

Review of probiotic treatment, including VSL#3® for ileoanal-pouchitis (DROP-List)

This is one of a number of bulletins providing further information on medicines contained in the PrescQIPP DROP-List (Drugs to Review for Optimised Prescribing). This bulletin focuses on probiotics and provides evidence for prescribing to be reviewed and stopped if ACBS prescribing criteria for VSL#3® are not met. Further bulletins, including the DROP-List itself¹ are available on the PrescQIPP website at www.prescqipp.info

Recommendations

- Ensure that prescribing of VSL#3® is in line with the Advisory Committee on Borderline substances (ACBS) approved indication, i.e. for the use under the supervision of a physician, for the maintenance of remission of ileoanal pouchitis induced by antibacterials in adults² (so after an intense course of antibiotics has induced remission of pouchitis).
- The dose is one to four sachets daily depending upon the number of bowel movements per day.^{3,4}
- The product information recommends taking VSL#3® for at least one month to allow for colonisation of the gut to become stable.³
- Review all patients on probiotics:
 - » Check the indications for using a probiotic.
 - » Advise any patients (including those who do not meet the ACBS approved indication for VSL#3®) to purchase probiotics over-the-counter (OTC), if they wish to try them. However, ensure patients understand there is a lack of evidence supporting a benefit of probiotics in any other indication.
 - » Regularly review effectiveness of VSL#3® in those patients who meet the ACBS criteria. Consider stopping therapy where there is insufficient clinical benefit.

Background

The PrescQIPP DROP-List is a list of medicines regarded as low priority for prescribing, poor value for money or medicines where there are safer alternatives. There are also medicines which could be considered for self-care, with the support of the community pharmacist, included on the DROP-List.

Bacteria or yeast generally ingested orally as therapy are termed probiotics. They may be administered as a single organism or a defined mixture, aiming to beneficially alter the microbial ecology of the gut.⁵ Probiotics (including VSL#3®) features on the DROP-List as an item which has limited clinical value. VSL#3® is an ACBS approved product for one indication only - for the use under the supervision of a physician, for the maintenance of remission of ileoanal pouchitis induced by antibacterials in adults.² There is insufficient evidence to recommend it for other indications. Patients not meeting the ACBS criteria should purchase VSL#3® OTC (or buy another probiotic of their choice). They should be counselled on the lack of evidence for benefit in any indication other than the ACBS approved one. See section on 'Rationale for stopping probiotic prescribing'.

The National Institute for Health and Care Excellence (NICE) have information on their website for the public on Irritable Bowel Syndrome (IBS) which states:

“If you want to try a probiotic product to see if it helps, your doctor should advise you to keep taking it for at least 4 weeks and to take the dose recommended by the manufacturer. You should also record whether it makes a difference to your symptoms. Your doctor should not recommend using the herbal medicine called Aloe vera for irritable bowel syndrome.”⁶

By advising to take the probiotic as per manufacturer’s dose recommendations, it is implied that the patient should purchase the probiotic OTC.

In the UK the estimated number of people with a diagnosis of ulcerative colitis (UC) is around 146,000⁷ and at least 115,000 with Crohn’s Disease.⁸ These two conditions come under the umbrella term Inflammatory Bowel Disease (IBD). The cause of UC is unknown. It can develop at any age, but peak incidence is between the ages of 15 and 25 years. UC usually affects the rectum and some of the colon next to the rectum.

The lifetime risk for surgery may be as high as 20-30% for UC, depending on disease severity and location.⁹ An ileal pouch is a surgically created chamber using the small intestine. This is sometimes necessary for patients with severe UC. When the lining of the pouch becomes inflamed, the condition is known as pouchitis. This is the most common long-term complication of an ileoanal anastomosis (surgical connection between two tubular structures) in ulcerative colitis.³ Up to 50% of patients who undergo ileal pouch surgery for UC suffer from pouchitis. Symptoms include increased frequency and looseness of stools, with or without bleeding. Urgency, tenesmus and pelvic floor discomfort may also occur in addition to fever and systemic upset. Diagnosis of pouchitis requires an appropriate clinical presentation in addition to endoscopic and histological confirmation of inflammation.⁵

The NICE clinical guideline on UC, focuses on drug treatment. It makes no mention of the use of probiotics in ileoanal pouchitis, nor does the clinical guideline on Crohn’s disease.^{7,8}

Clinical evidence

The nutritional supplement VSL#3®, is a powder containing 8 strains of live, freeze-dried, lactic acid bacteria. The ACBS indication is for use under the supervision of a physician, for the maintenance of remission of ileoanal pouchitis induced by antibacterials in adults (so after an intense course of antibiotics has induced remission of pouchitis).² This is a post-surgical condition associated with ulcerative colitis.⁵

There is a lack of evidence for probiotics in other IBD indications. The NICE draft Quality Standard for IBD is currently undergoing consultation and is due to be published in September 2014.¹⁰

Risk factors, genetic associations and serological markers of pouchitis suggest that a close interaction between the host immune response and the pouch microbiota, plays a relevant role in the aetiology of this inflammatory condition.⁹

In a small study partially supported by VSL Pharmaceuticals Inc, Mimura et al evaluated the effectiveness of a single daily high dose probiotic in maintaining antibiotic-induced remission in patients with recurrent or refractory pouchitis. They randomised 20 patients to VSL#3® treatment and 16 to placebo. Remission was maintained at one year in 17 patients (85%) on VSL#3® and in one patient (6%) on placebo ($p < 0.0001$). One patient withdrew from the trial due to abdominal cramps, vomiting and diarrhoea 10 days after starting the study medication. Three further attempts at taking the trial preparation resulted in the same symptoms. All patients in this study had previous recurrent or refractory pouchitis and had achieved remission after a four week course of intense antibiotic therapy. Antibiotic therapy would now appear to be the favoured form of treatment for active pouchitis. Although continuous antibiotics may be able to maintain remission induced by an acute course of antibiotics, this strategy has not formally been tested. The authors discuss that as an

imbalanced or excessive response to intraluminal bacteria seems to be involved in the pathogenesis of IBD, including pouchitis, probiotic therapy to modify the bacterial flora may be an attractive option. They conclude that VSL#3® is effective in maintaining antibiotic induced remission for at least a year.¹¹

In the clinical situation, probiotic products are generally recognised as safe and reported problems are rare. There are some case reports of infection by probiotic organisms, but in nutritionally-compromised patients. A systematic review cited 53 clinical trials in which 32 out of 4131 patients developed probiotic-related infection. Often these patients were acutely and severely ill.¹²

There is still no full mechanistic explanation for IBD, but people are starting to realise that the pathogenesis of IBD involves four fundamental components: the environment, gut microbiota, the immune system and the genome. So IBD development might be due to an altered immune response and a disrupted mechanism of host tolerance to the non-pathogenic resident microbiota, leading to an elevated inflammatory response. From the current literature reviewed by Sinagra et al, a benefit of probiotics remains unproven in Crohn's disease; a benefit of probiotics remains unproven in UC, even if *E. coli* Nissle 1917 (a probiotic in VSL#3®) seems promising in maintaining remission and it could be considered an alternative in patients intolerant or resistant to 5-ASA preparations. In pouchitis, small controlled trials suggest a benefit from VSL#3® in the primary and secondary prevention of pouchitis. In IBD-associated conditions, a benefit of probiotics remains unproven. Well-designed randomised control clinical trials are necessary to understand the undoubted role of these agents in the management of gut physiology in health and disease.¹³

Patients who do not meet ACBS criteria for VSL#3® prescribing who wish to continue to take probiotics should be asked to purchase OTC, but should be made aware that efficacy is unproven in any ACBS non-approved indications.

Rationale for stopping probiotic prescribing

- VSL#3® is the only probiotic with any evidence for treatment of the ACBS approved indication.
- British Society of Gastroenterology guidelines for the management of inflammatory bowel disease in adults state that VSL#3® probiotic therapy may be used to treat and prevent pouchitis. Its efficacy is lost soon after stopping the treatment.⁵
- A Cochrane review investigated use of probiotics to treat active UC. There is limited evidence that probiotics may reduce disease activity, but not enough to recommend them to treat active UC. Larger, well designed randomised controlled trials are needed to determine this.¹⁴
- There is no clear evidence to support any role of probiotics in the maintenance of Crohn's disease after surgically or medically-induced remission.⁵
- A more recent Cochrane review concluded that for the prevention of pouchitis, VSL#3® was more effective than placebo, but not more effective than no treatment. The reason for this discrepancy is not clear. Hence the efficacy of VSL#3® for prevention is questionable. Larger RCTs are needed to determine the optimal agent(s).¹⁵

Costs

In England over £872,500 was spent on all probiotics over the course of a year - VSL#3® is the most commonly prescribed (ePACT May 14). It is hoped that GPs will participate in making cost savings from reviewing probiotic therapy, as there is a substantial cost involved in prescribing these products. Table 1, on the following page, illustrates the cost per 28 days of treatment of VSL#3®, based on the lowest dose of one sachet daily.

Table 1: VSL#3® costs per pack⁴

Product	Cost per 28 days
VSL#3®	£32.98 for 30 sachets

Options to review therapy

Ensure all patients prescribed VSL#3® on FP10 prescriptions meet the ACBS criteria and treatment is reviewed regularly. As previously stated, the only ACBS approved indication is for use under the supervision of a physician, for the maintenance of remission of ileoanal pouchitis induced by antibacterials in adults.²

Discontinue any prescribing for probiotics other than VSL#3® and for those on VSL#3® who do not meet ACBS criteria or for those patients with pouchitis where it is ineffective.

Savings available

In England each year, over £863,000 is spent on VSL#3® alone and over £9,300 on other probiotics.

Prescribing 80% less VSL#3® and other probiotics would **save over £698,000 in England over 12 months**. If prescribing of probiotics stopped completely, this could release **savings of around £872,500 in England over 12 months**. **This equates to savings of £1,235 per 100,000 patients for 80% less prescribing and £1,544 per 100,000 patients if prescribing stopped completely.**

Summary

- A lack of evidence for using probiotics in IBD is highlighted by Cochrane reviews. This means that only prescribing of VSL#3® for the ACBS approved indication can be supported. All other prescribing should be discontinued.
- Substantial savings can be achieved by reviewing prescribing. Discontinue any prescribing for probiotics other than VSL#3® and for those people who do not meet ACBS criteria or for those patients with pouchitis where VSL#3® is ineffective. Advise OTC purchase for those who wish to continue using them, but emphasise the current lack of evidence for clinical benefit.

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Additional PrescQIPP resources



Briefing



Data pack



Patient letter, audit

Available here: <http://www.prescqipp.info/resources/viewcategory/260-probiotics>

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