Vancomycin or Metronidazole for Treatment of Clostridium difficile Infection: Clinical and Economic Analyses

EXECUTIVE SUMMARY

The Issue

*Clostridium difficile* (*C. difficile*) infection is the most common cause of nosocomial infectious diarrhea in adults. The spread of a hypervirulent strain of *C. difficile* has caused recent outbreaks of *C. difficile* infection. Metronidazole and vancomycin are the antibiotics of choice to treat *C. difficile* infection. An assessment was prepared to help guide the choice of therapy for *C. difficile* infection and to inform reimbursement policies in the Canadian publicly funded health care system.

Objectives

The research objectives were to evaluate the relative clinical effectiveness, the relative cost-effectiveness, and the budget impact of using vancomycin or metronidazole in the management of initial episodes of moderate to severe *C. difficile* infection in children or in adults. Clinical practice guidelines recommendations were also reviewed.

Methods

A search for systematic reviews, health technology assessments, randomized controlled trials, and observational studies that compared vancomycin and metronidazole was conducted. An analysis of the clinical studies was completed. A narrative synthesis of economic evaluations was performed. A primary economic analysis and a budget impact analysis were also prepared.

After the literature was searched, it was determined that none of the retrieved studies met the population inclusion criteria. The authors of this report decided to proceed with a systematic review of studies that included patients with an initial or recurrent episode of moderate or severe *C. difficile* infection. Other than this amendment, the original research protocol for the clinical review was followed.

Findings

**Clinical**

The goal of the clinical review was to compare vancomycin with metronidazole based on the outcomes of cure, recurrences, complications, and serious adverse events in adults or children with moderate or severe *C. difficile* infection.
One randomized controlled trial showed no difference in cure rate when comparing the use of metronidazole and vancomycin by adult patients with initial or recurrent episodes of moderate *C. difficile* infection. In adult patients with initial or recurrent episodes of severe *C. difficile* infection, the use of vancomycin increased the cure rate by 27% (relative risk [RR] 1.27; 95% confidence interval [CI], 1.05 to 1.53) compared with metronidazole in a randomized controlled trial conducted before the outbreak of a hypervirulent strain, NAP1/BI/027 (NAP1). In one randomized controlled trial where a third of patients were infected with NAP1, the use of vancomycin increased the cure rate by 31% (RR 1.31; 95% CI, 1.03 to 1.66) compared with metronidazole in adult patients with initial or recurrent episodes of severe *C. difficile* infection. Other outcomes were reported, but the comparisons between vancomycin and metronidazole yielded inconclusive findings, or the effect measures were not calculated because the number of events was too small for adequate comparisons.

**Clinical Practice Guidelines**

The two international clinical practice guidelines that were identified were rigorously developed and clearly presented. Both guidelines recommended the use of oral metronidazole for non-severe initial episodes of *C. difficile* infection. Both guidelines recommended the use of oral vancomycin for severe initial episodes of *C. difficile* infection.

**Economic**

A primary economic analysis based on the efficacy data from one randomized controlled trial compared the cost-effectiveness of first-line therapy with vancomycin versus metronidazole in patients with severe *C. difficile* infection. It was assumed that there was no difference between vancomycin and metronidazole in the incidence of serious complications. In the economic evaluation, it was estimated that each additional clinical cure that was attained through first-line vancomycin use would occur at an additional cost of $1,161 to the health care system.

Deterministic sensitivity analyses showed that the incremental cost per clinical cure increased during an outbreak of a hypervirulent strain of *C. difficile*. Increasing incremental costs were largely due to high doses of vancomycin being prescribed to an increasing proportion of patients who were initially treated with a lower dose of vancomycin and whose treatment failed. Another sensitivity analysis suggested that the substitution of oral vancomycin capsules with a lower cost generic intravenous formulation that was administered orally and available only to hospitals could decrease incremental cost-effectiveness ratios. Cost-effectiveness ratios that were estimated based on the assumption that treatment success leads to an earlier discharge suggest that treatment with vancomycin is cost-equivalent to treatment with metronidazole given small reductions in the length of stay among patients taking vancomycin. If serious complications occurred at equal rates among treatment failures, initial treatment with vancomycin may result in net health expenditure reductions to the health care system due to savings in hospital costs. It was also found that these results were sensitive to model assumptions about efficacy rates of initial therapy with metronidazole.

**Budget Impact**

The budget impact analysis compared the incremental costs of first-line treatment using vancomycin with the costs of first-line treatment using metronidazole in hospitalized patients with severe *C. difficile* infection. The probabilities of treatment success, relapse, failure, complications, and subsequent drug therapy were the same as those used in the base case of the
economic evaluation. The results showed annual incremental costs to hospital budgets of $734,826 at the national level, and annual incremental costs to community drug budgets of $398,454 after using vancomycin as first-line treatment.

In sensitivity analyses, the use of a lower-cost, generic intravenous vancomycin that was administered orally and only available to hospitals decreased incremental hospital costs to $72,646 at the national level. In an outbreak of a hypervirulent strain, the incremental costs to hospital budgets increased to $1.74 million, and those of community drug budgets increased to $3.2 million when accounting for a greater number of patients with uncomplicated treatment failures obtaining treatment in the community after hospital discharge. Differing complication rates between treatment groups resulted in a total incremental cost of $681,258 in hospital budget for first-line treatment using vancomycin. The incremental cost to community drug budget was $712,667. If vancomycin is more effective than metronidazole in reducing the rate of complications in severe disease, its use would result in net savings to hospital budgets of $8.5 million at the national level because of savings in hospital stays.

Generalizability of Findings

Of the RCTs that were found, none included patients with an initial episode of *C. difficile* infection exclusively, and none included children or were conducted in the community. Hence, the findings of the clinical and economic systematic reviews and economic analysis apply to hospitalized adult patients with initial or recurrent episodes of moderate or severe *C. difficile* infection.

Conclusions

Five randomized controlled trials included hospitalized adult patients with initial or recurrent episodes of *C. difficile* infection. Based on the limited data that were obtained from subgroup analyses, the use of metronidazole and of vancomycin leads to a similar clinical cure rate among hospitalized adult patients with initial or recurrent *C. difficile* infection of moderate severity. A higher clinical cure rate is reported after the use of vancomycin by hospitalized adult patients with initial or recurrent severe *C. difficile* infection. Conclusions about the outcomes of recurrences, complications, and serious adverse events cannot be made.

The use of oral vancomycin by patients with severe disease will incur an incremental cost of $1,161 per clinical cure, but the use of vancomycin may reduce net health expenditure, if it has an impact on hospitalization costs through reduced length of stay due to earlier discharge or reductions in serious complications.

The annual incremental costs of using vancomycin as first-line treatment in hospitalized patients with severe *C. difficile* infection are, at the national level, $734,826 for hospitals and $398,454 for community drug budgets.

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