**Paper #23770 (WJG)**

**Reviewer #68404**

This manuscript was conducted to compare AAD and CDI in pediatric and adult populations and determine significant differences and similarities that might impact clinical decisions. This is a carefully done systematic review, the topic is of considerable interest and has a good clinical significance, which can guide clinical work. The reference of this study is relatively sufficient and reasonable. The language of this article is relatively smooth and has readability. On the whole, this is a good article which deserves publication.

*Thank you for your kind remarks.*

**Reviewer #159305**

To the authors, Good piece of work, well written. I have no concern about your manuscript. P.S. However, I have one concern: the core-tip is lacking! (please, write it) In addition, please see page 4 line 8: to pediatric…, and page 19, last paragraph line 2: delete one increased!

*The core tip was included in the submission, but we will submit it again. Thank you for catching the two errors, these have been corrected.*

**Reviewer #504462**

I read your manuscript with great interest and your review has been a good effort to go through the bibliography and analyze it. However, your effort is lacking in some points that need some clarification: a) Your pediatric age group definition is a bit confusing as you wrote that "generally, the pediatric population is defined as aged one month to 18 years of age, but for pediatric CDI this age range has been shifted to 1-21 years old". However, you did not then proceed to state which age range you used for the rest of the analysis. It is a reality that there are many changes from birth through childhood and the adolescent years, and many authors divide the pediatric group into neonates (under 1 month in age), then for children from 1 month to 4 years, children 4 years to 10 years, and finally adolescence. (Your only reference is that "infants younger than one year old are typically excluded".)

*This has been clarified as suggested. We are reporting what is found in the literature, and we found there is a variation in the definitions used in different studies. However, we have clarified this as to what we used in the review. For AAD, pediatric ages include 4 months to 21 years old. For CDI, pediatric age range should start at 1 year old (excluding neonates). Although we agree that a more precise age stratification may be interesting (to reflect changes in intestinal flora), the few studies in the literature that have used age strata, typically only report incidence of CDI and not other characteristics by age strata. We have included this in the text and have clarified this age definition for AAD and CDI in the DEFINITIONS section. Thank you for this observation.*

b) If I understood correctly you are arguing that cdi is different from aad, but the articles you cite do not support this directly because the cited studies show that a risk factor for cdi is the use of antibiotics. Can you clarify this argument and look for more appropriate supporting studies?

*This review's goal was to describe both similarities and differences of AAD and CDI for pediatric and adult populations. There are many similar findings for pediatric and adults, namely that for CDI and AAD, both pediatric and adults share the major risk factor (exposure to antibiotics). But then, we go on to explore other ways that pediatric and adult disease differs. Please see Table 2 which shows more exposures in hospitals and a wider range of co-morbidities in adults.*

c) From the lack of good definitions, some of your data and conclusions are confusing.

*I hope that the clarification of the definitions clarifies this confusion. Also, we discuss differences in the risk factors of pediatric and adult CDI and AAD at the end of the epidemiology sections.*

d) The manuscript is also too long, maybe because of the precedent aspects, and I could suggest, maybe that you could rewrite it, and break it into 2 manuscripts. Alternatively, try to focus your definitions and objectives. Hope you can fix it and resubmit it soon.

*We agree, that this is a longer paper than a typical review. However, this is the first global synthesis of all the literature of pediatric and adult AAD/CDI studies and we felt that we needed to include all the data that was presented for a comprehensive analysis. Other reviewers have appreciated the comprehensive (albeit longer) text of the paper. We did eliminate some areas (methods of diagnosis, etc.) before the original submission was done, as we realized this is a long paper. We feel that by separating the paper into two publications, we would lose the message and convenience of having all the data in one paper. In addition, the online format of this journal supports longer papers, which we appreciate.*

**Reviewer #33739**

Dear authors: Thank you for allowing me to review your manuscript entitled “A Comparison of pediatric and adult antibiotic-associated diarrhea and Clostridium difficile infections.” I found your review article very well written covering several important topics including antibiotic-associated diarrhea in both children and adults as well as C. difficile infection in the pediatric and adult population. Your presentation was balanced and provided one of the more comprehensive groupings of data for these topics that I have seen to date. I felt that you should be commended for writing on important topics and covering all relevant sub-topics associated with these disease states. Including the pediatric population side by side with the adults differentiates your manuscript as unique and exposes a shortage of data in the pediatric

population for CDI and a true shortage of publications for antibiotic-associated diarrhea in both populations. I only had a couple of conceptual questions for you to consider and several minor changes to the document listed below.

*Thank you for your kind remarks.*

Major: 1. Adult CDI Severity: Consider adding information regarding white blood cell count, creatinine and albumin as commonly used indicators of disease severity for this population. These criteria should be initially described as a way of triaging disease severity (Cohen et al. 2010 and Surawicz et al. 2013). Once that has been described, then consider contextualizing that information into the discussion that already exists regarding how the various studies rated the disease severity so the reader has a better idea of how each study classified their patients.

*We have added a more precise definition of severity into the pediatric CDI section as suggested. While a more detailed presentation of severity for each paper may be of interest, we believe the length of this review precludes a detailed investigation into how 'severe' CDI should be defined. We do point out that regardless of how severity of CDI is defined, severe CDI is less frequent in the pediatric population. This is an ongoing focus of CDI research and remains under debate.*

Major 2. Table 4: The crude mortality and colectomy rates are a bit confusing since no time frame is provided for these. Are these all 30-day rates? If so, please label. If not, please consider adding the time frame for the rates for each of these studies to allow the reader a better understanding of the data presented.

*Thank you for this suggestion, the rates did vary by follow-up period by study and this was added to the text (not Table 4) under CDI consequences for both pediatric and adult CD and providing follow-up times for pediatric and adult mortality rates. Interesting, an increase in observation times did not correlate with a trend for increasing or decreasing mortality rates. Differences in observation times for colectomies rated to lengths of stay in the hospital, but no trends for changes in surgery rates were found by observation times. Surgery rates tended to lower for pediatric CDI compared to adults, but the numbers of studies were limited.*

Minor:

Introduction

1. Page 4, Paragraph 1, Line 8: Please add a space between “to” and “pediatric.”

*Revised as suggested.*

Epidemiology:

2. Pediatric CDI outbreaks: Page 10, Paragraph 2, Line 5: The sentence that starts with "While most studies…" reads strangely. Consider adding the word "in" between "While" and "most."

*Revised as suggested.*

3. Adult CDI outbreaks: Page 10, Paragraph 3, Line 4: Please consider changing the sentence to read "the 1980s, with as few as…"

*Revised as suggested.*

4. Page 18, Paragraph 2, Line 5: The sentence that starts with "Most AAD cases are mild-moderate…" reads strangely. Consider removing "AAD cases" at the end of the sentence and pluralizing the word adult.

*Revised as suggested.*

Consequences of Infection:

5. Page 19, Adult CDI Consequences, Paragraph 1, Line 2: The word increased is duplicated. Please consider removing one.

*Revised as suggested.*

6. Page 39, Table 4, Cost, Pediatric CDI: Please consider adding a hyphen between the two dollar sums.

*I think the data lines up better now.*

Treatment:

7. Page 24, Treatment of pediatric CDI, Line 7: Consider removing the word "cases" to improve the flow of the sentence.

*Revised.*

**Reviewer #2731212**

This review article compares pediatric and adult AAD, and also compares pediatric and adult CDI. This seems like a worthwhile comparison to make because (1) it has been suggested that these entities differ substantially in adults and children, and (2) gastroenterologists who practice at small hospitals may be called upon to serve both children and adults. Of course, it is challenging to make sensible comparisons across studies involving different populations (how, for example, can we draw conclusions by examining a study that tests the effectiveness of flagyl

vs vancomycin for CDI in adults and then another similar study in children?). However, the authors take a sober approach and, for the most part, the manuscript is successful.

MAJOR COMMENTS: 1. AAD is a diagnosis of exclusion and patients with AAD are heterogeneous: some have undiagnosed gastrointestinal infections, and others have non-infectious diarrhea which may be related to the loss of normal commensal bacteria. This is especially true for older studies of AAD, where the only testing may have been stool cultures. Because it is so hard to say much about AAD, I did not find these sections helpful. Why not focus exclusively on CDI, where the patients are more homogeneous?

*As CDI is part of the spectrum of AAD, we felt it useful to present what is known about both CDI and AAD to highlight where further research is needed. Also, it is interesting to see where CDI and non-C. difficile AAD differs.*

2. A style point. The frequent section breaks make the manuscript very choppy to read. Could the authors combine some of these sections?

*We will defer to the journal editors on this point, but we felt that the section breaks help to keep track of what's being presented.*

3. One of the interesting things about this comparison is that it may help to shed light on pathophysiological differences between children and adults for AAD/CDI. The authors touch on this (p. 15) but there is no section explicitly focused on pathophysiology.

*We have presented what we found from clinical studies on pediatric and adult AAD and CDI, but to cover the age-related differences in basic pathology and mechanisms-of-action is beyond the scope of this review. Unfortunately, we had to focus on more clinical data and less on basic pathology. Perhaps another paper? Thank you for this suggestion.*

MINOR: p. 4: “The burden and costs…” Actually, there are some studies and the authors cite some of them on page 8.

*This should have read pediatric AAD and was revised.*

p. 5, Definitions: I don’t find this helpful and would incorporate the definitions into the manuscript. I don’t think that “time to onset” requires such a long definition.

*As one reason why rates vary is due to differences in how things are defined, the definition section was added in the beginning to clarify the variability in the literature. It reads more as a methods section. Time of onset includes several factors and these are often not provided in studies. Every effort was made to be concise.*

p. 8: “Rates may also range…” This sentence is confusing. Rephrase.

*Revised.*

p. 11, Risk Factors: Modifiable risk factors are the most interesting and also the most useful. Can the authors be more specific than “broad spectrum” antibiotics?

*Revised.*

p. 11-13, CDI Risk Factors: What about acid suppression medications? These are a potentially modifiable risk factor and have been studied extensively in adults and studied at least somewhat in children.

*Added some text on PPI to the text and referred readers to Table 2.*

p. 14: “Adults with CDI have a more complex risk factor profile.” I think the authors mean that adults with CDI tend to have more comorbidities than children with CDI. But don’t adults always have more comorbidities than children?

*Co-morbidity is not necessarily a given as we age. Surprisingly, there do exist a proportion of adults with little co-morbidities, although as researchers, we tend to neglect this healthy population from our studies. C. difficile tends to take advantage of the predisposition due to co-morbidities and more hospitalizations in the older populations. However, there are pediatric populations with co-morbidities (cancer, chronic immune problems, etc.), but they do not appear to be of more risk of CDI than other children.*

p. 25, higher doses of vancomycin: Can the authors cite specific evidence supporting high dose vancomycin? My impression is that there is little evidence that doses higher than 125 mg qid result in substantial benefit. The authors make a similar statement elsewhere in the manuscript.

*This is cited in Surawicz (2000) and McFarland (2002) papers and has been added to the text.*

p. 24-26, CDI treatment: The authors breeze past FMT, which has strong evidence vs recurrence in adults. What about children?

*There have been only two phase 3 randomized trials for adults with CDI (presented in Table 5). We could find no randomized clinical trials using FMT in children.*

Tables. These contain useful information but are almost impossible to read—one can’t easily tell which piece of information goes with which reference. I would restructure these.

*We will defer to the journal editors, as the final formatting of the Tables are often clearer than in the original text.*

*We wish to sincerely thank the reviewers for their insightful and thoughtful review of our paper.*