CONTEXT AND POLICY ISSUES

Clostridium difficile (C. difficile) is a gram-positive, spore-forming, anaerobic bacterium. C. difficile is transmitted through spores or bacteria in stool or through spores in the environment. Healthy individuals who are colonized with C. difficile may be asymptomatic carriers; the colonization rates of C. difficile range from 2.4% to 13.0% among healthy adults in the community and from 20% to 50% in hospitalized adult patients. CDI symptoms range from mild diarrhea to fever or leukocytosis, which occur in severe disease. Complications include toxic megacolon, bowel perforation, colectomy, sepsis, shock, or death.

In Canada in 2004-2005, it was reported that the overall incidence rate of nosocomial Clostridium difficile infection (CDI) among adults was 4.6 cases per 1,000 patient admissions and 65 per 100,000 patient-days. The 30-day all-cause mortality rate was 16.3 deaths per 100 cases. The total attributable mortality was 5.7 deaths per 100 cases; 2.2 deaths per 100 cases were directly attributable, and 3.6 deaths per 100 cases were indirectly related to CDI. An aging population, an increase use of antibiotics, better diagnostic tests, and increased awareness and surveillance programs may explain the increase in CDI incidence.

Broad spectrum antibiotic exposure is a risk factor for CDI. Alteration of bowel flora allows C. difficile spores to germinate, multiply, bind to the gastrointestinal mucosa, and produce toxins that damage the colonic mucosa. Advanced age (≥65 years), immunosuppression, surgical procedures, comorbidities, hospitalization or residence in a long-term care facility, and possibly the use of gastric acid suppressive therapies such as proton pump inhibitors (PPIs) are other risk factors. PPIs are a class of medications which are frequently prescribed and a potential risk factor for CDI. The mechanism by which PPIs may increase the risk of CDI is unclear although several hypotheses have been suggested such as gastric acid suppression, altered host immune response, and antibacterial effects of PPI metabolites.
A probiotic is a natural health product composed of live microorganisms which when ingested in adequate amount may contribute to a healthy gut flora. Examples include Lactobacillus species, Bifidobacterium species, and Saccharomyces boulardii. The administration of a probiotic may prevent CDI by maintaining or restoring gut microecology, such as in patients exposed to antibiotics. Several recent systematic reviews and meta-analyses have shown that probiotics administered during or after antibiotic therapy are effective in preventing CDI. Whether or not probiotics and other natural health products could protect against CDI in patients administered a PPI is of interest to policy makers.

A previous CADTH report reviewed the clinical evidence and safety of probiotics for the prevention and treatment of CDI, not limited to patients on PPIs. Limited evidence from one meta-analysis suggested that treatment with Saccharomyces boulardii in addition to vancomycin or metronidazole could reduce the incidence of recurrent C. difficile infection versus antibiotics alone.

The objective of this report is to review the clinical effectiveness and cost-effectiveness of natural health products in the primary and secondary prevention of CDI in hospitalized adult patients administered proton pump inhibitors.

**RESEARCH QUESTIONS**

1. What is the clinical effectiveness of natural health products in the primary and secondary prevention of Clostridium difficile infection in hospitalized adult patients administered proton pump inhibitors?

2. What is the cost-effectiveness of natural health products in the primary and secondary prevention of Clostridium difficile infection in hospitalized adult patients administered proton pump inhibitors?

**KEY FINDINGS**

No relevant literature regarding the clinical effectiveness and cost-effectiveness of natural health products in the primary and secondary prevention of CDI in hospitalized adult patients administered proton pump inhibitors was identified.

**METHODS**

**Literature Search Strategy**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and August 20, 2014.
Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria outlined in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td>Hospitalized adult patients on proton pump inhibitors</td>
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<tr>
<td>Sub-groups:</td>
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<tr>
<td>• Patients with exposure to antibiotic therapy</td>
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<tr>
<td>• Patients with no exposure to antibiotic therapy</td>
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<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>Natural health products (probiotics, essential oils, herbal products, garlic / allecin extracts, energy medicine)</td>
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<tr>
<td><strong>Comparator</strong></td>
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<tr>
<td>Placebo or no treatment</td>
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<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td>• Reduction in symptoms generally associated with Clostridium difficile infection (diarrhea, infectious diarrhea, colitis)</td>
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<tr>
<td>• Reduction of relapse or recurrence of Clostridium difficile infection in hospitalized adult patients who have previously experienced one or more episodes of Clostridium difficile infection</td>
</tr>
<tr>
<td>• Costs and cost-effectiveness</td>
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<tr>
<td><strong>Study Designs</strong></td>
</tr>
<tr>
<td>Health technology assessment/ systematic review/ meta-analysis, randomized controlled trials, non-randomized trials, economic evaluations</td>
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</table>

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, or were published prior to 2009.

SUMMARY OF EVIDENCE

Quantity of Research Available

The selection of studies is summarized in Appendix 1. The literature search yielded 437 citations. After screening of titles and abstracts, 62 potentially relevant articles were selected for full text review. Three additional publications were identified from the grey literature. Of the 65 potentially relevant reports, none met the inclusion criteria.

Summary of Findings

There was no evidence found on the clinical effectiveness and cost-effectiveness of natural health products in the primary and secondary prevention of CDI in hospitalized adult patients administered proton pump inhibitors. Therefore a summary cannot be provided.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

No relevant literature was identified; therefore, no conclusions can be drawn about the clinical effectiveness and cost-effectiveness of natural health products in the primary and secondary prevention of CDI in hospitalized adult patients administered proton pump inhibitors.

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REFERENCES


APPENDIX 1: Selection of Included Studies

437 citations identified from electronic literature search and screened

375 citations excluded

62 potentially relevant articles retrieved for scrutiny (full text, if available)

65 potentially relevant reports

65 reports excluded:
- duplicate publication (1)
- irrelevant study design (17)
- irrelevant population (14)
- irrelevant intervention (1)
- irrelevant outcomes (3)
- no sub-group analysis of patients on a PPI (29)

0 reports included in review