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ORIGINAL ARTICLE

# Economic assessment of fidaxomicin for the treatment of *Clostridium difficile* infection (CDI) in special populations (patients with cancer, concomitant antibiotic treatment or renal impairment) in Spain

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**Abstract** The objective of this paper was to assess the cost–utility of fidaxomicin versus vancomycin in the treatment of *Clostridium difficile* infection (CDI) in three specific CDI patient subgroups: those with cancer, treated with concomitant antibiotic therapy or with renal impairment. A Markov model with six health states was developed to assess the cost–utility of fidaxomicin versus vancomycin in the patient subgroups over a period of 1 year from initial infection. Cost and outcome data used to parameterise the model were taken from Spanish sources and published literature. The costs were from the Spanish hospital perspective, in Euros (€) and for 2013. For CDI patients with cancer, fidaxomicin was dominant versus vancomycin [gain of 0.016 quality-adjusted life-years (QALYs) and savings of €2,397 per patient]. At a cost-effectiveness threshold of €30,000 per QALY gained, the probability that fidaxomicin was cost-effective was 96 %. For CDI patients treated with concomitant antibiotic therapy, fidaxomicin was the dominant treatment versus vancomycin (gain of 0.014 QALYs and savings of €1,452 per patient), with a probability that fidaxomicin was cost-effective of 94 %. For CDI patients with renal impairment, fidaxomicin was also dominant versus vancomycin (gain of 0.013 QALYs and savings of €1,432 per patient), with a probability that fidaxomicin was cost-effective of 96 %. Over a 1-year time horizon, when fidaxomicin is compared to vancomycin in CDI patients with cancer, treated with concomitant antibiotic therapy or with renal impairment, the use of fidaxomicin would be expected to result in increased QALYs for patients and reduced overall costs.

Key points for clinical decision-making

- Fidaxomicin is indicated for the treatment of *Clostridium difficile* infection (CDI) and has been shown to significantly reduce CDI recurrence compared to vancomycin ($p<0.005$) [1, 2].
- Two randomised controlled trials reported the efficacy of fidaxomicin compared to vancomycin in three CDI patient subgroups: those with cancer, treated with concomitant antibiotic therapy and with renal impairment [3–5].
- Previous studies have reported that CDI in these subgroups is associated with greater mortality [6], with higher recurrence rates and longer hospital stays than other CDI patients [7].
- The model demonstrated that the treatment of CDI with fidaxomicin would be cost-saving and lead to improved quality of life when compared to vancomycin in these patient subgroups. The probability of being cost-effective at the €30,000 per quality-adjusted life-year (QALY) threshold was 96 % for patients with cancer, 94 % for patients on concomitant antibiotic treatment and 96 % for patients with renal impairment.

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## Introduction

*Clostridium difficile* is a microorganism capable of proliferating and producing toxins in the intestinal lumen, and is the most frequent cause of hospital-acquired diarrhoea [8]. The clinical spectrum of *C. difficile* infection (CDI) ranges from symptoms of uncomplicated diarrhoea with benign evolution to symptoms of progressive severity that include pseudomembranous colitis and toxic megacolon [9]. The annual incidence of CDI in Spain is estimated at 3.2–3.5 cases per 10,000 hospitalised patients [10]. In a Spanish study, the crude hospital mortality rate was higher in cases with CDI (31 %) than in controls that did not present this infection (6.6 %) [11]. According to a different study, it is estimated that there are approximately 7,600 episodes of CDI per year in Spain, with a financial burden of €32,157,093 on the National Health System (NHS) [12].

The initial management of patients with CDI should include, if possible, the discontinuation of any antibiotic that might have affected the normal microbial ecology of the large intestine. In particular, those that favour the proliferation of *C. difficile*, the release of toxins and subsequent inflammatory response [8, 13]. Patients with clinical symptoms or signs consistent with CDI, positive diagnostic test and persistent diarrhoea despite discontinuation of the antibiotic should be treated with vancomycin or metronidazole [8]. Despite these measures, infection recurrence is frequent even when these antibiotics are used, which may occur in more than 25 % of the cases treated [14].

Fidaxomicin is an antibiotic that belongs to the class of the macrocyclics and is indicated for the treatment of CDI [15]. In clinical trials, fidaxomicin, when compared to vancomycin, was non-inferior for the clinical cure of patients with CDI and superior for the reduction of recurrence rates, with a greater sustained response after 30 days [1, 2]. Of the patients included in the clinical trials, additional subgroup analyses were performed in patient subgroups with a higher risk of recurrence than the overall CDI population. These subgroups were patients with cancer [odds ratio (OR)=0.37; $p$=0.018] [3], patients treated with concomitant antibiotic treatment (OR=0.492; $p$=0.0499) [4] and patients with renal impairment (OR=0.487; $p$<0.001) [5]. Moreover, in these patients, CDI had a greater impact on morbidity and mortality and increased hospital costs [7] compared to the overall CDI patient group.

The objective of this study was to estimate the costs and patient outcomes, and the cost–utility, of fidaxomicin compared to vancomycin in the initial treatment of CDI (when patients enter the model) in these three CDI patient subgroups.

## Methods

Cost–utility analysis, which is a type of cost-effectiveness analysis, is an important part of the commissioning process for the Spanish NHS [16], as it can be used to determine if new treatments represent good value for money for the healthcare provider. The Markov model used in this study was based on a previously published CDI model [17] (Fig. 1) with six health states fully described in Table 1. All the characteristics of the Markov model have been extensively described in the assessment reports by the Welsh and Scottish authorities in the United Kingdom [18, 19], as well as in several publications [17, 20, 21].

Patients in the model were treated orally with fidaxomicin [200 mg twice daily (BID) for 10 days] or vancomycin [125 mg four times daily (QID) for 10 days] [3–5, 18]. All patients initially had CDI and, following treatment, were either clinically cured or not clinically cured (i.e. a treatment failure, where 'failure' was defined as a patient who failed to experience a clinical cure after 10 days of treatment with fidaxomicin or vancomycin). Patients initially clinically cured either had or did not have a recurrence [defined as re-establishment of diarrhoea within 28 days (±2 days) of the last dose of the study therapy and detection of *C. difficile* toxin A or B in stools]. Oral vancomycin was recommended for severe CDI episodes and for any recurrence, other than the first non-severe CDI recurrence, where oral metronidazole was recommended at the dose of 500 mg three times a day (TID) (1,500 mg/day) [22].

All recurrences that occurred when the patient was still in hospital, and all severe recurrences, were treated in hospital. Non-severe recurrences after hospital discharge were treated in the community (two GP visits; one home visit and one office visit) (both arms). Patients with CDI, in whom the initial treatment failed, were treated with high doses of vancomycin (dose increased to 250 mg QID for 10 days in 80 % of patients and up to 500 mg QID for 20 %) (both arms). Patients without clinical cure after 10 days of treatment with vancomycin at high doses were subsequently given a tapering dose of vancomycin: 125 mg QID of oral vancomycin for 14 days, followed by 125 mg BID of oral vancomycin for 7 days, followed by 125 mg OD of oral vancomycin for 7 days and, finally, 125 mg of oral vancomycin every 3 days (a total of 8 weeks of treatment) (both arms) (Fig. 1).

Clinical experts consulted on suitable last-resort therapy (authors JCR, SGC, JMP, MSL) stated that, for patients in whom tapering dose of vancomycin failed, a faecal microbiota transplantation was the last-resort treatment for multi-recurring CDI, in accordance with the recommendations of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [22].

A final death state was included for patients who died from CDI or unrelated cause. In the model, it was assumed that mortality from the main disease (cancer, renal failure) would be equivalent in arms with fidaxomicin or vancomycin due to the effect of randomisation followed in the clinical trial.

Healthcare resource use and unit costs for the health states were obtained from Spanish sources and published literature

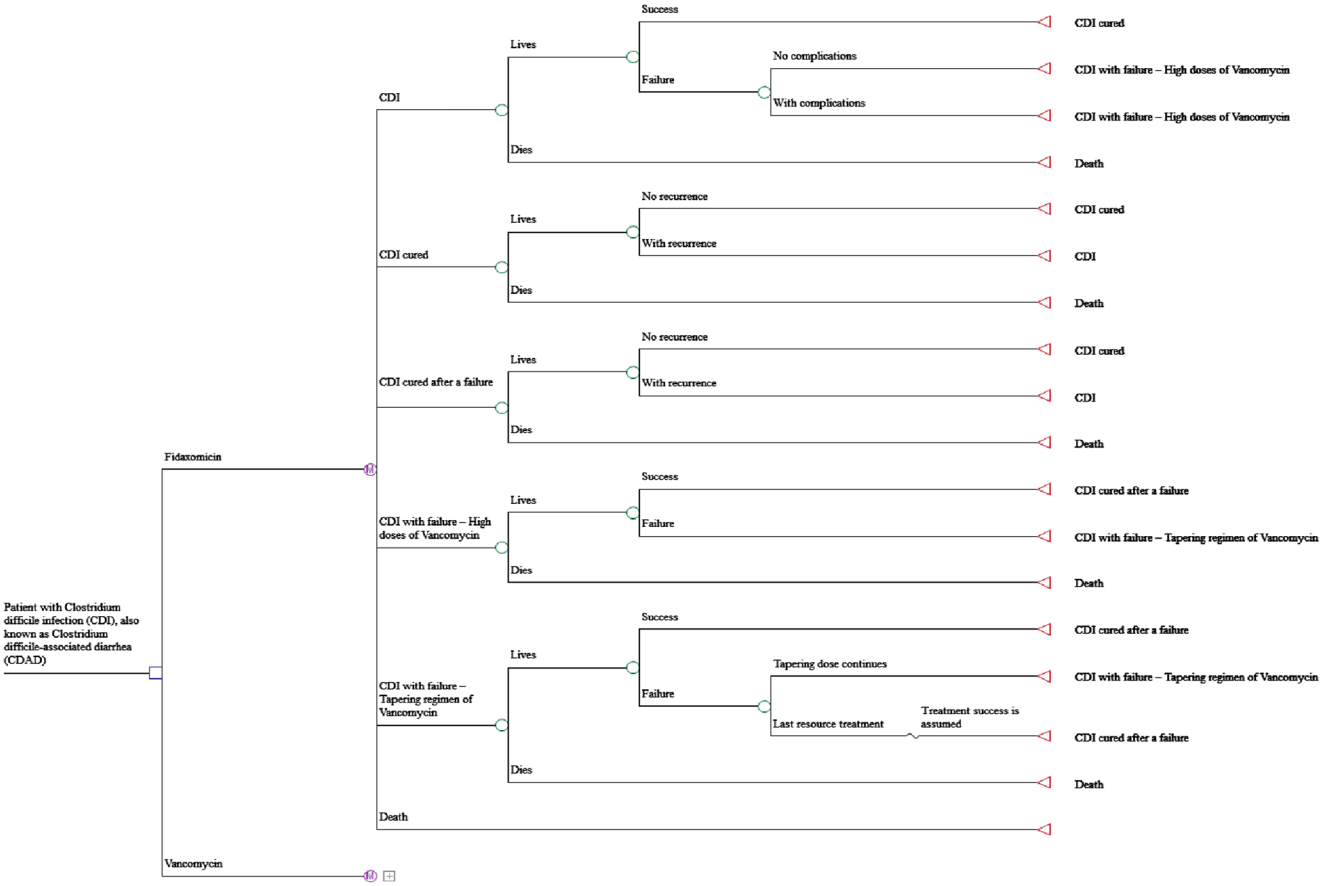


**Fig. 1** Markov model

(Table 2). The excess hospital stay for patients with initial or recurring CDI was taken from three studies performed in Spanish patients [6, 23, 24]. The probabilities of a patient with CDI being admitted into an intensive care unit (ICU) (first infection and recurrence) and of a recurrence in the 30 days after the CDI being treated in the hospital were obtained from

**Table 1** Health states included in the Markov model [18]

| Health state | Description |
|---|---|
| CDI[a] | Initial episode of infection and any subsequent recurrence; all the patients enter the model in this state. |
| CDI cured | Patient clinically cured after the initial treatment. |
| CDI cured after a failure | Patient clinically cured after a failure of the initial treatment. |
| CDI with failure: high doses of vancomycin[b] | Patient without clinical cure after 10 days of treatment with fidaxomicin (200 mg BID) or vancomycin (125 mg QID) which is, therefore, treated with high doses of vancomycin. It is assumed that the dose is increased to 250 mg QID for 10 days in 80 % of the patients and up to 500 mg QID in the remaining 20 %. |
| CDI with failure: tapering regimen of vancomycin | Patients without clinical cure after 10 days of treatment with vancomycin at high doses are subsequently given a tapering dose of vancomycin: 125 mg QID of oral vancomycin for 14 days, followed by 125 mg BID of oral vancomycin for 7 days, followed by 125 mg OD of oral vancomycin for 7 days and, finally, 125 mg of oral vancomycin every 3 days (a total of 8 weeks of treatment). |
| Death | Patients who die of CDI or an unrelated cause. |

*BID* twice daily, *CDI Clostridium difficile* infection, *OD* once daily, *QID* four times daily, *TID* three times daily

[a] In order to count the number of recurrences and their severity, the CDI status was divided into seven health substates: initial episode of CDI, first non-severe recurrence, first severe recurrence, second non-severe recurrence, second severe recurrence, as of the third non-severe recurrence and as of the third severe recurrence

[b] It is assumed that, when the first recurrence of CDI is not severe, the treatment is with metronidazole (in both the fidaxomicin and vancomycin arms) at the dose of 500 mg TID (1,500 mg/day)

**Table 2** Health resources, unit costs and utilities considered in the model (€ from 2013)

| Resources | Medium | Minimum | Maximum | References |
|---|---|---|---|---|
| Excess hospital stay in patients with initial CDI (days) | 15.31 | 10.00 | 26.00 | [6, 23, 24] |
| Excess hospital stay in patients with recurrence of CDI (days)[a] | 18.83 | 12.30 | 26.00 | [12] |
| Probability of a patient with CDI being admitted to the intensive care unit (first infection and recurrence) | 5 % | 2 % | 10 % | Experts Panel |
| Probability of a recurrence within the 30 days after the CDI being treated in the hospital | 66.7 % | 50.0 % | 100.0 % | [25] Experts Panel |
| Probability of a recurrence after the 30 days after the CDI being treated in the hospital | 66.7 % | 50.0 % | 100.0 % | Experts Panel |
| Unit costs | Medium | Minimum | Maximum | References |
| Drugs (PVL)[b] | | | | |
| Daily cost of fidaxomicin, 200 mg BID (PVL with deduction of 7.5 % in Dificlir®, 20 200-mg tablets) | €138.75 | €138.75 | €138.75 | [26] |
| Daily cost of vancomycin 125 mg QID (PVL of Vancomycin Hospira®, one 500-mg vial) | €3.45 | €3.45 | €3.45 | [26] |
| Daily cost of vancomycin 250 mg QID (PVL of Vancomycin Hospira®, one 500-mg vial) | €6.90 | €6.90 | €6.90 | [26] |
| Total cost of the tapering regimen of vancomycin (see Table 1) | €74.46 | €74.46 | €74.46 | [26] |
| Daily cost of metronidazole 500 mg TID (PVL of Metronidazole Normon®, 20 250-mg tablets) | €0.32 | €0.32 | €0.32 | [26] |
| Cost of last-resort treatment by faecal transplantation[c] | €1,191.40 | €1,191.40 | €1,191.40 | [27–29] |
| Other direct healthcare costs | | | | |
| One day of hospitalisation in the general ward | €604.50 | €525.47 | €685.00 | PP 11 CCAA |
| One day of hospitalisation in the intensive care unit | €1,134.46 | €1,021.01 | €1,247.91 | [12] |
| Severe CDI complication[d] | €9,898.44 | €7,584.58 | €12,212.31 | [12] |
| One visit to the primary care General practitioner | €35.54 | €21.54 | €53.72 | PP 9 CCAA |
| One home visit by the primary care general practitioner | €46.25 | €34.56 | €66.61 | PP 7 CCAA |
| Utilities in CDI | Medium | Minimum | Maximum | References |
| Initial, the first three days | 0.30 | 0.10 | 0.50 | [30] |
| Days 4–10 | 0.34 | 0.14 | 0.54 | [30] |
| The first 10 days after cure of CDI | 0.56 | – | – | [30] |
| After the first 10 days after cure | 0.78 | – | – | [30] |
| Reduction after a complication | 0.0 | 0.0 | 0.1 | Assumption |

*BID* twice daily, *CDI Clostridium difficile* infection, *PP CCAA* public prices of the autonomous communities, *PVL* manufacturer's selling price, *QID* four times daily, *TID* three times daily

[a] Estimated from the excess stay in Spanish patients with initial CDI, according to the proportionality of the excess stay in the patients with recurrence of CDI estimated in the CDI cost study in Spain [12]

[b] It was considered that the treatments with fidaxomicin, vancomycin and metronidazole would have a duration of 10 days

[c] It was estimated that the faecal transplantation would entail a donor blood culture (€28.45) and coproculture (€19.16), the preparation of the faeces (€53.00) and instillation in the recipient by colonoscopy (€975.38) [27–29]

[d] Toxic megacolon, perforated colon, sepsis or colectomy

UK data (Hospital Episode Statistics, HES), as Spanish data were not available [25].

The perspective of the analysis was the NHS Spanish hospital, so only direct healthcare costs were used. The currency was Euros (€) and the year for costs was 2013. The drugs acquisition cost was calculated from approved prices [26]. The cost of hospitalisations, admission to the ICU, severe CDI complications and visits to primary care general practitioners or home visits were obtained from the Spanish public healthcare prices [27–29] and from a Spanish study [12] (Table 2). The time horizon (the duration of the model) was 1 year, during which all the possible recurrences of a patient with CDI [18] were recorded.

Data on the effectiveness of the antibiotics in the treatment of CDI and the main probabilities of transition between health states used in the model were obtained from the clinical trial publications that reported the results in the specific populations studied [3–5] and from other published sources [1, 2, 31–35] (Table 3). Quality-adjusted life-years (QALYs) for the CDI patients were calculated from utilities obtained from Slobogean et al. [30] (Table 2). Whilst these utilities are from the USA rather than Spain, the values are likely to be

**Table 3** Main data on the effectiveness and safety of *Clostridium difficile* infection (CDI) treatments and the transition probabilities considered in the model

| Patients | Endpoint | OR/probability | LL 95 % CI | UL 95 % CI | References |
|---|---|---|---|---|---|
| Oncological | OR of recurrence with FID vs. VAN | 0.370 | 0.160 | 0.860 | [3] |
| | OR of recurrence with ≥2 recurrences | 0.370 | 0.160 | 1.000 | [a] |
| | OR of clinical success with FID vs. VAN | 2.000 | 0.950 | 4.220 | [3] |
| Concomitant antibiotic treatment | OR of recurrence with FID vs. VAN | 0.492 | 0.242 | 1.000 | [4] |
| | OR of recurrence with ≥2 recurrences | 0.492 | 0.240 | 1.000 | [a] |
| | OR of clinical success with FID vs. VAN | 2.333 | 1.008 | 5.402 | [4] |
| With renal impairment | OR of recurrence with FID vs. VAN | 0.487 | 0.348 | 0.682 | [5] |
| | OR of recurrence with ≥2 recurrences | 0.487 | 0.348 | 0.682 | [a] |
| | OR of clinical success with FID vs. VAN | 1.140 | 0.790 | 1.642 | [5] |
| All subjects | OR of clinical success with MET vs. VAN (first non-severe recurrence) | 1.000 | 0.030 | 2.220 | [35] |
| | OR of success with FID vs. VAN in patients with a first clinical success | 1.000 | 0.415 | 2.808 | [b] |
| | Probability of recurrence in patients without previous recurrence (30 days after the treatment) | 2.87 % | 0 % | 3.92 % | [b] |
| | Probability of the recurrence being severe | 12.2 % | 0 % | 34.3 % | [31] |
| | Probability of the complication with FID or VAN | 0.35 % | 0.10 % | 24.0 % | [1, 2, 33] |
| | Mortality attributable to CDI (day 40) | 2.04 % | 1.89 % | 2.19 % | [32] |
| | All-cause mortality | 0.019 % | 0 % | 0.241 % | [34] |

*FID* fidaxomicin, *CDI Clostridium difficile* infection, *LL 95 % CI* lower limit 95 % confidence interval, *UL 95 % CI* upper limit 95 % confidence interval, *MET* metronidazole, *OR* odds ratio; *VAN* vancomycin

[a] It was assumed that fidaxomicin reduces the probability of a first recurrence and subsequent recurrence equally, except in the UL 95 % CI of the OR with an estimated value of 1.00

[b] According to a meta-analysis of the main studies of fidaxomicin [1, 2]

representative of the Spanish population. The results from a study based on 83,000 assessments of 44 health states with EQ-5D, performed in six European countries, including Spain, demonstrated that there was greater variability among individuals than among countries [36].

Antibiotic adverse events were not included in the analysis, since the absorption of fidaxomicin and vancomycin is minimal, and no differences in the adverse events of both drugs have been observed [13, 18].

The results were presented as an incremental cost-effectiveness ratio (ICER), i.e. the cost of gaining one additional QALY with fidaxomicin compared to vancomycin. The threshold for cost-effectiveness from the Spanish NHS perspective is €30,000 per QALY gained, so for an ICER less than this, fidaxomicin would be considered a cost-effective treatment option [37]. Deterministic and probabilistic analyses were performed. Results for the base case were calculated using the median values in Table 2. Deterministic sensitivity analyses were performed: (i) using the minimum value of 10 days for the duration of the excess stay attributable to CDI [24]; (ii) calculating the estimated duration of the excess stay attributable to CDI in the three subgroups of patients at the cost-effectiveness threshold of €30,000 per QALY gained; (iii) using the assumption that the change of antibiotic treatment in the case of clinical failure would be carried out after 5 days and not after 10 days of treatment. The probabilistic analyses were performed using 2,000 Monte Carlo simulations. These simulations were performed for the following distributions of the variables: log-normal for odds ratios, beta for probabilities and gamma for resource use [38].

## Results

Fidaxomicin was found to be dominant in all three patient subgroups when compared to vancomycin. The QALYs were higher and the costs lower for patients on fidaxomicin compared to patients on vancomycin in all three subgroups.

For CDI patients with cancer, the QALYs gain for fidaxomicin patients was 0.016 QALYs and the cost saving was €2,397 per patient (Table 4A). The probability of being cost-effective was 96 % at a threshold of €30,000 per QALY gained (Figs. 2 and 3). For CDI patients with concomitant antibiotic treatment, the QALYs gained for patients treated with fidaxomicin was 0.014 QALYs and the cost saving was €1,452 per patient (Table 4B). The probability of fidaxomicin

**Table 4** Results of the cost–utility deterministic analysis. Patients with CDI and cancer (A), concomitantantibiotic treatment (B) or renal impairment (C)

| Item | Fidaxomicin | | Vancomycin | | Difference |
|---|---|---|---|---|---|
| A. Patients with cancer | | | | | |
| Clinical effects | | | | | |
| % of clinical cure without recurrence | 33.6 | | 28.1 | | 5.4 |
| % cure | 90.0 | | 86.8 | | 3.1 |
| % recurrence | 3.6 | | 5.0 | | −1.4 |
| % failure | 0.6 | | 0.9 | | −0.3 |
| % deaths | 5.8 | | 7.3 | | −1.4 |
| QALYs | 0.721 | | 0.704 | | 0.016 |
| Costs | | | | | |
| Medications | €2,384 | 14.37 % | €113 | 0.60 % | €2,271 |
| Hospitalisation | €14,131 | 85.18 % | €18,786 | 98.93 % | −€4,655 |
| Complications | €7 | 0.04 % | €10 | 0.06 % | −€3 |
| Visits to the GP | €69 | 0.41 % | €79 | 0.42 % | −€10 |
| Total costs | €16,591 | 100.00 % | €18,988 | 100.00 % | −€2,397 |
| Incremental cost-effectiveness ratio | Fidaxomicin was dominant versus vancomycin [a] | | | | |
| B. Patients with concomitant antibiotic treatment | | | | | |
| Clinical effects | | | | | |
| % of clinical cure without recurrence | 32.4 | | 28.1 | | 4.3 |
| % cure | 89.5 | | 86.8 | | 2.7 |
| % recurrence | 3.8 | | 5.0 | | −1.2 |
| % failure | 0.7 | | 0.9 | | −0.2 |
| % deaths | 6.0 | | 7.3 | | −1.3 |
| QALYs | 0.719 | | 0.704 | | 0.014 |
| Costs | | | | | |
| Medications | €2,501 | 14.26 % | €113 | 0.60 % | €2,388 |
| Hospitalisation | €14,958 | 85.30 % | €18,786 | 98.93 % | −€3,828 |
| Complications | €6 | 0.04 % | €10 | 0.06 % | −€4 |
| Visits to the GP | €71 | 0.40 % | €79 | 0.42 % | −€8 |
| Total costs | €17,536 | 100.00 % | €18,988 | 100.00 % | −€1,452 |
| Incremental cost-effectiveness ratio | Fidaxomicin was dominant versus vancomycin[a] | | | | |
| C. Patients with renal impairment | | | | | |
| Clinical effects | | | | | |
| % of clinical cure without recurrence | 32.3 | | 28.1 | | 4.2 |
| % cure | 89.3 | | 86.8 | | 2.5 |
| % recurrence | 3.8 | | 5.0 | | −1.3 |
| % failure | 0.7 | | 0.9 | | −0.2 |
| % deaths | 6.2 | | 7.3 | | −1.1 |
| QALYs | 0.717 | | 0.704 | | 0.013 |
| Costs | | | | | |
| Medications | €2,505 | 14.27 % | €113 | 0.60 % | €2,391 |
| Hospitalisation | €14,971 | 85.28 % | €18,786 | 98.93 % | −€3,813 |
| Complications | €9 | 0.05 % | €10 | 0.06 % | −1 |
| Visits to the GP | €71 | 0.40 % | €79 | 0.42 % | −9 |
| Total costs | €17,556 | 100 % | €18,988 | 100.00 % | −€1,432 |
| Incremental cost-effectiveness ratio | Fidaxomicin was dominant vancomycin[a] | | | | |

*QALYs* quality-adjusted life-years, *CDI Clostridium difficile* infection

[a] One medicinal product is dominant over another when the former is more efficacious and generates fewer costs than the latter

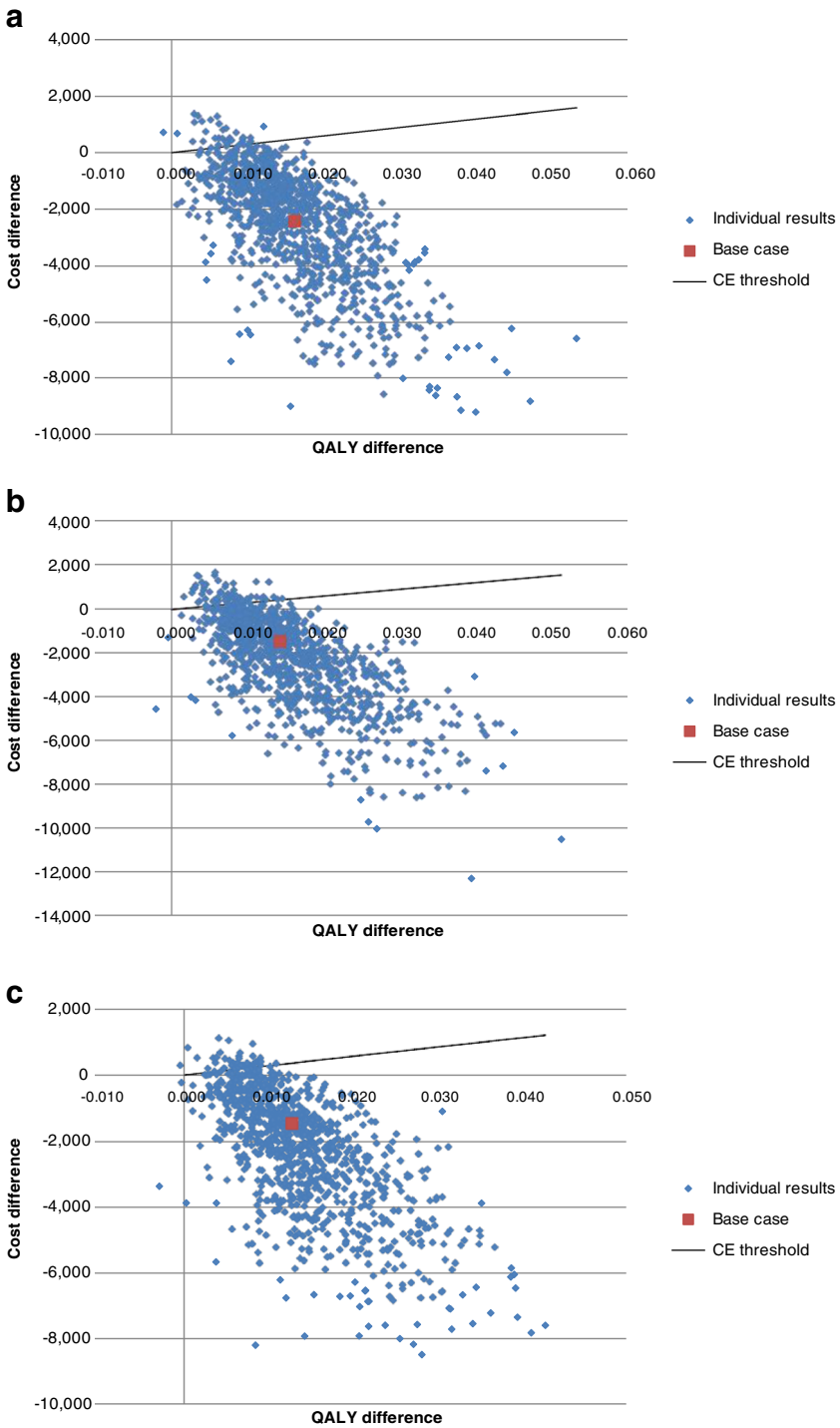


**Fig. 2** Results of the cost–utility probabilistic analysis. 2,000 Monte Carlo simulations were performed. Patients with *Clostridium difficile* infection (CDI) and cancer (a), concomitant antibiotic treatment (b) or renal impairment (c). For a cost-effectiveness (CE) threshold of €30,000 per quality-adjusted life-years (QALYs) gained, the probability of fidaxomicin being a cost-effective treatment in the Spanish populations analysed would be 96 % (a), 94 % (b) and 96 % (c)

being cost-effective was 94 % (Figs. 2 and 3). In patients with CDI with renal impairment, the QALY gain for patients treated with fidaxomicin was 0.013 QALYs and the cost saving was €1,432 per patient (Table 4C). The probability of fidaxomicin being cost-effective was 96 % (Figs. 2 and 3).

The results from the deterministic sensitivity analyses indicated that, for all the subgroups, fidaxomicin remained the dominant treatment when the mean duration of excess hospital stays attributable to CDI was 10 days, and also when the change of antibiotic treatment in the case of failure is carried out after 5 days of treatment instead of 10 days. At the cost-effectiveness threshold of €30,000 per QALY gained, the threshold duration of excess stay attributable to CDI, initial CDI or recurrent CDI, was 5.8 days

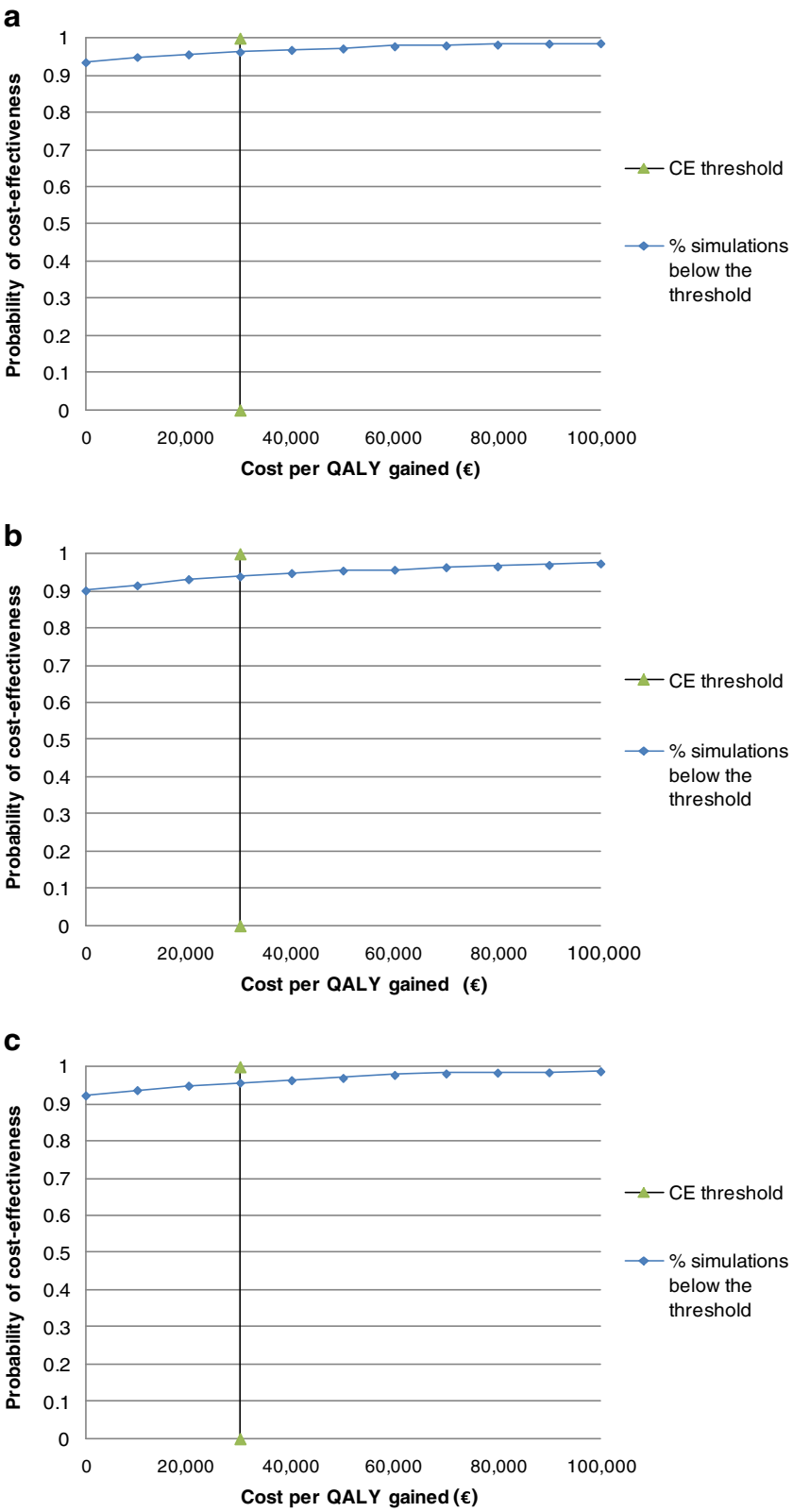


**Fig. 3** Acceptability curves obtained from the probabilistic cost–utility analysis. Patients with CDI and cancer (a), concomitant antibiotic treatment (b) or renal impairment (c). For a cost-effectiveness threshold of €30,000 per QALY gained, the probability of fidaxomicin being a cost-effective treatment in the Spanish populations analysed would be 96 % (a), 94 % (b) and 96 % (c)

in cancer patients, 7.8 days in concomitant antibiotic patients and 8.1 days in renally impaired patients. As these durations of excess stay are below the range of excess hospital stay observed in Spain [6, 23, 24], this analysis further demonstrates fidaxomicin to be a cost-effective treatment option for these patients.

## Discussion

This study found that fidaxomicin is a cost-effective treatment option compared to vancomycin in CDI patients with cancer or concomitant antibiotic treatment or renal impairment. This result is driven by the clinical data that have demonstrated that fidaxomicin is superior to vancomycin in preventing recurrences of CDI.

As with all economic analyses using decision analytic modelling, the results are subject to limitations based on the applicability of clinical trial data to clinical practice. In addition, there will also be aspects of clinical practice that are not accounted for in the model. However, these have been minimised by using economic analysis performed by means of a model recently published [17–21] with probabilistic Monte Carlo analyses [39], which made it possible to test the robustness of the results, in comparison with the deterministic models. All the costs used in the model were taken from Spanish sources [12, 26]. The cost-effectiveness analysis results of the model were very stable in the three subgroups according to the results of the probabilistic analysis.

It is widely acknowledged that the economic burden of CDI is driven by the number of hospitalisation days [40]. Several studies report a significant health economic burden associated with CDI, but with variable quality of data [41, 42]. A well-designed study published in 2013 [23] was performed to quantify additional hospital stay attributable to CDI in four European countries (England, Germany, Spain and The Netherlands) by analysing nationwide hospital episode data. Multivariate regression and propensity score matching models were developed to investigate the impact of CDI on additional length of hospital stay, controlling for confounding factors such as underlying disease severity [23]. According to the results of the propensity score matching techniques, attributable lengths of stay due CDI during hospitalisation range from 15.31 days (Spain) to 32.42 days (England). Therefore, this study confirms the high variability and uncertainty of this variable.

In our analysis, we chose to take as the value for the base case that obtained in the study of Eckmann et al. [23] (15.31 days). To perform probabilistic analysis (second-order Monte Carlo simulation), we selected a minimum and maximum value for this variable. The minimum value (10 days) was obtained from a retrospective matched-cohort study conducted among Spanish patients [24]. In the absence of Spanish data on the maximum value of the extended stay attributable to CDI, it was necessary to make an estimate based on the experience of the Spanish panel of clinical experts. According to a study on CDI cost in Spain [12], the extended stay due to CDI can be up to 27.3 days when recurrences or outbreaks occur. In this regard, the expert panel decided to take a value of 26 days. This value is equal to the crude median extended stay obtained in the cohort study by Monge et al. [6] but, in reality, it does not correspond to the crude value but, instead, the estimated value attributable to the CDI. According to the authors of this study, the maximum extended stay value used in the model is clinically plausible according to their experience. This assumption was conservative, since the alternative would have been to take the value of 27.3 days from the previous Spanish study [12] or the maximum value observed in England (32.42 days) [23]. However, as this is the most critical variable of the analysis (we must clarify that it is the same for both treatments), it was explored further in the deterministic and probabilistic sensitivity analyses. In this regard, in the deterministic sensitivity analysis, fidaxomicin was cost-effective versus vancomycin, even with excess stay as low as 5.8, 7.8 and 8.1 days for the cancer, concomitant antibiotic therapy and renal impairment subgroups, respectively. These values are below the minimum value used in the sensitivity analysis (10.0 days). This means that, even with extensions for CDI hospital stays well below those observed or estimated used in the model, fidaxomicin would remain cost-effective compared to vancomycin in the three subgroups of patients analysed. However, fidaxomicin would not be cost-effective for excess stay below those values.

The model does not include the comparison with metronidazole, because the clinical trials were limited to a comparison of fidaxomicin versus vancomycin. It is assumed, when the first recurrence of CDI is not severe, that the treatment is with metronidazole (in both the fidaxomicin and vancomycin arms) at the dose of 500 mg TID (1,500 mg/day). It is assumed that severe recurrences are treated with fidaxomicin (in the fidaxomicin arm) or with vancomycin (in the vancomycin arm). Both assumptions were validated by Spanish clinical experts.

The model was conservative in that it omitted costs associated with transmission, patient isolations or infection control measures (e.g. the use of disposable gloves, gowns and thermometers). If these factors were included in the model, the results would be expected to be more favourable for fidaxomicin due to the reduction in recurrences.

The structure of this model is the same as the model structure used in three European studies, performed in Scotland [19], Belgium [20] and Ireland [21]. These models did not analyse the subgroups of CDI patients with cancer, renal impairment or concomitant antibiotics. In the Irish and Scottish cost-effectiveness models, fidaxomicin was compared to oral metronidazole (in the initial treatment or in the first recurrence in patients with non-severe CDI) by means of an indirect treatment comparison [17, 21] and to oral vancomycin (in severe CDI or as of the second recurrence). According to the Irish analysis, fidaxomicin was the dominant treatment in comparison with the current management of the disease, with a probability of cost-effectiveness of 82 % at a cost-effectiveness threshold of €45,000 per QALY gained [21]. In the Belgium model, fidaxomicin was dominant versus metronidazole and vancomycin in all patients with CDI and also in

the subgroup of severe cases. In the Belgium model, at a willingness to pay threshold of €30,000 per QALY gained, the probability of fidaxomicin being cost-effective was 80 % [20]. In Scotland, the advice from the Scottish Medicines Consortium was for fidaxomicin to be used for the treatment of adults with a first CDI recurrence on the advice of local microbiologists or specialists in infectious diseases [19].

In an analytical decision model comparing four strategies in the management of recurring CDI, metronidazole, vancomycin, fidaxomicin and faecal microbiota transplantation (FMT) by colonoscopy, FMT was estimated to be the most cost-effective option [43, 44]. In one study, fidaxomicin was regarded as a cost-effective option when the acquisition cost did not surpass $1,359 at a willingness-to-pay threshold of $50 000 per QALY gained [43, 44]. The current acquisition cost of fidaxomicin in Spain is less than $1,818. The model used in this study included patients stratified by severity, but it was not applied to the specific patient subgroups (cancer, renal impairment, concomitant use of antibiotics). As the efficacy and safety profile of FMT in immunocompromised patients is unknown, the cost-effectiveness of FMT for these CDI patient subgroups is also unknown. Further studies on the clinical efficacy of FMT versus fidaxomicin for the treatment of CDI have been proposed [45].

One study reported that fidaxomicin could be regarded as a cost-effective option in countries where the isolation rates of the NAP1/BI/027 strains were below 50 % [46], an epidemic ribotype that has not been seen in Spain [9].

Fidaxomicin has been associated with lower rates of recurrences [−9.9 %; 95 % confidence interval (CI), −16.6 to −2.9 %; $p<0.005$] [2] and higher rates of sustained cure (13.2 %; 95 % CI, 5.3 to 21.0 %; $p=0.001$) [1] than vancomycin and is non-inferior to vancomycin in terms of clinical cure [1, 2]. The acquisition cost of fidaxomicin is greater than the acquisition cost of vancomycin. However, a medicinal product with a higher acquisition cost may be more cost-effective compared to a medicinal product with a lower acquisition cost, due to the economic impact of other variables that must be included in the cost calculation [47]. According to the model presented in this paper, this hypothesis appears to hold true for fidaxomicin compared to vancomycin in certain patient subgroups.

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**Contributions of the authors** A. Toledo, C. Rubio-Terrés and D. Rubio-Rodríguez made the adaptation of the economic model. C. Rubio-Terrés, D. Rubio-Rodríguez and A. Toledo wrote the first and subsequent versions of the manuscript. All the authors contributed to the fruitful discussion of the results and to the review of the different versions of the manuscript. C. Rubio-Terrés is the guarantor of the overall content of the paper.

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