeat test for *Clostridium difficile* toxin with enzyme immunoassay has little or no value. We amended our manuscript to clarify our recommendation in the following way:

"Therefore, because EIA is most often used in clinical practice, it is important to be aware that a high clinical suspicion for CDI may warrant empiric therapy or repeat testing with a more sensitive test in a patient with an initial negative test result."[3,21]

Any comments for duration of therapy?

Duration of treatment for initial CDI based on clinical severity is listed in Table 4.

Are there any differences for the duration of therapy in the first attack and recurrent episodes?

We did not address duration of treatment of recurrent *C. difficile* infection (CDI) because the focus of this paper is the treatment of an initial CDI. An accompanying paper on recurrent CDI is intended to be published in the same supplement as this paper.

Can C. difficile be resistant to metronidazole?

The decreased response of CDI to metronidazole is not believed to be attributable to vegetative *C. difficile* cell resistance, but rather to the pharmacokinetics of the drug as well as a variety of host factors such as immune status and underlying disease.

What about the role of nitazoxanide or probiotics in the treatment of CDI?

We did not include probiotics in our discussion of treatments for CDI, in part because current guidelines do not support their use.

*"*There is no compelling evidence that other probiotics are useful in the prevention or treatment of recurrent CDI." —Cohen SH et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431-455.

Similarly, we did not include nitazoxanide in our discussion because it has not shown significant clinical benefits over current conventional therapy. In one open-label, prospective, compassionate-use study, 75% of patients with CDI experienced a cure, but a third went on to relapse. (Aslam S et al. Treatment of *Clostridium difficile*-associated disease: old therapies and new strategies. *Lancet Infect Dis*. 2005;5(9):549-557.) In a more recent double-blind comparative study of nitazoxanide vs vancomycin treatment of CDI, nitazoxanide cure was noninferior to vancomycin, but sustained response with nitazoxanide was less than with vancomycin. (Musher DM et al. Nitazoxanide versus vancomycin in *Clostridium difficile* infection: a randomized, double-blind study. *Clin Infect Dis*. 2009;48(4):e41-e46.)

Do we need to perform control stool cultures or EIA before stopping the therapy?

No. This has been clarified in the amended manuscript, under "Principles of Diagnosis."

Any suggestions for infection control both in public and hospital?

A discussion of infection control policies is beyond the scope of our current paper. However, it is discussed in an accompanying paper intended to be published in the same supplement as this paper.

Reviewing: 2

General: The manuscript seeks to provide a contemporary overview of the initial recognition and management of patients with Clostridium difficile infection utilizing a case-based scenario. As the manuscript is a review, it is not particularly innovative. However, is easy to follow and relatively complete given word count limitations. Specific comments to be addressed by the author are as follows.

Thank you for your comments.

1. Risk factors for CDI
Pg 3, Line 18. While 1-4% of healthy adults are carriers, colonization in hospital environments or recent health care exposure may be much higher (10-40% depending on the study) . The author might consider revising this sentence to differentiate colonization rates from the commonality of CDI in the health care environment. This would also help clarify comments in Principles of Diagnosis section where author states that colonization rates are high.

We agree with your suggestion and for the sake of clarity revised the sentence about colonization in the following way:

"While colonization of *C. difficile* occurs in the community in only 1% to 4% of healthy adults, the rate of colonization in hospitalized adults is much higher, approximately 20% to 30%."[4]

2. Pg 3, Line 41. The epidemiology of CDI has changed in recent years from primarily a hospital acquired infection to a health care associated infection for a variety of reasons. Several large epidemiologic studies have identified rates of community onset (CO) and/ or health care associated community onset(CO-HCFA) 20-50% of cases. While this topic is partially addressed in the manuscript a stronger case for early triage and evaluation of new admissions and or outpatients would be beneficial.

Space and scope of this paper limit our ability to expand on the topic of early triage and evaluation of outpatients or new admissions. However, we did reinforce the concern you raised by amending the sentence in question:

"Healthcare professionals should consider CDI in patients who present with diarrhea and have a history of recent antimicrobial treatment in a hospital or as an outpatient."

3. Pg 4, Line 21. It may be informative to add a sentence that explains that patients who become colonized with a new strain are at increased risk for CDI, space permitting.

Symptomless carriers of toxinogenic *C. difficile* are generally considered to be protected against CDI. To our knowledge there are no data to indicate that their exposure to "a new strain" of *C. difficile* results in disease. Similarly, recurrent CDI may result from either the old or a new strain.

4. Pg 6, Line 28 " and confirmatory testing should be performed.

In response to your concern, we have edited the sentence you questioned under "Principles of Diagnosis." It now reads:

"Confirmatory testing should be performed, but only on watery or loose stools because the rate of symptomless colonization with C. difficile in hospitalized patients is high; a positive result on a normal stool sample proves only that the patient is colonized with C. difficile but not necessarily infected."[14]

5. Pg 7, Lines 15-20. CDI IDSA/SHEA guidelines recommend not doing repeat testing. This is huge problem for labs everywhere (although I concede that some ELISA assays have poor sensitivity)..Please clarify the discrepancy between the Guideline recommendation and that in the text. Consider adding description of two-stage approach the glutamate dehydrogenase + cytotoxin/culture assay.

We did not include a discussion of the two-stage approach to glutamate dehydrogenase (GDH) + cytotoxin/culture assay, in part because current guidelines call for more data on the sensitivity of GDH before they recommend this diagnostic approach.

6. Pg 7, Lines 33-34. While not yet widely applied, several studies have reported good predictive performance for severity indices that can aid in determining severity of illness. Severity indices aid in triage and description/reference may be beneficial.

A number of severity score indices have been proposed in the literature in the past few years, but to date none have been validated. We agree that a validated clinical prediction tool for severe CDI would be very welcome and useful.

7. Pg. 8-9. Fidaxomicin section. Further description of this agent should include mention that there was no difference in relapse rates for non-BINAP1 strains, which varies widely geographically. Also, it may be worthwhile to note the post hoc paper identifying a significant difference in outcome for patients with continued antibiotic therapy. (90.0 vs 79.4%) in favor of fidaxomicin. Finally, it is imperative to mention the disparity in cost (>$3,000 / course). While this agent is a welcome addition the cost-benefit analysis of this agent in select populations will take some time……

We complied with your recommendation and inserted a fifth table, which lists outcomes in one of the phase III trials of fidaxomicin versus vancomycin, including the subset analyses you suggested. We also included a sentence on the acquisition cost of fidaxomicin:

"While acquisition costs for this new antibiotic are a consideration, they may be offset by a reduction in recurrent CDI especially in high risk patients."

8. Finally, re-enforcement of infection control practices (soap and water as opposed to the eternal use of alcohol disinfectants), contact precautions, etc should be considered (space permitting).

A discussion of infection control policies is beyond the scope of our current paper. However, it is discussed in an accompanying paper intended to be published in the same supplement as this paper.

Reviewing: 3

This is an extremely important and timely topic, and you do a very good job of educating clinicians in the management of C. diff. However, I have a few content and formatting suggestions that may increase the article's impact.

Purpose: The introduction paragraph should describe the problem in more detail, perhaps with inclusion of current epidemiological trends that illustrate the burden of disease. Additionally, I suggest specifically stating the purpose of the article. Are you aiming to inform clinicians on the management of C. diff?

We followed your suggestion and amended the abstract and introduction to clarify the purpose and context of our paper.

Content
Case Study: Adding the case study adds interest to the topic and keeps the reader's interest. I very much like it, although, it is awkwardly inserted in the text. It might have more impact if it is presented in its entirety at the end of the article as a synthesis of evidence in practice. A concluding remark may be helpful also, commenting directly on whether the management was correct.

Message: It may help to inform members of the public health community reading this article if you succinctly emphasized prevention measures in long-term care facilities / hospitals. What can providers do to prevent outbreaks in the ICU or nursing homes? In my opinion, it would also be beneficial to briefly mention non-theraputic disease management (i.e. isolation).

On the advice of the Editor of *Journal of Hospital Medicine*, we are keeping the case study inserted throughout the text.

3. Citation: I suggest using some additional references to replace citations 1 and 2 in some instances. There was some over-reliance on these sources.

We have replaced a number of citations in our manuscript to the reviews, Kelly CP, *JAMA,* 2009;301(9):954-962, and Riddle DJ et al, *Infect Dis Clin North Am,* 2009;23(3):727-743, with citations to the original studies where appropriate.

I look forward to seeing your article in print, as I know it will help to inform the health community on a timely topic.

Thank you.

Reviewing: 4

Clostridium difficile colitis is a timely subject because of the frequency with which this problem is encountered in the hospital setting. However, this manuscript is basically a reiteration of previously published information on this subject in many current peer-reviewed journals. Specifically, reference #2 which is cited in this manuscript is one of this author's previous articles on C. difficile. The only difference is a brief discussion on fidaxomicin in the last paragraph on page 8 and the beginning 2 paragraphs on page 9. While fidaxomicin may be a new antimicrobial for C. difficile infection, the author did not discuss as to what circumstances should this drug may be more appropriately used instead of the standard and equally effective drug vancomycin. Considering the high cost of fidaxomicin (most recent average wholesale price is $168.00 /tablet or $3360 for a 10 day course) and given the current economic environment, the cost issue of this drug should be discussed in this paper.

We addressed your concerns about the section on fidaxomicin with the following sentences:

"In a phase III trial (N = 596) of fidaxomicin (200 mg orally every 12 hours) versus vancomycin (125 mg orally every 6 hours) for 10 days, fidaxomicin was shown to be noninferior to vancomycin in achieving an initial clinical response and significantly better at preventing recurrent CDI."[32]

The following sentence was added to the end of that paragraph:

"While acquisition costs for this new antibiotic are a consideration, they may be offset by a reduction in recurrent CDI especially in high risk patients."

I also have concerns about the scientific quality and accuracy of the referenced citations in this manuscript. There was an extensive citation of reference #2 in this submitted manuscript (pages 2-5, 7-10) which is the author's own paper in JAMA published as proceedings of a conference which took place at the Medicine Grand Rounds at Beth Israel Deaconess on November 15, 2007. An example of my concern is the statement on Page 3 Line 19 "This is because the normal colonic microflora limit C. difficile colonization and proliferation". This statement cited reference#2 where a similar statement was made on p.955 JAMA 2009 in sentence #2 last paragraph and which in turn cited "Bartlett JG. Antibiotic-associated diarrhea. N Engl J Med. 2002;346(5):334-339" as the reference. I read Dr. Bartlett's paper but I did not see any discussion on this issue nor was there a study cited in Dr. Bartlett's article to support the above statement. An article, preferably a study that supports this statement would be most helpful to the reader.

Another example is Page 9 Line 55 to 57 to Page 10 Line 3 "Normal pooled IV immunoglobulin has been used in patients with fulminant and/or refractory CDI in an attempt to avert surgery or death by providing passive immunotherapy against C. difficile toxins A and B." Again, there are many other current substantial references other than reference#2 which can be cited to support this statement.

We have replaced a number of citations in our manuscript to the review, Kelly CP, *JAMA,* 2009;301(9):954-962, with citations to the original studies where appropriate. Furthermore, we have checked all the citations in our manuscript and made the necessary changes to ensure the accuracy of the text and wherever appropriate to cite the original studies.

Review Editor

General comments:
Nicely written. Although the reviewers are critical of the lack of new information, the goal of this review is to concisely summarize existing literature for the Hospitalist audience, and this was done effectively. Revisiting the case periodically throughout the manuscript is effective and can stay as is. As mentioned by one of the reviewers, please ensure that there is no self-plagiarism, and that the references are accurately selected.

Thank you for your words of encouragement. As noted above, we have checked every reference for accuracy, and replaced citations to reviews, including the Kelly CP, *JAMA* 2009 review, with citations of the original studies where appropriate.

Specific comments and questions that arise in clinical practice:
1) Page 3, last paragraph: what is "colonization resistance"?

We have included the following definition of colonization resistance:

"However, balanced intestinal microflora normally confer colonization resistance, a host factor that limits the proliferation of pathogenic microorganisms such as C. difficile."[3]

2) What about proton pump inhibitor therapy as a risk factor for recurrent CDI?

Whether or not treatment with a proton pump inhibitor is a risk factor for CDI remains controversial. The potential mechanisms for increased risk include survival of the vegetative form of *C. difficile* as they pass through the stomach and/or an effect of proton pump inhibition on the intestinal microflora and hence colonization resistance.

3) In terms of treatment duration, should we "start the clock" when other antibiotic courses have been completed or from when the anti-CDI agent is initiated?

In a discussion of anti-CDI treatments, the time of treatment duration typically starts

when the anti-CDI treatment is initiated, not the time when other prior courses of antibiotic therapy have been completed.

4) A source of continued confusion among providers is whether repeat assays are needed; it might be worth discussing this rather than suggesting in the text that repeat tests should be considered without delving into more detail. Our laboratory, for instance, does PCR assays for the toxin B gene as a single testing modality; repeating within 7 days is not permitted due to high sensitivity of the assay (unless there was a new exposure suspected). Stool culture cannot be ordered without special permission. There is no testing for toxin A since there are no pathogenic strains known that make toxin A but not toxin B. Other laboratories may use different protocols.

You are fortunate to have access to the PCR assay for CDI toxins, which are more reliable than EIA assays, and thus would not typically require a repeat assay with a stool culture. Our recommendation for a repeat assay was following a negative EIA result, especially when clinical symptoms suggest otherwise. We hope our recommendation to repeat an assay has been clarified with this sentence:

"Therefore, because EIA is most often used in clinical practice, it is important to be aware that a high clinical suspicion for CDI may warrant empiric therapy or repeat testing with a more sensitive test in a patient with an initial negative test result."[3]

5) Some clinicians think that Hemoccult testing can help to determine whether there is active colitis. Do you know of any data to support or refute this?

Testing for occult blood in the stool is not useful to diagnose CDI as *C. difficile* is not invasive and bloody diarrhea is unusual in this infection.