Cost-effectiveness in *Clostridium difficile* treatment decision-making

Mark JC Nuijten, Josbert J Keller, Caroline E Visser, Ken Redekop, Eric Claassen, Peter Speelman, Marja H Pronk

**Mark JC Nuijten**, Ars Accessus Medica, 1546 LG Jisp, The Netherlands

Josbert J Keller, HAGA teaching hospital, 2545 CH Den Haag, The Netherlands

Caroline E Visser, Clinical Microbiologist AMC, 1105 AZ Amsterdam, The Netherlands

Ken Redekop, iMTA and BMG EUR, 3062 PA Rotterdam, The Netherlands

Eric Claassen, EUR, Rotterdam, 3062 PA Rotterdam, The Netherlands

Peter Speelman, AMC, 1105 AZ Amsterdam, The Netherlands

Marja H Pronk, Europe-ExPro, 81669 Munich, Germany

**Author contributions:** Nuijten MJC and Pronk MH designed research; Nuijten MJC and Pronk MH performed research; Keller JJ, Visser CE, Redekop K, Claassen E and Speelman P contributed for analytic tools; Nuijten MJC and Pronk MH analyzed data; Nuijten MJC, Keller JJ, Visser CE, Redekop K, Claassen E, Speelman P and Pronk MH wrote the paper.

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

**Data sharing statement:** None.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to:** Mark JC Nuijten, PhD, MD, MBA, Ars Accessus Medica, Dorpsstraat 75, 1546 LG Jisp, The Netherlands. marknuijten@planet.nl

**Telephone:** +31-620-427827

**Fax:** +31-756-422456

**Received:** August 26, 2014

**Peer-review started:** August 26, 2014

**First decision:** September 28, 2014

**Revised:** July 28, 2015

**Accepted:** August 4, 2015

**Article in press:** Published online: November 16, 2015

**Abstract**

**AIM:** To develop a framework for the clinical and health economic assessment for management of *Clostridium difficile* infection (CDI).

**METHODS:** CDI has vast economic consequences emphasizing the need for innovative and cost effective solutions, which were aim of this study. A guidance model was developed for coverage decisions and guideline development in CDI. The model included pharmacotherapy with oral metronidazole or oral vancomycin, which is the mainstay for pharmacological treatment of CDI and is recommended by most treatment guidelines.

**RESULTS:** A design for a patient-based cost-effectiveness model was developed, which can be used to estimate the cost-effectiveness of current and future treatment strategies in CDI. Patient-based outcomes were extrapolated to the population by including factors like, *e.g.*, person-to-person transmission, isolation precautions and closing and cleaning wards of hospitals.

**CONCLUSION:** The proposed framework for a population-based CDI model may be used for clinical and health economic assessments of CDI guidelines and coverage decisions for emerging treatments for CDI.
infection, by this spore forming bacterium, have been demonstrated. In 55% of hospitalized patients with CDI, hospital stay was prolonged to more than 4 wk[8].

Pharmacotherapy of an initial episode of CDI with oral metronidazole or oral vancomycin is the recommended treatment in most guidelines[9-11]. However, following antibiotic treatment of CDI, recurrence and re-infection within 30 doccurs in approximately 15%-35% of patients, while 33%-65% of patients with > 2 previous CDI episodes will recur[12]. Recurrence of CDI is a serious and difficult-to-treat problem, impacting on the length and overall cost of hospitalisation[13]. The guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) have identified recurrence as being the most important challenge in the treatment of CDI[14].

Recently published guidelines[11-13] have incorporated relatively new treatments strategies with the antibiotic fidaxomicin and fecal microbiota transplantation (FMT or donor feces infusion), although their role is restricted because of the high price of fidaxomicin and the complexity (unconventional and unstandardised nature) of FMT. The latest Netherlands guideline suggests weighing fidaxomycin’s high price versus the advantage of fewer recurrences[10,12,15]. English guidelines also recommends oral metronidazole for initial treatment in non-severe CDI, because it is cheaper than oral vancomycin, and because of concern about the selection of vancomycin resistant enterococci[13]. The median cost to treat a patient with CDI was €33840, showing an almost five fold higher and significant difference compared with the non-infected matched controls[16]. The estimated cost of CDI within the European Union (EU) is about €3 billion per year[27], and may further increase with aging. In most studies, hospitalisation is the main cost driver in patients with CDI[18]. Patients with CDI spend on average an extra 7-21 d in hospital, compared with non-infected controls[16,19,20]. The high rates of treatment failure and high rates of currently recommended antibiotics (metronidazole and vancomycin)[15,21,22] significantly affects costs[23]. The influence on clinical outcome and costs of this limited treatment efficacy is particularly apparent for patient groups with multiple comorbidities and a high risk of recurrence. In addition, minimizing the risk of person-to-person transmission of C. difficile in hospital wards seems of utmost importance. Taken together it is evident there is a large socio-economic and clinical unmet need to evaluate all these different factors in a single decision support model[24].

MATERIALS AND METHODS

Classic patient-based cost effectiveness model for infectious diseases tend to ignore the supra-patient social-economic consequences such as, for example, person-to-person transmission and closing of hospital wards due to infectious outbreaks. Preparing for an
Recurrence of CDI is a serious and difficult-to-treat problem. The cost of recurrence of CDI is high.

Clinical and economic relevant issues

Clinical and economic relevant issues are shown in Tables 1 and 2.

The clinical and economic consequences of CDI in terms of morbidity, survival and costs underline the therapeutic need for innovative cost-effective solutions. Payers require cost-effectiveness analyses when deciding whether or not to reimburse new therapies/approaches for CDI. In such an analysis the first step is typically to develop a patient-based cost-effectiveness model. Such a model for CDI is shown in Figure 1.

Instructions are defined possible different stages for a CDI patient (health states).

Treatment stages hospital setting: (1) In the hospital, discontinuation of the antibacterial therapy that may have precipitated CDI is often not possible; (2) Patients with CDI are usually treated with antibiotics (metronidazole); (3) Patients may die or stay alive and surviving patients may or may not respond to metronidazole; (4) Patients who respond to metronidazole may be cured or experience a recurrence (or re-infection), which may occur during the hospitalization period or after discharge. In both cases the initial treatment with metronidazole is restarted, or vancomycin or fidaxomicin is prescribed instead; (5) If no response to metronidazole is seen, patients may be switched to vancomycin or fidaxomicin; (6) Then again patients may die or stay alive and surviving patients may respond or not respond to vancomycin or fidaxomicin; (7) Patients who respond to vancomycin or fidaxomicin may be cured or experience a recurrence (or re-infection), which may occur during hospitalization or after discharge. In both cases the initial treatment with vancomycin or fidaxomicin is restarted; and (8) Patients not responding will be switched to third-line treatment. For patients failing on third-line treatment, not many treatment options are left. If third line treatment is FMT, this can be repeated several times. Otherwise, patients may have to use vancomycin more or less continuously.
Based model only provides a limited health economic outcome in terms of time horizon and perspective and more importantly, disregards the impact on other patients. The relevant economic issues, such as resistance, person-to-person transmission, isolation measures and closing of wards of hospitals, are all supra-patient effects. These consequences of CDI on hospitals, payers and society, that go beyond the individual scope of the patient, are not integrated in standard CEA's. Therefore, the outcomes of a patient-based cost-effectiveness model should be considered cautiously because they present only a conservative and limited outcome. For all-encompassing cost-effectiveness evaluations of CDI therapies, these supra-patient economic aspects cannot be disregarded. Therefore, we propose performing cost-effectiveness analyses for CDI using a population-based model, which incorporates all of the clinically important elements of the patient-based model as well as the supra-patient therapeutic and economic issues (Table 3).

**RESULTS**

The flow diagram (Figure 1) does not contain a particular choice for a specific therapy but serves as
a blueprint for cost-effectiveness modeling. Based on the developments in CDI treatment, we suggest applying different treatment sequences for testing the effects on cost-effectiveness outcomes. Other suggestions for application are stratification of the patient population according to potential co-variables, such as risk factors for recurrence (for example, prolonged hospital stay or ICU admission) or underlying diseases (for example, patients after surgery, patients with a malignancy receiving chemotherapy, and renally impaired patients).

Three types of recent therapies could be candidates for comparison using a population-based model: the antibiotic fidaxomycin, fecal microbiota transplantation (FMT), and preventive use of probiotics.

Fidaxomycin is a novel antibiotic with targeted activity against \textit{C. Difficile} with a similar safety profile as vancomycin. After treatment of an initial episode of CDI, the cure rate after 30 d was increased after fidaxomycin (82\%) compared to vancomycin (70\%)\textsuperscript{[16,17,24]}. FMT helps restore the normal colonic micro flora in patients with refractory and recurrent CDI\textsuperscript{[25,26]}. The procedure involves single or multiple infusions (\textit{e.g.}, by enema) of a feces based solution from a healthy donor. A recently published randomized trial confirmed the efficacy of FMT in patients with recurrent CDI. For assessment of preventive treatments, the framework (Figure 1) can be used to estimate the costs and benefits of co-prescription of probiotics with antibiotics to prevent CDI. Recently, a patient-based cost-effectiveness evaluation for probiotics showed probiotics "could lead to substantial cost savings"\textsuperscript{[27]}. To further investigate the economic consequences of the use of probiotics to prevent CDI, a population-based model could be applied and although the expected clinical benefit may be limited, total cost savings compared to no preventive treatment, and a predicted (Cochrane) drop in therapy induced side effects, may still be relevant.

**DISCUSSION**

Current clinical guidelines seldom include cost-effectiveness evaluations. Conclusions are typically based on clinical data only and sometimes referral is made to prices of therapies for justification of the treatment sequence advised. However, the price of a therapy as such is just a single criterion and does not reflect the balance between effectiveness and costs associated with the application of that therapy. This results often in a restricted position of new therapies in the treatment algorithm.

Among health authorities, it is common to include evidence of cost-effectiveness in decision-making about coverage under the health insurance package. Even though the cost per QALY outcome might fall below the threshold of a country, health authorities might decide to reject coverage based on the high weight they place on the budget impact\textsuperscript{[28]}. This may be considered a paradox, because the cost-effectiveness guidelines were written by the same authorities and payers.

Estimates of the cost-effectiveness of a medicine may only have a limited impact on the use of that medicine within a hospital, as a result of a "siloh mentality" found within the hospital as well as within the budget management structure existing at the payer, local and national levels. In that case, a treatment (medication or medical therapy) that is more expensive than existing treatments may exceed the amount of money reserved within the hospital budget or the pharmacy budget.

Another paradox, since exceeding this "local" budget might generate a multiplier and create substantial savings in the total system/hospital.

Achieving changes in the "siloh structure" within hospitals as well as the budget management struc-

---

**Table 3  Similarities and differences between a patient-based and population based cost-effectiveness model**

| Patient-based cost-effectiveness model | Population-based cost-effectiveness model |
|--------------------------------------|-------------------------------------------|
| **Similarities**                     | The relevant economic issues, as indicated for CDI like: |
| Patient-related therapeutic and economic measures for clinical and economic evaluations | increasing incidence of CDI, |
| Differences                          | 2. person-to person transmission of CDI, |
|                                      | 3. development of vancomycin-resistant enterococci (VRE), |
|                                      | 4. or other antibiotic induced resistant bacteria, |
|                                      | 5. impact for department of microbiology diagnostic testing |
|                                      | 6. isolation measures and |
|                                      | 7. closing of wards of hospitals |
|                                      | 8. other supra-patient effects |

Limited health economic outcome in terms of time horizon and perspective

The patient-based cost-effectiveness model only captures the short-term time horizon of the CDI episode within the hospital setting at a patient level

CDI: \textit{Clostridium difficile} infection.
ture by payers depends on the generation of basic information on these cost-effective aspects. We propose that usage of the current flow diagram will generate facts and figures, as well as enable motivated implementation of these facts into guidance documents from professional societies to policy makers and payers (locally or regionally as well as nationally).

Integration of cost-effectiveness using the population-based variant of cost-effectiveness evaluations as an instrument in guidelines for CDI should be considered.

This may help healthcare professionals, patients, hospitals, payers and society to make better decisions about the optimal way to reduce the health and economic impact of CDI.

COMMENTS

Background
Current clinical guidelines seldom include cost-effectiveness evaluations. Conclusions are typically based on clinical data only and sometimes referral is made to prices of therapies for justification of the treatment sequence advised. However, the price of a therapy as such is just a single criterion and does not reflect the balance between effectiveness and costs associated with the application of that therapy. This results often in a restricted position of new therapies in the treatment algorithm.

Research frontiers
Recent high rates of treatment failure and recurrent infection have vast economic consequences emphasizing the need for innovative and cost effective solutions in Clostridium difficile infections (CDI). The price of new therapies and approaches cannot always compete with the relatively low, generic prices of current standard therapies with metronidazole and vancomycin. The question is then, how should professional societies integrate new and more effective, but also more expensive, remedies into their guidelines and how health authorities make reimbursement decisions.

Innovations and breakthroughs
The cost-effectiveness outcome based on the patient-based model only provides a limited health economic outcome in terms of time horizon and perspective and more importantly, disregards the impact on other patients. The relevant economic issues, such as resistance, person-to-person transmission, isolation measures and closing of wards of hospitals, are all supra-patient effects. These consequences of CDI on hospitals, payers and society, that go beyond the individual scope of the patient, are not integrated in standard cost-effectiveness analyses. Therefore, we developed a guidance model for coverage decisions and guideline development in CDI based on a population-based cost-effectiveness model.

Applications
We propose performing cost-effectiveness analyses for CDI using a population-based model, which incorporates all of the clinically important elements of the patient-based model as well as the supra-patient therapeutic and economic issues.

Terminology
CDI is responsible for 15%-25% of cases of antibiotic associated diarrhea (AAD) and is typically seen in elderly hospitalised patients, resulting in significant morbidity and mortality. Pharmacotherapy of an initial episode of CDI with oral metronidazole or oral vancomycin is the mainstay for pharmacological treatment of CDI and is recommended by most treatment guidelines.

Peer-review
This guideline article is interesting and has a high scientific value.

REFERENCES

1. Barbis F, Petit JC. Epidemiology of Clostridium difficile-associated infections. Clin Microbiol Infect 2001; 7: 405-410 [PMID: 11591202 DOI: 10.1046/j.1198-743X.2001.00289.x]
2. Bauer MP, Notermans DW, van Benthem BH, Brazier JS, Wilcox MH, Rupnik M, Monnet DL, van Dissel JT, Kuijper EJ. Clostridium difficile infection in Europe: a hospital-based survey. Lancet 2011; 377: 63-73 [PMID: 21084111 DOI: 10.1016/S0140-6736(10)61266-4]
3. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frentette C, Kelly M, Viben A, Brassard P, Fenn S, Dewar K, Hudson R, René P, Monczak Y, Dascal A. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med 2005; 353: 2442-2449 [PMID: 16322602 DOI: 10.1056/NEJMoa051639]
4. Paltansing S, van den Berg RJ, Guseinova RA, Visser CE, van der Vorm ER, Kuijper EJ. Characteristics and incidence of Clostridium difficile-associated disease in The Netherlands, 2005. Clin Microbiol Infect 2007; 13: 1058-1064 [PMID: 17922780 DOI: 10.1111/j.1199-0691.2007.00793.x]
5. Pépin J, Valiquette L, Cossette B. Mortality attributable to nosocomial Clostridium difficile-associated disease during an epidemic caused by a hypervirulent strain in Quebec. CMAJ 2005; 173: 1037-1042 [PMID: 16179431 DOI: 10.1503/cmaj.050978]
6. Smith A. Outbreak of Clostridium difficile infection in a hospital in south east England linked to hypertoxin-producing strains in Canada and the US. Euro Surveill 2005; 10: E050630.2
7. Dodek PM, Norena M, Ayas NT, Romney M, Wong H. Length of stay and mortality due to Clostridium difficile infection acquired in the intensive care unit. J Crit Care 2013; 28: 335-340 [PMID: 23337482 DOI: 10.1016/j.jcrc.2012.11.008]
8. Draaijers Maatregelen ter preventie en bestrijding Clostridium difficile PCR-ribotype 027 - toxinoftype III-infectie buiten het ziekenhuis. December 2009 Landelijke Coördinatie Infectieziektebestrijding RIVM - Centrum Infectieziektebestrijding Bilthoven. Available from: URL: http://www.rivm.nl
9. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol 2010; 105: 478-498; quiz 499 [PMID: 23439232 DOI: 10.1038/ajg.2013.4]
10. Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K, Sears P, Gorbach S. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012; 12: 281-289 [PMID: 22321770 DOI: 10.1016/S1473-3099]
11. Wilcox MH. Updated guidance on the management and treatment of Clostridium difficile infection. London: Public Health England, 2013 [DOI: 10.1002/psb.1074]
12. Viswanathan VK, Mallozzi MJ, Vedantam G. Clostridium difficile infection: An overview of the disease and its pathogenesis, epidemiology and interventions. Gut Microbes 2010; 1: 234-242 [PMID: 21327030 DOI: 10.4161/gmic.1.4.12706]
13. Pépin J, Valiquette L, Alary ME, Villemure P, Pelletier A, Forget K, Pépin K, Chouinard D. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ 2004; 171: 466-472 [PMID: 15337727 DOI: 10.1503/cmaj.1041104]
14. Debast SB, Bauer MP, Kuijper EJ. 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 [PMID: 24118601 DOI: 10.1111/1469-0069.12418]
15. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, Sears P, Shue YK. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011; 364: 422-431 [PMID: 21288078 DOI: 10.1056/NEJMoa0910812]
16 Wilcox MH, Cunniffe JG, Trundle C, Redpath C. Financial burden of hospital-acquired Clostridium difficile infection. *J Hosp Infect* 1996; 34: 23-30 [PMID: 8880547 DOI: 10.1016/S0195-6701(96)90122-X]

17 Kuijper EJ, Coignard B, Tüll P. Emergence of Clostridium difficile-associated disease in North America and Europe. *Clin Microbiol Infect* 2006; 12 Suppl 6: 2-18 [PMID: 16965399 DOI: 10.1111/j.1469-0691.2006.01580.x]

18 Dubberke ER. Wertheimer AI. Review of current literature on the economic burden of Clostridium difficile infection. *Infect Control Hosp Epidemiol* 2009; 30: 57-66 [PMID: 19049438 DOI: 10.1086/592981]

19 Commission for Health care Audit and Inspection. Investigation 21 into outbreaks of Clostridium difficile at Stoke Mandeville Hospital. Buckinghamshire: Buckinghamshire Hospitals NHS Trust, 2006

20 Vonberg RP, Reichardt C, Behnke M, Schwab F, Zindler S, Gastmeier P. Costs of nosocomial Clostridium difficile-associated diarrhoea. *J Hosp Infect* 2008; 70: 15-20 [PMID: 18602185 DOI: 10.1016/j.jhin.2008.05.004]

21 Aslam S, Hamill RJ, Musher DM. Treatment of Clostridium difficile-associated disease: old therapies and new strategies. *Lancet Infect Dis* 2005; 5: 549-557 [PMID: 16122678 DOI: 10.1016/ S1473-3099(05)70121-0]

22 Musher DM, Aslam S, Logan N, Nallacheru S, Bhaia I, Borchert F, Hamill RJ. Relatively poor outcome after treatment of Clostridium difficile colitis with metronidazole. *Clin Infect Dis* 2005; 40: 1586-1590 [PMID: 15889334 DOI: 10.1086/430311]

23 McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. *Am J Gastroenterol* 2002; 97: 1769-1775 [PMID: 12135033 DOI: 10.1111/j.1572-0241.2002.05839.x]

24 European Medicines Agency. EPAR fidaxomicin. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002087/WC50019707.pdf

25 van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent Clostridium difficile. *N Engl J Med* 2013; 368: 407-415 [PMID: 23323867 DOI: 10.1056/NEJMoa1205037]

26 Van Nood E, Speelman P, Nieuwdorp M, Keller J. Fecal microbiota transplantation: facts and controversies. *Curr Opin Gastroenterol* 2014; 30: 34-39 [PMID: 24241245 DOI: 10.1097/MOG.0000000000000024]

27 Lenoir-Wijnkoop I, Nuijten MJ, Craig J, Butler CC. Nutrition economic evaluation of a probiotic in the prevention of antibiotic-associated diarrhoea. *Front Pharmacol* 2014; 5: 13 [PMID: 24596556 DOI: 10.3389/fphar.2014.00013]

28 Prong MH, Bonsel GJ. Out-patient drug policy by clinical assessment rather than financial constraints? The gate-keeping function of the out-patient drug reimbursement system in The Netherlands. *Eur J Health Econ* 2004; 5: 274-277 [PMID: 15714349 DOI: 10.1007/s10198-003-0223-0]

P- Reviewer: Di Lorenzo G, Kirshtein B, Yokoyama Y
S- Editor: Tian YL  L- Editor: A  E- Editor: Wang CH