Centre universitaire de santé McGill
McGill University Health Centre

Technology Assessment Unit of
the McGill University Health Centre

The use of probiotics in the prevention and treatment of *Clostridium Difficile* diarrhea: An Update

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by

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Invitation.

This document was developed to assist decision-making in the McGill University Health Centre. All are welcome to make use of it. However, to help us estimate its impact, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way.

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2 ABBREVIATIONS AND ACRONYMS

TAU	Technology Assessment Unit
MUHC	McGill University Health Centre
CDAD	*Clostridium difficile*-associated diarrhea
AAD	Antibiotic Associated Diarrhea
RCT	Randomized Controlled Trials

3 SOMMAIRE

En 2005, l'utilisation des probiotiques pour la prévention et le traitement des infections au C-difficile et de la diarrhée concomitante (CDDC) chez les adultes fut évaluée par l'Unité d'évaluation des technologies (TAU) du Centre universitaire de santé McGill (CUSM). L'on conclua à ce moment que les évidences d'un bénéfice quelconque étaient insuffisantes en regard de la prévention ou du traitement du CDDC et que l'utilisation des probiotiques au CUSM n'était pas recommandée. Le présent document est une mise à jour de ce rapport.

La revue de la littérature à partir de cette date jusqu'en 2009 ne révéla aucune nouvelle étude sur le *traitement* du CDDC par les probiotiques et identifia cinq nouvelles études sur l'utilisation des probiotiques pour la *prévention* du CDDC. Parmi les 10 études randomisées disponibles de nos jours, une seule souligna des bénéfices importants reliés à l'utilisation des probiotiques. Ainsi, il n'existe toujours pas d'évidences de bénéfices cliniques reliés à l'utilisation des probiotiques pour la prévention et le traitement du CDDC.

Recommandation :

L'utilisation des probiotiques pour la prévention et le traitement du CDDC au CUSM n'est pas recommandée.

4 EXECUTIVE SUMMARY

In 2005, the use of probiotics for the prevention and treatment of CDAD in adults was evaluated by the Technology Assessment Unit (TAU) of McGill University Health Centre (MUHC). It was concluded at that time that there was insufficient evidence of benefit for either prevention or treatment of CDAD, and the use of probiotics for this purpose at the MUHC was not recommended. The present document is an update of that report.

Review of the literature from that time up to September 2009 revealed no new studies on the *treatment* of CDAD by probiotics, and five studies of their use in *prevention* of CDAD. Of the 10 RCTs currently available for review, only one found significant benefit from the use of probiotics. Thus, there is still no good evidence of clinical benefit of probiotics for prevention or treatment of CDAD.

Recommendation: Use of probiotics for the prevention or treatment of CDAD at the MUHC is not recommended.

5 INTRODUCTION

Clostridium difficile-associated diarrhea (CDAD) is the most common form of nosocomial diarrhea. Length of hospital stay for patients with CDAD is found to increase by 8 days among adult inpatients and 36 days in geriatric patients[1]. The incidence and severity of CDAD has been increasing in Quebec[2].

A probiotic is a live microorganism or a mixture of various bacteria that is administered to improve the microbial balance in the gastrointestinal (GI) system of the host. In 2005, the use of probiotics was evaluated by the Technology Assessment Unit (TAU) of McGill University Health Centre (MUHC), focusing on the use of probiotics for prevention and treatment of CDAD in adults[2]. As there was very little evidence relating to the use of probiotics for either prevention or treatment of CDAD at that time, its use was not recommended at the MUHC. The present document is an update of that report.

6 METHODS

We followed the same literature search methodology and terms as our previous report in 2005[2]. Briefly, we limited our search to randomized controlled trials (RCTs) on the use of probiotics for the prevention and treatment of CDAD and antibiotic-associated diarrhea (AAD) in adult in-patients from January 1990 onward. We accepted studies published in English or French in which CDAD was either the primary or the secondary outcome. We assessed the quality of each RCT according to the Cochrane criteria and classified it into one of three categories, A (highest), B (medium) and C (lowest)[3]. The literature search ended on October 9th, 2009. When appropriate, we conducted meta-analysis using a random-effects model to pool relative risks of using probiotics versus placebo[4]. We also did a simple cost analysis to explore the economic implications of using probiotics in clinical practice.

7 RESULTS

Literature search: We identified five studies on the use of probiotics for CDAD in adult in-patients published between 2005 and October 2009[5-9]. All five studies used probiotics for the prevention of CDAD, rather than for its treatment. The primary and secondary outcomes were AAD and CDAD in these 5 studies. Since there have not been any new studies on the use of probiotics for the *treatment* of CDAD in recent years, our conclusions and recommendations remain unchanged from the previous report for treatment by probiotics[2]. Consequently, this report focuses on the use of probiotics for the *prevention* of CDAD.

Including four RCTs[10-13] identified in the former report, there are now 12 RCTs [5-17] on the use of probiotics for the prevention of AAD or CDAD (See Table 1). Ten[5-14, 16] out of 12 RCTs[5-17] reported on CDAD. However, with one exception[10] CDAD was the secondary outcome in these RCTs. Only three studies systematically tested for *C. difficile* toxin in all patients experiencing diarrhea [5, 10, 16]. Based on the Cochrane criteria , the qualities of these studies are good, (A or B)[3], but, there was obvious heterogeneity between studies, such as in terms of probiotics used, treatment duration, the definition of diarrhea, length of follow-up beyond the treatment period, and the average age of patients (See Table 1). Therefore we decided not to carry out a meta-analysis of this data.

AAD: The main results of these 12 RCTs are summarized in Table 2. For AAD prevention, eight[5-9, 13-15, 17] out of 12 studies found evidence of benefit from probiotic treatment, and 6 [5-7, 9, 13, 14, 17] found both statistically and clinically significant results; in the other 4 studies, two found lower rates of AAD with placebo (statistically insignificant) [12, 16] and in two the AAD rates in placebo and treatment groups were identical [10, 11]Though we chose not to carry out a meta-analysis, it would appear that there is a fairly consistent beneficial effect of probiotics for AAD across these studies. However, we cannot make any generalization about the magnitude of the benefit given the variability across studies.

CDAD: Most studies had few CDAD cases making results statistically non-significant. The sample sizes were calculated on the basis of the efficacy of probiotics on the primary outcome, AAD, so there was insufficient power to detect any protective effect of CDAD. Furthermore, only a subset of patients

who had diarrhea were tested for *Clostridium difficile* toxin in some studies[6, 8, 12]. For example, in the study by Beausoleil et al.[6], 7 patients in the probiotics group and 16 patients in the placebo group developed diarrhea, yet only 2 (28%) of these patients in the probiotics group and 13 (81%) from the placebo group were tested for CDAD. Thus, it is likely that CDAD was under reported in both groups in those studies. In some studies[12, 16], the descriptions of cases were brief, excluding important details, such as the number of patients with CDAD for each group.

One[5] out of the ten studies showed a statistically significant beneficial effect on CDAD from probiotics. In Hickson et al.[5], the absolute risk reduction of CDAD was 17% (p=0.001) with probiotic prophylactic treatment. However, there are some concerns about the generalizability of these results since the study excluded patients who were 'high risk' or who were taking 'high risk' antibiotics[5, 18]. The other 9 studies did not find statistically significant differences between probiotics and placebo (See Table 2). Due to the poor quality of evidence, as mentioned above, we did not perform a meta-analysis on the efficacy of probiotics for prevention of CDAD.

Adverse events: Seven[6, 8, 11-13, 15, 17] of the twelve studies reported adverse events. None of these found any increase of adverse events associated with using probiotics. The common side effects were abdominal pain and nausea in both groups [6, 8, 15]. In Beausoleil et al.[6], three patients died in the *lactobacillus* group, but these deaths were not related to the use of the study preparation. No other severe complications were observed in both groups.

Cost issues: Compared with usual medications, the price of probiotics is very low. We assumed that the average cost of probiotic therapies is 3 CAD $ per day, and the average duration of prophylaxis is 14 days. The expected average cost of probiotic prophylaxis is therefore, 42 $ per patient. It is well documented that CDAD is associated with longer hospitalization[1, 19]. However, AAD alone is not associated with additional hospitalization or other resource consumption.

8 CONCLUSIONS

There is no good evidence of clinical benefit in using probiotics for CDAD prevention. Probiotics may significantly decrease the risk of AAD in adult in-patients, but AAD is not associated with additional health care resource uses.

9 RECOMMENDATION

Probiotics use at the MUHC for prevention of CDAD or AAD is not recommended.

10 TABLES

10.1 Table 1: Clinical Background

Author (year)	Definition of diarrhea	Sample size pro; pla	Age (SD) Pro; Pla	Probiotics	Treatment duration	Follow up	Quality of study £
Safdar [8] (2008)	Either watery or liquid stools for 2 or more consecutive days.	23; 17	66.6 (14.5); 72.5 (11)	LA (Capsule)	Pro: 22.8(9.4) days; Pla: 24.5(4.8) days	0	A
Wenus[9] (2008)	At least three fluid stools/day for at least 2 days.	46; 41	58.8 (16.5); 56.2 (18.7)	LR, LA, B (Milk)	14 days	0	B
Beausoleil [6] (2007)	Three or more liquid stools in a 24-hour period.	44; 45	68.8 (14.5); 72.9 (13.4)	LA and LC (Milk)	Antibiotic therapy	3 weeks	B
Hickson[5, 14] (2007)	More than 2 liquid stools a day in excess of normal for 3 or more days.	69; 66	73.7 (11.1); 73.9 (10.5)	LC, LB, ST (yogurt)	Antibiotic therapy plus 7days	4 weeks	A
Conway[15] (2007)$	3 or more loose stools per day over 2 consecutive days.	Bio: 143; Comm: 127; Pla: 137	37.8 (25.3); 37.1 (23); 38.2 (23.5)	ST, LA, B (Bio-yogurt); ST, LB (Comm yogurt)	12 days	0	B
Can[7] (2006)	N.A.	73; 78	(25-50); (25-50)†	SB (N.A.)	Antibiotic therapy	4 weeks	B
Plummer[10] (2004) &	N.A.	Elder	Elder	LA and B (Capsule)	20 days	0	A
Beniwal[17] (2003)	2 or more loose stools per day, representing a change from the prior bowel pattern.	105; 97	69.5 (20-94); 70.5(19-92)†	LA, LB, ST (comm yogurt)	8 days	0	B

Thomas[11] (2001) &	Either watery or liquid stools for 2 or more consecutive days, or 3 or more bowel more than normal pattern.	133; 134	57.2 (18); 54.4 (17.4)	LA (Capsule)	14 days	1 week	A
Lewis[12] (1998) &	At least 3 loose stools per day.	33; 36	75 (71, 81)#; 77 (70, 85)#	SB (Capsule)	Antibiotic therapy	0	A
McFarland[13] (1995) &	At least 3 loose stools per day for at least 2 consecutive days.	97; 96	40.7 (16.0); 42.3 (17.7)	SB (Capsule)	Antibiotic therapy plus 3 days, up to 28 days	7 weeks	A
Heimburger [16] (1994)	The excretion of > 200g of stool in any 24-hour (Tube-feeding patients).	16; 18	Adult; Adult	LA, LB (Granules)	≥5 days	0	B

Abbreviations: N=number; Pro= probiotics; Pla= placebo; comm=commercial; N.A.= not applicable; LR=*Lactobacillus rhamnosus*; LA= *Lactobacillus acidophilus;* B=*Bifidobacterium;* SB=*Saccharomyces boulardii*; LC= *Lactobacillus casei*; LB= *Lactobacillus bulgaricus*; ST= *Streptococcus thermophilus;* BC= *B. clausii;* CB= *Clostridium butyricum*.

†: Mean (range).
#: Median (interquartile range).
&: Studies were included in our previous report[2].
£: We assessed the quality of RCT according to Cochrane criteria system, mainly focusing on selection bias, performance bias, attrition bias and diction bias [3]. The qualities of RCTs are categorized into 3 levels, A (highest), B (medium) and C (lowest).
$: The numbers of 1 to 14 years old children were 29, 26, and 23 in Bio yogurt, commercial yogurt and control groups, respectively.

10.2 Table 2: Summary of results of prevention of AAD or CDAD using probiotics in adults

Author (year)	AAD no./total no. (%)			CDAD† no./total no. (%)			Adverse effects	
	Pro	Pla	P	Pro	Pla	P	Probiotics	Placebo
Safdar[8] (2008)	4/23 (17)	6/16 (37)	>0.05	0/3 (0)	1 /4 (25)	>0.05	Fever: 2/23(9%); Nausea: 0/23 (0%).	Fever: 2/16(12%); Nausea: 3/16 (19%).
Wenus[9] (2008)	2/34 (6)	8/29 (28)	<0.05	0/34 (0)	1/29 (3.4)	--	N.A.	N.A.
Beausoleil[6] (2007)	7/44 (16)	16/45 (36)	<0.05	1/2 (50)	7/13 (53.8)	>0.05	21/44 (48%) patients experienced softened stools, taste disorder, abdominal cramping, etc. 3 mortalities not related with probiotics.	20/45 (44%) patients experienced softened stools, taste disorder, abdominal cramping, etc. No mortality.
Hickson[5, 14] (2007)	7/57 (12)	19/56 (34)	<0.05	0/56 (0)	9/53 (17)	<0.05	N.A.	N.A.
Conway[15] (2007)	Bio: 9/131 (7) Comm: 13/118 (11)	17/120 (14)	>0.05	-- --	-- --	-- --	Thrush: 10/131 (8%); abdominal pain 66/131 (46%); flatulence 86/131 (65%). Thrush: 6/118 (5%); abdominal pain 46/118 (39%); flatulence 71/118 (60%).	Thrush: 10/120 (8%); abdominal pain 60/120 (50%); flatulence 77/120 (64%).
Can[7] (2006)	1/73 (1.4)	7/78 (9)	<0.05	0/73 (0)#	2/78 (2.6)#	>0.05	N.A.	N.A.
Plummer[10] (2004) &	15/69 (22)	15/69 (22)	>0.05	2/15 (13)	5/15 (33)	>0.05	N.A.	N.A.

Beniwal[17] (2003)	13/105 (12)	23/97 (24)	<0.05	--	--	--	Bloating: 6/102 (6%)	Bloating: 8/97 (8%)
Thomas[11] (2001) &	39/133 (29)	40/134 (30)	>0.05	2/133 (1.5)	3/134 (2.2)	>0.05	No difference in nausea or abdominal. Gas or bloating: (28%).	No difference in nausea or abdominal. Gas or bloating: (39%).
Lewis[12] (1998) &	7/33	5/36	>0.05	In both groups, 4 cases in total.		--	No side effects contributable to probiotics.	
McFarland[13] (1995) &	7/97 (7)	14/96 (15)	<0.05	3/10 (30)	4/14 (29)	>0.05	No significant adverse reactions. Fever: 0.; intestinal gas: 0.	No significant adverse reactions. Fever: 5 (5%); intestinal gas: 7 (7%).
Heimburger[16] (1994)	5/16 (31)	2/18 (11)	>0.05	0/5 (0)	0/2 (0)	--	N.A.	N.A.

Abbreviations: no=number; bio=bio-yogurt; comm= commercial yogurt; N.A.= not applicable.
#*:* Only *Clostiridium difficile* toxin A was assayed in this study [7]. Information of toxin B was not reported.
†: Definition of CDAD: Diarrhea was present and *C. difficile* toxin was positive in stool samples.

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