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Royal Cornwall Hospitals NHS Trust

Probiotics (VSL#3) for Prevention of *Clostridium Difficile* Associated Diarrhoea (CDAD) Policy

V3.0

July 2019

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Summary of Probiotic policy

Probiotics: Live healthy microbial supplement.
The probiotic used in RCHT is VSL#3
Purpose: To reduce the incidence of Clostridium difficile associated (CDAD)

Indication: Responsibility:

1. Prescribe along with following antibiotics (in-patients >60yr)

   Piperacillin-Tazobactam, Ciprofloxacin, Levofloxacin, Meropenem, Ertapenem, Cephalosporins, Clindamycin, Co-amoxiclav, Amoxicillin

   All prescribers Prescribe through EPMA

2. GDH positive in-patients with any antibiotics (any age)

Check exclusion criteria: Immunosuppressed patient, organ transplantation, acute pancreatitis, asplenia, prosthetic heart valve, risk of aspiration, long term steroid, allergy to gluten or coeliac disease

Dose: 1 sachet a day for all in-patients throughout the period of antibiotic treatment. Continue probiotic even after deescalation from high risk to low risk antibiotics; i.e. Pip-Tazo to trimethoprim to cover the whole antibiotic period.

Administration: Orally mixed with cold non-fizzy drink or sprinkled on cold food Storage: In refrigerator (2-8^0)	Responsibility: Nurses
Procurement and stock maintenance Regular monitoring of uses and monthly audits of compliance	Responsibility: Pharmacy
Approval, implementation and review of the policy with regular updating (3 yearly)	Responsibility: Antimicrobial Stewardship committee

1. Introduction

1.1. Appropriate use of antibiotic and standard infection precautions are the two key elements for prevention of *Clostridium difficile* associated diarrhoea (CDAD) or *Clostridium difficile* infection (CDI) in acute care trusts. RCHT strongly promotes adherence to trust's antibiotic policy and guidelines while prescribing an antibiotic. All broad spectrum antibiotics should be reviewed every day by the appropriate clinical team and microbiology advice should be sought whenever necessary. Probiotic therapy (VSL#3) should be considered for all in- patients above sixty years without having certain risk factors when a broad spectrum antibiotic is prescribed in order to reduce the risk of *Clostridium difficile* infection.

1.2. It is estimated that adult human gut contains around 10^{14} bacterial cells and more than 1000 different bacterial species. However these proportions vary greatly among individuals based on age, diet and environment. *Clostridium difficile* is one of the common anaerobic, gram-positive, spore-forming bacteria which is found as part of the normal intestinal microflora in 5-30% of healthy human gut. Up to 50% of patients in a long-term care facility can be asymptomatic carriers of *C. difficile* (1). Symptomatic patients can release abundant spore in the environment which can be transmitted among other patients hospital. However, asymptomatic carriers also can play significant role in transmission of *C.difficile* spore in healthcare setting as well as community. Under normal conditions, commensal microbes and their hosts enjoy a symbiotic relationship. Antibiotics are the most common agents that can disrupt the gut microenvironment resulting overgrowth of pathogenic organisms including *Clostridium difficile*. Toxigenic *C. difficile* can produce Toxin A/B, a potent intestinal toxin which binds with intestinal epithelial cells leading to inflammation and diarrhoea. As the diversity of gut flora decreases with age, elderly population are more vulnerable to antibiotic mediated dysbiosis of gut flora and therefore prone to develop CDAD.

1.3. On average 30-40% of hospitalised patients receive antibiotics during their stay in hospital. 5-35% of patients receiving broad spectrum antibiotics can develop antibiotic associated diarrhoea. The incidence of CDAD is increasing because of gradual rise of broad-spectrum antibiotic usage driven by bacterial resistance. In a CDC analysis of data regarding antibiotic prescribing in hospitalised patients, Fridkin and colleagues estimated that a 30% reduction in use of broad spectrum antibiotics would result in a 26% reduction of *Clostridium difficile* infections (2). Effective antibiotic stewardship and standard infection prevention and control have been proven to be the key measure for preventing *C. difficile* cases in hospital as well as reducing bacterial resistance in longer term. However recent rise of CDAD cases poses a significant threat of transmission and further development of severe or complicated CDI to hospitalized patients, which necessitates new approaches for prevention and treatment of *C. difficile* disease.

1.4. The term "probiotic" was first used to describe "a live microbial supplement, which beneficially affects the host by improving its microbial balance." Probiotic organisms can colonize gut temporarily, produce anti-inflammatory peptides and promote colonization resistance by competing with unhealthy microbes for nutrients and epithelial adhesions. Various probioitcs supplements have been used for last two decades in the treatment of multiple diseases like inflammatory bowel diseases, antibiotic associated diarrhoea, irritable bowel syndrome etc. A recent meta-anlysis

(Hempel S et al, 2012) concluded that probiotic prophylaxis can significantly reduce antibiotic associated diarrhoea (3). Another review by Johnston et al, 2012 showed that in a population with a 5% incidence of antibiotic associated CDAD, probiotic prophylaxis would prevent 33 episodes per 1000 persons without an increase in clinically important adverse effect (4). Cochrane review (2017) summarized when probiotics are given with antibiotics they can reduce the risk of developing CDAD by 60% (5).

1.5. On the basis of these reviews and meta-analysis, RCHT promotes the use of probiotics for prevention of CDAD. Probiotic organisms can be bacterial (Lactobacillus, Bifidobacterium etc), fungal (Saccharomyces) or mixed. We avoided Saccharomyces (fungal probiotic) because of risk of safety issues if inadvertently it is given to immunocompromised patients. Among bacterial probiotics, VSL#3 is a multi-strain probiotic and has been well studied in many other disorders including IBD, IBS, pouchitis and liver disorders since last 10 years and found to be well tolerated and safe for clinical use. A recent trial from Manchester showed (Selinger et al 2013) VSL#3 can significantly reduce antibiotic associated diarrhoea in average risk hospital in-patients with the potential to reduce CDAD in high risk patients (6).

1.6. VSL#3 contains 450 billion CFU organisms of 8 different strains, including:

- Streptococcus thermophiles
- Bifidobacterium breve
- Bifidobacterium longum
- Bifidobacterium infantis
- Lactobacillus acidophilus
- Lactobacillus plantarum
- Lactobacillus paracasei
- Lactobacillus delbrueckii subsp. Bulgaricus

1.7. Data Protection Act 2018 (General Data Protection Regulation – GDPR) Legislation

The DPA18 covers how the Trust obtains, hold, record, use and store all personal and special category (e.g. Health) information in a secure and confidential manner. This Act covers all data and information whether held electronically or on paper and extends to databases, videos and other automated media about living individuals including but not limited to Human Resources and payroll records, medical records, other manual files, microfilm/fiche, pathology results, images and other sensitive data.

DPA18 is applicable to all staff; this includes those working as contractors and providers of services.

For more information about your obligations under the DPA18 please see the information use framework policy', or contact the Information Governance Team rch-tr.infogov@nhs.net

2. Purpose of the Policy

This policy has been developed to provide staff with the necessary information and knowledge to effectively prescribe and administer probiotics.

3. Scope

This policy applies to all RCHT, locum and agency staff who prescribe or administer antibiotics.

4. Definitions and Glossary

All definitions are contained within the text.

5. Ownership and Responsibilities

5.1 Divisional Directors, Specialty Directors, Divisional Nurses, Matrons, Ward Sisters/Charge Nurses

Are responsible for ensuring implementation within their area, and for ensuring all staff who work within the area adhere to the principles at all times

5.2 All clinical staff involved in the prescribing and administration of antimicrobials

Are required to adhere to this policy including full documentation on EPMA as detailed.

5.3 Antimicrobial Stewardship Committee

The Antimicrobial Stewardship Committee is responsible for the approval, implementation and monitoring of this policy

6. Standards and Practice

6.1 Criteria for receiving probiotics

Group 1

All of the following criteria should be met before considering probiotic therapy:

- Patients over 60 years of age
- Patient is an in-patient
- Patient has been prescribed any of the following antibiotics
    - Tazocin (Piperacillin-tazobactam)
    - Ciprofloxacin
    - Levofloxacin
    - Meropenem/Ertapenem
    - Clindamycin
    - Cephalosporins
    - Co-amoxyclav
    - Amoxicillin

Probiotic supplement is NOT required when these antibiotics are used as single dose surgical prophylaxis. In some circumstances where clinical assessment indicates high risk of CDI, probiotic can be considered in younger adult (<60yr) with high risk antibiotics.

Group 2

All patients who have been diagnosed GDH positive in any stool sample (in current

or previous admissions) and require **any** antibiotic in current admission

6.2 Exclusion criteria

- Immunosuppressed pt (haematology pts, HIV, chemotherapy or taking any immunosuppressants for example:
    - Azathioprine
    - Methotrexate
    - Ciclosporin
    - Tacrolimus
    - Serolimus
    - Mercaptopurine
    - Infliximab
    - Adalimumab
    - Mycophenolate

- Patient with organ transplantation
- Acute pancreatitis
- Patient with prosthetic heart valve
- Patient with risk of aspiration
- Patient with no spleen
- Allergy to diary products, soy or gluten
- Patient with long term (> 1 month) high dose systemic steroid (equivalent to 20mg prednisolone)
- Patients who have coeliac disease.

6.3 Dose

VSL #3 sachet: 1 sachet daily.

6.4 Duration

VSL#3 should be continued for the duration of antibiotic treatment only.

Patients, who are discharged during treatment, should continue the VSL#3 on discharge until the antibiotic course is complete. The duration of VSL#3 for patients on long term antibiotics (e.g. TB therapy, Bone & joint infection, Home IV antibiotic therapy) and for other situations should be reviewed on an individual basis by the microbiology and infection control team – where the need for VSL#3 will be determined.

6.5 Administration

VSL#3 can be taken orally or via an enteral feeding tube. It should be mixed with a cold (non-fizzy) drink, or sprinkled on cold food.

6.6 Storage

VSL#3 sachets should be stored in a fridge ($2\text{-}8^{0}$).

6.7 Adverse effects

Occasional bloating and flatulence sensation may be experienced while taking VSL-3, however these are usually mild and subside with continuous use. The dose frequency may be reduced if patient suffers significant discomfort after intake.
One theoretical concern associated with probiotics includes the potential for these

viable organisms to move from the gastrointestinal tract and cause systemic infections and although rare, probiotic related bacteraemia have been reported. However these are isolated reports and none of the clinical trials have reported any serious adverse effect or systemic infection with probiotics. It is estimated that the risk of developing bacteremia from ingested lactobacilli probiotics is less than 1 per 1 million users (7). However we recommend to follow all exclusion criteria before prescribing VSL#3 for patient safety.

6.8 Dietary considerations

VSL#3 may contain traces of gluten and dairy products. A small amount should be tried first if patient reports allergy to gluten or dairy products.

7. Dissemination and Implementation

The guidance will be part of RCHT antibiotic guide and can be accessed via RCHT antibiotic webpage and microguide app. Information about the policy will be sent to all ward managers, nurses, doctors and pharmacists. Adherence to the policy will be encouraged through posters, routine pharmacy round, antibiotic review round, grand round and FY1/2 teaching. VSL-3 can be prescribed through EPMA following appropriate inclusion and exclusion criteria. VSL-3 will be stored in ward drug refrigerator and regular ward stock will be maintained jointly by ward staff and pharmacy.

8. Monitoring compliance and effectiveness

Element to be monitored	Prescribing and administration of probiotics for the patient group identified in section 6.
Lead	Antibiotic Pharmacist
Tool	Report generated from EPMA
Frequency	Monthly
Reporting arrangements	Results reported to Antimicrobial Stewardship Group
Acting on recommendations and Lead(s)	Members of the Antimicrobial Stewardship Committee will undertake subsequent recommendations and action planning for any or all deficiencies and recommendations within reasonable timeframes Required actions will be identified and completed within a month.
Change in practice and lessons to be shared	Required changes to practice will be identified and actioned immediately where necessary. The relevant Divisional Representative will be identified to take each change forward where appropriate. Lessons will be shared with all the relevant stakeholders.

9. Updating and Review

This policy will be reviewed no less than every three years.

10. Equality and Diversity

10.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the 'Equality, Inclusion & Human Rights Policy' or the Equality and Diversity website

10.2. The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Document Title	Probiotics (VSL#3) for Prevention of Clostridium Difficile Associated Diarrhoea (CDAD) Policy V3.0					
Date Issued/Approved:	July 2019					
Date Valid From:	July 2019					
Date Valid To:	July 2022					
Directorate / Department responsible (author/owner):	Dr P Chakrabarti, Microbiologist					
Contact details:	01872 254960					
Brief summary of contents	This policy has been developed to provide staff with the necessary information and knowledge to effectively prescribe and administer probiotics.					
Suggested Keywords:	Probiotics, antibiotics, clostridium difficile.					
Target Audience	RCHT	KCCG	CFT			
	✓					
Executive Director responsible for Policy:	Medical Director					
Date revised:	July 2019					
This document replaces (exact title of previous version):	Probiotics for prevention of *Clostridium difficile* associated diarrhoea (CDAD) V.1					
Approval route (names of committees)/consultation:	Hospital Infection Prevention & Control Committee Meeting (08.02.16) CSSC Governance DMB					
Divisional Manager confirming approval processes	Robin Jones CSCG					
Name and Post Title of additional signatories	Not Required					
Name and Signature of Divisional/Directorate Governance Lead confirming approval by specialty and divisional management meetings	{Original Copy Signed}					
	Name Kevin Wright, Governance Lead CSCG					
Signature of Executive Director giving approval	{Original Copy Signed}					
Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet & Intranet	✓	Intranet Only			

Document Library Folder/Sub Folder	Clinical / Pharmacy
Links to key external standards	CQC Regulation 12
Related Documents:	1. Riggs, M.M., A.K. Sethi, T.F. Zabarsky, E.C. Eckstein, R.L. Jump and C.J. Donskey. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic Clostridium difficile strains among long-term care facility residents. *Clin Infect Dis*, 2007. 45(8): p. 992-8. 2. Fridkin S, Baggs J, Fagan R, et al. Vital signs: improving antibiotic use among hospitalized patients. *MMWR Morb Mortal Wkly Rep*. Mar 7 2014;63(9):194-200. 3. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, Johnsen B,Shekelle PG. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA*. 2012 May 9;307(18):1959-69. 4. Johnston BC, Ma SS, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, Guyatt GH. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. *Ann Intern Med*. 2012 Dec 18;157(12):878-88. 5. Goldenberg JZ, Ma SS, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC. The use of probiotics to prevent Clostridium difficile diarrhoea associated with antibiotic use. *Cochrane Database Syst Rev*.2017 19th December. 6. Selinger CP, Bell A, Cairns A, Lockett M, Sebastian S, Haslam N. Probiotic VSL#3 prevents antibiotic-associated diarrhoea in a double-blind, randomized,placebo-controlled clinical trial. *J Hosp Infect*. 2013 Jun;84(2):159-65. 7. Borriello SP, Hammes WP, Holzapfel W et al. Safety of probiotics that contain lactobacilli or bifidobacteria. *Clin Infect Dis*. 2003; 36:775–80.

Training Need Identified?	No

Version Control Table

Date	Version No	Summary of Changes	Changes Made by
13.05.14	1.0	New Policy	Dr P Chakrabarti
04.01.16	2.0	Additions made to the criteria for receiving probiotics	Dr P Chakrabarti
04.07.19	3.0	No changes – formatted onto latest trust template	Ronan Sheehan

All or part of this document can be released under the Freedom of Information Act 2000

This document is to be retained for 10 years from the date of expiry.

This document is only valid on the day of printing

Controlled Document

This document has been created following the Royal Cornwall Hospitals NHS Trust Policy on Document Production. It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Initial Equality Impact Assessment Form

Name of the strategy / policy /proposal / service function to be assessed Probiotics (VSL#3) for Prevention of Clostridium Difficile Associated Diarrhoea (CDAD) Policy V3.0	
Directorate and service area: Pharmacy	**New or existing document:** Existing
Name of individual completing assessment: Ronan Sheehan	**Telephone:** 01872 252590

1. *Policy* Aim* *Who is the strategy / policy / proposal / service function aimed at?*	To provide staff with the necessary information and knowledge to effectively prescribe and administer probiotics.				
2. *Policy* Objectives*	To reduce antibiotic associated diarrhoea and subsequent Clostridium difficile cases.				
3. *Policy* – intended Outcomes*	To ensure those patients who are over the age of 60 years and those patients who are or who have previously been colonised with GDH and who meet the recommended inclusion criteria are prescribed and receive VSL#3				
4. *How will you measure the outcome?	Monthly audits from EPMA.				
5. Who is intended to benefit from the *policy*?	Patients				
6a Who did you consult with	Workforce	Patients	Local groups	External organisations	Other
	X				
b). Please identify the groups who have been consulted about this procedure.	**Please record specific names of groups** Antimicrobial Stewardship Committee Trust Management Committee				
What was the outcome of the consultation?	**Agreed**				

7. The Impact
Please complete the following table. **If you are unsure/don't know if there is a negative impact you need to repeat the consultation step**.

Are there concerns that the policy **could** have differential impact on:

Equality Strands:	Yes	No	Unsure	Rationale for Assessment / Existing Evidence
Age		**X**		

Sex (male, female, trans-gender / gender reassignment)		**X**		
Race / Ethnic communities /groups		**X**		
Disability - Learning disability, physical impairment, sensory impairment, mental health conditions and some long term health conditions.		**X**		
Religion / other beliefs		**X**		
Marriage and Civil partnership		**X**		
Pregnancy and maternity		**X**		
Sexual Orientation, Bisexual, Gay, heterosexual, Lesbian		**X**		

You will need to continue to a full Equality Impact Assessment if the following have been highlighted:

- You have ticked "Yes" in any column above and
- No consultation or evidence of there being consultation- this excludes any *policies* which have been identified as not requiring consultation**. or**
- Major this relates to service redesign or development

8. Please indicate if a full equality analysis is recommended.	**Yes**		**No**	**X**

9. If you are **not** recommending a Full Impact assessment please explain why.

None of the equality strands have been identified in the initial impact assessment.

Date of completion and submission	4th July 2019	Members approving screening assessment	Policy Review Group (PRG) **APPROVED**

This EIA will not be uploaded to the Trust website without the approval of the Policy Review Group.

A summary of the results will be published on the Trust's web site.