Is Fidaxomicin Worth the Cost? An Economic Analysis

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Background. In May 2011, the Food and Drug Administration approved fidaxomicin for the treatment of Clostridium difficile infection (CDI). It has been found to be noninferior to vancomycin; however, its cost-effectiveness for the treatment of CDI remains undetermined.

Methods. We developed a decision analytic simulation model to determine the economic value of fidaxomicin for CDI treatment from the third-party payer perspective. We looked at CDI treatment in these 3 cases: (1) no fidaxomicin, (2) only fidaxomicin, and (3) fidaxomicin based on strain typing results.

Results. The incremental cost-effectiveness ratio for fidaxomicin based on screening given current conditions was >$43.7 million per quality-adjusted life-year and using only fidaxomicin was dominated (ie, more costly and less effective) by the other 2 treatment strategies explored. The fidaxomicin strategy tended to remain dominated, even at lower costs. With approximately 50% of CDI due to the NAP1/BI/027 strain, a course of fidaxomicin would need to cost ≤$150 to be cost-effective in the treatment of all CDI cases and between $160 and $400 to be cost-effective for those with a non-NAP1/BI/027 strain (ie, treatment based on strain typing).

Conclusions. Given the current cost and NAP1/BI/027 accounting for approximately 50% of isolates, using fidaxomicin as a first-line treatment for CDI is not cost-effective. However, typing and treatment with fidaxomicin based on strain may be more promising depending on the costs of fidaxomicin.

Keywords. fidaxomicin; Clostridium difficile; treatment; economics; cost.

Clostridium difficile is a nosocomial infection that causes substantial morbidity, mortality, and healthcare costs [1–3]. Clostridium difficile infection (CDI) causes a wide range of clinical disease and is the leading cause of infectious diarrhea in hospitalized patients, particularly affecting elderly and frail patients [2, 3]. Treatment of CDI is challenging [2, 4, 5], even though several treatment strategies exist. Recurrences are of primary concern and add an additional complication to treatment of CDI [6].

In May 2011, the Food and Drug Administration (FDA) approved fidaxomicin, a new macrocyclic antibiotic, for the treatment of CDI [7]. Clinical studies have shown this drug to be just as efficacious as vancomycin in the clinical treatment of CDI [8, 9]. It has a similar cure rate but results in a lower incidence of recurrence when used in the treatment of the non–North American pulsed field type 1 and polymerase chain reaction ribotype 027 (NAP1/BI/027) strain [8, 9].

The NAP1/BI/027 strain is quite widespread and has been implicated in outbreaks worldwide; it accounts for approximately 50% of isolates and is prevalent in North America, having been identified in 40 states, several provinces in Canada, and throughout Europe [10–12]. The NAP1/BI/027 strain has increased production of toxins A and B, production of binary toxin, and fluoroquinolone resistance [2]. Although this strain is thought to cause more severe episodes of CDI, as opposed to nonsevere disease, debate remains as some studies show that severity is not different by strain [2, 10, 13].
Recurrent CDI is a difficult and increasingly common challenge associated with CDI management; up to 25% of patients have a recurrence and this rate may increase with the number of CDI episodes a patient experiences [4, 14]. Costs of CDI also increase with the number of CDI episodes [15–18]. The cost per episode to treat recurrent CDI is an estimated $4948, but varies on the basis of management (ie, inpatient vs outpatient treatment) [19, 20]. Thus, although comparative effectiveness studies have been performed on various C. difficile treatments, finding no antimicrobial agent to be superior for the initial cure of nonsevere CDI, treatment with fidaxomicin does result in fewer recurrences in non-NAP1/BI/027 strains [21]. This begs the question of whether the use of fidaxomicin might be a cost-effective treatment for CDI despite its higher drug costs when compared to metronidazole and, to a lesser extent, oral vancomycin.

The cost-effectiveness of fidaxomicin for the treatment of CDI remains undetermined. In this study, we constructed a decision analytic simulation model to evaluate the economic value of fidaxomicin for the treatment of CDI (either first episode or first recurrence), comparing the cost-effectiveness of CDI treatment in these 3 cases: (1) no use of fidaxomicin, (2) only use of fidaxomicin, and (3) fidaxomicin use based on strain typing results. Our hope is that clinicians, policy makers, and third-party payers would be able to use the results of this model to determine the best treatment strategy and reimbursement rates.

METHODS

We developed a decision analytic simulation model using TreeAge Pro 2009 (TreeAge Software, Williamstown, Massachusetts) to determine the economic value of fidaxomicin for the treatment of C. difficile from the third-party payer perspective. Figure 1 provides an outline of our model, and Table 1 displays its input parameters with values and sources.

All patients entering the model had CDI (either first episode or first recurrence) and could receive fidaxomicin as drug treatment in 1 of the following 3 scenarios:

1. No fidaxomicin: a patient’s drug regimen was based on disease severity and he/she could receive either metronidazole (nonsevere CDI) or vancomycin (severe CDI).

2. Only fidaxomicin: all CDI patients received fidaxomicin, regardless of disease severity and C. difficile strain (as strain typing is currently not standard of care and is not included in this scenario; therefore, patients with the NAP1/BI/027 strain would receive fidaxomicin in this scenario).

3. Fidaxomicin based on strain typing results: screening for the NAP1/BI/027 strain utilized the Xpert C. difficile/Epi test, manufactured by Cepheid (Sunnyvale, California) and assumed a turnaround time of <1 day [22]; patients with the NAP1/BI/027 strain (positive test result) received either metronidazole or vancomycin based on CDI’s severity, whereas those with negative tests received fidaxomicin.

The CDI cases were defined by the studies providing our probability input data; CDI was classified as severe if it caused or contributed to the patient’s death (within 30 days), required an intensive care unit admission, or resulted in a colectomy [23, 24]. All other cases were classified as nonsevere CDI. Treatment and dosing followed the Society for Healthcare Epidemiology of America and Infectious Diseases Society of America clinical practice guidelines [25]. Patients treated with oral metronidazole received 500 mg, 3 times daily for 10–14 days, and those treated with oral vancomycin received 125 mg, 4 times daily for 10–14 days. Patients receiving fidaxomicin were given 200 mg orally, 2 times daily for 10 days [8]. Patients had a probability of clinical cure (defined as resolution of symptoms and no need for further therapy as of the second day after the end of the therapy course) and a probability of recurrence, based on the treatment regimen used (Table 1). These clinical outcomes were based on C. difficile strain for vancomycin and fidaxomicin, but were determined by severity for metronidazole, due to a lack of published data for metronidazole efficacy and recurrence rates by strain. The model considered only 1 recurrence of CDI.

Each simulation run sent 1000 CDI patients (≥18 years old) through the model 1000 times for a total of 1 000 000 trials. For each run, the following formula calculated the incremental cost-effectiveness ratio (ICER):

\[
\text{ICER} = \frac{\text{Cost}_{\text{Option A}} - \text{Cost}_{\text{Option B}}}{\text{Effectiveness}_{\text{Option A}} - \text{Effectiveness}_{\text{Option B}}}
\]

where A and B are 2 of the 3 different fidaxomicin treatment options and effectiveness was measured in quality-adjusted life years (QALYs). ICERs ≤$50 000 per QALY were considered to be cost-effective [26]. A treatment option was deemed to dominate another treatment option when it saved both costs and QALYs (ie, more cost savings and health benefits).

Patients received QALY values based on their age and CDI severity for the duration of their illness. QALY decrements for noninfectious diarrhea were used as a proxy for diarrhea caused by C. difficile due to lack of more specific estimates. Patient age was determined by statistics for C. difficile, Internal Classification of Diseases, Ninth Revision code 008.45, from the Healthcare Utilization Project (HCUP) [27]. Those who experienced a recurrence were also attributed a QALY decrement for the duration and severity of their recurrence.

The third-party payer perspective considered the direct costs of illness (ie, hospitalization, drug treatment, and diagnosis)
and when performed, the cost of strain typing. The hospitalization cost, derived from HCUP [27], includes all service charges (converted to costs) associated with a patient’s hospital stay, including room and board (eg, if the patient had additional charges for being in a private room that should be included). Costs that do not lead to charges for a specific patient (eg, general infection control) should not be included. For patients experiencing a recurrence, only the cost of hospitalization for that episode was considered, as the subsequent drug treatment would be unknown. All costs were in 2012 US$, using a 3% discount rate to convert costs from other years.

Sensitivity analysis varied key parameters in the model to determine their effect on the cost-effectiveness of CDI treatment strategies and select parameters were tested jointly in a 2-way sensitivity analysis. The cost of fidaxomicin was varied from a baseline of $3360 (current cost) [21] to half of this value ($1680) for the full course and was also set to the cost of vancomycin and metronidazole. We also varied the probability of having the NAP1/BI/027 strain, the probability of CDI recurrence given the NAP1/BI/027 strain, and the cost of strain typing. In addition, probabilistic sensitivity analysis simultaneously varied all the parameters throughout their ranges listed in Table 1.

RESULTS

Figure 2A is a region graph of the net benefits for the 3 drug treatment strategies tested as the cost of fidaxomicin, and the probability of the NAP1/BI/027 strain are varied across the ranges of the sensitivity analysis. The regions of the plot denote the strategy that is most effective (ie, optimal) within the $50 000 per QALY threshold for the given values (ie, it is the
Table 1. Model Input Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range or Standard Error</th>
<th>Reference</th>
</tr>
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<tr>
<td>Costs, US$ 2012</td>
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<tr>
<td>Hospitalization</td>
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<td>Ages 18–44 y</td>
<td>8815</td>
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<td>[27]</td>
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<td>Ages 45–64 y</td>
<td>11158</td>
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<td>[27]</td>
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<tr>
<td>Ages 65–84 y</td>
<td>11820</td>
<td>254.3</td>
<td>[27]</td>
</tr>
<tr>
<td>Age ≥85 y</td>
<td>10634</td>
<td>222.1</td>
<td>[27]</td>
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<tr>
<td>Strain typing</td>
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<td>Treatment, per d</td>
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<tr>
<td>Metronidazole, oral</td>
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<td>2.51</td>
<td>[31]</td>
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<tr>
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<td>[31]</td>
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<tr>
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<td>[21]</td>
</tr>
<tr>
<td>Probabilities</td>
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<td></td>
<td></td>
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<tr>
<td>NAP1/BI/027 strain</td>
<td>0.517</td>
<td>0.189</td>
<td>[8, 12, 13, 23–37]</td>
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<td>Severe disease</td>
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<tr>
<td>NAP1/BI/027 strain</td>
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<td>0.0679</td>
<td>[23, 24, 35]</td>
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<tr>
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<td>0.0642</td>
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<tr>
<td>NAP1/BI/027 strain</td>
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<td></td>
<td></td>
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<tr>
<td>Vancomycin</td>
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<td>0.018</td>
<td>[8, 9]</td>
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<td>Fidaxomicin</td>
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<td>0.102</td>
<td>[8, 9]</td>
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<td>0.029</td>
<td>[8, 9]</td>
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<tr>
<td>Fidaxomicin</td>
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<td>0.014</td>
<td>[8, 9]</td>
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<td>Nonsevere disease</td>
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<tr>
<td>Metronidazole</td>
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</tr>
<tr>
<td>Recurrence</td>
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<td>NAP1/BI/027 strain</td>
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<tr>
<td>Vancomycin</td>
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<td>0.121</td>
<td>[8, 9]</td>
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<td>Fidaxomicin</td>
<td>0.247</td>
<td>0.035</td>
<td>[8, 9]</td>
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<td>Other strain(s)</td>
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<td>0.005</td>
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<td>Fidaxomicin</td>
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<td>[8, 9]</td>
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<td>Xpert sensitivity</td>
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<td>[22]</td>
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<tr>
<td>Xpert specificity</td>
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<td>[22]</td>
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<tr>
<td>Durations, d</td>
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<tr>
<td>Length of stay</td>
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<tr>
<td>Ages 18–44 y</td>
<td>5.2</td>
<td>0.1</td>
<td>[27]</td>
</tr>
<tr>
<td>Ages 45–64 y</td>
<td>6.4</td>
<td>0.1</td>
<td>[27]</td>
</tr>
<tr>
<td>Ages 65–84 y</td>
<td>7.4</td>
<td>0.1</td>
<td>[27]</td>
</tr>
<tr>
<td>Duration of drug treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole, oral</td>
<td>10–14</td>
<td></td>
<td>[25]</td>
</tr>
<tr>
<td>Vancomycin, oral</td>
<td>10–14</td>
<td></td>
<td>[25]</td>
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<tr>
<td>Fidaxomicin</td>
<td>10</td>
<td></td>
<td>[8, 21]</td>
</tr>
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<td>Utilities, QALY weights</td>
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<td></td>
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<tr>
<td>Baseline QALY, ages 18–64 y</td>
<td>0.92</td>
<td></td>
<td>[39]</td>
</tr>
<tr>
<td>Baseline QALY, ages ≥65 y</td>
<td>0.84</td>
<td></td>
<td>[39]</td>
</tr>
<tr>
<td>Nonsevere disease</td>
<td>0.88</td>
<td></td>
<td>[40, 41]</td>
</tr>
<tr>
<td>Severe disease</td>
<td>0.817</td>
<td></td>
<td>[40–42]</td>
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</table>

Abbreviation: QALY, quality-adjusted life year.

strategy that “buys” the most QALYs for $50,000). It should be noted that the most effective strategy is not necessarily the most cost-effective or the one with the lowest ICER. As can be seen, drug treatment with only fidaxomicin is the optimal strategy only when it cost < $496 for a full course and the probability of NAP1/BI/027 is < 48%. As the figure shows, fidaxomicin based on strain type is most effective only under narrow conditions, at the test’s current cost. In general, and under current economic and epidemiologic conditions (denoted in the Figure), not giving fidaxomicin (ie, treatment with only metronidazole or vancomycin) is the most effective drug regimen for the treatment of C. difficile. The ICER value for fidaxomicin based on strain typing given current conditions was $43.7 million/QALY. Giving everyone fidaxomicin was dominated by the other 2 treatment strategies, which were less costly and more effective.

Even when the cost of fidaxomicin was varied across relatively wide ranges, ICER values remained high and the “only fidaxomicin” strategy tended to remain more costly and less effective than the other treatment strategies. Even at the same cost as the full course of vancomycin (ie, $1032), “no fidaxomicin” was still the best strategy (other strategies were dominated by “no fidaxomicin” or had ICERs > $8.8 million per QALY), given the baseline probability of NAP1/BI/027 and assuming that metronidazole is equally effective for both NAP1/BI/027 and non-NAP1/BI/027 strains. At lower costs, use of fidaxomicin becomes the optimal strategy (Figure 2). Fidaxomicin based on strain typing (baseline cost: $35.50) becomes the dominant strategy (ie, less costly and more effective) when the cost of fidaxomicin was between $160 and $400 for a full treatment course, given the baseline probability of the NAP1/BI/027 strain. At costs ≤ $150 for a full treatment course (including when fidaxomicin was the same cost as a full course of metronidazole, $59), giving all CDI patients fidaxomicin was the best strategy (baseline values).

For testing strategies where strain type is unknown, if fidaxomicin were to reduce the recurrence rate for the NAP1/BI/027 strain as effectively as it does for other strains (about 10% recurrence rate), the full treatment course would have to cost < $430 (Figure 2B) in order to be the optimal treatment strategy. As shown, when the probability of recurrence with the NAP1/BI/027 strain given fidaxomicin treatment reaches 14%, treatment with fidaxomicin is no longer the most effective at any tested cost (≥ $5).

Varying the cost of molecular typing had little impact and showed a similar trend to that shown in Figure 2A. The strain typing strategy was cost-effective when typing cost $5 or $15 and fidaxomicin cost ≤ $481, when typing was $50 and fidaxomicin ≤ $445, and when typing cost $100 and fidaxomicin cost ≤ $390. The probability of having the NAP1/BI/027 strain had a negligible effect on this result.
DISCUSSION

Our results show that given the current CDI epidemiologic conditions (approximately 50% of isolates NAP1/BI/027) and fidaxomicin’s cost, treatment with fidaxomicin is not cost-effective. Given these conditions, fidaxomicin would need to cost ≤$150 to be cost-effective in the treatment of all CDI cases and between $160 and $400 to be cost-effective for those with a non-NAP1/BI/027 strain (ie, treatment based on strain typing). Even when changing the proportion of CDI that is the NAP1/BI/027 strain, fidaxomicin treatment remained not cost-effective at its current cost. Unpublished data presented at IDWeek 2012 suggest that 28% of CDI is NAP1/BI/027 (from sites across 10 states) [28]; under these conditions, giving fidaxomicin to all CDI patients...
was the optimal strategy when a full course cost <$500; at higher costs “no fidaxomicin” was still the most effective treatment regimen.

Treatment of CDI with fidaxomicin should be considered for recurrent infection when (1) C. difficile typing is available and a non-NAP1/BI/027 strain is identified and (2) typing is not available and a patient does not respond to the treatment regimen used during his/her first episode [29]. However, using a molecular typing test to identify the NAP1/BI/027 strain is not standard of care. Our model utilizes the Xpert C. difficile/ Epi test, which has been approved by the FDA for epidemiologic purposes and has a turnaround time of about 45 minutes [22]; however, other strain typing tests may take longer to perform. As tests evolve and become faster, strain typing for clinical purposes may become a practical option. In addition, many factors may influence the use of fidaxomicin to treat CDI including a clinician’s willingness to prescribe, safety data, local incidence patterns of CDI and recurrences, and costs, including both drug costs and recurrence costs [21].

The economic value of fidaxomicin may change with changes in the proportion of C. difficile infections that are NAP1/BI/027 versus non-NAP1/BI/027 strains, changes in the treatment recommendations offered by guidelines, or changes in the cost of alternative therapies. For example, if the NAP1/BI/027 strain becomes more widespread, causing more outbreaks and potentially causing more severe disease, the cost-effectiveness of fidaxomicin may become lower, giving its lesser effectiveness for the NAP1/BI/027 strain. Additionally, if the cost of vancomycin were to decrease (eg, generic oral vancomycin becomes available), the value of fidaxomicin would become even less favorable. The economic value may also change if CDI treatment recommendations were altered (eg, if vancomycin became the recommended first-line treatment for all CDI per national guidelines).

The use of fidaxomicin for the treatment of CDI would be cost-effective if its current price were to decrease. An epidemiologic study estimated the warranted price per day of fidaxomicin compared to various formulations of vancomycin, finding that fidaxomicin would need to cost <$400 for a full course of treatment [30].

Our model attempted to be conservative about the drug treatments utilized. We only considered 1 recurrence and the hospitalization costs associated with it. Only those clinical outcomes affected by drug treatment (ie, clinical cure and recurrence) were considered; we did not look at more severe outcomes such as surgery or mortality. The use of vancomycin may be underestimated in our study as it is often used as first-line therapy for patients with additional complications such as acute renal failure or a high white blood cell count, which were not factors that were considered in the studies available that defined severe CDI. Additionally, the only QALY estimates available for diarrhea are for noninfectious diarrhea and may be conservative, as these values may underestimate the health effects of the more acute and severe diarrhea caused by C. difficile.

Limitations
Models, by definition, are simplifications of real life and cannot represent every CDI event or outcome. We did not consider the impact of CDI treatments in less typical presentations, such as in those with irritable bowel syndrome or immunosuppression. Our model inputs were derived from different studies of varying quality. There is a lack of data on the effectiveness of fidaxomicin compared to metronidazole and on the effectiveness of metronidazole on CDI’s strains; we assumed that metronidazole was equally effective in the treatment of both the NAP1/BI/027 and non-NAP1/BI/027 strains.

CONCLUSIONS
Our model suggests that, on average, when approximately 50% of isolates are NAP1/BI/027, when patients are having their first CDI episode or recurrence, and given the current costs of fidaxomicin, its use in the treatment of CDI is not cost-effective; however, it may be beneficial in some specific circumstances, such as when patients have had multiple recurrences in the setting of guideline-recommended treatments with metronidazole and vancomycin. Molecular typing and treatment with fidaxomicin based on strain may be more promising depending on the costs of fidaxomicin and typing. Future research should examine the effectiveness of treatment, stratifying by both strain and severity, as well as compare the use of fidaxomicin to metronidazole for the treatment of nonsevere disease.

Notes
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Potential conflicts of interest. All authors: No reported conflicts.

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