

**South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Alimentary conditions**

EVIDENCE REVIEW:

1. Executive Summary

Date: 5 April 2018
Indication (ICD10 code): Enterocolitis due to Clostridium difficile (A04.7)
Medicine (INN): Antibacterials for systemic use
Medicine (ATC): J01
Patient population: Adults
Level of Care: Secondary level
Prescriber Level: Doctors
Current standard of Care: Metronidazole oral and vancomycin parenteral used orally. No clear delineation in terms of severity of disease.
Efficacy estimates: (preferably NNT): n/a
Motivator/reviewer name(s): Dr R Coetzee, Prof L Bamford
PTC affiliation: Dr R Coetzee: Western Cape Provincial PTC

2. Name of author(s)/motivator(s)

Primary reviewers: Dr R Coetzee, assisted by Ms TD Leong (AGREE assessment of guidelines)

Secondary reviewer: Prof L Bamford

3. Author affiliation and conflict of interest details

Dr R Coetzee: Western Cape Provincial Pharmacy and Therapeutics Committee, Adult Hospital Level Committee (2017-2020); no conflicts of interest declared.

Ms TD Leong: National Department of Health, Essential Drugs Programme; Secretariat to the Adult Hospital Level Committee (2017-2020); no conflicts of interest declared.

Prof L Bamford: NEMLC Committee member; no conflicts of interest declared.

4. Introduction/Background

Unlike most (international) guidelines, the current guidelines do not delineate treatment by severity of infection. In a 2016 article reviewing five international societies' *Clostridium difficile* infection (CDI) management recommendations, all guidelines differentiated treatment by mild-moderate disease and severe disease.¹ Although the change in differentiating disease severity does not form part of this review, it should be noted that it does inform the decision of the ultimate purpose of this review. Therefore, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) will be adopted, as it also includes a list of clinical and laboratory markers in the presence of which severe CDI may be established, such as older age, serious comorbidity, immunodeficiency and ICU admission (full definition below).²

ESCMID definition of severe *Clostridium difficile* infection (CDI) ²

"Severe CDI is defined as an episode of CDI with (one or more specific signs and symptoms of) severe colitis or a complicated course of disease, with significant systemic toxin effects and shock, resulting in need for ICU admission, colectomy or death. Clostridium difficile infection without signs of severe colitis in patients with greater age (≥65 years), serious comorbidity, Intensive Care Unit (ICU) admission, or immunodeficiency may also be considered at increased risk of severe CDI."

The inclusion of immunodeficiency is especially important in the South African population as patients may not be able to mount an immune response against the *C. difficile* toxins, leading to poor outcomes.

5. Scope of Review

Establish the current best evidence for the management of severe *Clostridium difficile* infection in adults.

- P** Adults with active, symptomatic *Clostridium difficile* infection (based on ESCMID definition)
- I** Treatment with antibiotics
- C** Standard of care: empiric metronidazole, followed by vancomycin, oral in non-responders
- O** Resolution of infection /mortality reduction

6. Method

Review the current literature on the management of CDI. Literature search focussed on systematic reviews and clinical practice guidelines.

A search was performed in the following databases: MEDLINE (2000 to 2018), the Cochrane Database of Systematic Reviews (2000 to 2018), TRIP Database (unrestricted) and Google Scholar (unrestricted). Only English language publications of systematic reviews or meta-analyses comparing antibiotics were selected. Keywords for the search included, but not limited to diarrhoea, *Clostridium difficile* infection, treatment, recurrence (MeSH terms). Abstracts for presentations at conferences were excluded.

An analysis of the clinical practice guideline for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), 2017 (see appendix A).

7. Evidence Synthesis

Recently, a 2017 Cochrane review found vancomycin to be more effective than metronidazole for achieving symptomatic cure in **all disease types**; 72% (318/444) of metronidazole patients achieved symptomatic cure compared to 79% (339/428) of vancomycin patients (RR 0.90, 95% CI 0.84 to 0.97; moderate quality evidence).³

Stevens et al., recommends the addition of vancomycin in patients with severe CDI reduce the risk of mortality. “Among patients in the any severity cohort, those who were treated with vancomycin were less likely to die (adjusted relative risk, 0.86; 95%CI, 0.74 to 0.98; adjusted risk difference, –0.02; 95%CI, –0.03 to –0.01). No significant difference was found in the risk of mortality between treatment groups among patients with mild to moderate CDI, but **vancomycin significantly reduced the risk of all-cause 30-day mortality among patients with severe CDI** (adjusted relative risk, 0.79; 95%CI, 0.65 to 0.97; adjusted risk difference, –0.04; 95%CI, –0.07 to –0.01).”⁵

The Cochrane authors stated, “No firm conclusions can be drawn regarding the efficacy of antibiotic treatment in severe CDI as most studies excluded patients with **severe** disease.” Therefore, the significant efficacy of vancomycin in the Cochrane review applies to patients with mild-moderate disease. The author’s subsequent statement that “differences in effectiveness between these antibiotics were not too great,” also applies primarily to patients with mild-moderate disease. Therefore, in patients with **mild-moderate disease**

metronidazole may still be considered as first line therapy, as it is less expensive, despite the Cochrane review finding vancomycin to be more effective overall in all disease types. A 2018 update of treatment algorithms recommended vancomycin as first-line therapy for when CDI treatment is necessary and the severity of the disease is difficult to assess.⁴

Vancomycin as first line therapy in patients with severe disease has been standard in the evidence based ESCMID guidelines and the evidenced based IDSA/SHEA guidelines.

Cost is a consideration and recognized in the Cochrane review. The cost reference about vancomycin being more expensive refers to oral vancomycin tablets, not administering the IV solution by mouth, which is much less expense.

AGREE II assessment was done for the following guideline:

Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), 2017.

For a full AGREE II assessment review Appendix A. It is recommended that based on the AGREE II finding to adapt the recommendations from IDSA and SHEA to reflect the local context.

EVIDENCE TO DECISION FRAMEWORK

| | JUDGEMENT | SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS | | | | | | | | |
|--|---|---|----------|------------|---|-------|--|----------|--------------------------------------|---------|
| QUALITY OF EVIDENCE | <p>What is the overall confidence in the evidence of effectiveness?</p> <p>Confident Not confident Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> | | | | | | | | | |
| BENEFITS & HARMS | <p>Do the desirable effects outweigh the undesirable effects?</p> <p>Benefits outweigh harms Harms outweigh benefits Benefits = harms or Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> | | | | | | | | | |
| THERAPEUTIC INTERCHANGE | <p>Therapeutic alternatives available:</p> <p>Yes No</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>List the members of the group: n/a</p> <p>List specific exclusion from the group: n/a</p> | <p>Rationale for therapeutic alternatives included:</p> <p>References: n/a</p> <p>Rationale for exclusion from the group: n/a</p> <p>References: n/a</p> | | | | | | | | |
| VALUES & PREFERENCES / ACCEPTABILITY | <p>Is there important uncertainty or variability about how much people value the options?</p> <p>Minor Major Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> | | | | | | | | | |
| RESOURCE USE | <p>How large are the resource requirements?</p> <p>More intensive Less intensive Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p> | <p>Direct cost of medicines/ treatment course:</p> <table border="1"> <thead> <tr> <th>Medicine</th> <th>Cost (ZAR)</th> </tr> </thead> <tbody> <tr> <td>Metronidazole, oral, 400 mg 8hrly x 10d</td> <td>4.30*</td> </tr> <tr> <td>Vancomycin, oral, 125 mg 6hrly x 10d (parenteral formulation given orally)</td> <td>630.00**</td> </tr> <tr> <td>Metronidazole, IV 500 mg 8hrly x 10d</td> <td>175.62*</td> </tr> </tbody> </table> <p>* RT301-2017 ** RFQ sourced from WC medical depot 13Jun18 (R63.00/vancomycin 500 mg vial). Additional resources: n/a</p> | Medicine | Cost (ZAR) | Metronidazole, oral, 400 mg 8hrly x 10d | 4.30* | Vancomycin, oral, 125 mg 6hrly x 10d (parenteral formulation given orally) | 630.00** | Metronidazole, IV 500 mg 8hrly x 10d | 175.62* |
| Medicine | Cost (ZAR) | | | | | | | | | |
| Metronidazole, oral, 400 mg 8hrly x 10d | 4.30* | | | | | | | | | |
| Vancomycin, oral, 125 mg 6hrly x 10d (parenteral formulation given orally) | 630.00** | | | | | | | | | |
| Metronidazole, IV 500 mg 8hrly x 10d | 175.62* | | | | | | | | | |
| EQUITY | <p>Would there be an impact on health inequity?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p> | | | | | | | | | |
| FEASIBILITY | <p>Is the implementation of this recommendation feasible?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> | | | | | | | | | |

| | | | | | |
|-------------------------------|---|--|---|---|--|
| Type of recommendation | We recommend against the option and for the alternative <input type="checkbox"/> | We suggest not to use the option or to use the alternative <input type="checkbox"/> | We suggest using either the option or the alternative <input type="checkbox"/> | We suggest using the option <input type="checkbox"/> | We recommend the option <input checked="" type="checkbox"/> |
|-------------------------------|---|--|---|---|--|

Recommendation:

Based on this review, the Adult Hospital Level Committee recommends that severe and recurrent CDI be treated as follow:

- *For severe cases:* Vancomycin parenteral administered orally and metronidazole, IV if unable to take oral treatment.
- *For recurring cases:* Pulse and tapered vancomycin therapy.

Rationale:

- Systematic review evidence showed no significant difference in the risk of mortality between treatment groups among patients with mild to moderate CDI, but vancomycin significantly reduced the risk of all-cause 30-day mortality among patients with **severe** CDI.
- Recommendations aligned with clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), taking into consideration the costs of the medicines.

Level of Evidence: I Systematic review, Guidelines

Review indicator:

| | | |
|-------------------------------------|--------------------------|--------------------------|
| Evidence of efficacy | Evidence of harm | Price reduction |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

VEN status:

| | | |
|--------------------------|-------------------------------------|--------------------------|
| Vital | Essential | Necessary |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> |

NEMLC MINUTES OF THE MEETING OF 27 SEPTEMBER 2018:

NEMLC accepted the evidence review and proposed recommendation at the NEMLC meeting of 27 September 2018

Monitoring and evaluation considerations

Resource requirements for the management of severe and recurrent CDI.

Research priorities

References

1. Fehér C, Mensa J. A Comparison of Current Guidelines of Five International Societies on Clostridium difficile Infection Management. *Infect Dis Ther* 2016;5(3):207-30. doi: 10.1007/s40121-016-0122-1 [published Online First: 2016/07/28]
2. Debast SB, Bauer MP, Kuijper EJ, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. *Clin Microbiol Infect* 2014;20 Suppl 2:1-26. doi: 10.1111/1469-0691.12418
3. Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults. *Cochrane Database Syst Rev* 2017;3:CD004610. doi: 10.1002/14651858.CD004610.pub5 [published Online First: 2017/03/04]
4. Ooijsaar RE, van Beurden YH, Terveer EM, et al. Update of treatment algorithms for Clostridium difficile infection. *Clin Microbiol Infect* 2018 doi: 10.1016/j.cmi.2017.12.022 [published Online First: 2018/01/05]
5. Stevens VW, Nelson RE, Schwab-Daugherty EM, et al. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with Clostridium difficile infection. *JAMA Intern Med* 2017;177(4):546-553. doi: 10.1001/jamainternmed.2016.9045
6. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) [published online February 15, 2018]. *Clin Infect Dis*. doi: 10.1093/cid/cix1085

APPENDIX A

Review of clinical practice guideline:

AGREE II assessment of the Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Refer to the attached AGREE II assessment report.

General agreement on all domains was reached between the two appraisers of these guidelines; and both appraisers recommended that these Guidelines could be adapted for the South African setting



AGREE_Appraisal_I AGREE_Appraisal_I
DSA_CDdiff_CPG_201; DSA_CDdiff_CPG_201;