SUPPLEMENT ARTICLE

A Decade of Experience in Primary Prevention of *Clostridium difficile* Infection at a Community Hospital Using the Probiotic Combination *Lactobacillus acidophilus* CL1285, *Lactobacillus casei* LBC80R, and *Lactobacillus rhamnosus* CLR2 (Bio-K+)

Pierre-Jean Maziade,[1] Pascale Pereira,[2] and Ellie J. C. Goldstein[3,4]

[1]Infectious Diseases and Microbiology Department, and [2]Nutrition Department, Pierre-Le Gardeur Hospital, Lachenaie, Quebec, Canada; [3]David Geffen School of Medicine at UCLA, Los Angeles, and [4]R. M. Alden Research Laboratory, Santa Monica, California

In August 2003, the 284-bed community hospital Pierre-Le Gardeur (PLGH) in Quebec experienced a major outbreak associated with the *Clostridium difficile* NAP1/027/BI strain. Augmented standard preventive measures (SPMs) were not able to control this outbreak. It was decided in February 2004 to give to every adult inpatient on antibiotics, without any exclusion, a probiotic (Bio-K+: *Lactobacillus acidophilus* CL1285, *Lactobacillus casei* LBC80R, and *Lactobacillus rhamnosus* CLR2) within 12 hours of the antibiotic prescription. Augmented SPMs were continued. The use of the probiotic in addition to SPMs was associated with a marked reduction of *C. difficile* infection (CDI). During the 10 years of observation, 44 835 inpatients received Bio-K+, and the CDI rate at PLGH declined from 18.0 cases per 10 000 patient-days and remained at low mean levels of 2.3 cases per 10 000 patient-days. Additionally, 10-year data collected by the Ministry of Health in Quebec comparing the CDI rate between Quebec hospitals showed that CDI rates at PLGH were consistently and continuously lower compared with those at similar hospitals. Blood cultures were monitored at PLGH for *Lactobacillus* bacteremia through the 10 years' experience, and no *Lactobacillus* bacteremias were detected. Despite the limitation of an observational study, we concluded that the probiotic Bio-K+ was safe and effective in decreasing our primary CDI rate.

Keywords. *C. difficile* infection; primary prevention; Bio-K+; probiotic; diarrhea.

In March 2003, the recognition that hospitals in metropolitan Montreal and the surrounding Quebec region had a marked increase in the incidence of *Clostridium difficile* infection (CDI) to 28.2 CDI cases per 1000 patient admissions (almost 5 times the 2001 rate of 5.7 CDI cases per 1000 patient admissions) publicized the emergence of the fluoroquinolone-resistant epidemic *C. difficile* strain NAP1/027 [1, 2]. This outbreak was associated with an increased severity of disease and increased mortality. Consequently, increased surveillance and infection control measures were regionally instituted at most affected institutions.

Pierre-Le Gardeur Hospital (PLGH), in Lachenaie, Quebec, Canada, a 284-bed community hospital without heart, thoracic, neurosurgery, or transplant units, had established a policy of standard protective measures (SPMs) in 1998 and, in response to the outbreak in August 2003, instituted an augmented SPM (aSPM) program (Table 1). After an initial 6-month observational

Correspondence: Pierre-Jean Maziade, MD, FRCPC, 911 Montee Pionniers Terrebonne, Québec, Canada J6V 2H2 (pierre-jean.maziade@ssss.gouv.qc.ca).
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Table 1. Augmented Standard Preventive Measures for the Prevention of *Clostridium difficile* Infection Used August 2003–February 2004 Without Response but Continued Throughout the Study

Isolation of CDI patients
• *Clostridium difficile*–infected patients were rapidly identified • Isolation was in a dedicated area • Dedicated hospital staff was assigned for CDI patients
Cleansing and disinfection
• Rigorous cleaning program was implemented, including disinfection of bathrooms, toilets, floors, and walls with PerCept (hydrogen peroxide) • Special attention was paid to rooms previously occupied by patients with diarrhea • Disinfection of medical equipment (cuffs, bedpans, etc) was performed after each use to reduce patient-to-patient contamination
Monitoring of antibiotic use
• Monitoring of antibiotic use, ie, second- and third-generation cephalosporins • Moxifloxacin removed from the formulary
Hand washing and hand disinfection
• A team took care of washing hands of inpatients twice a day, 7 days a week, using a waterless antibacterial sanitizer • This was done in addition to normal patient hand hygiene

Source: Adapted from Maziade et al [3] with permission.

Abbreviation: CDI, *Clostridium difficile* infection.

period that showed apparent ineffectiveness of the aSPM alone to decrease CDI rates, PLGH instituted a novel probiotic bundle in January 2004. This 8-year intervention resulted in a 73% reduction of CDI cases ($P < .001$), of severe cases of 76.4% ($P < .001$), and of relapse of 39% ($P < .001$) [3].

In this article, we include an additional 2 years of follow-up from our previous report covering an 8-year period [3] and summarize the 10-year experience with our quasi-experimental, prospective cohort study of patients in a community hospital where the probiotic bundle was routinely used from 30 April 2004 to 31 March 2014. A specific probiotic formula of *Lactobacillus acidophilus* CL1285, *Lactobacillus casei* LBC80R, and *Lactobacillus rhamnosus* CLR2 (Bio-K+) was administered to all adult patients who were prescribed antibiotics in addition to aSPMs for the prevention of CDI. Additionally, we accumulated safety information with regard to *Lactobacillus* species bacteremia during the study period.

METHODS

In 1998, and before the outbreak, SPMs that had previously been reported as components of successful bundled approaches to control CDI were instituted at PLGH. In 2003, aSPM measures were instituted by PLGH as described in Table 1. The details of this quasi-experimental program and initial results have been previously reported [3]. The pharmacy dispensed a daily oral dose of a probiotic formula containing 50 billion colony-forming units (CFU) of *L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2 (Bio-K+, Bio-K Plus International, Quebec, Canada) to all adult inpatients who were prescribed any antibiotics, within 2–12 hours after the start of any antibiotic prescription. This was continued for a minimum of 30 days or until completion of the antibiotic prescription. No adult patients (≥18 years of age) were excluded from the program, and patient compliance was verified during hospitalization by the pharmacy where the capsules remaining in the bottles were counted. Patient compliance could not be verified after hospital discharge. However, a written prescription for the probiotic was given to all patients at discharge. At the beginning of 2011, we gave 2 capsules per day (100 billion CFU) to patients aged ≥50 years according to a recently published randomized controlled study [4]. For patients aged 18–49 years, we continued to give 1 capsule per day. The probiotic was continued for 5 days after the end of antibiotic treatment.

The aSPMs and probiotic administration, without adding any other interventions, were continued during the study period. The project was considered to be a quality improvement initiative, and ethical review was waived. The microbiology laboratory was monitored for any *Lactobacillus* bacteremia. Additionally, the CDI incidence rate at PLGH was compared with that of all 95 hospitals of the 16 Quebec administrative regions following the early 2005 initiative of the Ministry of Health and Social Services of Quebec, which independently collected and analyzed all these data [5–7].

CDI was defined by either (1) the presence of an episode of diarrhea (at least 3 liquid stools within 24 hours) or (2) the sudden onset of liquid stools lasting >24 hours with no alternative explanation and a positive assay for *C. difficile*, or a diagnosis of pseudomembranous colitis on the basis of endoscopy or by histology. Patients were monitored for recurrence (2 months) postdischarge. Multiple recurrence was defined as >2 recurrences after adequate treatment. A case was considered hospital acquired (nosocomial) if symptoms started ≥72 hours after a patient was admitted or if CDI was diagnosed within 1 month after hospital admission, whether the patient was still in the hospital or released. Potential probiotic-related bloodstream infections were to be identified by monitoring microbiologic laboratory blood culture results for any sample positive for *Lactobacillus* species, and preparations for phenotypic evaluation and speciation by a reference laboratory were made.

The 10-year data collected by the Ministry of Health in Quebec comparing the CDI rate between Quebec hospitals and PLGH were expressed as initial episodes per 10 000 patient-days, which became the accepted norm for between-institution comparisons.

RESULTS

During the combined observational phase (30 April 2005 to 31 March 2014), data were published annually by the Ministry of Health, and were expressed as cases per 10 000 patient-days. Figure 1 shows that the average annual incidence rate of CDI at PLGH remained at values much lower than those observed in the conglomerate of other Quebec network hospitals (2.3 vs 7.5 cases per 10 000 patient-days). These values are also lower than those from equivalent hospitals (≥250 beds) (8.3 cases per 10 000 patient-days) as well as from a similarly sized hospital with comparable services (12.8 cases per 10 000 patient-days) located close to PLGH. All rate reductions observed during the initial utilization of Bio-K+ were maintained for 9 years.

For the first 18 months using Bio-K+, we noted a reduction of recurrences of 39% (38.5% to 23.4%). We found no nosocomial multiple recurrent cases. In fact, those cases are referred to the infectious disease specialists to consider stool transplant, and the list so far is empty. In addition, compared to a similar hospital in the same territory, we observed almost no variation in our rate of CDI during the 10-year experience (Figure 1). The microbiology laboratory had no episodes of *Lactobacillus* bacteremia during the entire 10-year experience.

DISCUSSION

The efficacy of various probiotics in the prevention of CDI and antibiotic-associated diarrhea has been reported by several meta-analyses [8–11]. The data presented in this investigation strongly suggest that the probiotic formulation namely Bio-K+ given to patients receiving antibiotics may have been an effective adjunct intervention in reducing the incidence of overall and severe CDI at PLGH. This is supported by the lack of significant change in the control of CDI by the aggressive aSPM approach alone, especially compared with the rates seen at other regional hospitals. The choice of *L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2 proved to be fortuitous, given recently published data from randomized controlled trials using this same formulation [4, 12, 13]. It also should be noted that the probiotic plus an SPM intervention appeared to be effective in preventing NAP1/027 CDI. The NAP1 strain, recognized for its virulence, was documented to account for 50%–70% of Quebec network hospital isolates [7]. CDI strains from PLGH were also found to be NAP1/027 [7].

The combined program also had a financial impact from the prevention of CDI. Analysis of the results of a randomized clinical trial using the same probiotic showed that the use of the probiotic formula would result in estimated mean per-patient savings up to US$2769 [14]. These savings could be much more significant in the US healthcare system.

The reduction of CDI recurrences was noted starting in the first months after initiating Bio-K+ use. During the observational period, cases of multiple nosocomial recurrences of CDI were absent in PLGH. Since 2013, the protocol for multiple recurrent cases at our hospitals has been to refer them to the infectious disease service to consider a new PLGH fecal transplant treatment in accordance with a recently published article [15]. Consequently, due to our low rates, this protocol was employed only twice for community cases.

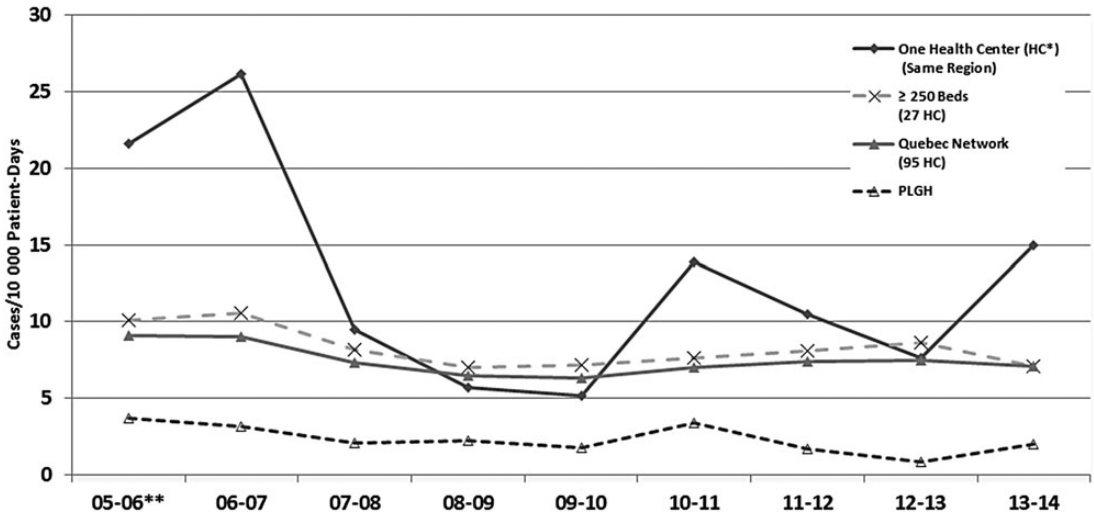

Figure 1. Comparative rates of *Clostridium difficile* infection from 1 August 2005 to 31 March 2014 at Pierre-Le Gardeur Hospital (PLGH) and hospitals in the Quebec Network, hospitals with ≥250 beds, and One Health Centers (HC; same region).*Adapted from Maziade et al [3] with permission.**Data source: 2005–2014 surveillance data on *C. difficile* infection in Quebec hospitals from the Ministry of Health and Social Services of Quebec.

The continuous lower CDI rate with only small variation from 2005 to 2014 might be explained by the direct protection conferred by the probiotic against CDI. The probiotic was taken by inpatients, with a high compliance rate (>99.5%). Comparatively, there was a wide variation in CDI rate through time at a similar hospital near PLGH, suggesting that our unique intervention may have been a factor. It is possible that the other regional hospitals experienced an uneven quality and compliance of SPM through that time [16]. Alternatively, the existing hand hygiene interventions at the other hospitals may have used techniques with limited activity against *C. difficile* spores [17].

Our observational study is limited, as are all observational studies. This type of trial was initiated instead of a properly designed randomized controlled trial because, in 2003, we were experiencing an outbreak of CDI. In those days, even with the implementation of aSPM, many patients died because of CDI. We wanted to rapidly modify our medical practices to control CDI, and probiotic administration was a very promising therapy to prevent this nosocomial infection. Because Bio-K+ was in the process of being evaluated at Maisonneuve-Rosemont hospital in Montreal, we assumed it was an interesting probiotic product to implement in our bundle of preventive measures. However, after 10 years of observation, the maintenance of a constant reduction of CDI and lack of toxicity suggests that the probiotic Bio-K+ is effective in primary prevention of CDI.

Our experience suggests that the addition of a combination probiotic formulation of *L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2 to a bundle of aSPMs and antibiotic surveillance program appears to be an effective and safe method for reducing CDI incidence.

Notes

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Potential conflicts of interest. P.-J. M. is a member of the Bio-K Plus International advisory board. E. J. C. G. is a member of the Bio-K Plus International advisory board and speaker's bureau. P. P. reports no potential conflicts.

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References

1. Warny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. Lancet **2005**; 366:1079–84.
2. Eggertson L. *C. difficile* hits Sherbrooke, Que., hospital: 100 deaths. CMAJ **2004**; 171:436.
3. Maziade PJ, Andriessen JA, Pereira P, et al. Impact of adding prophylactic probiotics to a bundle of standard preventative measures for *Clostridium difficile* infections: enhanced and sustained decrease in the incidence and severity of infection at a community hospital. Curr Med Res Opin **2013**; 29:1341–7.
4. Gao XW, Mubasher M, Fang CY, et al. Dose–response efficacy of a proprietary probiotic formula of *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* LBC80R for antibiotic-associated diarrhea and *Clostridium difficile*-associated diarrhea prophylaxis in adult patients. Am J Gastroenterol **2010**; 105:1636–41.
5. Ministère de la Santé et des services sociaux. Surveillance data on *Clostridium difficile* infection in Québec hospitals. News Bulletin No. 24, **2011**. Available at: http://publications.msss.gouv.qc.ca/acrobat/f/documentation/2011/11-209-01A_no24.pdf. Accessed 17 March 2015.
6. Ministère de la Santé et des Services sociaux. Surveillance data on *Clostridium difficile* infection in Québec hospitals. News Bulletin No. 18, **2009**. Available at: http://publications.msss.gouv.qc.ca/acrobat/f/documentation/2008/08-209-01Ano18.pdf. Accessed 17 March 2015.
7. Ministère de la Santé et des Services sociaux. Surveillance data on *Clostridium difficile* 2012–2013. News Bulletin No. 30. Institut National de Santé Publique, **2013**. Available at: http://publications.msss.gouv.qc.ca/acrobat/f/documentation/2013/13-209-03A_no30.pdf. Accessed 17 March 2015.
8. Johnson S, Maziade PJ, McFarland LV, et al. Is primary prevention of *Clostridium difficile* infection possible with specific probiotics? Int J Infect Dis **2012**; 16:e786–92.
9. Johnston BC, Ma SS, Goldenberg JZ, et al. Probiotics for the prevention of *Clostridium difficile*–associated diarrhea a systematic review and meta-analysis. Ann Intern Med **2012**; 157:878–88.
10. McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of *Clostridium difficile* disease. Am J Gastroenterol **2006**; 101:812–22.
11. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA **2012**; 307:1959–69.
12. Beausoleil M, Fortier N, Guenette S, et al. Effect of a fermented milk combining *Lactobacillus acidophilus* Cl1285 and *Lactobacillus casei* in the prevention of antibiotic-associated diarrhea: a randomized, double-blind, placebo-controlled trial. Can J Gastroenterol **2007**; 21: 732–6.
13. Psaradellis E, Sampalis J, Rampakakis E. Efficacy of Bio K+ CL1285 in the reduction of antibiotic-associated diarrhea—a placebo controlled double-blind randomized, multi-center study. Arch Med Sci **2010**; 6:56–64.
14. Kamdeu Fansi AA, Guertin JR, LeLorier J. Savings from the use of a probiotic formula in the prophylaxis of antibiotic-associated diarrhea. J Med Econ **2012**; 15:53–60.
15. Nood EV, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med **2013**; 368: 407–15.
16. Deshpande A, Sitzlar B, Fertelli D, et al. Utility of an adenosine triphosphate bioluminescence assay to evaluate disinfection of *Clostridium difficile* isolation rooms. Infect Control Hosp Epidemiol **2013**; 34: 865–7.
17. Edmonds SL, Zapka C, Kasper D, et al. Effectiveness of hand hygiene for removal of *Clostridium difficile* spores from hands. Infect Control Hosp Epidemiol **2013**; 34:302–5.