



RESEARCH ARTICLE

EFFECTIVENESS AND SAFETY OF PROBIOTICS IN THE TREATMENT OF CLOSTRIDIUM DIFFICILE INFECTION IN EUROPEAN COUNTRIES: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Although the incidence of Clostridium difficile infection (CDI) has significantly reduced, people still contract this infection and it remains a burden to the health care system. However, medical interventions such as probiotics, and faecal transplants are still being explored and evaluated in a bid to ameliorate this condition.

Aim: The aim of this study is to establish quality evidence on the effectiveness and safety of probiotics in the treatment of C. difficile infection in European Countries.

Method: A systematic search for articles and journal literature published between 2010 and 2015, relevant to this research study was conducted on: COCHRANE LIBRARY, DISCOVER, EMBASE, GOOGLE SCHOLAR, MEDLINE, MESH, PUBMED, SCIENCE CITATION INDEX and SCIENCE DIRECT from June, 2015 – August, 2015. Included studies were randomised control trials and case studies assessing probiotics and Faecal Microbial Transplant (F.M.T.) in the prevention and treatment of CDI

Result: 7 studies were reviewed. 4 examined the effectiveness of faecal microbial transplant (F.M.T.) in the treatment of CDI In a population experiencing recurrence while 3 assessed the effectiveness of one or more probiotic strains in the treatment/ prevention of CDI

All studies demonstrated that either of these treatment options is effective in the management of CDI however, 2 studies that showed that specific probiotics such as Sacchomyces boulardii or a multi-strain probiotic is not effective in the treatment of Clostridium difficile associated diarrhoea (C.D.A.D.). All reviewed studies suggested that the adverse effects associated with probiotics and F.M.T are mild in severity.

Conclusion: Probiotics including F.M.T, appear: to be effective in the treatment and prevention of CDI, particularly after a short regimen of antibiotic/ bowel lavage. There are limited clinical trials on these treatment measures perhaps as a result of the plunge in the incidence of CDI However, more studies are required to boost the available evidence.

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INTRODUCTION

Clostridium difficile (C. difficile) is an anaerobic spore forming bacterium, found in the human intestine. This bacterium is present in approximately 3% of healthy adults and two-thirds of babies causing no symptoms, (P.H.E., 2013). C. difficile is present in a small percentage of healthy people as a result of metabolites produced by bacteria that make up the normal flora of the large intestine which creates a hostile medium unfavorable to this bacterium, (Gould, 2010).

Nevertheless, an upset in the balance (Dysbiosis) of the normal flora present in the gut – often by specific antibiotics, stimulate the rapid multiplication of C. difficile which subsequently produce toxins that causes illness (P.H.E., 2013) such as C. difficile associated diarrhoea (C.D.A.D.), which is the most frequent clinical presentation in patients and accounts for 10 - 20% of all cases of such diarrhoea (Aziz, 2013; Dietrich et al., 2014; Hickson, 2011). While eubiosis is associated with health, dysbiosis is associated with several health problems both within the gastro intestinal tract such as diarrhoea and inflammatory bowel disease. Outside the gastro intestinal tract it is associated with obesity and allergy, (Vandenplas et al., 2015).

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Clinical Symptomology

The colon is mainly affected resulting in diarrhoea and in severe cases where the colon is inflamed (Pseudomembranous colitis) bleeding ensues with excruciating pain, (Denton *et al.*, 2014). Other associated clinical signs range from mild symptoms, (nausea, vomiting, dehydration) to severe symptoms, (perforated intestine, toxic mega colon and shock-may also present (Stoelting *et al.*, 2013). Advanced age, underlying illness, prolonged hospitalisation, prolonged antibiotic administration (Kristin and Monson 2012; Dietrich *et al.*, 2014), immune-compromised person, immune suppressed therapy, gastrointestinal surgery (Loo *et al.*, 2011) and the use of antiulcer medication, (Islam *et al.*, 2013; Allen *et al.*, 2013; Wong *et al.*, 2013) are some risk factors associated with *C. difficile* infection. In their meta-analysis of 12 observational Studies and clinical trials, Le – Monnier *et al.* (2014) found that the simultaneous use of antimicrobials for the treatment of infections other than C.D.I was significantly linked with increased risk of C.D.I recurrence.

Epidemiology

Despite the increasing incidence of CDI as a result of antibiotic over use and abuse, this infection remains rare in paediatrics mostly because younger children are inadequately susceptible to the actions of the *C. difficile* toxins, (Esposito *et al.*, 2015). Clostridium Difficile Infection (CDI) has remained a challenge particularly in healthcare despite advances in the diagnosis and treatment of CDI (Evans and Johnson, 2015). The result of a 2011 survey on Healthcare Associated Infection, (H.A.I.) involving randomly selected patients from 183 hospitals, in 10 states showed that among the 11, 282 participating patients, 4.0% had 1 or more H.A.I. The most commonly identified pathogen was *C. difficile*, responsible for 12% of all H.A.I. Conclusively, the study suggests continuous CDI surveillance and prevention activities by the public health department, (Magill *et al.*, 2014). According to Evans and Johnson (2015), most infection control approaches however, lay emphasis on the disruption of horizontal transmission of *C. difficile* between patients, their environment and health care personnel. They therefore suggest that further improvement in prevention of CDI will likely need to focus on prevention of diseases in those populations who continue to be exposed to the organism. Moreover, they point out that a potential effective strategy in the control of CDI is antibiotic stewardship and the use of probiotics, which minimise the antibiotic associated complications, although this probiotic approach is less studied. In line with the horizontal transmission of *C. difficile* as pointed out by Evan and Johnson *et al.* (2015), Hughes *et al.* (2013) and Islam *et al.* (2013), maintain that *C. difficile* infection (CDI) can be transferred between patients and their surroundings on the hands of health care workers by chance, (Hughes *et al.*, 2013; Islam *et al.*, 2013).

Hospital surfaces, harbour *C. difficile* spores, which can be ingested by health care providers and transferred to patients, thus increasing patients' risk. The colonisation rate can rise from 2% - 5% to 30% - 50% (Stanley *et al.*, 2013). A study revealed that 60% of hospital staff uniforms were colonised by potential pathogenic bacteria, (Weiner-Well *et al.*, 2011). Another study found percentages of certain pathogens on the hands of healthcare workers. These were: - 19.5-78.6% Rotavirus, 23-81% Yeasts, 14-59% *C. difficile*, 17% Klebsiella spp., 16.9% MRSA, 41% Vancomycin Resistant Enterococcus

(V.R.E), 1.3-25% Pseudomonas spp. and 3-15% Acinetobacter spp. (Curtis, 2008). Stoelting *et al.* (2012) links this to the spore forming ability of *C. difficile* bacterium and its ability to survive in an environment for months or years despite the application of various infection control methods, (Mitchell *et al.*, 2014; Breathnach, 2013; Agha, 2012; Dancer, 2009). Studies reveal that by the 30th day post diagnosis of this infection, approximately 17% of patients die and an estimated 1:12 (8%) of this mortality is directly associated with CDI (Planche, 2013; Bauer *et al.*, 2011). A Hungarian based study conducted by Kurti *et al.* (2015) on the trends in C.D.I between 2010 and 2013 shows that the crude incidence of CDI was 21.0% per 1000. These cases all resulted in hospital admission and 4.45% of the total inpatient days were related to CDI (4,326/ 96,284 days equal 25.6 cases per 10,000 patient days). The majority of the patients were 60 years or older (< 40 years old – 4.7%, 40 – 60years old – 11.9%, > 60 years – 83.4%). According to the study the rate of community acquired CDI was 45.3%, symptoms were identified at hospitalisation in 82 patients (33.2%) and within 3 days from admission in an additional 30 patients (12.1%).

However, the average time to present CDI symptoms was 2.75 ± 5.3 days from hospitalisation. The study found varying incidence of CDI across the different hospital units with the highest incidence rate per 1000 admissions in haematology (32.9), gastroenterology (25) and nephrology (24.6) and the lowest rate was in 1.4% (33/2312) in endocrinology and the general internal medical unit, (14.2 and 16.9 per 1000 admissions). However, the study showed no difference in incidence between genders. Concerning severe CDI, Kurti *et al.* (2015) highlights that the incidence was 12.6% (2.63/ 1000 of all causes of hospitalisation), severe CDI was found among older patients, (Severe: 84.2% Vs. all: 69.9% of patients were > 65years old, p < 0.001) and length of hospital stay was longer compared to other patients. According to a CDI European report (2014), Hospital acquired infection (H.C.A.) including CDI lengthens hospitalisation by 2 weeks and can add up to € 14,000 to the cost per hospitalization care. The report states that CDI accounts for an estimated sum of €3, billion across Europe and that 1:10 cases of CDI causes or contributes to death, intensive care admission or bowel surgery. Furthermore, the report suggests that CDI doubles the risk of death within 30 days of diagnosis and as such causes or contributes to 40% of deaths that occur within 3 months of diagnosis. Similarly, In the U.S, an estimated sum of \$ 3.2 billion is spent on the treatment of CDI annually with nearly 333,000 cases and 15,000 to 20,000 deaths yearly, (Boyle *et al.*, 2015).

Another European clinical infectious disease study (E.U.C.L.I.D.), involving 482 hospitals in 20 European Countries in 2013, indicates that the average incidence of CDI across Europe is 6.6 per 10, 000 patient bed days and also suggests that while the incidence of CDI has decreased in some countries such as the U.K. (H.P.A., 2014), it remains high in other European countries (Karrie *et al.*, 2014; Kurti *et al.*, 2015). Statistics in the U.K. reveal that in 2010, 23,253 CDI cases were recorded and 19,603 cases were recorded in 2011, indicating a 16% decrease in prevalence, (H.P.A., 2011; N.I.C.E., 2014). Likewise, from April 2012 – March 2013 a total of 5,980 CDI cases were reported and 5,546 CDI cases were reported from April 2013 – March 2014, signifying a 7.2% decrease in cases (HPA, 2014). Statistics revealed that in 2011, 2,053 CDI related deaths were recorded and 1,646 CDI related deaths in 2012 indicating a decrease of 19.8%, (O.N.S.,

2013). Fig.1 below is a bar chart showing the decrease in the rate of CDI in the U.K. from 2010 – 2013. CDI remains a burden in health care nationally, despite the decrease recorded and It has remained a burden internationally following increased incidence in other countries, (N.I.C.E., 2011, Cohen *et al.*, 2015). CDI According to Denton *et al* (2014), CDI is associated with increased mortality and increased health care costs.

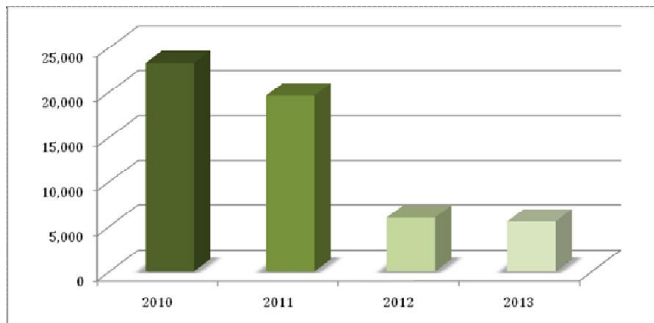


Figure 1. Decrease in the rate of CDI in the U.K. from 2010 – 2013

In the U.K., an estimated £5,640 is spent on the treatment of a patient with CDI (D.O.H., 2013) and approximately £75million is spent annually, (Doan *et al.*, 2012). In the U.K., infection prevention and control is at the forefront of health care initiatives following the burden of cost associated with CDI and similar infections, (Edwards *et al.*, 2012). A battery of preventive measures has been put in place. These include: mandatory surveillance, a H.A.I. reduction programme, publication of evidence based recommendations (Denton *et al.*, 2014), use of the Bristol stool chart, (Statish and Culver, 2011), discreet antibiotic prescription, antibiotic/antimicrobial stewardship, hand hygiene, (N.H.S., 2012; Allegranzi and Pittet, 2009; W.H.O, 2009).

The use of chlorine based or sporicidal-based products in environmental decontamination, (Donskey *et al.*, 2014), isolation of CDI patients, use of personal protective equipment, (D.O.H., 2010; N.I.C.E., 2011). Also role restructuring within the N.H.S. has been put in place in order to improve the quality of care, (Royal College of Nursing (R.C.N.), 2013). CDI is a national and international issue (Denton *et al.*, 2014) and remains a burden for health care (N.I.C.E., 2011). CDI is the most common cause of diarrhoea in hospitals and health care environments and it is accountable for increased hospitalisation, particularly in older people, increased morbidity and mortality (D.O.H., 2013).

According to Planche (2013), 17% of patients confirmed with this infection die by the 30th day, post diagnosis and they account for 1: 12 (8%) of deaths. An estimated £5,640 is spent in the treatment of one *Clostridium difficile* infected patient and there is a total spend of £75million per year, (Doan *et al.*, 2012). Furthermore, studies show that there is a 20% prevalence of asymptomatic colonisation in hospitals as a result of the long-term survival of the *Clostridium difficile* spore and its resistance to common disinfectants, (Hines and Marshall, 2012). This increases the risk of infection to both patients and health care workers. Although certain antibiotics have been found effective in the management of this condition (Stanley *et al.*, 2013), studies reveal a 10 – 40% recurrent rate among patients, (C.D.C., 2014; Boyle *et al.*, 2015) coupled with the fact that there is little evidence supporting existing treatment

options, (Goldenberg *et al.*, 2013) hence more researches relating to the treatment of CDI have been suggested and existing ones such as probiotics and faecal transplant are still being assessed for effectiveness, which is one purpose of this study. For these reasons the researcher decided to search available literature systematically in order to establish quality evidence on the effectiveness and safety of probiotics in the treatment of *C.difficile* infections in the U.K. and other European countries.

Research Design and Methodology

The research was designed to focus on the efficacy and safety of probiotics in the treatment of *Clostridium difficile* infection. The aim of the study is to establish the quality of available evidence on the effectiveness and safety of probiotics in the treatment of *C. difficile* infection in the U.K. and other European Countries. A systematic review was used to examine the effectiveness and safety of probiotics in the management of CDI. A systematic review is regarded as a distinctive overview of primary research on a precise research question that seeks to identify, synthesize and appraise all high quality research evidence applicable to that question in order to answer it (Higgins and Green, 2012). Fundamentally, it entails using explicit search and appraisal methodology in the selection of studies, synthesis and reporting of data, (Higgins and Green 2012; Daly *et al.*, 2013). Melynck and Fineout - Overholt (2015), maintain that a systematic review seeks to gather all evidence that addresses pre- specified eligibility criteria in order to address a specific research question, thus this process aims to minimise bias by adopting clear systematic methods.

Search Strategy

A systematic search for articles and journal literature published between 2010 and 2015, relevant to this research study was conducted on the following databases: COCHRANE LIBRARY, DISCOVER, EMBASE, GOOGLE SCHOLAR, MEDLINE, MESH, PUBMED, SCIENCE CITATION INDEX and SCIENCE DIRECT from June, 2015 – August, 2015 using such search terms as: “probiotics”, “*Clostridium difficile*”, “probiotics and *clostridium difficile*”, “probiotics in CDI”, “faecal transplant and *Clostridium difficile* diarrhoea”, “faecal micro biota”. For a more precise and wider search for literatures, Boolean Logic – AND, OR, * - were employed. MeSH terms (“*Clostridium difficile*” OR “*Clostridium*”, “CDI” AND “Probiotics”, “Diarrhoea” OR “probiotics” OR “pseudomembranous colitis”) were used during this search. Grove *et al.* (2013) and Chiappelli (2014), suggests that identification of inclusion and exclusion criteria enables researcher to direct their literature search and therefore suggests that the use of the “P.I.C.O.” format may be effective in ascertaining key terms to be included in the search process, which ensures that basic components of a study are considered. Thus, researchers considered study subjects comprising both adults and children. Trials in which the occurrence of CDI/ C.D.A.D. (with probiotics or F.M.T. as a treatment option) was the primary or secondary outcome were searched for.

Study Inclusion and Exclusion Criteria

Selected literature included recent articles relevant to the research topic that addressed the prevention or treatment of CDI using probiotics or faecal transplants. Only R.C.T.s and case studies addressing the use of probiotics and faecal

transplant in the prevention and treatment of CDI, that was conducted within the U.K. and Europe and published in English between 2010 and 2015, were included in this study. Correspondingly, literature addressing the prevention and treatment of CDI with probiotics and faecal transplant that were non – R.C.T.s or case studies, not published in English between 2010 and 2015, that were reviews or commentary or animal studies or abstract only, were excluded from this study. Furthermore, studies that did not examine clinical endpoints such as onset of diarrhoea and did not confirm the presence of *C. difficile* either by microbial culture or detection of toxin A and B were also excluded.

Data Extraction

Preferred Reporting Items for Systematic Review and the Meta - Analysis (P.R.I.S.M.A.) flow chart was used in the abstraction of literature from all databases for this study. Extraction on data was strictly based on the outlined inclusion and exclusion criteria of this study. A lone researcher carried out the entire process and built up a table consisting of specific criteria.

Overall, the selection process generated 7 studies, (5 R.C.T.s and 2 Case studies), that meet the study inclusion criteria (See Figure 2). The 7 included articles were further grouped and described under 3 headings: Faecal transplant for recurrent CDI, Probiotics for the prevention of CDI and the Safety of probiotics in the treatment of CDI

Faecal Microbial Transplant for recurrent CDI

4 of the 7 included studies demonstrated the effectiveness of F.M.T. in the treatment of recurrent CDI Cammorata *et al.* (2015) in their study allocated 39 participants with recurrent CDI who tested positive to *C. difficile* toxin, to receive F.M.T. (20) or a vancomycin regime, (19). Study results indicate that 13 of 20 patients (65%) in the F.M.T. group were cured after the initial faecal infusion, and out of these 13 patients, none developed P.M.C. However, the remaining 7 were diagnosed with P.M.C. and 6 of these 7 patients had multiple infusions while 1 had only one infusion. Altogether, 5 of the 7 patients with P.M.C. were cured, while the remaining 2 experienced a recurrence. A gradual disappearance of P.M.C. was observed by using an endoscope. Overall, F.M.T. cured 18 of the 20 patients (90%).

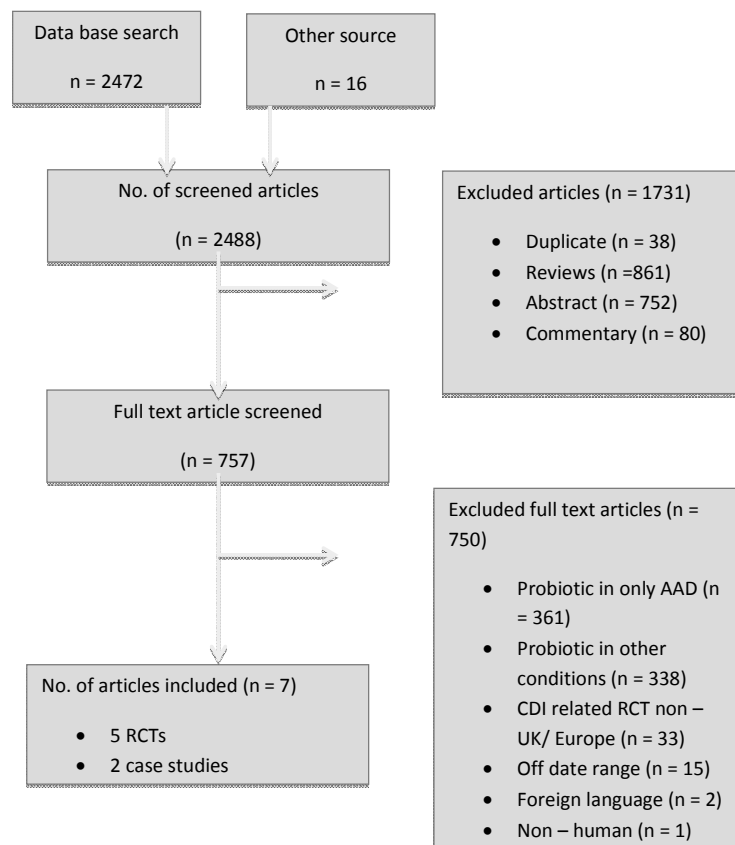


Figure 2. P.R.I.S.M.A. Flow Chart for Selected Literature

RESULTS

The total literature search yielded 2,488 articles, which was screened to exclude abstract only literature (n = 752), duplicates (n = 38), reviews (n = 861) and commentaries (n = 80). Articles were further screened to exclude certain full text literature that did not meet required criteria. Hence, probiotic in A.A.D. only (n = 361), probiotic in other conditions (n = 338), non – U.K./ Europe published CDI related R.C.T.s/ case studies (n = 33), out of date literatures (n = 15), foreign language (n = 2) and non-human trial (n = 1) were excluded.

In the vancomycin group, 5 of the 19 participants (26%) were cured while 12 had a *C. difficile* recurrence 10 days after the end of the vancomycin therapy. Further follow ups revealed that these 12 patients had undergone cycles of a repeated antibiotic regimen comprising metronidazole and vancomycin, to combat further recurrence of CDI. However, resolution of symptoms occurred in 7 of these patients and 3 were lost to follow up without data on their CDI status. 26 outpatients with relapsing CDI; were treated by Kelly *et al.* (2012) with F.M.T.

Table 1. List of 7 Incorporated Studies

| Authors | Study design | Method of analysis | Intervention | Results |
|--------------------------------|--------------|-----------------------------|---|--|
| Allen <i>et al.</i> (2013) | RCT | Intention to treat analysis | Lactobacilli and bifidobacteria in the prevention of A.A.D. and C.D.D. | Multi-strain probiotic ineffective in prevention of A.A.D. and C.D.D. |
| Commorata <i>et al.</i> (2015) | RCT | Intention to treat analysis | Faecal microbiota transplantation vs. vancomycin for recurrent CDI | Resolution of C.D.A.D. Resolution of P.M.C. |
| Lönnemark <i>et al.</i> (2010) | RCT | Intention to treat analysis | Lacobacillus plantarum Vs. placebo in certain G.I symptom during antibiotic treatment including CDI | Reduced G.I symptoms |
| Pozzoni <i>et al.</i> (2012) | RCT | Intention to treat analysis | Sacchromyces boulardii on the occurrence of A.A.D. and C.D.A.D. | S. boulardii not effective in prevention of A.A.D. and CDI |
| Van Nood <i>et al.</i> (2013) | RCT | Intention to analysis | Duodenal infusion of faeces vs. vancomycin for recurrent CDI | Resolution of C.D.D. No significant differences in side effects Improved faecal bacterial diversity. |
| Fuentes <i>et al.</i> (2014) | Case study | Intention to treat analysis | Fecal transplant in recurrent CDI | Resolution of CDI Restored healthy microbiota |
| Kelly <i>et al.</i> (2012) | Case study | Descriptive analysis | Faecal transplant for CDI | CDI and diarrhoea free |

Table 2. Assessment of Bias across Incorporated Papers

| AUTHORS/ STUDIES | SELECTION BIAS | PERFORMANCE BIAS | DETECTION BIAS | ATTRITION BIAS | PUBLICATION BIAS | TRANSFER BIAS | COMMENTS |
|--------------------------------|----------------|------------------|----------------|----------------|------------------|---------------|---|
| | | | | | | | |
| Cammarota <i>et al.</i> (2015) | Low risk | High risk | Unclear | Low risk | Low risk | Low risk | Study populations was clearly identified with similar baseline characteristics An open label trial, personnel and patients were not masked owing to the basic contrast between the treatments. Although this study was funded, an ethical committee approved the study protocol and the study was also registered at clinical trial.gov. A third party used online software to generate numbers for randomisation. There was no loss to follow up |
| Kelly <i>et al.</i> (2012) | Low risk | High risk | High risk | Low risk | High risk | Low risk | Participant shared similar base line characteristics. Study protocol was in place but not clear whether study was registered or not. All participants were accounted for and no inconsistency in date was noticed. No blinding and no control Adequate follow up. Follow up information obtained through office visits, telephone or email. |
| Pozzoni <i>et al.</i> (2012) | Low risk | Low risk | High risk | Low risk | Low risk | Low risk | Clearly defined base line characteristics, identified possible confounding factors Approved study protocol and study was funded but registered under I.S.R.C.T.N. Process of group allocation was by randomisation. Distribution and dispensing of products was in a double-blinded approach. All participants discharged or in – hospital were well accounted for. Study was reported based on C.O.N.S.O.R.T. Records were used to establish compliance to intervention. |

Continue.....

| AUTHORS/ STUDIES | SELECTION BIAS | PERFORMANCE BIAS | DETECTION BIAS | ATTRITION BIAS | PUBLICATION BIAS | TRANSFER BIAS | COMMENTS | |
|---------------------------------|-------------------|---------------------|-------------------|-------------------|---------------------|------------------|---|---|
| Lönnermark <i>et al.</i> (2010) | | Low risk | Low risk | Low risk | Low risk | High risk | High risk | <p>Similar base line characteristics considered across both study groups.</p> <p>Study was double blinded and randomisation to ensure allocation concealment was done by a third party, using a computer generated list, hospital staff who at no time had direct contact with participants or investigators, labelled the intervention or placebo.</p> <p>Drop out rate was specified with reasons. Diary was given to participants to document certain observation related to intervention/ placebo based on instruction and some inconsistency in diary data was noted thus may have influenced the outcome of intervention.</p> <p>Study was funded but whether or not study was registered, was unclear.</p> |
| Allen <i>et al</i> (2013) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | <p>Similar base line characteristics were ensured. Study protocol was in place.</p> <p>To ensure allocation concealment, patients were assigned to either the treatment arm or placebo arm based on a computer generated random sequence carried out by a third party statistician and remained unavailable to the members of the research group until databases had been completed and locked.</p> <p>Participants, study staff, specimens and data analyst were blinded to tasks.</p> <p>Drop out was identified and excluded. All participants were accounted for.</p> <p>This study was registered and although funded, the study declared that the funding institution played no role in the study design, collection of data or report writing.</p> | |
| Van Nood <i>et al</i> (2013) | High risk | High risk | High risk | Low risk | Unclear | Low risk | <p>An open label randomized study. Process of randomization was unclear but a study physician allocated participants, who had been admitted by referring hospitals, to either study groups.</p> <p>Stool diaries were kept by patients, follow - up was conducted.</p> <p>All patients were accounted for and excluded patients were not included in analysis.</p> <p>Investigators performed data analysis.</p> | |
| Fuentes <i>et al</i> (2014) | Low risk | High risk | High risk | Low risk | Unclear | Low risk | <p>Participants were recruited based on records. Baseline characteristics were similar.</p> <p>No form of blinding was applied</p> <p>Adequate follow up and all participant accounted for.</p> <p>No source of funding was indicated and study was not registered.</p> | |

All except 1 patient had C.D.I after treatment with antibiotics and during hospitalisation. All the patients had received at least 12 weeks of vancomycin and the mean duration of CDI before receiving F.M.T. was 12.6 months. However, after the F.M.T., no complications were observed as all patients tolerated the procedure. Patients were followed up for an average of 10.7 months post F.M.T. and 21 patients were completely symptom free with reports of instant improvement within hours to a few days post F.M.T. 3 patients experienced very mild/ irregular stool and they were *C. difficile* toxin negative. Of the remaining two patients, 1 experienced brief episodes of

diarrhoea that was linked to trimethoprim-sulphamethoxazole 2 months after F.M.T. *Clostridium difficile* toxin was not confirmed in stool, but the patient was treated with a week-long course of vancomycin by another provider, consequently CDI did not reoccur thereafter. The other patient self - commenced vancomycin despite repeated negative tests for *C. difficile* toxins however, 11 months later this patient had a recurrence following a course of cephalixin. Van Nood *et al* (2013) conducted a study on duodenal infusion of donor faeces for recurrent CDI They described the primary outcome of the investigation as the resolution of *C. difficile* associated

diarrhoea with no recurrence after 10 weeks. 43 patients were recruited and grouped to receive treatment under one of 3 conditions: an initial vancomycin regimen followed by bowel lavage and subsequent infusion of donor faecal solution through nasoduodenal tube, a standard vancomycin regimen or a standard vancomycin regimen with bowel lavage. The study revealed that 13 out of 16 patients (81%) in the infusion group had a resolution of *C. difficile* associated diarrhoea after the first treatment. 3 patients had a second faecal infusion with resolution occurring in 2 patients. However, in the vancomycin group 4 out of 13 patients (31%) showed resolution of CDI while a similar effect was evident in 3 of 13 patients (23%) in the vancomycin with bowel lavage. Furthermore, faecal microbial analysis of stool samples obtained from participants established increased variety of faecal bacterial similar to that in healthy donors, with an increased species of bacteroidetes, clostridium cluster IV and XIVa and a decreased species of proteobacteria.

This is in line with a study on the reset of a critically disrupted microbial biome that focused on using faecal transplant in recurrent CDI Feuntes *et al* (2014) studied 9 patients with confirmed recurrent CDI who were treated with F.M.T. in a randomised open label trial. Of the 9 patients 5 were randomly selected for F.M.T. and 4 were randomly selected for the vancomycin group, but later received F.M.T. following failed antibiotic therapy. However, analysis of the patients' faecal samples pre F.M.T. revealed a contrast in the normal faecal microbial composition as compared to that of healthy donors. Nevertheless, after the F.M.T all 9 patients were cured with no recurrence of CDI during their 10 weeks post F.M.T. follow up. Subsequent post F.M.T. faecal microbial analysis revealed richness, diversity and evenness of patients' microbita similar to the donors'.

Probiotics for the prevention and treatment of CDI

Allen *et al.* (2013), in a multicentre randomised double blind, placebo trial on the effectiveness of lactobacilli and bifidobacteria in the prevention of A.A.D. and C.D.A.D. in older inpatients, recruited and screened 17, 420 patients of which 1,493 patients were randomly allocated to the microbial group and 1,488 were assigned to the placebo group. Overall, 1,470 and 1,471 were included in the primary endpoint (occurrence of A.A.D./ C.D.A.D.) analysis respectively. The analysis indicated that 159 (10.8%) of participants in the microbial group had A.A.D. and C.D.A.D. compared to 153 (10.4%) participants in the placebo arm. However, in the microbial group C.D.A.D. occurred in 12 (0.8%) participants compared to 17 (1.2%) in the placebo group and the side effects of treatments were similar in both groups. Another study conducted by Lönnermark *et al.* (2010) on the effect of lactobacillus plantarum intake on certain gastrointestinal symptoms during treatment with antibiotics randomised 163 patients to either lactobacillus plantarum (80) or placebo (83). According to the study, more patients in the treatment group tested positive with the *C. difficile* toxin on inclusion. However, diary data was available for an average of 22 days in both groups. The study period was evaluated as a whole, but divided into 3 sections: the period of antibiotic treatment for which all participating patients (163) provided data, the period of continued intake of test drink following cessation of test drink (140) and the follow up period (87). In their study, Lönnermark *et al* defined diarrhoea as at least 3 loose or watery stools in 24 hours for about 2 days; nonetheless they

found that the occurrence of diarrhoea was infrequent in the participants, (only 6 patients in the treatment group and 5 in the placebo group). Before the inclusion of patients in their study, CDI was found in 5 patients, (4 in the treatment group and 1 in the placebo group) however, after the treatment, 6 patients tested positive for CDI. They therefore reveal that few patients harboured *C. difficile* toxin and colonisation did not differ between both study groups, thus they concluded that the intake of *L. plantarum* could have a preventive effect on milder gastrointestinal symptoms during treatment with antibiotics. In a study on *Saccharomyces boulardii* for the prevention of A.A.D. and C.D.A.D. in hospitalised adult patients involving 562 patients, Pozzoni *et al* (2012) randomised the patients either to a placebo group (134) or to the *S. boulardii* group (141). 287 were excluded from the study mostly due to their inability to provide consent. Of the 275 who were randomised, 71 did not complete the study owing to death unrelated to diarrhoea or CDI bringing the total number of participants to 204 who completed the follow up, (98 in the placebo group and 106 in the *S. boulardii* group). The result of the study confirms that 5 patients with diarrhoea had *C. difficile* toxin (2 in the placebo group and 3 in the treatment group). Consequently, Pozzoni *et al* concluded that the low number of patients developing CDI prevented the evaluation of the effect of *S. boulardii* on the development of CDI.

Safety of probiotics

In the F.M.T. group, Van Nood *et al.* (2013) showed immediate diarrhoea in 94% post F.M.T., cramping in 31%, belching in 19%. However, these symptoms were resolved within 3 hours and constipation was found in 19% of the patients. Similarly, Cammarota *et al.* (2015) confirmed an immediate occurrence of diarrhoea in 19 of 20 patients. (94%) following donor faeces infusion, bloating and abdominal cramping in 12 of 29 (60%) participants. Fuentes *et al.* (2014) and Kelly *et al.* (2012) recorded no adverse events in their studies. In the probiotic group, Allen *et al.* (2013) found bloating and flatus common in the microbial group, but adverse effects such as P.M.C., colectomy, recurrence or death was not found in patients with CDI. Pozzoni *et al.* (2012) revealed that a 94% adverse event occurred in patients: 13 in the *S. boulardii* group and 10 in the placebo group had constipation, abdominal pain in 9 of the *S. boulardii* group and 7 in the placebo group. 10 participants in the *S. boulardii* group against 11 in the placebo group experienced headache. 5 in the *S. boulardii* group compared to the 2 in the placebo group presented with cutaneous rash while fever not associated with underlying infection was recorded in 3 patients in the *S. boulardii* group and 4 patients in the placebo group. No incident of fungemia was recorded. However, the study indicates that all adverse effects were mild in severity. Lönnermark *et al.* (2010) identified nausea, abdominal pain, vomiting and constipation as side effects that occurred in their study. However they upheld that because constipation is common in connection with illness and immobilization, then it is unlikely that it is associated with the treatment effect.

Research Outcomes

F.M.T. was found safe and effective in the prevention and treatment of CDI (Cammarota *et al.*, 2015; Kelly *et al.*, 2012). The latter established that F.M.T. was 92% effective in preventing further diarrhoea or CDI recurrence in their study. Findings from Van Nood *et al.* (2013) and Feuntes *et al.* (2014) suggest that F.M.T. increases bacterial diversity in patients who

receive it. This is comparable to that of a healthy donor with increased beneficial/ essential bacteria species, (Bacteroidetes, clostridium cluster IV, XIVa) and decreased non-essential bacteria species such as proteobacteria. In contrast to the above findings, Pozzoni *et al.* (2012); Allen *et al.* (2013) demonstrated that specific probiotics such as *S. boulardii* or multiple strains of probiotics are ineffective in preventing both A.A.D. and C.D.A.D. whereas Lönnemark *et al.* 2010 in their study conclude that the use of *Lactobacillus plantarum* may exert a prophylactic effect on milder gastro intestinal symptoms during antibiotic treatment. All included studies confirm that the adverse effects associated with F.M.T. or probiotics is mild in severity and rarely leads to death.

The International Committee of Medical Journal Editors (I.C.M.J.E.) in view of publication bias suggests that it is pertinent that all R.C.T.s be pre- registered with an approved clinical trial registry (Pannucci *et al.*, 2010). However, not all of these 7 studies had a study protocol or were registered with relevant health authorities although a relevant ethical committee approved the studies. It therefore implies that the studies without an approved protocol and/ or not registered, are prone to publication bias, whereas those with an approved protocol and/ or are registered are not subject to this bias. The populations of these studies were mainly patients and all shared similar base line characteristics relevant to each study. Eligible participants were screened to either confirm the presence or absence of *C. difficile* toxin before inclusion. Outcome measures were similar across each study. 3 of the included studies are double blind R.C.T.s, 2 are open label R.C.T while 2 are case studies. While the double blind studies are less prone to some form of bias the open label R.C.T.s and case studies are more prone to forms of bias, which threatens the quality and internal validity of the studies.

Cammarota *et al.* (2015); Pozzoni *et al.* (2012); Allen *et al.* (2013) and Lönnemark *et al.* (2010) used a computer generated random sequence (randomisation) -conducted by a third party- to generate lists to allocate patients to either the intervention arm or placebo arm. The major strength of this method of randomisation is that it ensures adequate allocation concealment, which reduces the risk of selection and outcome bias across the studies. However, of the included 7 articles, Pozzoni *et al.* (2015), Allen *et al.* (2013) and Lönnemark *et al.* (2010) were the only double blind R.C.T. included in this research. The double blind approach (blinding of participants and personnel) adopted by these studies ensures that performance bias is minimised. However, of all 7 included studies, only one (Allen *et al.*, 2013), indicated a blinding of outcome assessment which minimises detection bias in their study whereas the absence of this approach in other studies places them at a higher risk of detection bias which may influence the study result. Nevertheless, Allen *et al.* (2013) multi-centered study appears to be a more reliable study based on the total population (1,470). Thus findings of this study could be generalised although it did not favour probiotics as an effective intervention for C.D.A.D. In contrast, Kelly *et al.* (2012) and Fuentes *et al.* (2014) were case studies with no control group. Hence in the absence of a study comparison, intervention often appears to have an association with the study outcome. Moreover, the fact that there is no form of blinding in these studies predisposes them to performance bias, as investigators automatically believe that the treatment can affect outcome. However, although the findings of their studies corresponded with their outcome measure, the weakness of

these studies lies in the fact that few participants were involved hence they lack external validity, as findings cannot be generalised. Furthermore, in the hierarchy of evidence, case studies are considered less rigorous with regard to the methodologies and so are susceptible to bias, (Daly *et al.*, 2013). However, an average of 4 weeks follow up was conducted in all studies except Lönnemark *et al.* (2010) who followed up patients for a brief length of time (2weeks), which is not sufficient time to prove the effectiveness of the intervention as regards CDI, as it takes as long as 2 months after antibiotics use for A.A.D. or C.D.A.D. to develop (Mozaffari *et al.*, 2014). Inconsistency was also noticed in the diary data of Lönnemark *et al.* study. This inconsistency may have influenced the outcome of their study. However, all other studies accounted for lost participants/ data and subsequently excluded lost participants from overall results. All 7 studies except Kelly *et al.* carried out a post treatment stool analysis to rule out *Clostridium difficile* toxin in patients. This failure on the part of Kelly *et al.* might have affected the overall outcome of his study regarding the cure rate of F.M.T. in his participants. 5 of these studies were funded by various health organizations, which might have influenced the publication of results of these respective studies. One study was not funded and another study did not disclose any source of funding.

DISCUSSION AND FINDING

This study aimed to evaluate the efficacy and safety of probiotics in the treatment of CDI, which is said to be the key cause of A.A.D. in patients and in hospitals, and remains a global burden in health care. The incidence of this infection necessitated several strict control measures to curb it, (N.H.S., 2010; W.H.O., 2009; Dentol *et al.*, 2014; N.I.C.E., 2011; D.O.H., 2014) with significant impact as indicated by available literature particularly in the U.K. (O.N.S., 2013; H.P.A., 2014).

However, the diminished population that are still being plagued by this infection is a call for concern as such treatment options are still being explored. Probiotics and F.M.T. respectively are one of such treatment option that has been found to have a key role in the management of CDI, though evidence for its efficacy is limited. However, the findings of this study were grouped and discussed under 3 subjects: Effectiveness of probiotics and F.M.T., Single or combination probiotic treatment and Safety.

Effectiveness of Probiotics and Faecal Microbial Transplant

The focus of current evidence in the management of CDI centres on the maintenance of the intestinal microbiota and optimisation of the immune response to CDI and *C. difficile* toxin (Vecchico and Zacur, 2012), which is obviously one function of probiotics and F.M.T. However, other treatment options such as active vaccination, intravenous immunoglobulin and monoclonal antibodies targeted against *C. difficile* toxin are still being researched, (Kim, 2012). While Kubiszewska *et al.* (2014); Kechagia *et al.* (2013) and William (2010) in their review argue that the best documented effects of probiotics include its use in the treatment of bowel disorders such as lactose intolerance, A.A.D., pouchitis and infectious diarrhoea. Findings from this study reveal that both F.M.T. and probiotics are safe and effective in the management of CDI (Cammarota *et al.*, 2015; Kelly *et al.*, 2012; Van Nood *et al.*, 2013; Feuntes *et al.*, 2014) which parallels existing findings such as the conclusions of McCune *et al.* (2014);

Theodorapoulou *et al.* (2013) and Avadhani and Miley, (2011). Whereas Kee (2012) opines that probiotic *S. boulardii* is the only strain with proven efficacy in the treatment of CDI. However, none of the literature reviewed in this study correlated with the findings of Kee, (2012). In line with the findings of this study as regards F.M.T., a U.S based study confirms that for over 50 years F.M.T. has been used infrequently in the U.S.A and Europe in the treatment of CDI and related symptoms with a high efficacy rate, (Borody *et al.*, 2012). Another study also found F.M.T. effective particularly in immunosuppressed patients and with reduced adverse effects and deaths, (Kelly *et al.*, 2014; Youngster *et al.*, 2014; Mattila *et al.*, 2012). In their Washington – U.S based case series, Rohlke *et al.* (2010), evaluated the effectiveness of F.M.T. in 19 patients with recurrent CDI and found that 18 of these patients were cured after the first infusion while one of these patients was cured after the second infusion. They maintained that all 19 patients showed prolonged cure status ranging from 6 – 5 years; consequently they concluded that F.M.T. is effective in the treatment of CDI. Tanriover *et al.* (2012) and Isolauri *et al.* (2008) maintain that the modification of gut microbiota composition with probiotics might have positive effects with regards to the prevention of allergic, atopic and auto immune diseases. Intestinal micro flora has been linked with the occurrence of type I diabetes; therefore factors such as probiotics and F.M.T. capable of impacting on the constitution of the intestinal micro flora might be a therapeutic intervention (Tanriover *et al.*, 2012).

Besides the modulation of gastrointestinal diseases, probiotics are assuring in terms of their diverse beneficial effects on human health. High quality animal research confirms a relationship between modulated gut micro flora constitutions and normal gut permeability, levels of plasma endotoxicity, fat gain, inflammation and glucose tolerance, (Tuohy *et al.*, 2009). F.M.T. does not only cure CDI, but also increases bacterial diversity in patients who had this form of treatment so that they compare to the healthy donor as revealed in the findings of Van Nood *et al.* (2013) and Feuntes *et al.* (2014). However, 3 studies (Khorust *et al.*, 2010; Chien – Chang *et al.*, 2010 and Kubiszewska *et al.*, 2014) confirm the findings of Van Nood *et al.* and Feuntes *et al.* regarding the increased bio diversity of patients' microbiome. Only one study (Selinger *et al.*, 2013) was unable to conclude whether or not probiotics was effective in the treatment of CDI. This was linked to the marked reduction in the incidence of CDI but they were unable to detect enough cases to draw reliable conclusions. However, despite the available evidence - though insufficient, some individuals argue that the conventional treatment (Metronidazole, vancomycin and fidaxomicin) remains the gold standard for the treatment of CDI (Ciorba, 2012; Kee, 2012).

Single or combination probiotic treatment

Regarding dosage of probiotics, whether or not single or multiple strains of probiotic is effective in the treatment of CDI remains controversial. However while Pozzoni *et al.* (2012) and Allen *et al.* (2013) in their studies established that specific probiotics or multiple strains of probiotics is ineffective in the prevention and management of both A.A.D. and C.D.A.D. Other existing studies, such as 2 studies that were carried out in China by Ouwehand *et al.* (2014) and Gao *et al.* (2010) and Hickson *et al.* (2007) contradict the finding of Allen *et al.* and Pozzoni.

Ouwehand *et al.* in their study found a combination of 4 strains of probiotic effective in lowering the risk of A.A.D. and C.D.I together with gastrointestinal symptoms in a dose dependent approach. Similarly, Gao *et al.* found a proprietary probiotic to be efficacious in reducing the likelihood of A.A.D. and specifically C.D.A.D. in patients that were hospitalised also in a dose ranging manner. They found that the dispensing of the proprietary probiotic at a dose of 10 billion c.f.u yielded a more positive effect compared to 50 billion c.f.u. Hickson *et al.* demonstrated that a probiotic preparation comprising of *L. casei*, *L. bulgarius*, *S. thermophilus*) can lower the occurrence of A.A.D. and C.D.A.D., related morbidity and health costs as well as related mortality if used regularly in patients over 50 years of age. Hickson must have suggested the regular use of this preparation in older people because these age groups are susceptible to CDI as established by available studies such as Allen *et al.* (2013) and Kristin and Moson (2012). Furthermore, Lönnermark *et al.* (2010) in this study indicated that the use of a single strain probiotic (*Lactobacillus plantarum*) might exert a prophylactic effect on milder gastrointestinal symptoms during treatment with antibiotics. Nonetheless, Chapman *et al.* (2011) show that a combination of probiotics is effective not only in the treatment of CDI, but also in the treatment of a range of other conditions and this result is consistent with the findings of Ohland and MacNaughton (2010). Critically ill patients comprise a specific group who are disposed to infection and as such require parenteral nutritional support. The probiotic VSL# 3 was found to be efficacious in reducing the frequency of watery stools in patients that were critically ill, who were fed parenterally, (Frohman *et al.*, 2010) and also that *S. boulardii* yields the strongest evidence for the prevention of C.D.A.D. (Tanriover *et al.*, 2012).

Issue of Safety

One concern related to probiotics that has constantly been raised by the public is the issue of safety for this form of treatment particularly with regard to its potential for causing bacteremia and fungemia, by using live organisms on immune-suppressed patients and the transferring of an antibiotic resistant gene (Suresh *et al.*, 2013). It has been claimed that probiotic strains may act as a reservoir to hold resistant genes and may have the potential to transfer these genes to the pathogenic bacteria in the human body. *Lactobacilli*, due to their broad environmental distribution, may interchange resistance genes among themselves, but might also interact with transient bacteria to acquire and transmit an antibiotic – resistance gene, (Tanriover *et al.*, 2012). Similarly the safety of F.M.T. is questioned, as it is associated with the potential for transmission of virus, bacteria and parasites present in donor stools to patients, (Orenstein *et al.*, 2013). There have also been case reports of patients who ingested probiotics prior to the manifestation of symptoms associated with infections caused by microbes homogeneous with probiotic strains (Doron and Snyderman, 2015). Suresh *et al.* (2013) maintains that systemic infections caused by probiotics are rare. They point out that the likelihood of bacteremia occurrence from the intake of *Lactobacillus* probiotics is estimated at less than 1 in 1 million consumers and the likelihood of fungemia occurrence from consumption of *S. boulardii* is approximately 1 in 5.6 million consumers whereas these infections are much lower in healthy person. However, all included studies confirm that the adverse effects associated with F.M.T. or probiotics is mild in severity and rarely leads to re – infection or death. Consistently, Tvede *et al.* (2014) in their case series in Denmark also found F.M.T.

safe with minor side effects such as abdominal pain, which is the major complaint in their study, although 3 deaths were recorded out of 55 patients. A recent survey conducted by Baker *et al.* (2015) also showed that probiotics (*L. acidophilus*, *Bifidobacteria*) are safe. They expounded that they have been available for 30 years and have been widely accessible on the North American market for over 15 years with no history of danger to humans. This concurs with a survey conducted in Finland that revealed no episodes of bacteremia or any antibiotic resistant gene issues. One study (Kelly *et al.*, 2012) failed to conduct a post treatment stool analysis on its patients during a follow up period and they explained that this was because patients were considered cured if they were CDI symptom free, this failure might have influenced the rate of cure attributed to F.M.T. in their study. Interestingly and parallel to the above failure, a European under diagnosis of *Clostridium difficile* study (E.U.C.L.I.D.) involving 482 hospitals in 20 European Countries in 2013 identified a discrepancy in the incidence of CDI across Europe between 2011 – 2012 (the average incidence of CDI across Europe is 6.6 per 10, 000 patient bed days), when compared to the previous European *Clostridium Difficile* Infection Study (E.CDIS.) that was conducted in 2008 - 2009 that showed an average incidence of 4.1 cases per 10, 000 patient bed days in 87 hospitals (Bauer *et al.*, 2011). Thus the E.U.C.L.I.D. study linked this discrepancy to “under diagnosis” which is capable of skewing epidemiological data.

Consequently, E.U.C.L.I.D.'s findings suggests that on a single day across Europe, 82 patients with diarrhoea due to *C. difficile* toxin are not detected as a result of lack of clinical suspicion. Thus, under testing and under detection likely accounts for a huge disparity between reported and actual rates of CDI across Europe. Moreover, the study points out that potentially incorrect diagnosis in up to 23% of patients may result in inadequate treatment of patients and inappropriate infection control measures, (Kerries *et al.*, 2014). Of interest in this study is the fact that the included studies recruited more females than males, hence suggesting that more females perhaps suffer from CDI than males. However, during the search for literature, no literature was found addressing CDI in a particular gender. This might be an area for further research.

Ethical Approval

Formal ethical approval for this study was granted by the University of Sunderland Ethics Committee.

Conflicts of Interest

There were no potential conflicts of interest in relation to the execution of this project.

Funding of Research

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