CHAPTER 15 COMPLEMENTARY NUTRITION THERAPIES

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Complementary therapies are defined as medicinal products containing active ingredients such as herbs, vitamins and minerals, nutritional supplements, homoeopathic medicines and aromatherapy products each of which have a clearly established identity and traditional use in medicine [694]. The use of complementary therapies in chronic disease has increased significantly over the last twenty years and is continuing to gain medical, economic and sociological importance [695]. Recent estimates suggest that up to 75 percent of children with CF [696,697] and up to 70 percent of adults with CF [698] have used complementary therapies in addition to conventional treatments.

Complementary therapies are regulated in Australia by the Therapeutic Goods Administration under the Therapeutic Goods Act 1989 [694] and in NZ by the Ministry of Health under the Natural Health and Supplementary Products Bill 2012 [699]. This chapter will discuss evidence for the use of probiotics, glutathione, coconut oil and herbal supplements in people with CF.

15.1 Probiotics

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A diverse range of over 100 trillion microorganisms colonizes the human gastrointestinal tract. The composition of the microbiota is influenced by factors including age, disease and diet [700]. The gut microbiota profile of an individual (i.e. bacteria living within the gut) begins to develop as early as *in utero* and progresses rapidly in richness and diversity during the first twelve months of life and beyond. By the end of the first three years of life, the microbiota of healthy children converges toward the characteristic diverse adult microbiota profile [701-703]. The adult microbiota is more distinct and stable and whilst it may continue to change, it does so at a much slower rate than in early childhood [704]. It has been postulated that for permanent change to gut microbiota, alterations to the host's microbiome must occur within the first few months and years of life [705].

Gastrointestinal microbiota play an important role in health and disease. A well-balanced gut microbiota has been associated with good immune function, prevention of infection from pathogenic or opportunistic microbes, and metabolic homeostasis [706]. Disruption to healthy gut microbiota, known as dysbiosis, has been associated with a number of inflammatory conditions including inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) as well as respiratory conditions such as allergic airway inflammation [707]. Probiotic efficacy has also been shown in the treatment of antibiotic and *Clostridium difficile*-associated diarrhoea [703,708].

A person's native gut microbiota may not always be able to perform its immune and metabolic functions optimally and therefore modulation of the gut microbiota is being increasingly considered a viable therapeutic strategy. Modulation of the gut microbiota can be achieved through the administration of probiotic supplements [703].
Probiotics are defined by the World Health Organisation as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [709]. The mechanism and efficacy of probiotics are strain-specific [710]. General health effects of probiotics cannot be extrapolated from one strain to another strain, nor are all probiotics indicated for the same health conditions [703].

The most common bacterial genera marketed as probiotics are lactic bacteria, such as *Lactobacillus* and *Bifidobacterium* [703]. Due to their strain-specific effects, probiotics must be identified and characterised to the level of the phyla, genus, species and strain [709]. An example of this is outlined in figure 15a below.

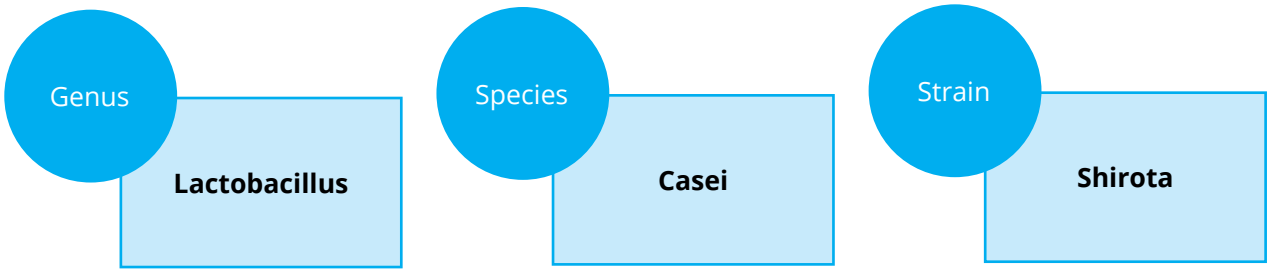

Figure 15a. Example of probiotic identification according to genus, species and strain.

Probiotics are now widely available to the general population and exist in many forms, including food and dietary supplements. Probiotic products vary considerably not only in their form, but in their intended health claim, quality, dose and storage requirements. In recent years, several clinically tested probiotic products have become available with quality-controlled production and are marketed by reputable companies, however, regulatory issues remain a challenge [708].

In Australia and New Zealand, probiotic products are considered as either functional foods, regulated by Food Standards Australia New Zealand (FSANZ), or complementary medicines, regulated by the Therapeutic Goods Administration (TGA) and New Zealand Ministry of Health. Under the Food Standards Code, fermented milk beverages and yoghurts that claim to be probiotic must have a minimum of one million live bacteria per gram. While complementary medicines must show the amount of an active ingredient, foods do not have to disclose the number of probiotic bacteria in a product, which can make it difficult for consumers to make an informed purchase. Of concern is the significant variability in product quality, purity and viability, with some products likely to have fewer probiotics than they claim [700,711].

Disease Aetiology

The gut microbiota in people with CF is thought to be different from those without CF. A state of dysbiosis has been demonstrated in the CF gut with an abundance of potentially pathogenic bacteria and a reduction in beneficial bacteria [236,712-714].

Gut microbiota profiles can be affected by numerous factors associated with CF including viscous mucus, intestinal dysmotility, reduced intestinal pH, reduced bile salt secretion, intestinal inflammation, chronic antibiotic and pancreatic enzyme use and bacterial overgrowth [236]. It is hypothesised that the intestinal mucosa in CF acts as the primary interface between the gut microbiota, immune and metabolic systems [712]. Abnormal intestinal mucosa is also likely to be associated with dysbiosis which may contribute to chronic pulmonary and intestinal inflammation and to the later development of gastrointestinal malignancies [712]. For these reasons, manipulation of the gut microbiota may have therapeutic potential in reducing chronic inflammation seen in CF [236].

The 'lung-gut axis' is a new area of research into the interconnectedness of pulmonary and gastrointestinal microbiomes [168,715]. It is suggested that gut microbiota in CF may be related to bacterial colonisation in the respiratory tract and the regulation of respiratory outcomes [712,716]. One proposed mechanism is by the action of T-cells, whereby alteration of the gut microbiota with probiotics improves respiratory disease via initiation of a T-cell regulatory mediated mechanism in the gut [716]. Chronic respiratory inflammation in CF may therefore benefit from strategies targeting the gut microbiota that influence the entire immune environment [716].

Does dietary supplementation with probiotic genus *Lactobacillus* improve nutritional and/or respiratory status in people with CF? PICO 15.1.1

[Grade C] Dietary supplementation with a *Lactobacillus* genus probiotic (single or as part of a mixture) may have health benefits for people with CF, particularly in regards to intestinal inflammation, the intestinal microbiota and risk of pulmonary exacerbation. [164-171]

The potential mechanisms of action by which probiotics may benefit individuals with CF include their effects on the gut microbiota, changes to gut motility, improved intestinal barrier function, inhibition of the colonisation of pathogenic bacteria, improved metabolic process and modulation of gut and systemic immunity [712,717].

Beneficial effects of probiotic supplementation have been demonstrated in CF, on a number of health outcomes, as outlined below [707]. However, it is important to note that the existing evidence is underpowered, of low quality and is inconsistent with regards to the health outcomes, population, probiotic strain and duration of supplementation examined. Care should be taken at this time when applying this evidence to clinical practice.

INTESTINAL INFLAMMATION

A reduction in intestinal inflammation (as measured indirectly by faecal calprotectin) has been demonstrated in people with CF, after supplementation with *Lactobacillus* as a single species/strain of probiotic [164,166,167,169] or as part of a probiotic mixture with a prebiotic [169].

INTESTINAL MICROBIOTA

Partial restoration of the normal intestinal microbial profile has been reported post probiotic supplementation in people with CF [164,167].

PULMONARY EXACERBATIONS

A reduction in the incidence and/or risk of pulmonary exacerbations has been shown in people with CF taking *Lactobacillus* probiotic supplements as a single strain/species [165,168,170,171].

Overall there were no beneficial effects of probiotics on FEV_1 [165,167,168,171]; inflammatory markers IL-8 and TNF-α [167,168,171]; or nutritional status as measured by BMI [165,167,171].

Assessment

DIET

Current or previous use of probiotics and their effects should be noted as part of a nutrition assessment. Probiotic intake may be from a supplement, in tablet, capsule or powder form and/or as a component in foods such as some yoghurts and fermented dairy drinks.

Many yoghurts contain live-active *Lactobacillus* cultures and are considered functional food products, however, most are not considered probiotics *per se*. The live cultures are added to milk to make yoghurt and are often called 'starter cultures'. A yoghurt therefore is not necessarily a probiotic unless it is fortified with an adequate number of viable bacteria shown to exert benefit in controlled trials [708].

CLINICAL

SAFETY CONSIDERATIONS

Definitive data on the safety of probiotics is limited. Species of *Lactobacilli* and *Bifidobacteria* are normal residents of, or common transients through, the human digestive system and as such do not display infectivity or toxicity [703]. These lactic bacteria are generally considered safe for oral consumption as part of foods and supplements for the generally healthy population and at levels traditionally used [703].

Overall there does not appear to be a risk in using probiotics however the reporting of side effects and adverse events in studies is generally poor. A large systematic review of probiotic safety in a range of population groups and a review in immune compromised adults, found no significant effect of probiotics on adverse events experienced [718,719]. However the literature is not well equipped to answer questions on the safety of probiotic interventions with confidence [718]. Until there is more robust evidence regarding the safety of probiotics in CF, they should continue to be used with caution in high risk patients such as those with severe lung disease [707]. Care should also be taken administering probiotics to those with venous catheters due to risk of sepsis [719].

Intervention

Should routine or targeted use of probiotic supplements be recommended for people with CF? PICO 15.1.2

[Grade C] The body of evidence to support health benefits from probiotic supplementation in CF is growing, however there is insufficient high quality evidence to support the *routine* or *targeted* supplementation of probiotics in individuals with CF. [164-171]

There is insufficient evidence at this time to recommend any specific probiotic species and strain, dose or frequency, as being the most promising for improving health outcomes in CF. Large well powered randomised controlled trials investigating specific probiotic strains and duration of probiotic supplementation on individual health outcomes in CF are required to further guide clinical practice.

Monitoring & Evaluation

If probiotic supplements are being consumed, it may be helpful to monitor subjective outcomes pre and post supplementation to assess whether they have been effective. The outcomes most amenable to monitoring in the clinical environment and which are important to individuals are functional gastrointestinal symptoms such as bloating, flatulence, abdominal pain and altered bowel motions.

Many probiotic strains do not permanently colonise the gut and at one to four weeks post cessation of the probiotic supplement, the probiotic strain/s are no longer recoverable in the faeces [720]. This is an important point to consider if recommending and reviewing probiotic supplements as they will likely need to be continued in the long-term for a sustained benefit [708]. Future work is required to develop practice resources based on region specific product availability, to assist clinicians to choose the best available probiotic product and regimen [707].

Practitioners are encouraged to ask about complementary therapy use and to be familiar with the evidence for both benefits and adverse reactions [721]. Potential interactions between traditional and complementary medicine and therapy use should be considered.

Practice Points PICO 15.1.1 and 15.1.2

Mechanism of action

- Probiotics are used as a therapeutic option to modulate the composition and actions of the gut microbiota.

Probiotic species, strain and dose

- Mechanism of action and efficacy are strain specific.
- Insufficient evidence to recommend any particular probiotic species or strain, single or mixed, as being superior for beneficial health outcomes in CF.
- The beneficial dose of probiotics varies depending on the particular species and strain used and the reported benefit – in most cases dose and duration should be based on manufacturer's recommendation.

Other considerations

- Impact on burden of treatment and medication adherence.
- Cost – probiotics can be expensive and not subsidised in Australia or New Zealand.
- Concerns regarding reported variability in quality control, efficacy and viability of probiotic microbes in different products.
- Storage – probiotics are sensitive to temperature, air, light and moisture and often require refrigeration.
- Probiotics are often marketed via their trade name (e.g. *Lactobacillus rhamnosus* is marketed as *Lactobacillus GG).*
- Recommend that if trialled, probiotics are taken for at least 4 weeks. If after this time they have no impact on symptoms, cease or trial an alternative preparation.
- Potential health benefits are thought to subside shortly after supplementation is ceased.
- Use probiotics with caution with high risk patients such as those with severe respiratory function.
- Care should also be taken administering probiotics to those with venous catheters due to risk of sepsis.

Translating into Practice

- Where a trial of a probiotic is indicated or requested, recommend (if possible);

  (i) A probiotic species and strain for which there is evidence for the particular health condition

  (ii) Reputable brand products which contain adequate therapeutic numbers of bacteria [707]

- Recommended dosage and duration of probiotic supplements will vary depending on the probiotic strain used and the health effect it is reported to have. In most cases dose and duration should be based on the manufacturer's recommendation.

- It is most likely that probiotics are required to be taken daily for best effect. Regular consistent intake may be required to achieve ongoing effects.

- The cost can be considerable and therefore it is important that people with CF understand the limitations of the available evidence which prevent clinicians from making specific product recommendations with certainty [707].

- Recommend that probiotics if trialled are taken for at least 4 weeks and if they do not work to try another brand or stop taking them [722].

- It is important to note that probiotic products may be identified, particularly from a marketing perspective, by their trade name; for example: LGG® rather than by the genera, species and strain.

- Probiotics are very sensitive to temperature, air, light and moisture and need to be stored correctly to ensure that they contain sufficient live organisms and remain viable. Read the package for storage instructions. Buy probiotics well before the expiration date as the longer a product has been sitting on the shelf the lower the number of viable microorganisms.

  The probiotic product should indicate the number of live cells of the probiotic strain/s it contains. For example: 6.5 billion or 6.5 x 10^9. The dose of a probiotic, instead of a number of milligrams or grams as used for a medicine in a tablet, is the number of cells or CFUs. CFUs stands for colony-forming units and is the way in which, the number of probiotic microbes is measured and described. It is an estimate of the number of "viable" bacteria or fungal cells in a sample.

15.2 Glutathione

C. Miles

Glutathione is a thiol-containing tripeptide, found in both plants and animals, with a number of important biological functions. It is the most abundant intracellular antioxidant and is synthesised by the liver from dietary cysteine sources [173]. Dietary sources of cysteine include meat, dairy, poultry, fish and soy-based products. Cysteine is a non-essential amino acid as it can be synthesised in the body.

Glutathione is a water-soluble antioxidant and therefore has important functions in the epithelial lining fluid of the lungs and intestines, the primary function of which is to inhibit free radicals [356]. Glutathione also plays a pivotal role in the immune system, particularly for chemotaxis and phagocytosis [356] as well as in ameliorating gastrointestinal inflammation[172].

Disease Aetiology

Reduced glutathione levels in the blood, neutrophils, lymphocytes and epithelial lining fluid have been reported in people with CF [173]. This profound glutathione depletion is believed to affect neutrophil recruitment to the lungs of people with CF and may contribute to the chronic inflammatory response described in these patients [173]. Total glutathione levels can be 10-50% of normal and therefore people with CF may not be receiving the full antioxidant or mucolytic benefits of glutathione [723]. Research has also shown that low levels of glutathione can lead to the release of

pro-inflammatory cytokines and in combination with affected neutrophil recruitment, may partly explain the excessive inflammation observed in CF [723].

A number of forms of glutathione supplementation have been trialled in humans including reduced glutathione and a glutathione precursor N-acetylcysteine. The precursor provides the amino acid cysteine for the replenishment of systemic glutathione. Both local treatments (inhalations) and systemic administration (oral formulations) of glutathione and N-acetylcysteine have been proposed to be of benefit to people with CF [356].

Assessment

DIET

Intake of glutathione supplements and reported effects in people with CF should be noted as part of a dietary assessment.

Intervention

Does antioxidant supplementation with oral glutathione or N-acetylcysteine improve nutritional and/or respiratory status in people with CF? PICO 15.2

[Grade C] Dietary supplementation with oral antioxidant glutathione or its precursor N-acetylcysteine may improve nutritional status in individuals with CF. There is inconsistent evidence to suggest that dietary supplementation of either of these treatments improves respiratory status. The currently available evidence does not support the use of glutathione therapy in people with CF [78,172-176].

Studies investigating antioxidant supplementation with oral glutathione or its precursor N-acetylcysteine in people with CF are heterogeneous in nature with varying formulations, doses, durations and outcome measures studied, making meta-analysis and consensus recommendations difficult [356].
There is limited evidence from a small case series study [176] including adults and children and a larger RCT including children only [172] that oral glutathione may improve weight percentile and BMI [176] and weight, height and BMI percentiles and z-scores [172].

Studies investigating effects of oral glutathione and its precursor N-acetylcysteine on improvements in respiratory function found inconsistent results for improvements in FEV_1 [174-176] pulmonary exacerbations [173,176] and sputum neutrophils [173,175]. There were no significant improvements in inflammatory markers with supplementation of oral glutathione or N-acetylcysteine [173-175].

Monitoring and Evaluation

Of the completed trials using glutathione and N-acetylcysteine supplementation in people with CF, a number of CF-related mild-moderate adverse events have been reported including gastrointestinal symptoms and pulmonary exacerbations [172-174,176]. Dauletbauev et al. (2009) reported one serious adverse event of a gastrointestinal bleed, however, it remains unclear as to whether this was related to N-acetylcysteine supplementation [174].

Practice Points PICO 15.2

Mechanism of action

- Glutathione is a water-soluble antioxidant.
- N-acetylcysteine provides the amino acid cysteine (non-essential amino acid) for systemic glutathione replenishment.

Sources of supplementation

- Dietary sources of cysteine include meat, dairy, poultry, fish and soy-based products.
- There is insufficient evidence to support the use of glutathione therapy in CF.

Other considerations

- Impact on burden of treatment and medication adherence

15.3 Coconut Oil

C. Miles & J. Heyward

Coconut oil has had a recent resurgence in both mainstream and CF diets with health claims reporting benefits of coconut oil in the prevention or mitigation of a wide range of health conditions. In terms of CF, the health claims relate specifically to the medium-chain triglyceride (MCT) properties of coconut oil and the hypothesis that coconut oil is more easily absorbed in people with pancreatic insufficiency.

Coconut oil is a type of saturated fat made up of two major saturated fatty acids; lauric acid and myristic acid. Lauric acid is technically a MCT and makes up approximately half of the fatty acids constituents in coconut oil. Whilst lauric acid is considered a MCT, it is metabolised differently and in digestion, behaves more like a long chain fatty acid. Approximately 4% of the fatty acids found in coconut oil behave as true MCT. Conversely, commercially manufactured MCT oils, which are generally derived from coconut or palm oils, contain approximately 95% MCT [724].

Assessment

DIET

Intake of coconut oil and reported effects in individuals with CF should be noted as part of a dietary assessment.

Intervention

Is there evidence that dietary supplementation with coconut oil improves nutritional status in pancreatic insufficient people with Cystic Fibrosis? PICO 15.3

[Ungraded] There is insufficient evidence to support a CF-specific recommendation

At present no experimental trials of coconut oil supplementation for improving health outcomes in individuals with CF have been conducted.

Monitoring and Evaluation

People taking coconut oil should be monitored for potential side effects such as loose bowel motions.

Practice Points PICO 15.3

Coconut oil composition:

- Lauric acid (45 - 48%) – medium chain triglyceride (MCT)
- Myristic acid (14 - 18%) – long chain triglyceride (LCT)

Lauric acid is considered a MCT, however, it is metabolised differently. In digestion, lauric acid behaves more like a long chain fatty acid.

Commercially manufactured MCT oils are generally derived from coconut or palm oils and contain approximately 95% MCT.

15.4 Herbal Supplements

C. Miles

The use of herbal supplements in people with CF is based upon the hypothesis that herbal products and their components have antioxidant and/or antimicrobial properties [725]. The most common herbal supplements that have been reviewed in the literature for people with CF are garlic, curcumin and ginseng.

Garlic has long been recognised among Chinese medicine and natural therapists for its medicinal and in particular antimicrobial properties. *In vitro* and animal studies have demonstrated that garlic has an inhibitory effect on the growth of *pseudomonas aeruginosa*. It has been hypothesised that garlic supplementation in individuals with CF and chronic *pseudomonas aeruginosa* infection may render this pathogen less virulent and more susceptible to the action of antibiotics [177,726].

Curcumin is a component of the Indian spice turmeric and has been extensively examined in the literature for its antioxidant and anti-inflammatory properties [727]. A number of *in vitro* and animal studies have investigated the role of curcumin in increasing CFTR-regulated channel activity in CF, with inconclusive results [728-735].

Ginseng is thought to have antioxidant, antimicrobial and immune-modulating effects [725]. In vitro and animal studies of ginseng supplementation have demonstrated that like garlic, ginseng can have an inhibitory effect on the growth of *pseudomonas aeruginosa* [736,737].

Assessment

DIET

Intake of herbal supplements and reported effects in individuals with CF should be noted as part of a dietary assessment.

Intervention

Is there evidence that dietary supplementation with specific herbal products or their components improves health outcomes in people with Cystic Fibrosis? PICO 15.4

[Grade D] There is no evidence that dietary supplementation with specific herbal products or their components improve health outcomes in individuals with CF [177].

A double-blind, placebo-controlled RCT in 26 children and adults with CF chronically infected with pseudomonas aeruginosa investigating the effect of garlic supplementation on lung function found a small improvement in lung function, weight and symptom score. These findings did not reach statistical significance [177]. Adverse events were reported to be mild and were either predictable side effects of garlic supplementation or intrinsic features of CF [177].

To date no human trials of curcumin or ginseng supplementation have been conducted in people with CF.

Monitoring and Evaluation

People with CF should be encouraged to discuss herbal supplement use with their treating team. If an individual with CF chooses to take herbal supplements, they should be monitored for both adverse and positive effects. Post lung transplant, there are a large number of drug-nutrient interactions between complementary and alternative medicines and medications used, therefore all supplements should be clinically indicated and confirmed with the treating team, including pharmacy, prior to commencement. Refer to Chapter 16 for more information.

Practice Points PICO 15.4

People with CF should be encouraged to discuss herbal and complementary therapies with their interdisciplinary CF team prior to commencing any form of supplementation. Specific enquiry by the CF pharmacist or dietitian may be helpful. Limited evidence surrounding dosing, safety or efficacy of most herbal supplements.