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# USE OF PROBIOTICS IN PREVENTING ANTIBIOTIC ASSOCIATED DIARRHOEA AND *CLOSTRIDIUM DIFFICILE* ASSOCIATED DIARRHOEA IN SPINAL INJURY CENTRES: AN INTERNATIONAL MULTICENTRE SURVEY

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**ABSTRACT:** ***Probiotics may prevent antibiotic-associated- and Clostridium difficile-associated- diarrhoea (AAD/CDAD). Many spinal cord injury centres (SCICs) practitioners consider probiotics generically and may not realise that efficacy can be strain-, dose-, and disease-specific. One to four SCICs per country (depending on population size) were contacted (UK:4; the Netherlands:3; Belgium:1; Republic of Ireland:1) to (a) determine if they stocked probiotics; (b) determine whether the use of those probiotics was evidence-based; and (c) document their C. difficile infection (CDI) practices. All nine SCICs responded to the survey (7 physicians, 3 microbiologists, 1 nurse and 2 dietitians). Five (55.5%) stocked probiotics; five different probiotics were identified. Four probiotics were preferred choice prevention of AAD/CDAD were Lactobacillus casei Shirota (44.4%), L. casei DN-114001 (22.2%), L. acidophilus (22.2%) and a mixed-strains probiotic (Ecologic Pro-AD) (11.1%). Only one evidence base study was identified supporting the use of probiotic for prevention of AAD in SCI patients. Mean CDI cases per 10,000 patient-days were 0.307 (s.d: 0.486, range 0.00 to 1.08). Definitions of diarrhoea and CDI varied among SCICs. Stocking probiotics for the prevention of AAD/ CDAD is not common. There is only one single study showing efficiency of a particular strain in SCI populations. The study highlighted the importance of using a standardised definition of diarrhoea when conducting AAD/ CDAD research.***

**KEY WORDS**: Antibiotic-associated diarrhoea, *Clostridium difficile*' Probiotics, Spinal cord injury, Survey

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## INTRODUCTION

Probiotics are live organisms that, when administered in adequate amounts, confer a health benefit on the host (FAO / WHO, 2001). They are increasingly available as capsules and dairy-based food products sold in supermarkets and health food shops. Although there are numerous commercially available probiotics, there is much debate as to what beneficial effects these provide and which specific organisms may be most effective in any specific patient group. (Hempel *et al.,* 2012; Todorov *et al.,* 2011; Ohashi and Ushida, 2009) Microorganisms commonly used in probiotic preparations include bacteria of the genera *Lactobacillus*, *Bifidobacterium*, *Escherichia*, *Enterococcus* or *Bacillus,*and the fungal genus *Saccharomyces*. (Ohashi and Ushida, 2009)

Different probiotic species and strains can have substantially different effects on the host. (Hickson, 2011; Hill *et al.,* 2014) Several species- and strain-specific factors play a role in determining what benefits, if any, a probiotic may confer. To exert a beneficial effect, a probiotic must first be able to colonise the gastrointestinal (GI) tract. The initial step required for GI colonisation by probiotics is adhesion to the GI mucosa. (Van and Miller, 2011) Although not fully understood, current evidence suggests that the adhesive characteristics of probiotics may be due to differences in the expression of large surface

proteins and their interaction with mucus-binding proteins. (Van and Miller, 2011) Probiotics have been suggested as a mean of preventing adverse GI conditions such as antibiotic-associated diarrhoea (AAD) and *Clostridium difficile*-associated diarrhoea (CDAD). (Hempel *et al.,* 2012; Todorov *et al.,* 2011; Hickson, 2011; Wong et al., 2014) However, this is not a characteristic that is shared among all probiotic strains (Ohashi and Ushida, 2009; Hickson, 2011; Hill et al., 2014; Van and Miller, 2011) and effects may differ with different patient groups. (Hill *et al.,* 2014; Wong *et al.,* 2014) One example where the use of probiotics is particularly likely to be beneficial is in patients with spinal cord injury (SCI) who not only require an extended period of stay in hospital, but also have increased risk of infection due to the use of urinary catheters for long-term bladder management. If diarrhoea develops, rehabilitation will be delayed, impacting not just on the patient but also causing significant extra healthcare costs. Given the severe loss of quality of life for SCI patients, if any probiotic is effective, their low cost as well as the low incidence of adverse events (Hempel *et al.,* 2012) render probiotics an attractive intervention to prevent AAD / CDAD.

Probiotics that colonise the GI tract effectively help resist gut colonisation by potentially harmful bacteria. Such probiotics often have additional properties that benefit the host. (Ohashi and Ushida, 2009; Hill et al., 2014) Certain *Lactobacillus* strains can produce antimicrobial compounds, known as bacteriocins, which may inhibit pathogens such as *Bacillus*, *Staphylococcus* and *Enterococcus* species. A specific strain of *Lactobacillus acidophilus* produces a bacteriocin that has shown to inhibit strains of *Listeria innocua* and *Listeria monocytogenes*. (Todorov *et al.,* 2011)

With this in mind, it is important to recognise that there is no "generic equivalency" between probiotic species and strains. For example, one *Lactobacillus casei* strain cannot be assumed to be equivalent to another *Lactobacillus casei* strain in terms of its effectiveness in a human host. Therefore, it is important for clinicians to use or recommend specific commercially available probiotics that have specifically been shown to have beneficial effects in clinical trials.

Anecdotally, it has been noted that many practitioners consider probiotics in generic terms, not recognising that there may be differences between different products. Similarly, some of the healthcare facilities stock a probiotic, but will not substitute one commercial probiotic for another based on cost or availability, and without regard for any scientific evidence to support the probiotic in question.

To address this issue, we conducted a survey of specialist Spinal Cord Injury Centres (SCICs) in four European countries to determine which specific probiotics were stocked most commonly in SCICs. On the basis of the survey results, we then conducted a systematic literature review according to expert consensus (Hill *et al.,* 2014) to determine whether the probiotics that were stocked were supported by any clinical research. Our aim was to determine whether SCICs are currently using probiotics that are specifically supported by reliable evidence. Furthermore, to facilitate future AAD / CDAD research, we endeavoured to obtain an understanding of *Clostridium difficile* infection (CDI) management strategies (including diagnostic procedures and presence of national surveillance) followed in European SCICs.

## MATERIALS AND METHODS

### Survey Instrument

A 30 item cross-sectional questionnaire was distributed to each SCIC's lead clinician. The questionnaire consisted of three sections: the first section was aimed at all professional groups (medical staff, microbiologist, nursing staff and dietitian); the second section was aimed at the SCIC's medical lead and the last section was aimed at the lead microbiologist. In addition to gathering demographic data, we enquired about the SCIC's practice (for example, we asked them to provide epidemiological data, including numbers of patient-days, admission and use of gastric protection). To understand which commercial probiotics are stocked in the European SCICs, each SCIC's lead was asked to identify which specific products they stocked or used in their facility, the indications and dose for the probiotic they used, their diagnostic criteria for diarrhoea and stool sample testing for CDI in October 2014, and technical data such as which assays and culture methods were used. Formal ethical permission to conduct the study was not required by the Stoke Mandeville Hospital review board as this was considered to be a clinical audit not involving active patient participation (Health Research Authority, 2013); this was accepted by the other centres. The local clinical audit departments approved the questionnaires. In addition, we sent the pilot questionnaire to three members of our staff to assess the content and time required to complete the questionnaire; feedback from this guided the drafting of the final version of the questionnaire.

### Survey administration

The survey was administered to SCIC's medical leads in four European countries with a covering letter addressed to the local medical lead explaining that our findings would be used to identify current CDI practice and to establish if SCICs clinicians supported the use of probiotics. We aimed to include one SCIC for each country with fewer than 10 million inhabitants or fewer, two for countries with between 10 and 20 million inhabitants, and four for those with more than 20 million inhabitants, with a balance between academic and non-academic institutions. Participants were reassured that all findings would be treated anonymously and in confidence to encourage respondents to answer honestly. Completed questionnaires were anonymised prior to analysis. Two reminders were sent (at eight weeks and twelve weeks after the initial survey distribution).

### Statistical analyses

The incidence rate of healthcare-associated CDI for all SCICs was obtained by dividing the number of healthcare-associated occurrences by the number of patient-days during the period

covering 1st April 2013 to 31st March 2014. Healthcare-associated CDI incidence rates were also calculated with the total number of admissions as the denominator. Descriptive statistics were used to calculate response frequency. Data were reported as mean (s.d.) or median (ranges). Generally, statistical significance was declared for $p$ values less than 0.05. Data were analysed with Mintab 15 (Minitab Ltd, Coventry, UK).

## RESULTS

All nine SCICs responded to the survey. The centres contained a total of 383 SCI beds (20 in Belgium, 36 in the Republic of Ireland, 78 in the Netherlands, and 249 in the United Kingdom.) Ten consultants (eight physicians and two microbiologists), one nurse (with special interest in infection and prevention control) and two dietitians returned the questionnaires.

Of the nine responding SCICS, seven (77.8%) SCICs reported using gastric protection to SCI patients when they were admitted (Lansprazole (n=3); Omeprazole (n=4); Ranitidine (n=5) and others (n=2)). Four (44.4%) SCICs did not stock any probiotic products. Three SCICs stocked only one probiotic product, and two SCIC stocked more than one probiotic product (Fig. 1). Of the five SCICs that stocked probiotics, the products were used for preventing AAD (n=4);

**TABLE 1. Summary of probiotic use in SCICs in four European countries.** Patient days (excluding day-care treatment) during 1.4.2013 to 31.3.2014; AAD: antibiotic-associated diarrhoea; CDAD: *Clostridium difficile* associated diarrhoea

| | Centre 1 | Centre 2 | Centre 3 | Centre 4 | Centre 5 | Centre 6 | Centre 7 | Centre 8 | Centre 9 |
|---|---|---|---|---|---|---|---|---|---|
| No. of SCI beds | 48 | 42 | 20 | 25 | 115 | 28 | 44 | 36 | 25 |
| No. patients days | 15768 | 13797 | 7300 | 8213 | 35678 | 9198 | 14454 | 13140 | 7000 |
| Gastric protection to new admission | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No |
| Stocked probiotics | No | Yes | Yes | Yes | No | Yes | No | Yes | No |
| Single strain | | X | X | | | | | | |
| Commercial products | | | | X | | X | | X | |
| Agree probiotic is worthwhile to prevent AAD | No | Yes | Yes | Yes | Yes | No | Yes | Yes | No |
| Agree probiotic is worthwhile to treat AAD | No | Yes | Yes | No | Yes | No | Yes | Yes | No |
| Agree probiotic is worthwhile to prevent CDAD | No | Yes | No | No | Yes | No | Yes | Yes | No |
| Agree probiotic is worthwhile to treat CDAD | Yes | Yes | No | No | No | No | Yes | Yes | No |

**TABLE 2: Summary of *Clostridium difficile* management in SCI centres.** CDI: *Clostridium difficile* infection; SCIC: spinal cord injury centre; [a]*C. difficile* diagnostic criteria: 1: EIA for C. diff toxin A and / or toxin B; 2: EIA for C. diff toxin A only; 3: Cytotoxicity test; 4: culture for toxin producing C. difficile; 5: Enzyme for *C. difficile*- specific glutamate dehydrogenase; 6: PCR; [b]1.Cysloserin-cefoxtin-fructose agar; 2: Cycloserin-cefoxitin-mannitol agar; 3: Brazier medium; 4: Polymerase chain reaction; [c]First line treatment of CDI: 1: Vancomycin 125mg 6 hourly PO for 10-14 days; 2: Metronidazole 800mg loading dose then 400mg 8 hourly PO for 10-14 days; and [d]Definition of diarrhoea: 1: ≥2 watery liquid stools type 5,6 or 7 (Bristol stool scale) over 24 hours; 2: 2: ≥ 2 stools per day for ≥3 days; 3: ≥ 3 loose or liquid stools per day; 4 other.

| | Centre 1 | Centre 2 | Centre 3 | Centre 4 | Centre 5 | Centre 6 | Centre 7 | Centre 8 | Centre 9 |
|---|---|---|---|---|---|---|---|---|---|
| *C. difficile* policy | * | Yes | Yes | * | Yes | Yes | Yes | Yes | Yes |
| *C. difficile* outbreak | No | No | No | * | No | No | No | No | No |
| Number of CDI in SCIC | 0 | * | 0 | * | 2 | 1 | 1 | 1 | 0 |
| CDI cases per 10,000 patient days (SCIC) | 0 | - | 0 | - | 0.56 | 1.08 | 0.63 | 0.76 | 0 |
| *C. difficile* diagnostic criteria[a] | 1 | 1 | 1,5,6 | 1 | 1 | 1 | 1 | 1 | 1 |
| Medium for culturing *C. difficile*[b] | 1 | 1 | 1 | 1 | 3 | 4 | 1 | 4 | 1 |
| First line treatment of CDI [c] | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 1 |
| Criteria for diarrhoea[d] | 1 | 2 | 3 | 2 | 1 | 4 | 1 | 1 | 2 |

preventing CDAD (n=2) and/or constipation (n=1). (Fig. 2)

Of those SCICs which did not stock probiotic, the reasons given were insufficient evidence (n=1), financial reason (n=1) and because probiotic use was not in their centre's treatment policy (n=4) (Table 1).

Five SCICs agreed that a probiotic was worthwhile in preventing and/or treating AAD / CDAD, but the length of

**FIGURE 1. Summary of probiotics stocked in SCICs in four European countries.**

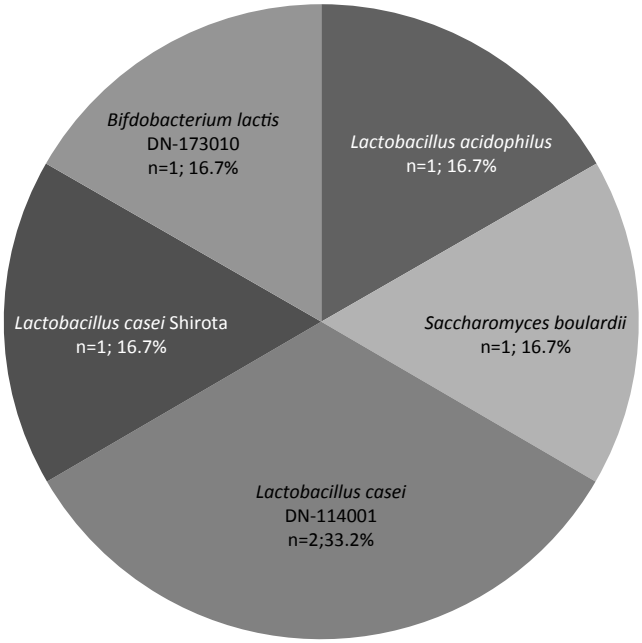



**FIGURE 2. Summary of condition for which probiotics were prescribed**. AAD: antibiotic-associated diarrhoea; CDAD: *Clostridium difficile*-associated diarrhoea; 3: constipation

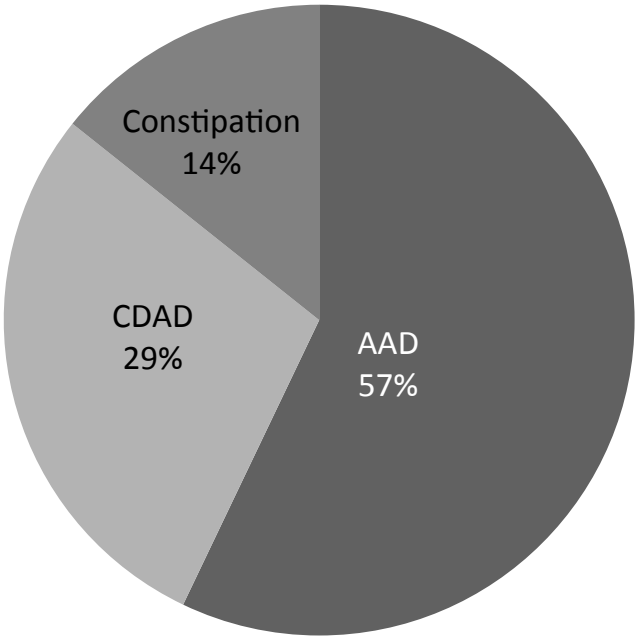



**FIGURE 3A. Summary of preferred probiotic used by the SCICs for antibiotic-associated diarrhoea**

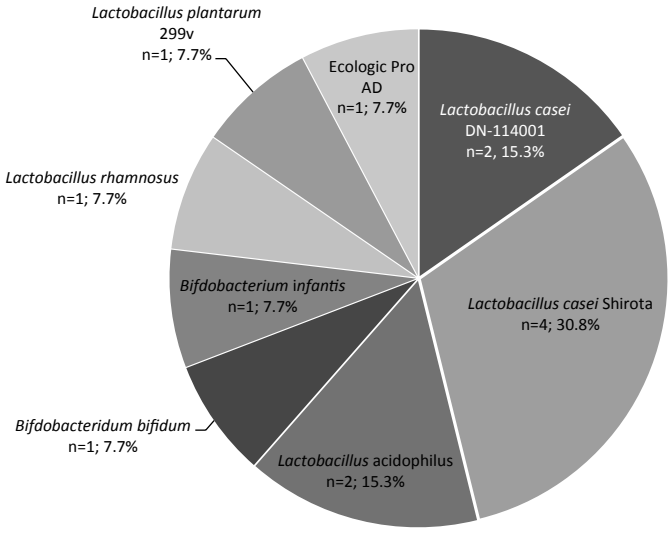
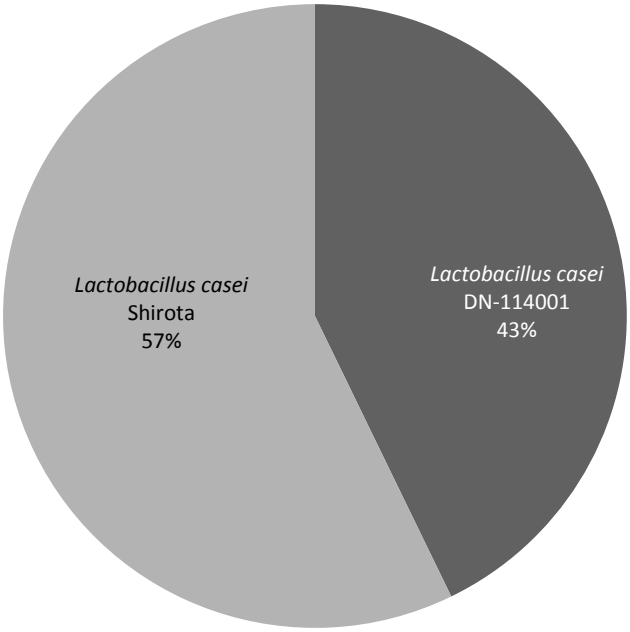



**FIGURE 3B. Summary of the preferred probiotic used by the SCICs for *Clostridium difficile*-associated diarrhoea**




the prescribed probiotic course varied (n=2 (40%) 7 days after antibiotic course; n=2 (40%) for the duration of antibiotics and; n=1 (20%) dependent on each individual case). Different probiotic strains were identified as potential agents for preventing AAD (n =8); and CDAD (n=2). (Fig 3A and Fig 3B).

No SCIC reported any CDI outbreak during the survey period. Five SCICs reported they have a CDI policy. Five SCICs reported CDI cases and the median CDI cases per 10,000 days were 0.56 (range: 0-1.08). The methods for diagnosing CDI, medium for culturing *C. difficile*, first line treatment for CDI and diagnostic criteria for diarrhoea varied, are summarised in Table 2.

## DISCUSSION

CDI is one of the most problematic gastrointestinal infections and one of the main infectious causes of morbidity in hospital. Prevention of CDI relies on methods to reduce transmission of the pathogen through effective hand hygiene, barrier precautions, isolation of patients, adequate nutrition and hydration and environment cleaning. (Public Health England., 2013) Perhaps even more important are attempts to reduce host susceptibility to infection by reducing unnecessary antibiotic use. (Kelly and LaMont, 2008) Antibiotic use disrupts and depletes the normal gastrointestinal flora, allowing C. *difficile* to thrive and generate clinical disease. (Kelly and LaMont, 2008) When antibiotic treatment is unavoidable, reinforcement of the colonic microbiota could be another means to decrease susceptibility of patients to CDI. Definitive restoration of the colonic ecosystem through faecal microbiota transplantation has potential important impact in the treatment of established CDI and prevention of recurrence. (Van Nood *et al.,* 2013) A more palatable approach to boost colonic defences is the use of non-pathogenic microbial supplements, known as probiotics. Probiotics have been shown to elicit various biological effects through their ability to colonise the GI tract, produce antimicrobial compounds, and other strain-specific actions such as immune modulations. Because these effects are specific for each probiotic strain or combinations of strains, any benefits reported in clinical studies are not generalisable to other probiotics, even within the same microbial species. (Hickson, 2011; Hill et al., 2014) Therefore, a reliable evidence base specific to that probiotic product should support use of any probiotic in SCIC.

The nine SCICs responding to the survey reported use of five different probiotic strains in their centres. In an attempt to locate evidence specifically to SCI patients, we preformed a systematic literature search restricted our search to randomised controlled trials that assessed probiotic in SCI patients exposed to antibiotics. We searched Cochrane Central Register of Controlled Trials, Health Technology Assessment Database; CINAHL; PsycINFO; EMBASE; Medline; AMED and DARE from date of inception to Feb 2015 used the following terms (with synonyms and closely related words): "spinal cord injuries" combined with "antibiotic-associated diarrhoea" and "probiotic". (Wong *et al.,* 2015) Our search identified only one study reporting evidence of probiotic benefit against AAD in an SCI population, which was one of those probiotics: *Lactobacillus casei* Shirota. (Wong *et al.,* 2014) Our review did not find any studies conducted in SCI populations that investigated use of probiotics for preventing or treating CDAD and constipation in the SCI population, although there are several studies with the general population (Hempel *et al.,* 2013; McFarland, 2007). Overall, no probiotic was supported by a strong evidence base, mainly due to the lack of consistent benefit from different studies. *L. casei* Shirota and *L. Casei* DN-14001 appear to be the choice of probiotic for prevention of AAD / CDAD. Only 25% and 50% of SCICs stocked *L. casei* Shirota and *L. Casei* DN-14001, respectively, whereas 50% of SCICs stocked at least one probiotic that was supported by low or no evidence. These results suggested that a majority of SCICs stock a probiotic that lacks reliable evidence. Although we only found only one study reported the efficacy of probiotic in preventing AAD in SCI patients, the other probiotic strains may also be effective. Further studies are warranted to evaluate the use of a specific probiotic strain in SCI populations.

Barbut and colleagues reported a mean incidence of CDI in 23 European hospitals of 2.45 per 10,000 patient-days (range: 0.1 to 7.1), (Barbut et al., 2007) which is higher than the figure of 0.56 per 10,000 patient-days in our study thus the CDI incidence rates of participating SCIC were not representative of national incidence rates. The low incidence of CDI could be due to the continuing year-on-year fall of overall CDI cases. Indeed, the overall CDI rate for England has fallen from 4.85 per 10,000 in 2009 to 2.29 per 10,000 in 2013. (Public Health England, 2014)

The present study found that the incidence of CDI, choice of CDI treatment and definition of diarrhoea vary greatly between SCICs. At this present time, no consensus exists on optimal testing for CDI since uniform diagnostic (and culture) methods do not exist. To involve the international microbiology association in setting standards would not just help in identifying and treating patients with SCI but also for future AAD / CDAD research.

This study has some limitations. Firstly, the selection of the SCICs in each country was at discretion of the principal investigator and the number of SCICs per country was small. However, the SCICs selected represented approximately 40% of the SCICs in the Belgium, UK and the Netherland, and 100% in the Republic of Ireland. Therefore, results derived from this sample of SCICs could be considered representative of each country. Secondly, there may have been differences in physicians' awareness of infection and probiotics between SCICs and countries.

## CONCLUSIONS

Stocking probiotics for the prevention of AAD/ CDAD is not common. There is only one single study showing efficiency of a particular strain in SCI populations. SCICs should review the supporting evidence for each probiotic prior to stocking. Further research of specific probiotic strains is needed to provide more data that SCIC can use to make informed formulary and purchasing decisions. The data also emphasised the importance of using a standardised definition of diarrhoea when conducting future AAD / CDAD research.

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