Savings from the use of a probiotic formula in the prophylaxis of antibiotic-associated diarrhea

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Original article

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Antibiotic-associated diarrhea – Clostridium difficile-associated diarrhea – Cost-minimization analysis – Nosocomial infections

Abstract

Objective:
Antibiotic-associated diarrhea (AAD) and particularly Clostridium difficile-associated diarrhea (CDAD) are the most common causes of healthcare associated infectious diarrhea. A double-blind, dose response, placebo-controlled trial of the probiotic formula (Bio-K+ Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R formula) for prophylaxis of AAD and CDAD was published in 2010. The Bio-K+ Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R formula is a registered trademark of Bio-K Plus International Inc. (Laval, Quebec, Canada). Results indicated that the incidence of AAD and CDAD were lower for patients assigned to the probiotic formula compared with the placebo option. The present study aims to estimate the savings in direct medical costs that might result from the use of two different doses of the probiotic formula vs placebo.

Methods:
A cost-consequence analysis was conducted to compare the two doses of the probiotic formula compared to placebo. The analysis was based upon published data and adjusted to the North American context.

Results:
economic analyses showed that the use of the probiotic formula would result in estimated mean per patients savings of US$1968 for the single dose and US$2661 for the double dose compared with the placebo option if used an average of 13 days by all patients at risk of developing AAD and CDAD.

Limitations:
Several key parameters considered within the economic model were not captured within the Gao et al. study. Numerous sensitivity analyses were conducted to address this issue.

Conclusion:
The use of the probiotic formula in prophylaxis of AAD and CDAD would lead to estimated savings in direct medical costs that would substantially offset its acquisition cost. Treating 1000 hospitalized patients on antibiotics with the double dose of the product compared to current practice would save a single payer system the sum of $2,661,218.

Introduction

Antibiotic-associated diarrhea (AAD) is a leading complication of the administration of the majority of antibiotics1. Particularly, Clostridium Difficile-associated diarrhea (CDAD), a form of AAD, is a common cause of healthcare-associated infectious diarrhea in acute and chronic care facilities2. The spectrum of symptoms caused by Clostridium difficile (CD) is extremely wide ranging from the asymptomatic carrier status to fulminant colitis, toxic megacolon, and death3. The epidemiology of CD has changed through time, with a clear tendency towards increased incidence and prevalence as well as the
appearance of an extremely virulent strain. Between 300,000–500,000 cases occurred in the US in 2005, which corresponds to a 200% rise in number of cases within a 5-year period.

Probiotic products have been proposed as a preventive measure to avoid AAD as well as CDAD. The World Health Organization and the Food and Agriculture Organization of the United Nations define a probiotic as living micro-organisms that, when administered in sufficiently high concentration, have benefits for the health of the host.

Until now published trials on the use of probiotic products to prevent AAD and CDAD have not been conclusive. In particular they are under-powered due to inadequate sample size.

Recently, Gao et al. published a randomized, double-blind, dose response, placebo-controlled trial using a probiotic formula (Bio-K+ Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R) for prophylaxis of AAD and CDAD. The Bio-K+ Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R formula is a registered trademark of Bio-K Plus International Inc. (Laval, Québec, Canada). This trial, conducted in 2008–2009, showed that this proprietary probiotic formula reduces, in a dose-dependent manner, the incidence of AAD and CDAD in hospitalized patients receiving antibiotics.

The objective of the present study was to estimate the consequences in direct medical costs that might result from the use of the probiotic formula in two different doses to reduce the risk of AAD and, in particular, CDAD in hospitalized patients on antibiotics in a North American context. The study was done from the perspective of a single payer system. A sensitivity analysis was done to evaluate the applicability of our results to a North American context. A sub-analysis was also done from the perspective of a hospital pharmacy.

**Methods**

**Patients and economic-effectiveness outcomes**

The Gao et al. trial was conducted in 2008–2009 in China. Details of the trial's protocol have been published in the American Journal of Gastroenterology. Briefly, 255 patients were chosen, aged from 50–70 years, hospitalized for 5 or more days, for various types of infections, and who received antibiotic therapy (penicillin, cephalosporin, or clindamycin (lyncomycin) for at least 3 days but no more than 14 days. Patients were randomized into one of the three study groups: two probiotic formula capsules per day (Pro-2, n = 86), one probiotic formula capsule and one placebo capsule per day (Pro-1, n = 85), or two placebo capsules per day (Placebo, n = 84). Each capsule contained 50 billion colony-forming units. Patients received the initial dose of the assigned intervention within 36 h of their prescribed antibiotic therapy, and continued daily usage of the product for 5 additional days after completion of their antibiotics (13 days, on average). Patients were then followed for an additional 21 days after completion of the assigned intervention.

Hence, the study compared the three groups to each other Pro-2, Pro-1, and Placebo. Placebo was considered, in the absence of other alternative drug currently and universally accepted for prophylaxis, as the best comparator. The pertinent economic effectiveness variables and outcomes and their baseline estimates and ranges used in the economic model are summarized in Table 1. They were the incidence of AAD, the incidence of CDAD, the length of anti-CDAD treatment, and the number of days with diarrhea which, in our analysis, we used as a proxy for the length of the hospitalization.

**Healthcare costs**

We only estimated the direct medical costs of AAD and CDAD from a single-payer perspective and we did not consider direct non-medical costs, indirect costs, or intangible costs. We actualized all values into 2009 US$ using the appropriate medical care components of the Consumer Price Index.

Total costs included hospital costs. The hospital costs included those of the microbiological testing to identify CD bacteria, the pharmaceutical agents, and the hospitalization stay. The pharmaceutical agents which were part of our evaluation included the probiotic formula and the antibiotics used in the case of CDAD infections, metronidazole, and/or vancomycin. Antibiotic costs were estimated using the average wholesale prices derived from the 2006 Edition of the Red Book.

The hospitalization costs were calculated using the median cost of a hospitalization for a CDAD-infected patient in the US derived from the study by Song et al.

Although none of the patients in the original study experienced a CDAD reinfection in 21 days following discharge, our economic model estimated a possible reinfection and subsequent rehospitalisation in the 2 months following the initial discharge based upon the Sunenshine and McDonald review paper.

**Model description**

Figure 1 presents the decision tree of our economic model. Our economic model was developed using the Oracle Crystal Ball program (Oracle, Redwood Shores, CA), an add-on Microsoft Excel (Microsoft Corp., Redmond, WA) based program. The decision tree shows that, within each option, a patient could end up in any of the eight different sub-branches (Figure 1). For example, a patient model...
could develop AAD. The AAD could or could not be caused by CD. If the AAD is caused by CD, the patient will receive anti-CDAD antibiotics which could be either metronidazole or vancomycin as a first line treatment. If a patient receives metronidazole, the infection could be sensitive to metronidazole and then subside following treatment with this drug. If the infection is resistant to metronidazole, the patient will be treated with a vancomycin regimen as a second line intervention, or he may have received vancomycin as a first line treatment, in both cases the infection is assumed to subside following the vancomycin regimen. The model also assumes that, regardless of the treatment used in the initial infection, patients may develop a reinfection within 2 months of discharge and will be treated with an in-hospital 10-day vancomycin regimen. The reinfection is assumed to subside following the 10-day vancomycin regimen.

Cost of AAD

The cost of screening for CD of all patients with AAD was included. The cost of AAD patients screening for CDAD was calculated for the different options (Placebo, Pro-1, and Pro-2) by multiplying the number of patients with AAD in the different groups (Placebo group [44.1%], Pro-1 group [28.2%], Pro-2 group [15.5%]) by the cost of the screening for CD. We also added the cost of all the sequences incorporated when CDAD developed.

Cost of CDAD

The cost of the Placebo option was calculated by multiplying the number of CDAD cases in the Placebo group (23.8%) by the cost of 10 days of anti-CDAD antibiotic treatment (metronidazole and/or vancomycin). The cost of the probiotic formula options was calculated by multiplying the number of CDAD cases in the Pro-1 and Pro-2 groups by the cost of the probiotic treatment.
groups (respectively, 9.4% and 1.2%) by the cost of 10 days anti-CDAD antibiotics treatment (metronidazole and/or vancomycin). In addition, the cost of a 13 day probiotic formula treatment (one or two tablets depending on group assignment) was added to each patient in the active treatment groups.

Hospitalization costs for patients with CDAD were also added. These costs were calculated by multiplying the cost of a day in hospital for patients with CDAD ($1424.16) by the length of the hospitalization.

In the model, we added the costs of rehospitalisation for reinfection. Our model did not consider the cost of the antibiotics that caused the AAD or CDAD.

Analysis overview

The primary outcome was the cost-consequence of prophylactic utilization of the probiotic formula of patients administered antibiotic therapy predisposing to AAD. In this instance we calculated the difference in cost per patient using one and two tablets of the probiotic formula (Pro-1 and Pro-2) vs Placebo. To calculate the costs per patient for each option, we combined resources used with their corresponding unit costs to obtain the total costs of the Placebo and the two prophylactic options. Then, we calculated the difference in the costs between the three groups. We compared the active treatments to placebo since there are no other treatments which have been clinically proven for the prophylaxis of AAD and CDAD.

Assumptions of the model

- Assumption 1: We assumed that all patients with AAD will be tested with the microbiological screening test to identify the presence of CD.
- Assumption 2: In our base-case analysis, we assumed that 58% of patients initiating an anti-CDAD antibiotic regimen would be assigned to metronidazole and 42% to vancomycin. Based upon published literature, we estimated that metronidazole therapy would fail in 26% of cases.
- Assumption 3: CD resistance to metronidazole was assumed to be identified at the fifth day of treatment, patients for which metronidazole was effective remained on this antibiotic for the last 5 days of the drug regimen. Patients for which CD was resistant to the metronidazole therapy were assumed to be switched to a 10-day vancomycin regimen.
- Assumption 4: As mentioned above, patients positive for CDAD were assumed to remain hospitalised for the length of their AAD symptoms (6.4 ± 1.8 days for the Placebo group, 4.1 ± 1.5 days for the Pro-1 group, and 2.8 ± 0.8 days for the Pro-2 group). These durations were obtained from the Gao et al. paper.
• Assumption 5: Following the initial CDAD infection, we estimated that 18% of these patients would experience CDAD reinfection in the 2 months following the initial discharge. Patients experiencing a CDAD reinfection were assigned a 10-day vancomycin regimen and we assumed that they would be re-hospitalized and would remain hospitalized for the duration of the antibiotic treatment.

Probabilistic sensitivity analyses
A probabilistic costing model was built in which all parameters were varied simultaneously to evaluate the impact of joint second-order uncertainty on the results. We specified probability distributions for each of the model’s parameters (see Table 1 for details) and then carried out 100,000 Monte Carlo simulations using the Oracle Crystal Ball software for all the analyses. The main advantage of probabilistic sensitivity analyses is that the distributions around point estimates are used instead of a point estimate alone. Results are calculated by selecting inputs from each parameter distribution for each iteration. Results of the probabilistic sensitivity analyses can thus be expressed in terms of probability distributions which are much more informative than point estimates alone.

Results

Base case analysis
The Pro-2 option resulted in a cost of $152 per patient, while the Pro-1 option resulted in a cost of $845 per patient and the Placebo option resulted in a cost of $2813 per patient (Table 2). Therefore, prophylactic utilization of the probiotic formula by all patients at risk of developing antibiotic-induced CDAD generated expected costs savings of $1968 per patient for Pro-1 and $2661 per patient for Pro-2 compared with Placebo. Results favored Pro-2 and Pro-1 since these options greatly reduce the proportion of patients who develop CDAD and, therefore, reduce the need for anti-CDAD antibiotics, prolonged hospitalisations and microbiological screenings compared to Placebo despite the cost of the probiotic formula.

Multivariate sensitivity analyses
The result of the multivariate sensitivity analyses showed that use of the probiotic formula would be cost-saving under a wide range of scenarios, confirming that the findings were robust (Table 2). The largest impact on the difference in costs between Placebo and Pro-1, Pro-2 groups originated from the probiotic formula’s capacity to prevent CDAD infections and the rate of CD re-infection at 2 months.

Table 2. Average cost per patient treated with an antibiotic that is at risk of developing AAD and CDAD.

<table>
<thead>
<tr>
<th>Base case</th>
<th>Multivariate sensitivity analyses</th>
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<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
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<tr>
<td>Placebo</td>
<td>$2813</td>
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<tr>
<td>Pro-1</td>
<td>$845</td>
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<td>Pro-2</td>
<td>$152</td>
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AAD, Antibiotic-associated diarrhea; CDAD, Clostridium difficile-associated diarrhea; IQR, Interquartile range; Placebo, Patient treated with two placebo pills; Pro-1, Patient treated with the one Lactobacillus acidophilus CL1285 and Lactobacillus casei/LBC80R probiotic pill and one placebo pill; Pro-2, Patient treated with two Lactobacillus acidophilus CL1285 and Lactobacillus casei/LBC80R probiotic pills; SD, Standard deviation.

Probabilistic sensitivity analyses
The probabilistic cost analysis confirmed that the prophylactic utilization of probiotic formula was a cost-saving option. The mean (SD) saving per subject was:
- For Pro-1 vs Placebo $1899 (SD $981);
- For Pro-2 vs Placebo $2647 (SD $833); and
- For Pro-2 vs Pro-1 $747 (SD $535).

Figure 2 shows that every simulated differences were cost-saving for Pro-2 compared with Placebo; while over 97.7% of simulated differences were cost-saving or cost-neutral for Pro-1 compared with Placebo.

For the difference in costs between Pro-2 and Placebo, the variables that had the most impact on the cost variation per subject were the incidence of CDAD in the placebo group, the length of hospitalisation in the Placebo group, and the incidence of CDAD re-infection at 2 months. In the case of Pro-2 vs Placebo, the incidence of CDAD in the Placebo group has to be 1.17%, in comparison to 23.8% in the Gao et al. paper, for the costs to be equal in the two groups.

Deterministic sensitivity analysis
The incidence of AAD and CDAD (44.1% and 23.8%) reported for the Placebo group in the Gao et al. paper may be greater than what would be expected in the US. Lower incidences of AAD and CDAD have been published in Canada and in the UK. A deterministic sensitivity analysis shows that if we assign incidences reported by Beausoleil et al. to the placebo group, while keeping all the other parameters constant, Pro-2 would save $1689 per patient compared with Placebo.

Hospital pharmacy perspective
Figure 3 shows how the variation in the utilization rate of metronidazole and the acquisition cost of vancomycin impact the hospital pharmacy budget when Pro-2 is compared to Placebo. So, as seen in our base-case analysis, with...
a metronidazole utilization rate of 58% and a vancomycin utilization rate of 42%, the pharmacy cost-savings were estimated at $15; had vancomycin been used in 100% of patients, the cost-savings would be estimated at $59. If metronidazole is given as a first line treatment to every patient and if vancomycin is offered at no charge to the hospital pharmacy, assigning a patient to the Pro-2 group would cost for the hospital pharmacy an estimated $37 per patient.

Discussion

Using Gao et al.\textsuperscript{10} trial findings, estimates of probabilities and costs from published literature, we found that prophylactic utilization of two capsules per day of the probiotic formula by all patients who receive antibiotics who put them at risk of developing AAD and CDAD results in an important reduction of the overall costs from the perspective of a single payer in North America. These savings
are presented in a wide variety of scenarios and are associated with fewer CDAD cases (82 fewer cases per 1000 patients treated with the Pro-1 option and 143 fewer cases per 1000 patients treated with the Pro-2 option compared with the Placebo option).

Conducting an economic analysis based on a clinical study realised in a given setting and then extrapolating these results to another setting involves important challenges. First, some important information might not be available in the report of the clinical trial. Secondly, it is necessary to determine if there are important differences between the incidence of the disease and the response to the probiotic formula in the trial, and what we expect to find in a usual North American context care. Thirdly, it is necessary to determine what antibiotic regimens are used to treat CDAD (vancomycin vs metronidazole) in a usual North American context care.

Thus, one of the key elements not reported in the Gao et al.\textsuperscript{10} trial was the duration of patients’ hospitalisation. Lacking this information, we estimated the duration of symptoms of AAD as a proxy for the duration of the hospitalisations. We assumed that patients would remain hospitalised as long as the AAD symptoms would be present. In our study, the imputed duration was 6.4 (SD = 1.8) days for the Placebo group. This duration in the Placebo group seemed quite reasonable in view of the North American literature\textsuperscript{15,20}. Although some studies estimate the duration of hospitalization to be up to and over 20 days\textsuperscript{21,22}, most studies estimate it at 6–13.5 days\textsuperscript{7,15,20,21}. It would thus appear that using duration of symptoms as a proxy for duration of hospitalisation produces credible and conservative results. The value we used (6.4 days) is in the lower range of what has been reported in the North American literature, and the longer the hospitalisation the larger the savings obtained by preventing AAD and CDAD\textsuperscript{7}.

Another variable not available in the Gao et al.\textsuperscript{10} paper was the possibility of re-hospitalisation due to recurrence of CDAD at 2 months post-discharge from the hospital. Investigators followed the patients for only 21 days post-discharge and did not observe any recurrence during this period of time. The 2 months incidence of recurrence we used (18%) was obtained from the Sunenshine and McDonald\textsuperscript{14} paper. The fact that all the patients with recurrence of CDAD had to be re-hospitalised was obtained from expert opinion. We conducted an additional sensitivity analysis in which we omitted re-hospitalisation for recurrences from the analysis in order to assess the impact of this assumption. In this case, the difference in costs between Placebo and Pro-2 would be $2082 per patient, a difference of $565 with the base case scenario.

The incidence of AAD and CDAD (44.1% and 23.8%) reported for the placebo group in the Gao et al.\textsuperscript{10} paper is greater than what has been reported in the North American literature. However, our sensitivity analysis shows that if we lower the incidence of AAD and CDAD to published North American levels\textsuperscript{7}, while keeping all the other parameters constant, the Pro-2 option would remain cost-saving compared to the Placebo option.

In addition, our study estimated that a hospitalised patient assigned to the Placebo group who developed CDAD would cost $9115 (6.4 [SD = 1.8] hospitalized days in addition to the cost of associated treatments). Similar costs ranging from $10,000–$15,000 were found by other authors\textsuperscript{23–25}. These analyses support the transferability of our results to the North American setting.

Another important question is whether the efficacy in the prevention of AAD and CDAD reported by Gao et al.\textsuperscript{10} would also be present in a North American setting. We are confident that this would be the case since the efficacy of the probiotic formula as reported by Gao et al.\textsuperscript{10} is similar to the one reported by Beausoleil et al.\textsuperscript{7} in a Canadian teaching hospital.

In regard to the rate of antibiotic utilization used as a first line treatment, we assumed in our base-case analysis that 58% of patients initiating an anti-CDAD antibiotic regimen would be assigned to metronidazole and 42% to vancomycin\textsuperscript{15}. This rate of utilization of metronidazole and vancomycin varies in different hospitals. With the newer, more resistant strains of CD, the vancomycin utilization rate as a first line anti-CDAD antibiotic is likely to increase. However, increasing the vancomycin utilization rate results in additional cost-savings for both the single payer’s perspective and the hospital’s pharmacy perspective compared with the base case scenario (Figure 3).

Our study was done in the single payer perspective and we did not take into account the societal costs of the illness. Of course, a very important issue which has not been taken into consideration in this evaluation is the human cost associated with the morbidity of the disease and subsequent possible death. Although omitted from our model, if we reduce the rate of CDAD infections in the hospital, we also reduce the risk of infecting other individuals. These issues also greatly support the use of the probiotic formula for prophylaxis of AAD and CDAD.

Conclusions

We can thus conclude that the use of the probiotic formula to hospitalised patients who receive antibiotics would produce substantial cost-savings in a North America single payer system. Our results indicate that under the base case scenario treating 1000 hospitalised patients on antibiotics with Pro-2 would save a single payer system the sum of $2,661,218. Assuming the CDAD rate observed in North America, this sum will be $1,688,993.
**Transparency**

**Declaration of funding**

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**Declaration of financial/other relationships**

None of the authors have any other financial relationships pertaining to this study to disclose.

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**References**
