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Commentary

The need for a holistic view on management of *Clostridioides difficile* infection

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Since the implementation of innovative treatment options for the management of CDIs during the recent decades, controversy exists regarding the most cost-effective treatment pathways. The study by Chen and colleagues, not sponsored by industry, analysed the health-economic impact of using bezlotoxumab and fidaxomicin for initial CDI compared to oral vancomycin, based on the US societal perspective [1]. As one of the main study results, the authors highlighted cost-effectiveness of standard treatment with fidaxomicin, mainly due to a low rate of CDI recurrences (between 13% and 15%) within the observed timeframe of the two clinical trials by Cornely et al. and Louie et al. [2,3]. Vancomycin used alone was inferior to bezlotoxumab in combination with vancomycin, extended-pulsed fidaxomicin and standard fidaxomicin for treatment of initial CDI, mainly because of the higher recurrence rates. One major strength of the study by Chen et al. is the consideration of both direct treatment and indirect costs (productivity losses) and the calculation of outcome and costs over a lifetime horizon, including the impact of CDI recurrences. The prevention of recurrences is one of the major challenges in the treatment of patients with CDI. A recently conducted pan-European health-economic evaluation of 615 inpatients and outpatients across 12 countries (COMBACTE-CDI), a collaborative approach of the Innovative Medicines Initiative (IMI) and pharmaceutical partners, demonstrated the great importance of preventing CDI recurrences [4]. Patients with one or more CDI recurrences had a median overall hospitalization of 43 days during a 6-month follow-up period, meaning a 3.5-fold prolonged length of hospital stay (LOS) compared to patients who did not develop a CDI recurrence (median overall LOS 12 days). This prolonged hospitalization results in a 3.5-fold increased economic burden of €18,000 per patient (the median overall costs in both groups were €24,400 versus €6800, respectively).

With respect to the international readership, caution is needed for interpretation of study results due to the perspective and methodology used by Chen et al. First, the defined willingness to pay (WTP) threshold per patient for cost-effectiveness was US$150,000 per quality-adjusted life-year (QALY), meaning that this value is above the WTP threshold of countries with a lower gross domestic income. The adequate use of a WTP threshold per QALY is frequently discussed [5], as the historical WTP threshold range from one-to three-fold per capita gross domestic income, i.e. approximately US$50,000–US$150,000 in the US. However, health-economic

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evaluations from different countries should be designed based on the (national) budget available for decision-makers for improvements in health. Looking at the participating countries of COMBACTE-CDI, only Belgium, France, Ireland, Sweden, the Netherlands, and the United Kingdom have comparable gross domestic incomes, whereas Eastern and Southern European countries tend to have lower incomes. Additionally, prices for healthcare services (including direct treatment costs for pharmaceutical agents) vary largely between different countries, which further limits an international comparison of study results. Two studies by the Organisation for Economic Cooperation and Development (OECD) demonstrated large differences in price levels for healthcare services and health expenditures per capita between the US and the majority of European countries, especially those from the Eastern and Southern part of Europe [6,7]. The considerable differences in drug acquisition costs between different US healthcare perspectives (e.g. private versus statutory) might also have an impact on cost-effectiveness and should be considered for interpretation of the study results [8]. Furthermore, the access to innovative treatment options (such as bezlotoxumab and fidaxomicin) for treating physicians is hampered in countries with lower gross domestic incomes, especially due to the large differences in acquisition costs for bezlotoxumab and fidaxomicin compared to vancomycin. It should be noted that, in general, the clinical assessment of available pharmaceutical agents against CDI by decision-makers (e.g. physicians, hospital managers) should not be limited by the economical view on acquisition costs. Consequently, patients with a likely risk of developing a CDI recurrence should receive optimal treatment with evidence-based associated lower CDI recurrence rates to prevent an adverse clinical outcome and significant costs, e.g. patients in the intensive care unit (ICU). In those cases, higher acquisition costs for innovative agents, such as bezlotoxumab and fidaxomicin, will be rapidly balanced by e.g. lower personnel cost for physicians and nurses on hospitals wards. As demonstrated in the health-economic evaluation of COMBACTE-CDI, a patient with one or more CDI recurrences causes median additional direct and indirect treatment costs of €18,000, which is significantly higher compared to the acquisition costs for one treatment cycle of bezlotoxumab or fidaxomicin. In most European countries, direct treatment costs for a one-day treatment on the ICU vary between €1500 and €3200, meaning that a regular treatment cycle of 10 days with fidaxomicin (200 mg tablet twice daily) or a single infusion of bezlotoxumab will be balanced if this prevents an ICU stay of 1–2 days. This is particularly important for patients with haematopoietic stem-cell transplantation or solid-organ transplantation who are *per se* treated on high-cost wards due to the need for specialized care medicine. Such a holistic view on the management of CDI should be embraced by physicians, hospital managers, and further decision-makers. Another important aspect of the model structure by Chen and colleagues is the missing consideration of faecal microbiota transplantation (FMT). This limits the interpretation of study results regarding the most cost-effective treatment option for CDI by the lifetime horizon perspective in the US, especially because several recently published studies have demonstrated the effectiveness of FMT in reducing the incidence of recurrent CDI, resulting in a decreased health-economic burden [9–11].

The update of CDI treatment guidelines is also likely to have an impact on health-economic outcomes. For example, the current CDI treatment guideline by the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) was recently updated in 2021, and metronidazole is no longer recommended for first-line treatment of CDI [12]. It is well known that metronidazole is the cheapest antibiotic agent available for CDI treatment. Consequently, if the cheapest antibiotic agent is excluded from a guideline, overall drug costs in patient treatment might increase if CDI management is compliant with the guideline. On the other hand, it is well known that the currently available low-priced antibiotic agents against CDI had lower clinical success rates in some patient cohorts. This mainly includes the elderly, patients with severe CDI, and patients taking concomitant antibiotic agents, mostly resulting in increased overall treatment costs due to an increased likelihood of CDI recurrences. Again, these two viewpoints raise questions regarding the most cost-effective treatment strategy for a healthcare system, which should include the most granular view on patient outcome and treatment costs over a lifetime horizon. The 2021 update of the clinical practice guideline for CDI by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has nearly completed the public consultation phase, and it will be interesting to see whether the update will have a potential impact on health-economic outcomes due to recommendation or non-recommendation of pharmaceutical agents. The ESCMID CDI guideline committee also considered potential economic restraints for prescribing, and will offer alternative treatment options or risk stratification strategies for the selective use of innovative agents, so that local cost-effective considerations can be made. Further results of the health-economic evaluation of COMBACTE-CDI demonstrated the importance of guideline compliance due to improved health-economic outcomes [4]. Since CDI-attributable mortality and hospital LOS may decrease under adherence to guidelines [13], barriers of physician adherence to CDI treatment guidelines should be identified and overcome, for instance by the implementation of a CDI electronic order set and alert bundle [14].

The above-mentioned differences between healthcare systems—including the national access and economic possibility of implementing innovative treatment strategies against CDI—results in several limitations to the comparison of treatment cost-effectiveness between countries. Since no uniform pan-European access towards innovative CDI treatment options exists (e.g. due to national budget restrictions and reimbursement barriers), we expect future national studies to identify the best clinically and economically sound strategy for the prevention and treatment of CDI, including the impact of guideline adherence on cost-effectiveness as a reduction of hospital LOS is anticipated [13]. The most effective pathway to reach this target is to maximize the response of initial CDI treatment for prevention of CDI recurrences. The study by Chen et al. is a good example of a well-designed health-economic evaluation in line with international standards, demonstrating cost-effective CDI treatment in the US, which is primarily influenced by the prevention of recurrent CDI. Bezlotoxumab and fidaxomicin were found to be cost-effective agents in this context. Of note, fidaxomicin can also be administered as an extended-pulsed regimen (20 fidaxomicin doses distributed as follows: twice daily on days 1–5, then once daily on alternate days on days 6–25) or a tapered form (fidaxomicin 200 mg once daily for 7 days followed by 200 mg fidaxomicin every other day for a remaining 13 doses) [15,16]. Even though particularly low CDI recurrence rates were observed using these new treatment regimens, a direct comparison with a standard course of fidaxomicin does not exist. Future head-to-head comparisons may overcome possible bias in cost-effectiveness analyses due to differences in baseline patient characteristics of the included trials.

Author contributions

All authors have made substantial contributions in conception and design and to drafting the manuscript and revising it critically for important intellectual content; all have given their final approval for submission.

Transparency declaration

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References

[1] Chen J, Gong CL, Hitchcock MM, Holubar M, Deresinski S, Hay JW. Cost-effectiveness of bezlotoxumab and fidaxomicin for initial *Clostridioides difficile* infection. Clin Microbiol Infect 2021;27(10):1448–54.
[2] Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K, et al. 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;12:281–9.
[3] Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364:422–31.
[4] Wingen-Heimann SM, Viprey V, Davies K, Cornely O, Bandinelli PA, Wilcox M et al. 31th European congress of clinical Microbiology & infectious Diseases (ECCMID 2021). A pan-European cost-of-illness analysis of patients with *Clostridioides difficile* infection: results of COMBACTE-CDI. Abstract ID 02962.
[5] Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 2014;371:796–7.
[6] Organisation for Economic Co-operation and Development OECD. International comparisons of health prices and volumes: new findings. 2017. https://www.oecd.org/health/health-systems/International-Comparisons-of-Health-Prices-and-Volumes-New-Findings.pdf.
[7] Koechlin F, Konijn P, Lorenzoni L, Schreyer P. Comparing hospitals and health prices and volumes across countries: a new approach. Soc Indic Res 2017;131:43–64.
[8] Hay JW, Smeeding J, Carroll NV, Drummond M, Garrison LP, Mansley EC, et al. Good research practices for measuring drug costs in cost effectiveness analyses: issues and recommendations: the ISPOR Drug Cost Task Force report—Part I. Value Health 2010;13:3–7.
[9] van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med 2013;368:407–15.
[10] Konijeti GG, Sauk J, Shrime MG, Gupta M, Ananthakrishnan AN. Cost-effectiveness of competing strategies for management of recurrent *Clostridium difficile* infection: a decision analysis. Clin Infect Dis 2014;58:1507–14.
[11] Varier RU, Biltaji E, Smith KJ, Roberts MS, Jensen MK, LaFleur J, et al. Cost-effectiveness analysis of treatment strategies for initial *Clostridium difficile* infection. Clin Microbiol Infect 2014;20:1343–51.
[12] Johnson S, Lavergne V, Skinner AM, Gonzales-Luna AJ, Garey KW, Kelly CP, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. Clin Infect Dis 2021.
[13] Crowell KT, Julian KG, Katzman M, Berg AS, Tinsley A, Williams ED, et al. Compliance with *Clostridium difficile* treatment guidelines: effect on patient outcomes. Epidemiol Infect 2017;145:2185–92.
[14] Attaar A, Wei J, Brunetti L. Evaluating adherence to guideline-directed *C. difficile* infection management pre- and postimplementation of an electronic order set. J Pharm Pract 2020. 897190020903854.
[15] Guery B, Menichetti F, Anttila VJ, Adomakoh N, Aguado JM, Bisnauthsing K, et al. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. Lancet Infect Dis 2018;18:296–307.
[16] Skinner AM, Tan X, Sirbu BD, Danziger LH, Gerding DN, Johnson S. A tapered-pulsed fidaxomicin regimen following treatment in patients with multiple *Clostridioides difficile* infection recurrences. Clin Infect Dis 2021.