

# Pharmacoeconomic Analysis of Guidelines for Treating Mild Diabetic Foot Infections: A Decision-Tree Model for Canada

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## ABSTRACT

**Background:** Foot infections represent a serious complication of diabetes and are associated with substantial morbidity, health care costs, and risk of death. However, limited information exists to guide clinicians in selecting antibiotics to treat such infections.

**Objectives:** To determine, from the perspective of Ontario's provincial ministry of health, the cost-effectiveness of treatments recommended by the Infectious Diseases Society of America for mild diabetic foot infections.

**Methods:** A decision-tree model was developed using commercial software. Probabilities of success were derived from published randomized controlled trials. Drug costs were determined from the 2007 Ontario Drug Benefit Formulary and McKesson Canada (a logistics and distribution company in the health care sector), amputation costs from the Canadian Institute for Health Information database for fiscal year 2002/2003, and hospital costs from Sunnybrook Health Science Centre's 2003/2004 database. All values were adjusted to 2007 dollars using the Canadian Consumer Price Index.

**Results:** The quality of evidence used in the model was weak, and success rates were based on small studies. Expected success rates were 99.4% for clindamycin, 97.8% for cephalexin, 95.4% for amoxicillin-clavulanate, 95.2% for cloxacillin, and 95.0% for levofloxacin. The expected cost for clindamycin was \$361.33 per treatment, which was substantially lower than the next best alternative, cephalexin (\$1239.99); the cost difference was \$878.66 per successful treatment. In this model, clindamycin was the most cost-effective drug, dominating all other choices. In sensitivity analyses, the decision tree model was sensitive to changes in efficacy rates but not changes in cost.

**Conclusions:** In this cost-effectiveness model, clindamycin dominated other oral antibiotics for the treatment of mild diabetic foot infections. However, this observation should be interpreted with caution because the model was based on evidence from relatively few studies with small sample sizes.

**Key words:** diabetic foot infection, antibiotic, cost-effectiveness, pharmacoeconomics, Canada, oral therapy.

## RÉSUMÉ

**Contexte :** Les infections du pied représentent de sérieuses complications du diabète et sont associées à une morbidité, à des coûts de santé et à un risque de mortalité considérables. Or, les cliniciens ont accès à très peu d'information pour les guider dans le choix des antibiotiques pour traiter ces infections.

**Objectifs :** Déterminer, du point de vue du ministère de la Santé de l'Ontario, le rapport coût-efficacité des traitements recommandés par l'Infectious Diseases Society of America contre les infections légères du pied diabétique.

**Méthodes :** Un modèle d'arbre décisionnel a été mis au point à l'aide d'un progiciel. Les probabilités de réussite du traitement ont été dérivées de résultats d'essais cliniques comparatifs aléatoires. Les coûts des médicaments ont été déterminés à partir de la liste de médicaments de 2007 du Programme de médicaments de l'Ontario et de McKesson Canada (une entreprise de logistique et de distribution dans le domaine des soins de santé), les coûts d'amputation à partir de la base de données de l'Institut canadien d'information sur la santé pour l'exercice financier 2002-2003, et les coûts hospitaliers à partir de la base de données de 2003-2004 du Sunnybrook Health Science Centre. Toutes les valeurs ont été converties en dollars de 2007 sur la base de l'indice canadien des prix à la consommation.

**Résultats :** Les données probantes utilisées dans le modèle étaient de piètre qualité, et les taux de réussite étaient basés sur de petites études. Les taux de réussite attendus étaient de 99,4 % pour la clindamycine, de 97,8 % pour la céphalexine, de 95,4 % pour l'amoxicilline-clavulanate, de 95,2 % pour la cloxacilline et de 95,0 % pour la lévofloxacine. Les coûts prévus pour la clindamycine étaient de 361,33 \$ par traitement, ce qui était considérablement inférieur au coût de la deuxième meilleure option, la céphalexine (1239,99 \$); la différence de coût par traitement réussi était de 878,66 \$. Dans ce modèle, la clindamycine avait un rapport coût-efficacité favorable, surpassant toutes les autres options. Les analyses de sensibilité ont révélé que le modèle d'arbre décisionnel était sensible aux changements dans les taux d'efficacité, mais non aux changements de coûts.

**Conclusions :** Dans ce modèle d'analyse coût-efficacité, la clindamycine a surpassé d'autres antibiotiques par voie orale dans le traitement des infections légères du pied diabétique. Cependant, il faut interpréter cette observation avec prudence, car le modèle était basé sur des données issues d'un nombre relativement limité d'études assorties de petits échantillons.

**Mots clés :** infection du pied diabétique, antibiotique, coût-efficacité, pharmacoeconomie, Canada, traitement oral

[Traduction par l'éditeur]



## INTRODUCTION

Diabetes mellitus and its associated complications cause significant morbidity and mortality, have a negative impact on quality of life, and lead to substantial costs for the health care system.<sup>1,2</sup> The prevalence of diabetes worldwide is projected to reach 300 million people by the year 2025.<sup>3</sup> In Canada, more than 2 million people are living with diabetes, and this number is expected to increase to 3 million by 2010.<sup>4</sup> In 1998, the estimated total economic burden of diabetes in Canada was reported to range from US\$4.76 billion to US\$5.23 billion.<sup>5</sup> These values would translate to \$7.04 billion to \$7.74 billion in Canadian dollars, given the mean exchange rate of Can\$1.48 = US\$1 in 1998. If these values are projected to 2007, the total economic burden would be approximately Can\$9.25 billion to Can\$10.2 billion. However, extrapolation of 1998 results to the present would likely result in an underestimation of costs. In a more recent report, the Canadian Diabetes Association<sup>4</sup> estimated, using data from a US study, that diabetes and its complications cost Canada's health care system Can\$13.2 billion annually. This value was projected to increase to Can\$15.6 billion/year by 2010 and to Can\$19.2 billion/year by 2020.<sup>4</sup>

In addition to the increasing prevalence and economic burden of this disease, patients with diabetes face numerous complications throughout their lifetime. One common complication is foot ulceration, leading to infection and amputation. The annual incidence of foot ulceration ranges from 1% to 4%,<sup>3,6</sup> and the lifetime risk may range from 15% to 25%.<sup>1,3</sup> With ulceration, tissues are exposed to bacterial colonization, which can eventually progress to infection.<sup>6,7</sup> *Staphylococcus aureus* and *Streptococcus* spp. are the predominant microorganisms that colonize tissues and cause acute infections in previously untreated patients.<sup>6,7</sup> In patients with chronic wounds or infections involving deep tissues, gram-negative bacilli, enterococci, and anaerobic species may become important pathogens.<sup>8</sup>

Clinicians face many challenges in the treatment of diabetic foot infections, especially in the choice of antibiotic regimen. The guidelines of the Infectious Diseases Society of America (IDSA)<sup>7</sup> can guide clinicians in choosing empiric antibiotic regimens, but they provide no recommendations on specific antibiotic regimens, because of the poor quality of data available in the literature. Given this lack of direction, management of diabetic foot infections is often suboptimal or inadequate.<sup>6</sup>

One consequence of inadequately managed diabetic foot infections is amputation. Every 30 seconds, somewhere in the world, a lower limb is lost as a complication of diabetes,<sup>1</sup> and the incidence of amputation reportedly ranges from 2.1 to

13.7 per 1000 persons.<sup>3</sup> More than 50% of nontraumatic amputations of the lower extremity involve patients with diabetes.<sup>9</sup>

Individuals who have already undergone amputation of one limb are at high risk for amputation of the contralateral limb.<sup>10</sup> Within 5 years of an initial major amputation, 50% of patients will have died, and 30% to 50% of first-episode amputations will progress to subsequent amputations within 1 to 3 years.<sup>11</sup>

In 2003, O'Brien and colleagues<sup>12</sup> provided a comprehensive cost estimate of several complications of diabetes in Canada. They noted that the cost of a first lower-extremity amputation in a patient with diabetes was Can\$24 583 per year in 2000.<sup>12</sup> Extrapolated to 2007, that cost would be Can\$30 896 per year.

Considering the substantial economic burden of diabetic foot infections and their associated consequences, optimal management is needed to reduce the incidence of limb amputations and infection-related morbidity and mortality. Canadian guidelines<sup>13</sup> for the treatment of diabetic foot infections have been developed and published; however, they have not been updated since the 1990s. Conversely, the IDSA has published guidelines more recently,<sup>7</sup> but it is not known if these guidelines lead to cost-effective decisions.

Therefore, this study was undertaken to examine the following research question: What drug or drugs recommended by the IDSA guidelines are cost-effective for the treatment of mild diabetic foot infections in Canada? It was hoped that this cost information would be helpful to clinicians considering options for the treatment of diabetic foot infections. In theory, such information should allow better management of diabetic foot infections and should reduce the associated complications, while limiting drug expenditures.

## METHODS

### Literature Search

To obtain an evidence basis for the analysis, a literature search was performed to identify all randomized controlled trials (RCTs; level 1 evidence) dealing with treatment of mild diabetic foot infections. Two researchers (E.V.L., P.M.) independently performed a comprehensive search of the MEDLINE, EMBASE, and Cochrane databases using the key terms "diabetes or diabetic" and "foot or lower limb" and "ulcer or infection or cellulitis". Studies of both IV and oral antibiotics versus an active comparator were included. As well, references from all retrieved articles and reviews were searched by hand. Discrepancies were settled through consensus; if the 2 researchers could not achieve consensus, a third reviewer was enlisted to make the final decision.



## Pharmacoeconomic Model

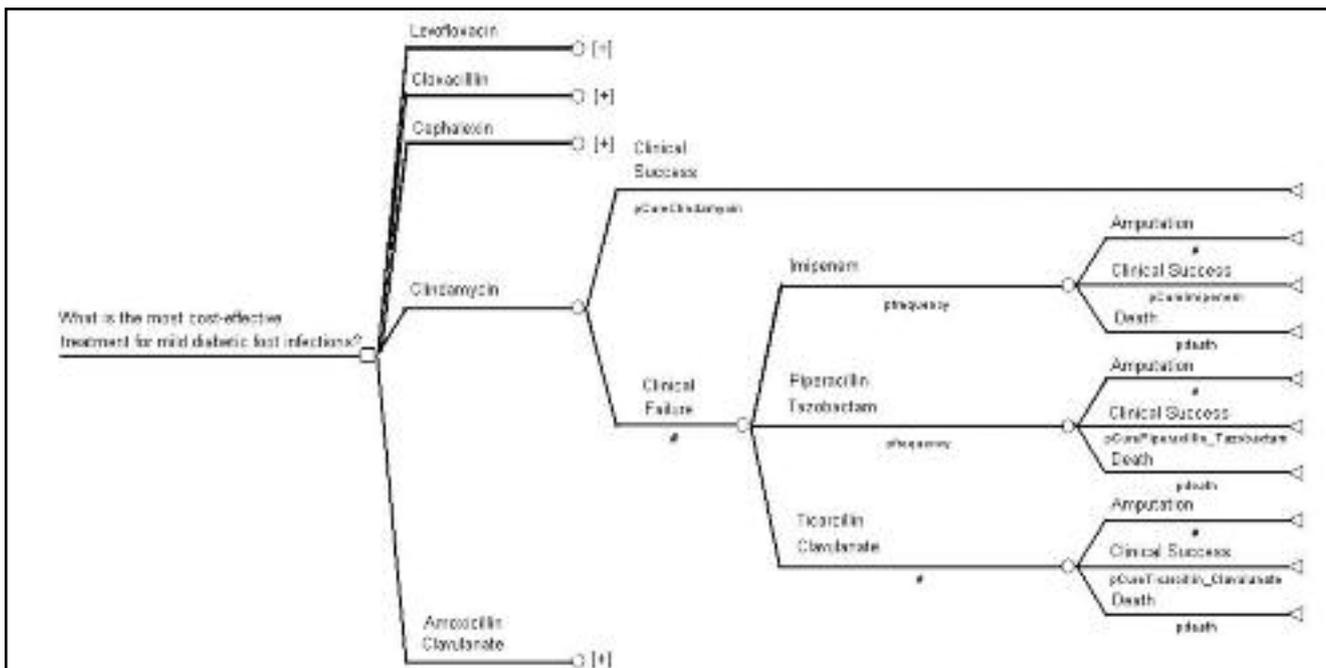
The information from RCTs and the 2004 IDSA guidelines<sup>7</sup> was used to construct a decision tree (Figure 1) to determine which antibiotic regimens were cost-effective in treating mild diabetic foot infections. TreeAge Pro 2007 software (TreeAge Software Inc, Williamstown, Massachusetts) was used for this purpose. As well, 3 Canadian infectious diseases experts, based in Toronto, Ontario, and Vancouver, British Columbia, were consulted (personal communications, October 29, 2007); these experts confirmed that they followed the IDSA guidelines for the treatment of diabetic foot infections.

The population for the model consisted of patients with type 1 or type 2 diabetes and acute but mild foot infections who were able to take oral antibiotics. Mild infections were defined as those limited to the skin or superficial tissues with the presence of 2 or more manifestations of inflammation (e.g., purulence, erythema, pain, tenderness, warmth, or induration) or any cellulitis up to 2 cm around the ulcer; patients with systemic illnesses, osteomyelitis, gangrene, or extensive deep tissue infections were excluded.<sup>7</sup> Conversely, if oral antibiotic therapy failed, the patient's infection was considered moderate to severe. Moderate to severe infections were defined as cellulitis extending beyond 2 cm, deep tissue involvement, gangrene, and/or involvement of muscle, joint, tendon, or bone requiring admission to hospital for debridement and parenteral administration of antibiotics.<sup>7</sup>

The first branch of the decision tree (Figure 1) reflects the oral antibiotics recommended by the IDSA as empiric therapy for the treatment of mild diabetic foot infections. Sulfamethoxazole–trimethoprim was excluded from the model because no RCTs involving this drug were found. The remaining antibiotics—cephalexin, clindamycin, cloxacillin (in place of dicloxacillin, which is no longer available in Canada), amoxicillin–clavulanate, and levofloxacin—were included. The regimens for these antibiotics, as reported in the RCTs<sup>14-17</sup> and the IDSA guidelines,<sup>7</sup> are listed in Table 1.

Probabilities for clinical success were obtained from the RCTs identified.<sup>14-17</sup> However, only the probabilities of clinical success for evaluable patients were used in the decision tree, because probability values from the literature were most complete for this group. Clinical success was defined as both microbiological and clinical resolution of the infection. Clinical success rates for amoxicillin–clavulanate were not available; therefore, the probability was extrapolated from cure rates. If more than one RCT studied the drug of interest, the average of the reported clinical success rates was used as the probability in the model. A list of event probabilities used in the decision-tree model is presented in Table 2.

The next branch of the decision tree reflects the pathways of either clinical success or clinical failure after a 10-day course of oral antibiotics. If clinical success occurs, then treatment ends. If clinical failure occurs, the patient is admitted to hospital for IV administration of antibiotics (on the basis of expert opinion). Antibiotics for the treatment of moderate to



**Figure 1.** Decision tree for treatment of mild diabetic foot infections in Canada. Definitions of symbols: +, expandable branch; square, decision node; circle, chance node; triangle, terminal node; #, calculated probability value based on other model inputs.

**Table 1. Model Inputs: Doses and Durations of Antibiotic Therapy for Mild Diabetic Foot Infections**

Antibiotic	Dose	Duration (days)	Reference
<b>Oral</b>			
Amoxicillin–clavulanate	500 mg q8h	10	Lipsky and others <sup>14</sup>
Cephalexin	500 mg qid	10	Lipsky and others <sup>15</sup>
Clindamycin	300 mg qid	10	Lipsky and others <sup>15</sup>
Cloxacillin	1000 mg qid	10	Lipsky and others <sup>16</sup>
Levofloxacin	750 mg daily	10	Graham and others <sup>17</sup>
<b>Parenteral</b>			
Imipenem	500 mg q6h	14	Grayson and others <sup>18</sup> Bouter and others <sup>19</sup>
Piperacillin–tazobactam	3.375 g q6h	14	Lipsky and others <sup>20</sup>
Ticarcillin–clavulanate	3.1 g q6h	14	Graham and others <sup>17</sup> Tan and others <sup>21</sup>

**Table 2. Inputs: Clinical Success Rates and Costs**

Variables	No. of Study Participants	Probability (95% CI)*	Cost (2007 Can\$)	Reference
<b>Clinical success</b>				
Amoxicillin–clavulanate	108	0.7130 (0.621–0.790)		Lipsky and others <sup>14</sup>
Cephalexin	29	0.8621 (0.694–0.945)		Lipsky and others <sup>15</sup>
Clindamycin	27	0.9630 (0.817–0.993)		Lipsky and others <sup>15</sup>
Cloxacillin	27	0.7037 (0.515–0.841)		Lipsky and others <sup>16</sup>
Levofloxacin	26	0.6923 (0.500–0.835)		Graham and others <sup>17</sup>
Imipenem	69	0.9033 (0.788–0.940)		Grayson and others <sup>18</sup> Bouter and others <sup>19</sup>
Piperacillin–tazobactam	196	0.8265 (0.767–0.873)		Lipsky and others <sup>20</sup>
Ticarcillin–clavulanate	37	0.7857 (0.515–0.804)		Graham and others <sup>17</sup> Tan and others <sup>21</sup>
Infection leading to death	183	0.0098		Nelson and others, <sup>2</sup> Amato and others <sup>22</sup>
<b>Cost</b>				
Amoxicillin–clavulanate			\$0.67/tablet (500 mg amoxicillin, 125 mg clavulanate)	ODB/CDI <sup>23</sup>
Cephalexin			\$0.24/500-mg tablet	ODB/CDI <sup>23</sup>
Clindamycin			\$0.78/300-mg capsule	ODB/CDI <sup>23</sup>
Cloxacillin			\$0.19/500-mg capsule	ODB/CDI <sup>23</sup>
Levofloxacin			\$5.19/500-mg tablet	ODB/CDI <sup>23</sup>
Imipenem			\$26.00/500-mg vial	McKesson Canada <sup>24</sup>
Piperacillin–tazobactam			\$18.00/3.375-g vial	McKesson Canada <sup>24</sup>
Ticarcillin–clavulanate			\$11.00/3.1-g vial	McKesson Canada <sup>24</sup>
Lower extremity amputation (except toe)			\$12,334.37/procedure	CIHI CMGs <sup>25</sup>
Pronouncement of death			\$31.45/death	MOHLTC <sup>26</sup>
Admission to hospital, medical bed			\$430.30/day	Sunnybrook <sup>27</sup>
Admission to hospital, surgical bed			\$517.05/day	Sunnybrook <sup>27</sup>
Admission to hospital, ICU bed			\$2041.67/day	Sunnybrook <sup>27</sup>

CI = confidence interval; CIHI CMGs = Canadian Institute for Health Information Case Mix Groups; ICU = intensive care unit; MOHLTC = Ontario Ministry of Health and Long-Term Care; ODB/CDI = Ontario Drug Benefit Formulary / Comparative Drug Index. \*95% confidence interval from randomized controlled trials.



severe foot infections suggested by the infectious disease experts included imipenem, piperacillin–tazobactam, ticarcillin–clavulanate, ciprofloxacin (or another fluoroquinolone) plus clindamycin or metronidazole, and ceftriaxone (or another third-generation cephalosporin) plus clindamycin or metronidazole. Ertapenem was also mentioned by the experts, but only for finishing a course of treatment on an outpatient basis, because of the convenience of once-daily dosing, provided the microorganisms involved are susceptible. From the list of antibiotics provided by the infectious diseases experts, only the antibiotic regimens that had been evaluated in RCTs were included in the model: imipenem, piperacillin–tazobactam, and ticarcillin–clavulanate.<sup>17-21</sup> Treatment duration was 14 days, as suggested in the IDSA guidelines provided there was no bone involvement. Three outcomes were possible after 14 days of IV antibiotic therapy: clinical success, amputation, or death. The probabilities of clinical success for the secondary treatments (i.e., following failure of primary drug therapy) were also obtained from RCTs,<sup>17-21</sup> and the probability of death was obtained from an abstract<sup>22</sup> and a recent systematic review of diabetic foot infections.<sup>2</sup> Probabilities of amputation were calculated from the probabilities of clinical success and death within that branch of the decision-tree model. That is, if patients were not cured and did not die, it was assumed that amputation would be necessary. The total time horizon of the model was 24 days: 10 days for the primary antibiotic therapy and an additional 14 days for subsequent secondary antibiotic therapy, if the primary therapy failed.

All costs are reported in 2007 Canadian dollars. Only direct costs were included in this model, to reflect the perspective of the Ontario Ministry of Health and Long-Term Care. Drug costs were determined from the 2007 Ontario Drug Benefit Formulary/Comparative Drug Index<sup>23</sup> and McKesson Canada.<sup>24</sup> Amputation costs were obtained from the Canadian Institute for Health Information database using case mix group (CMG) methodology for the fiscal year 2002/2003<sup>25</sup>; values were adjusted to 2007 by means of the Canadian Consumer Price Index. The CMG methodology is designed to aggregate acute inpatient data in terms of various Canadian resources, such as the procedural costs in the model created in this study. Only the direct costs of lower-extremity amputations (excluding the toe) were used in the model. Physician fees were obtained from the 2007 Ontario Schedule of Benefits for Physician Services.<sup>26</sup> Hospital costs were obtained from the 2003/2004 database of the Sunnybrook Health Sciences Centre<sup>27</sup> and were adjusted to 2007 with the Consumer Price Index. Costs of admission to a medical, surgical, or intensive care unit were obtained, but only the cost of admission to a medical bed (excluding overhead costs) was used in calculating the costs of 14 days of parenteral antibiotic therapy in hospital. Costs were not discounted, as the duration of all treatment

periods was less than 1 year. Table 2 summarizes the costs of antibiotics, hospitalization, amputation, and death that were input into the model.

## Data Analysis

The analysis was conducted on an intention-to-treat basis: all costs and outcomes were ascribed to the initial drug used, regardless of downstream events. The economic outcome was the expected cost per patient treated for each regimen (i.e., once started on the antibiotic). Clinical outcomes calculated were the expected rates of success (i.e., the sum of all rates across all branches of the tree that ended in success) and expected rates of amputation (calculated in a similar manner). In the case of dominance, the expected cost per success was calculated for each drug. In the case of incremental cost and incremental benefit, the incremental cost-effectiveness ratio (ICER) was calculated.

One-way and two-way sensitivity analyses were performed to test the robustness of the decision-tree model, with variation in clinical success rates, costs of antibiotics, and length of hospital stay. Probabilistic sensitivity analyses were also performed using Monte Carlo simulations over 10 000 iterations across presumed distributions of variables (mean  $\pm$  10%). We used log-normal distributions for all antibiotic costs and beta distributions for clinical success rates.

## Model Assumptions

Several assumptions were made in this model. First, the model examined the cost-effectiveness of oral antibiotic regimens for mild foot infections, which generally excluded patients with osteomyelitis, gangrene, or extensive deep tissue infections. However, moderate to severe infections, which might have included osteomyelitis, gangrene, and deep tissue infections, were considered if the 10-day course of oral antibiotic failed. Low resistance rates were assumed, and the most common organisms involved with mild infections were assumed to be aerobic gram-positive microorganisms, specifically staphylococci and streptococci. Another assumption was that once oral antibiotic therapy had failed, the patients were admitted to hospital for the full 14 days before the outcome of clinical success, amputation, or death occurred. The possibility of parenteral antibiotics or step-down therapy to oral antibiotics (to complete therapy on an outpatient basis) was considered but not included in this model, because once oral therapy had failed and the patients were admitted to hospital, the infections were considered moderate to severe and potentially limb-threatening, which could lead to an overestimation of costs. To test whether shorter hospital stays would change the decision of the model, a sensitivity analysis was performed. The last assumption of the model was that adverse effects were low. This assumption was based on the studies used



to construct the model, which reported low incidences of adverse effects and mild to moderate adverse effects that resolved spontaneously without treatment; in addition, the rate of discontinuation of therapy because of antibiotic-associated adverse effects was low. However, this may represent a limitation, since these studies had small sample sizes and were underpowered, rather than reflecting current incidences of antibiotic-associated adverse events.

## RESULTS

Data on probability of clinical success were obtained from RCTs, but the quality of these studies was weak, and the total number of patients in the studies used to construct the model was very small (Table 2). Also, some studies had patients with diabetic foot infections only as a subgroup, and the results may not necessarily be comparable.

The decision-tree model indicated that clindamycin was the primary cost-effective oral antibiotic for the treatment of mild diabetic foot infections. Clindamycin dominated the

other oral antibiotics with a primary efficacy rate of 96.3% and an overall success rate of 99.4% (the additional successes being due to backup drugs, i.e., parenteral antibiotics administered when primary oral drugs failed). In terms of the cost of 10 days of oral antibiotic therapy, clindamycin was more expensive than cephalexin, cloxacillin, and amoxicillin-clavulanate (\$31.20 versus \$9.60, \$15.20 and \$20.10, respectively). However, because of the higher primary efficacy rate (96.3% versus 86.2%, 70.4%, and 71.3%, respectively), clindamycin was still the most cost-effective agent overall.

Amputations and deaths were also substantially lower among patients receiving clindamycin than among patients receiving other oral antibiotics (Table 3).

The expected total cost, as estimated by the decision-tree model, was substantially lower for clindamycin (\$361.33) than for the other oral antibiotics (Table 4). Clindamycin had a cost-effectiveness ratio of \$363.50 per treatment success, and the ICERs for cephalexin, cloxacillin, amoxicillin-clavulanate and levofloxacin were all dominated by clindamycin, the primary comparator (Table 4).

**Table 3. Expected Rates of Clinical Success, Amputation and Death for Each Comparator**

Antibiotic	Clinical Success (%)			Amputations (per 1000)	Deaths (per 1000)
	Primary	Secondary	Total (95% CI)*		
Amoxicillin-clavulanate	71.3	24.1	95.4 (94.1–96.6)	43.6	2.7
Cephalexin	86.2	11.6	97.8 (96.9–98.7)	20.9	1.5
Clindamycin	96.3	3.1	99.4 (98.9–99.9)	5.6	0.3
Cloxacillin	70.4	24.8	95.2 (92.3–98.2)	45.0	3.0
Levofloxacin	69.2	25.8	95.0 (91.8–98.3)	46.7	3.0

\*95% confidence interval (CI) from sensitivity analyses.

**Table 4. Results of Cost-Effectiveness Analysis of Oral Antibiotics Used for Mild Diabetic Foot Infections**

Antibiotic	Cost (2007 Can\$)		Success (%)		CE	ICER
	Expected	Difference*	Expected (%)	Difference* (percentage points)		
Clindamycin†	361.33	Comparator	99.4	Comparator	363.50	NA
Cephalexin	1239.99	878.66	97.8	-1.6	1268.23	Dominated by clindamycin
Amoxicillin-clavulanate	2580.81	2219.48	95.4	-4.0	2706.25	Dominated by clindamycin
Cloxacillin	2658.88	2297.55	95.2	-4.2	2792.52	Dominated by clindamycin
Levofloxacin	2823.25	2461.92	95.0	-4.4	2970.89	Dominated by clindamycin

CE = cost-effectiveness ratio, ICER = incremental cost-effectiveness ratio, NA = not applicable.

\*Relative to clindamycin.

†Primary comparator.

**Table 5. One-Way Sensitivity Analyses of Clindamycin and Cephalexin: Impact of Variations in Clinical Efficacy and Cost**

Comparison of Estimated Cost of Treatment (2007 Can\$)			
Success or Cost	Clindamycin	Cephalexin	Difference
<b>Clinical success (%)</b>			
<i>Clindamycin</i>			
50	4492.36	1239.99	+3252.37
75	2512.94	1239.99	+1272.95
87	1193.33	1239.99	-46.66*
<i>Cephalexin</i>			
50	361.33	4470.76	-4109.43
75	361.33	2463.24	-2101.91
95	361.33	455.72	-94.39
97.5	361.33	232.66	+128.67†
<b>Unit cost</b>			
<i>Clindamycin</i>			
\$0.10/300-mg capsule	330.23	1239.99	-909.76
\$50.00/300-mg capsule	380.22	1239.99	-859.77
\$950.00/300-mg capsule	1280.13	1239.99	+40.14†
<i>Cephalexin</i>			
\$0.10/500-mg tablet	361.33	1230.49	-869.16
\$50.00/500-mg tablet	361.33	1255.48	-894.15

\*Cephalexin no longer dominates.

†Clindamycin no longer dominates.

Varying the cost of clindamycin in a one-way sensitivity analysis (Table 5) did not affect the treatment decision, except at the extreme (i.e., \$950 per 300-mg capsule of clindamycin), which is an unlikely scenario. Likewise, changing the cost of cephalexin did not affect the final decision (Table 5). Although the 95% confidence interval for cephalexin success (69.4% to 94.5%) suggested that clinical success greater than 97% would be unlikely, it is important to note that this success rate was based on an observation of only 29 patients.<sup>15</sup> In comparison, variation of the success rate for clindamycin showed that cephalexin would be the dominant agent if clindamycin had an efficacy rate less than 87%. Given the 95% confidence interval for success for clindamycin (81.7% to 99.3%, obtained from one observation of 27 patients),<sup>15</sup> it is possible that clindamycin might have a success rate less than 87%. Two-way sensitivity analyses were also performed (Figures 2A and 2B).

The assumption that once oral antibiotics had failed, the patient would be admitted to hospital for 14 days of antibiotic therapy might have overestimated total cost; therefore, a sensitivity analysis was performed to determine if varying the length of hospital stay would change the result. When length of stay was varied from 1 day to 14 days, the overall cost-effectiveness ranking was still dominated by clindamycin; however, the per-patient cost was lower with shorter length of stay. The per-patient cost ranged from \$159 to \$364 for

clindamycin, \$494 to \$1268 for cephalexin, \$1055 to \$2706 for amoxicillin-clavulanate, \$1085 to \$2793 for cloxacillin, and \$1195 to \$2971 for levofloxacin, depending on the number of hospital days required for secondary treatment.

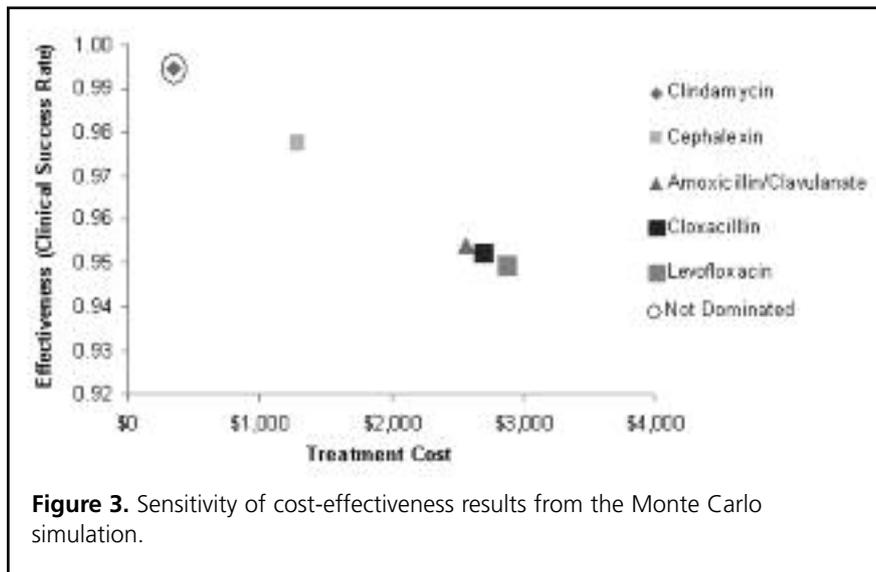
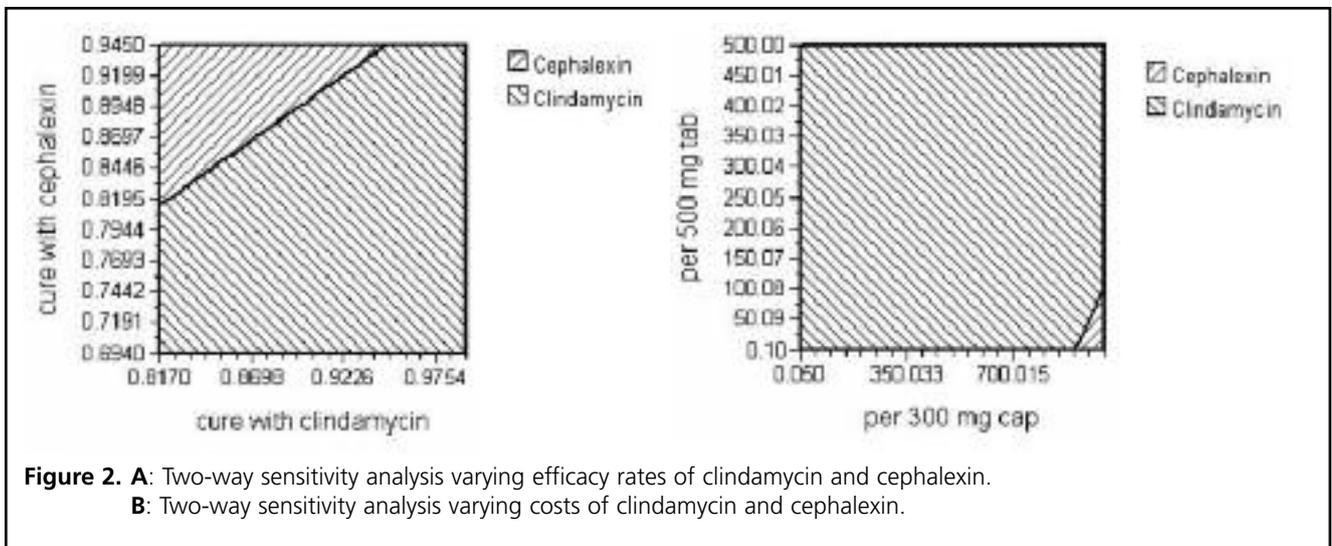
When Monte Carlo simulations were performed with variations of means by 10%, the treatment decision was still dominated by clindamycin (Figure 3).

## DISCUSSION

To the authors' knowledge, this decision-tree model based on the IDSA guideline is the first to be created for Canada. However, its limitations and assumptions may limit its clinical utility. Overall, the decision model presented here may represent an oversimplification of the complexity of treatment of diabetic foot infections, and a model based on guidelines may differ from actual clinical practice.

Although clindamycin was the cost-effective agent in this academic model, the clinical success rates for this drug were taken from a small study (total  $n = 56$ ).<sup>15</sup> In addition, that study showed no significant difference in primary success rates between the 2 drugs studied (clindamycin and cephalexin). It must be remembered that the decision-tree model includes not only the primary success rates, but also the effects of subsequent drugs. Monte Carlo simulations confirmed clindamycin's position, but there is still a strong possibility that the 2 drugs





are very similar clinically (i.e., in practice) and that the cost-effectiveness result is an artifact. Unfortunately, the quality of the evidence for the oral antibiotics recommended by the IDSA guidelines is weak because of small sample sizes and because patients with diabetic foot infections were only a subgroup in some studies. In addition, some of the studies were done in the early 1990s, when the choice of antibiotics and resistance rates would have differed from current standards of practice. Larger and better-designed RCTs for the antibiotics recommended in the IDSA guidelines are needed to bridge these gaps and also to help clinicians to choose the most cost-effective agents for the treatment of mild diabetic foot infections.

Other limitations of this decision model included obtaining the clinical success rates from evaluable patients rather than from the intention-to-treat group. Also, clinical success (i.e., efficacy) rates were used, rather than cure rates,

which might have overestimated the effectiveness rates of the antibiotics included in the model. Most of the clinical success rates used in this model were obtained from single RCTs of the antibiotic. In some cases, patients with diabetes constituted only a subset of patients in the RCT. Many of the trials were underpowered, and the clinical success rates reported could be overestimations of the true clinical success rates of the antibiotics included in the model. Only one large RCT involving diabetic patients was identified in the literature search, a comparison of ertapenem and piperacillin-tazobactam.<sup>20</sup>

Low resistance rates were assumed, but current epidemiology of diabetic foot infections indicates that resistance rates are increasing, especially for community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). If MRSA is suspected, antibiotic regimens would have to include agents that are active against MRSA, such as linezolid or vancomycin or, if local

resistance patterns suggest susceptibility of community-acquired MRSA, rifampin, doxycycline, clindamycin, or sulfamethoxazole–trimethoprim.

Another concern is the serious adverse effects associated with clindamycin (e.g., pseudomembranous colitis), which could limit the use of this antibiotic; other antibiotics with more benign adverse effect profiles are available. Also, the cost of treating these adverse effects could offset the cost benefits of clindamycin in the decision model.

Finally, the costs presented here may represent an underestimation or an overestimation because overhead costs of hospital care were not factored in and because it was assumed that all patients treated in hospital received the full 14-day course of parenteral antibiotics. For patients whose condition is stable, home parenteral antibiotic therapy is a possibility; if this is considered, costs would be lower than projected with the current model. An ideal model should factor in the percentage of patients who would complete the course of therapy with parenteral or oral antibiotics on an outpatient basis, and this should be a consideration in future models.

Because the model was intended to examine treatment of mild infections only, and because moderate to severe infections in the current model represented only a subset analysis if oral antibiotic therapy failed, future work should include designing a model for moderate to severe diabetic foot infections in Canada. Other enhancements, including obtaining intention-to-treat values, would provide a better estimate of the true clinical success rates of the antibiotics included in this model.

Despite the limitations discussed above, the model did reveal that treatment costs associated with diabetic foot infections increase with treatment failure, as well as with increased rates of amputation and death. This finding concurs with the current literature and with recommendations for prompt and optimal management to reduce the incidence of infection-related morbidity and mortality and its associated costs.

## CONCLUSIONS

In the decision-tree model developed in this study, clindamycin dominated other oral antibiotics recommended by the IDSA guidelines for treating mild diabetic foot infections, but this observation should be interpreted with caution. The evidence used to build the model was based on a small number of studies with small sample sizes. Therefore, more clinical studies evaluating oral antibiotics for treating mild diabetic foot infections are needed. Also, given the other limitations and assumptions of the model, the results should not be applied in isolation; rather, they should be combined with clinical experience and current standards of practice.

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