Reviewer's report

Title: Antibiotic susceptibility of Clostridium difficile is unchanged despite widespread use of broad spectrum antibiotics

Version: 1 Date: 13 May 2014

Reviewer: Nitish Khanna

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Discretionary Revisions
1. General: Terminology has been changed from CDAD to Clostridium difficile infection (CDI)
2. Line 68: Introduction: "CDADs" = Colloquial - suggest changing to CDAD cases (or CDI cases)
3. Line 69: As above
4. Table 2: It would also be more informative to illustrate how many patients received combination of antibiotics, as well as DDD data
5. Line 187 - some evidence that antifungals may predispose to CDI. Worth commenting on, and even informing reader what antifungals were used?
6. Line 212 – “In the 1980s....” - Can this be referenced?
7. Line 269 – remove “lucky”

Minor Essential Revisions
1. Line 78: introduction: Colloquial - "Strong" microbial activity? Classification of antibiotic activity into strong and weak is too simplistic. Recommend altering this.
2. Line 166: Do you have lab records to prove that stool samples were diarrhoeal when tested for C.diff toxin? Testing of non-diarrhoeal samples will confound results.
3. Table 2: spelling mistakes in Suppl Table 2 - eg ceftazidime/metronidazole/glycopeptide
4. Suppl table 2: Anti-mykotic should be antifungal
5. Line 187 – Antifungal instead of anti-mycotic
6. Line 196 – metronidazol spelling
7. Line 199 – “Strains were in>90%....” – Does not make sense
8. Line 202 – “where” should be “were”
9. Line 233 – spelling of cephalosporins

10. Line 238 The patients suffering from CDADs – colloquial

11. Line 248 – remove additional words “reviewed in”

12. Line 258 -The OR 95% CI for Vanc and Septrin crossed the 1 point suggesting that the effect may not be stat significant?

13. Line 265 - Not all penicillins have activity versus C.difficile? What about Pen V/Amoxicillin?

Major Compulsory Revisions

1. Table 2: It would have been better to list certain individual antibiotics as opposed to classes as eg: Augmentin is more likely to pre-dispose to CDI than Amox.

   Also antibiotics in preceding 3 months have been shown to be able to pre-dispose patients to CDI, even a single prophylactic agent - Do you have antibiotic history for each patient that goes back 3 months before index toxin positive? If not, this needs to be acknowledged.

2. Table 2: It would also be more informative to illustrate how many patients received antibiotic monotherapy, combination of antibiotics, as well as DDD data

3. Line 189 – As above, It would be useful to the reader to give more information on what penicillins were used as each have different propensity to induce CDI.

4. Materials and Methods: Any exclusion criteria? Are these index cases only with no patients with recurrent disease? Although this may not have an impact on MICs, it is important to state whether these are recurrent CDI cases or not.

5. Line 171-173 and materials and methods: In these 17 patients, culture positive, cytotoxin neg, but PCR positive - PCR detects presence of gene and not direct toxin production, so are you inferring that presence of toxin gene in patient with diarrhoea and c.difficile positive culture has CDI? As far as I'm aware Cytotoxin assay is still gold standard, so a negative Cytotoxin assay is concerning. Would it have been better to do toxin PCR first, followed by cytotoxin assay to confirm? Can you suggest reasons as to why the cytotoxin assay was negative?

6. There should be a Limitations paragraph as part of the discussion.

7. Line 313-314 - The fact that cephalosporins and carbapenems are high risk for causing CDI is not new - This has been reviewed in other papers - most recently: Slimings and Riley, J Antimicrob Chemother
doi:10.1093/jac/dkt477, Dec 2013 - This paper provides a systematic review and meta-analysis of antibiotics as risk factors for CDI
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I have received funding for research and fees for public speaking from AstraZeneca