Providing the evidence for the 2017 Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand

TECHNICAL REPORT
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**T1.0 Introduction**

This technical report accompanies the ‘2017 Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand’, developed by cystic fibrosis dietitians in conjunction with the Thoracic Society of Australia and New Zealand (TSANZ). The report provides a detailed record of the evidence review process. More specifically, it outlines:

- the guideline development process and methodology (see T2.0 guideline development),
- the clinical questions covered (see T2.3 development of practice questions),
- detailed summary of studies answering each PICO question (see T5.0 evidence review),
- the quality assessment tools used (appendices B and C American Dietetic Association quality assessment tools), and
- an overarching timeline of the guideline development process (see T4.0 timeline).

A simplified version of the guideline development process appears in the methods section of the guideline itself.

**T1.1 Purpose, Goals and Objectives**

This guideline document has been created to:

- ensure current best-practice guidelines for management of nutrition and pancreatic enzyme replacement therapy (PERT) are accessible to all health professionals providing care to people with CF and their families/whanau;
- ensure the nutritional and PERT education and care provided to all infants, children and adults with CF is evidence based where possible, and reflects current knowledge;
- standardise the nutritional and PERT care of infants, children and adults with CF;
- be widely and readily available in order to support isolated practitioners; and
- promote nutritional and PERT care as a priority in service provision to people with CF.

The **goals** of the guideline document are to:

- facilitate optimal outcomes for all infants, children and adults with CF by promoting best practice in clinical nutrition; and
- promote consistency and equity of healthcare and evidence based practice throughout Australia and NZ.

The **objective** of this guideline is to provide guidance to practitioners to enable them to:

- implement comprehensive and timely nutrition assessments in order to improve and maintain healthy living standards and identify nutritional deterioration early;
- optimise the management of nutrition and PERT, including the management of concurrent diseases and complications;
- support people with CF to achieve and maintain optimal nutritional status;
- encourage people with CF to follow a healthy diet tailored to their individual CF needs and to have positive eating behaviours; and
- improve quality of life of the person with CF, their carer/carers, and family/whanau.

**T2.0 Guideline Development Process**

In July 2012, a steering group comprised of Australian and New Zealand Dietitians, with clinical experience in assessing evidence and in the nutritional management of cystic fibrosis (CF), was formed to update the 2006 ‘Australasian clinical Practice Guidelines for Nutrition in Cystic Fibrosis’ (Dietitians Association of Australia, 2006). Shortly afterwards, in January 2013, a group of clinical experts and consumers was convened to provide specific content expertise. To better describe the scope of the updated guideline, the title was changed to the ‘Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand’. The nutrition guidelines project was completed by a volunteer workforce, with limited financial (<$5000) support being provided for teleconference meetings.
**T2.1 Guideline Development Group**

The primary custodian of the '2017 Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand is TSANZ. The following professional organisations were collaborators:

- Dietitians Association of Australia (DAA)
- Dietitians New Zealand (DNZ)
- Cystic Fibrosis Australia (CFA)
- Cystic Fibrosis Association of New Zealand (CFANZ)

Following a consultation process with all the above mentioned stakeholders, the first step in this project was formation of the dietitian steering group (July 2012). Expressions of interest (EOI) were circulated to all Australian and New Zealand dietitians who specialised in managing CF and to the broader dietetic community through the DAA and DNZ (see appendix A: EOI for the dietitian steering group). Acceptance to the dietitian steering group was based on merit.

The dietitian steering group was responsible for the overall management and strategic leadership of the guideline development process; later, they were to also become the authorship group. On the 29th November 2012, the steering group submitted a project proposal for the development of these nutrition guidelines to the TSANZ Clinical Care and Resources Subcommittee. This proposal was successful with TSANZ agreeing to champion the project, providing support with evidence review processes where necessary. In 2014, in collaboration with the interdisciplinary clinical expert committee, a decision was made to submit the project proposal to the National Health Research Medical Council (NHMRC) so that on completion the guidelines could be considered for their approval. The dietitian steering group was predominantly made up of dietitians however, three members of the interdisciplinary group provided sufficient input into the guidelines to be considered authors and thus part of this group. The dietitian steering group reported to the interdisciplinary clinical expert committee for feedback and consultation on the guidelines.

The interdisciplinary expert committee was formed in January 2013, following the distribution of EOIs through TSANZ and other professional organisations (see appendix B: EOI for the interdisciplinary clinical expert committee’). Membership of the interdisciplinary expert committee was comprised of medical, nursing allied health and consumer representatives. The responsibilities of the interdisciplinary group were to provide expert knowledge and guidance in their special areas, provide input into the clinical questions being covered, to help develop practice recommendations and to provide feedback on drafts of the guidelines and other publications.

**T2.2 Steps in preparing the clinical practice guidelines to NHMRC criteria**

The ‘2011 NHMRC standard for clinical practice guidelines document’ (National Health and Medical Research Council, 2011) was used as a reference document to ensure high standards as required by NHMRC for guideline development were met. Where more detailed information on specific guideline development processes were required (e.g. how to review the evidence) then other NHMRC resources and handbooks were consulted (National Health and Medical Research Council, 1999, National Health and Medical Research Council, 2000a, National Health and Medical Research Council, 2000b). Checklists contained in these documents were completed during the final stages of the guideline development process.

For most topic area (i.e. Guideline Chapters 4, 6, 7, 8, 9, 10, 11, 13, 14, 15) the steps below were followed:

1. Clinical (PICO) questions were set and confirmed
2. List of keywords created
3. Systematic literature searches for each clinical question were undertaken
4. Studies screened for suitability
5. Studies appraised both quality and level of evidence by two independent appraisers
6. Data extracted for each included study
7. Summary spreadsheet of all included studies completed inclusive of evidence and quality summaries
8. Check for discrepancies between appraisers carried out
9. Discrepancies reviewed by methodological expert/s
10. Evidence matrices, statement of evidence and recommendations/practice points drafted and graded
11. Leadership team (i.e. project co-chairs, project facilitators, methodological experts) reviewed evidence matrices and recommendation statements for consistency for consistency with the evidence
12. Evidence statements and practice recommendations/points approved by the steering group and the interdisciplinary clinical expert committee
13. Draft chapter content written up

Each guideline development step is described in greater detail in the following sections. Templates we created to help undertake these tasks are also provided (see appendices C and F). Due to low levels of evidence available, and/or contentious nature of subject matter and/or continuously evolving changes to practice – the following chapters 5 nutrition assessment, 12 CF-related diabetes and 16 lung transplantation were completed as narrative reviews.

In relation to the mandatory NHMRC requirement C3 ‘The population groups specified in the search strategy include Aboriginal and Torres Strait Islander peoples and any population subgrats that have been identified’ (National Health and Medical Research Council, 2011), it should be noted that CF almost exclusively affects individuals of Caucasian decent with an average life expectancy of 37 years. Thus, the authorship group did not feel that it was appropriate to specifically search for literature on Aboriginal and Torres Strait Islanders or for older individuals. Search strategies did ensure that both paediatric and adult populations were covered.
T2.3 Development of Practice Questions

In August 2012, the dietitian steering group proposed a wide range of clinical questions. The clinical questions and their search strategies focused on the identified relevant components of nutrition management, and encompassed screening for nutrition-related problems (e.g. CF-related diabetes, reduced bone mineral density), nutrition diagnosis (e.g. undernutrition, vitamin D deficiency), prevention (e.g. of undernutrition, DiOS, salt depletion), and treatment (various nutrition interventions are included. Input from the interdisciplinary expert committee helped to further refine the PICO questions. All proposed questions were reviewed on the basis of their purpose, scope and clinical importance to the target audience and were structured according to the PICO (populations, interventions, comparisons, outcomes) framework. A list of the final PICO questions can be seen in table 1, below.

It is worth noting that screening, prevention and diagnosis of CF are outside the scope of this guideline.

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Section</th>
<th>PICO question</th>
<th>Aetiology</th>
<th>Assessment</th>
<th>Intervention</th>
<th>Monitoring</th>
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<tbody>
<tr>
<td>1 Introduction</td>
<td>Nil</td>
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<td>2 Methods</td>
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<td>3 Role of nutrition</td>
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<td>4 Service Delivery</td>
<td>4.2</td>
<td><strong>What is the level of dietetic service required for people with CF?</strong></td>
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<td>5 Assessment</td>
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<td>6 Nutrition interventions</td>
<td>6.1.1</td>
<td><strong>Compared to standard nutritional care, do behavioural interventions around food and mealtimes improve behaviours, diet variety, and weight or nutrition status in children with CF?</strong></td>
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<td></td>
<td></td>
<td><strong>When should behavioural interventions around food and mealtimes be considered for children with CF?</strong></td>
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<td></td>
<td></td>
<td><strong>Do appetite stimulants, megesterol acetate and cyproheptadine, improve nutritional status in CF?</strong></td>
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<td></td>
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<td><strong>Does the use of recombinant growth hormone improve nutritional status in pre-pubertal people with CF?</strong></td>
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<td><strong>Is there any rationale for the use of commercial oral nutritional supplements over food or mealtime strategies to improve nutritional intake, weight or pulmonary function in CF?</strong></td>
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<td><strong>Should enteral feeding be considered to improve nutrition outcomes for people with CF?</strong></td>
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<td><strong>Should enteral feeding be considered to improve pulmonary status in people with CF?</strong></td>
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<td></td>
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<td><strong>When should enteral feeding be introduced for someone with CF?</strong></td>
<td></td>
<td>✓</td>
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<td></td>
<td><strong>What is the ideal enteral feeding regimen for someone with CF?</strong></td>
<td></td>
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<td><strong>What are the risks associated with enteral feeding in CF compared to the general population?</strong></td>
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<td>7 Macronutrients</td>
<td>7.1.1</td>
<td><strong>Are energy requirements elevated in the CF population compared to the general population?</strong></td>
<td></td>
<td>✓</td>
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<td></td>
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<td><strong>Are protein requirements elevated in the CF population compared to the general population?</strong></td>
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<td><strong>What is the evidence to support the routine recommendation of a high fat diet for people with CF?</strong></td>
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<td><strong>What are the recommendations for fibre in people with CF?</strong></td>
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<tr>
<td>Chapter</td>
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<td>7.2.1</td>
<td>8.1.1</td>
<td>How should vitamin A be assessed for people with CF?</td>
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<td>8 Fat soluble vitamins</td>
<td>8.1.2</td>
<td>What is the role for routine supplementation of vitamin A in people with CF and pancreatic insufficiency?</td>
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<td>8.1.3</td>
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<td>What vitamin A supplementation dose should be prescribed to treat vitamin A deficiency in people with CF?</td>
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<td>8.1.4</td>
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<td>What is the safe upper limit for vitamin A supplementation in people with CF?</td>
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<td>8.1.5</td>
<td></td>
<td>How often should vitamin A levels be measured in people with CF?</td>
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<td>✓</td>
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<td>8.2.1</td>
<td></td>
<td>Is vitamin D status associated with measures of respiratory health (lung function, pulmonary exacerbations, markers of inflammation) in people with CF?</td>
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<td>8.2.2</td>
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<td>Is there an ideal serum 25-hydroxyvitamin D level to aim for in people with CF?</td>
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<td>8.2.3</td>
<td></td>
<td>Is the time of year, specifically the season, important when measuring and interpreting an individual’s serum vitamin D level?</td>
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<td>8.2.4</td>
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<td>Should supplemental vitamin D be given to individuals with pancreatic sufficient cystic fibrosis as part of routine care?</td>
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<td>✓</td>
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<tr>
<td>8.2.5</td>
<td></td>
<td>What doses of vitamin D are needed to prevent deficiency in people with CF?</td>
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<td>✓</td>
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<td>8.2.6</td>
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<td>What doses of vitamin D are needed to correct deficiency in people with CF?</td>
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<td>8.3.1</td>
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<td>How should vitamin E levels be assessed for people with CF?</td>
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<td>8.3.2</td>
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<td>What is the role for supplementation of Vitamin E in people with CF?</td>
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<td>8.3.3</td>
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<td>What is the safe upper limit for vitamin supplementation for people with CF?</td>
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<td>8.3.4</td>
<td></td>
<td>How often should vitamin E levels be measured in people with CF?</td>
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<td>8.4.1</td>
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<td>How should vitamin K status be assessed for people with CF?</td>
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<td>8.4.2</td>
<td></td>
<td>Should vitamin K supplementation be recommended for all pancreatic insufficient people with CF?</td>
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<td>8.4.3</td>
<td></td>
<td>How often should vitamin K levels be measured in people with CF?</td>
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<td>Chapter</td>
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<td>9 Minerals</td>
<td>9.1.1</td>
<td>How should iron status be assessed in people with CF?</td>
<td></td>
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<td>9.1.2</td>
<td>How should iron deficiency be treated in people with CF?</td>
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<td>9.1.3</td>
<td>Is iron supplementation contraindicated in people with CF who are chronically colonised with pseudomonas aeruginosa?</td>
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<td>9.2.1</td>
<td>Does supplementing magnesium above the RDI improve nutrition and/or respiratory outcomes in people with CF?</td>
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<td></td>
<td>9.4.1</td>
<td>How do environmental factors and exercise impact on sodium requirements for people with CF compared to those without CF?</td>
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<td>✓</td>
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<td>9.4.2</td>
<td>What is the recommended daily sodium requirement for people with CF compared to those without CF?</td>
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<td>9.5.1</td>
<td>How should Zinc status be assessed for people with CF?</td>
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<td>9.5.2</td>
<td>What are the recommendations for zinc supplementation in people with CF?</td>
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<td>9.5.3</td>
<td>What is the safe upper limit for zinc supplementation in CF?</td>
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<td>10 Pancreatic enzyme replacement therapy</td>
<td>10.1.1</td>
<td>Does gastric emptying rate impact PERT efficacy in people with CF?</td>
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<td>✓</td>
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<td>10.1.2</td>
<td>Does the timing of PERT administration in relation to a meal impact PERT efficacy in people with CF?</td>
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<td>10.1.3</td>
<td>How should PERT be dosed for people with CF to support optimal fat absorption?</td>
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<td>10.1.4</td>
<td>Is there evidence to support the use of acid suppression medications to improve PERT efficacy for people with CF?</td>
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<td>10.1.5</td>
<td>What are the risks and long-term health implications associated with phthalate exposure via PERT to Australian and NZ people with CF?</td>
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<tr>
<td>11 Gastrointestinal and Hepatobiliary Considerations</td>
<td>11.1.1</td>
<td>What are the nutrition considerations for the management of gastro-oesophageal reflux (GOR) in CF?</td>
<td></td>
<td>✓</td>
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<td>11.2.1</td>
<td>What are the nutrition considerations for the prevention and management of Distal Intestinal Obstruction Syndrome (DIOS) in Cystic Fibrosis (CF)?</td>
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<td>✓</td>
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<td>11.2.2</td>
<td>What are the nutrition considerations for the prevention and management of constipation in CF?</td>
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<td>Chapter</td>
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<td>PICO question</td>
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<td>11.3.1</td>
<td>What are the nutrition considerations for colon cancer screening in CF? PICO</td>
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<td>11.4.1</td>
<td>Should vitamin K supplementation be recommended for all people with CF related liver disease?</td>
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<td>11.4.2</td>
<td>What are the requirements for effective supplementation in episodes of Vitamin A deficiency in patients with CF related liver disease?</td>
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<td>12 CF-related diabetes</td>
<td>Nil – narrative review only</td>
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<td>13 CF-related bone disease</td>
<td>13.1</td>
<td>How and when should bone health and disease be assessed for people with CF?</td>
<td>✓</td>
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<td>13.2</td>
<td>What are the calcium requirements in CF to reduce the risk of low bone mineral density?</td>
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<td>13.3</td>
<td>Does supplementing calcium above the RDI improve bone mineral density in CF?</td>
<td>✓</td>
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<td>14 Special Considerations</td>
<td>14.1.1</td>
<td>What are the nutrition considerations of the management of pregnancy in CF?</td>
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<td>14.1.2</td>
<td>What recommendations around vitamin A supplementation and monitoring should be provided to females with CF who are pregnant or planning a pregnancy?</td>
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<td>14.2.1</td>
<td>What are the implications of Ivacaftor on nutritional status in children &gt;2 years and adults with cystic fibrosis who have at least one G551D or other gating mutation allele?</td>
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<td></td>
<td>14.2.2</td>
<td>Are there any other nutritional considerations (energy, salt intake) that practitioners should take into consideration for people on Ivacaftor therapy?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.2.3</td>
<td>What is role of gastrointestinal and/or other nutritional outcome measures in individuals with CF receiving Ivacaftor therapy?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Complementary Therapies</td>
<td>15.1.1</td>
<td>Does dietary supplementation with probiotic genus Lactobacillus improve nutritional and/or respiratory status in individuals with CF?</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.1.2</td>
<td>Should routine or targeted use of probiotic supplements be recommended for people with CF?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.2</td>
<td>Does antioxidant supplementation with oral glutathione or its precursor N-acetylcysteine improve nutritional and/or respiratory status in individuals with Cystic Fibrosis?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.3</td>
<td>Is there evidence that dietary supplementation with coconut oil improves nutritional status in pancreatic insufficient individuals with Cystic Fibrosis?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapter</td>
<td>Section</td>
<td>PICO question</td>
<td>Aetiology</td>
<td>Assessment</td>
<td>intervention</td>
<td>Monitoring</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>15.5</td>
<td></td>
<td>Is there evidence that dietary supplementation with specific herbal products or their components improves health outcomes in individuals with CF?</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>16</td>
<td>Transplantation</td>
<td>Nil – narrative review only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Implementation</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Evidence Matrices</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
T2.4 Systematic Search Strategy

Electronic databases (Embase, CINAHL, PubMed, AustHealth, and Cochrane) were searched from January 2002 to August 2015 for each clinical practice question. Key recently published research, after August 2015, was also included if it was of vital significance to recommendations and/or practice points. This broad search strategy was developed by the project co-chairs with assistance from the methodological experts and appropriately trained medical librarians.

Up until June 2015, all systematic literature searches were completed by either the project chair or one of the project facilitators. In July 2015, in an effort to enhance the literature search process, a medical librarian assumed responsibility of completing the remaining literature searches. Between January 2012 and June 2016, twice yearly automatic updates of new literature that met the search criteria were set up to ensure that final guideline recommendations were contemporary at the time of publication. In addition, all literature searches were completed within 12 months of the public consultation period.

T2.5 Screening of literature results

All retrieved literature searches underwent a two stage screening process against pre-defined inclusion and exclusion criteria.

First screening

The first screening round was completed by the one or two of the project co-chairs/project facilitators. Screening involved review of titles and abstracts of all retrieved journal articles. All irrelevant, incorrect, non-English, and duplicates were removed (i.e. articles not meeting inclusion criteria).

Second screening

Full articles were then retrieved and a second screen was undertaken. The section leader of the topic and one other group member assessed each article for inclusion against the pre-defined inclusion and exclusion criteria for each PICO question. Journal articles meeting inclusion criteria were then forwarded on to members of the dietitian steering group for critical appraisal and data extractions.

T2.6 Literature Critique, Development of Evidence Statements and Grading of Recommendations

Each journal article was appraised independently by two members of the dietitian steering group for level of evidence and quality. Levels of evidence were rated using the NHMRC criteria as shown in table 2a and quality rankings assigned using the American Dietetic Association (ADA) tool as shown in table 2b (i.e. positive, neutral or negative quality)(National Health and Medical Research Council, 2009, American Dietetic Association, 2005). A completed example of a data extraction and quality assessment for one study, Beghin et al. 2005 can be found in the appendix C (CF Study Template) and appendix D (ADA quality criteria checklist for primary research). Likewise, the ADA quality assessment tool used to assess review articles is provided in appendix E. If consensus was unable to be reached after the first review, the dietitians critiquing the evidence were asked to complete a second review using the same tools, and if required a third reviewer (i.e. methodological expert) critiqued the article using the ADA tool and acted as an arbitrator to make the final determination of study quality.
The body of evidence for each practice question was synthesised into an evidence statement and rated using the NHMRC evidence matrix as shown in table 2c (National Health and Medical Research Council, 2009). When forming the practice recommendations, consideration was given to the volume of evidence, consistency of results and potential clinical impact. Generalisability and applicability of the recommendation to Australian and New Zealand healthcare context was also considered, including relatability to both the ‘Cystic Fibrosis Standards of Care for Australia’ and ‘Cystic Fibrosis Standards of Care New Zealand’ (Bell and Robinson, 2008, Cystic Fibrosis Association of New Zealand, 2011). A summary spreadsheet was developed to collect and collate the evidence and quality summary statements for each clinical practice question – these are shown later in this technical report.

Table 2a. NHMRC Levels of Evidence for Intervention and Prognosis Studies (National Health and Medical Research Council, 2009).

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Intervention Study</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Evidence obtained from a systematic review of all relevant randomised controlled trials</td>
<td>A systematic review of level II studies</td>
</tr>
<tr>
<td>Level II</td>
<td>Evidence obtained from at least one properly designed randomised controlled trial</td>
<td>A prospective cohort study</td>
</tr>
<tr>
<td>Level III-1</td>
<td>Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)</td>
<td>All or none (All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect)</td>
</tr>
<tr>
<td>Level III-2</td>
<td>Evidence obtained from comparative studies with concurrent control and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group</td>
<td>Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial</td>
</tr>
<tr>
<td>Level III-3</td>
<td>Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel group</td>
<td>A retrospective cohort study</td>
</tr>
<tr>
<td>Level IV</td>
<td>Evidence obtained from case studies, either post-test or pre- and post-test.</td>
<td>Case series, or cohort study of persons at different stages of disease</td>
</tr>
</tbody>
</table>

Table 2b Assessing primary research quality using tools from the ADA evidence analysis manua (American Dietetic Association, 2005).

<table>
<thead>
<tr>
<th>Quality</th>
<th>Definition of Quality for Primary Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>If most of the answers to the above validity questions are yes (including criteria 2,3,6, 7 and at least one additional yes), the report should be designated with a plus symbol (+)</td>
</tr>
<tr>
<td>Neutral</td>
<td>If the answers to validity criteria questions 2,3,6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral symbol (Ø)</td>
</tr>
<tr>
<td>Negative</td>
<td>If most (six or more) of the answers to the above validity questions are no, the review should be designated with a minus symbol (-)</td>
</tr>
</tbody>
</table>

Table 2c Assessing review article quality using tools from the ADA evidence analysis manual (American Dietetic Association, 2005).

<table>
<thead>
<tr>
<th>Quality</th>
<th>Definition of Quality for Review Articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>If most of the answers to the above validity questions are yes (must include criteria 1,2,3,4), the review should be designated with a plus symbol (+)</td>
</tr>
<tr>
<td>Neutral</td>
<td>If the answers to any of the first four validity questions (1-4) is no, but other criteria indicate strengths, the review should be</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality</th>
<th>Definition of Quality for Review Articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>If most of the answers to the above validity questions are yes (must include criteria 1,2,3,4), the review should be designated with a plus symbol (+)</td>
</tr>
<tr>
<td>Neutral</td>
<td>If the answers to any of the first four validity questions (1-4) is no, but other criteria indicate strengths, the review should be</td>
</tr>
</tbody>
</table>
**Table 2d NHMRC Evidence Matrices and Forming Grades of Recommendation (National Health and Medical Research Council, 2009)**

<table>
<thead>
<tr>
<th>Component</th>
<th>A - Excellent</th>
<th>B - Good</th>
<th>C - Satisfactory</th>
<th>D - Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence base</td>
<td>-</td>
<td>One or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias</td>
<td>One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias</td>
<td>Level IV studies, or level I to III studies/SRs with a high risk of bias</td>
</tr>
<tr>
<td>Consistency</td>
<td>All studies consistent</td>
<td>Most studies consistent and inconsistency may be explained</td>
<td>Some inconsistency reflecting genuine uncertainty around clinical question</td>
<td>Evidence is inconsistent</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>Very large</td>
<td>Substantial</td>
<td>Moderate</td>
<td>Slight or restricted</td>
</tr>
<tr>
<td>Generalisability</td>
<td>Population/s studied in body of evidence are the same as the target population for the guidelines</td>
<td>Population/s studied in body of evidence are similar to the target population for the guideline</td>
<td>Population/s studied in body of evidence differ to the target population for guideline but it is clinically sensible to apply this evidence to target population</td>
<td>Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population</td>
</tr>
<tr>
<td>Applicability</td>
<td>Directly applicable to Australian healthcare context</td>
<td>Applicable to Australian healthcare context with few caveats</td>
<td>Probably applicable to Australian healthcare context with some caveats</td>
<td>Not applicable to Australian healthcare context</td>
</tr>
</tbody>
</table>

**T2.7 Weak/low-quality Evidence and Evidence Gaps**

The ‘2017 Guidelines’ are mostly based on lower level evidence (i.e. NHMRC recommendation levels C and D). Many nutritional studies are not completed in a blinded fashion. Furthermore, like other areas of CF research, often the sub group that would have been likely to benefit from intervention were excluded for ethical concerns (e.g. there are few randomised control trials (RCTs) of enteral feeding as it would be unethical to not offer treatment to a control arm, where the target group is malnourished. In other words, it would be of poor judgement to withhold the intervention in those allocated to a control group as this would result in a delay in treatment of malnutrition). Until, better quality evidence is available, it is important that lower level evidence is still included to guide best practice.

Poor study quality is another area of concern for guideline developers. A recent review revealed that even when nutritional randomised controlled trials are completed in people with CF that their study quality is often suboptimal (Daitch et al., 2016). More specifically, nutritional randomised RCTs are frequently characterised by lower quality methodology, small sample sizes (insufficient to provide clinically meaningful data), have short intervention timelines and fail to examine outcome parameters that are important to people with CF. The evidence matrices located within this technical report, and also the guideline itself, will help clinicians to identify where and how lower quality evidence has been included in these guidelines.

It is worth bringing the readers attention to the fact that there is little literature in CF that specifically examines, or even evaluates as secondary outcomes issues outlined in the ‘2011 NHMRC standard for clinical practice guidelines document’ (National Health and Medical Research Council, 2011) – more specifically evidence related to:

- culturally and linguistically diverse communities or other groups for whom specific sociocultural factors in treatment or prevention outcomes should be considered;
- consumers’ perceptions and experiences; and
• cost effectiveness and resource implication for practice.

Standard practice for the assessment, monitoring and supplementation of fat soluble vitamins and minerals vary internationally. Where evidence is low this guideline includes considerations from a number of international consensus papers. The recommendations have been formulated from the available evidence, international practice and application to the Australian and NZ environments.

Step 1 Practice points

Where there was insufficient quantity or quality of evidence and recommendations could not be made in the guidelines, practice points developed by consensus of the dietitian authorship group and interdisciplinary clinical expert committee are provided. Dietitians and other disciplines still require guidance to ensure good and consistent clinical practice.

Step 2 Creation of position papers

It is anticipated that in 2018, following the release of these guidelines, that a Delphi process will be completed to formally reach consensus across Australian and NZ CF experts in topic areas where insufficient evidence was identified. Recommendations based on this Delphi process will be published separately as a follow-up position statement.

T2.8 Writing the Content

For each topic area, the section leaders were asked to draft their guideline chapter using the following format (for full template see Appendix F). PICO questions were inserted under the relevant headings with successive numbering, and included evidence grading for each recommendation provided.

- **Title**
- **Introduction**: significance in CF? and why is the topic important? Includes background information.
- **Disease aetiology**: What is the relationship to CF? What are the causes? What does it influence?
- **Assessment**: Diet, clinical and biochemical and laboratory considerations.
- **Intervention**: This section also notes information about implications of any practice recommendations made, including how it may impact usual care, and resource implications
- **Monitoring and evaluation**: How do we know that our care was successful?
- **Translation to practice**: Succinct information supporting practice recommendations
- **References**

Literature used for the background sections (i.e. narrative text) was not systematically reviewed and does not include any clinical recommendations. Background sections were written by the section leaders under direction of the project co-chairs and the interdisciplinary clinical expert committee. Where available and current, existing TSANZ endorsed guidelines and position paper recommendations have been utilised within this guideline. This helps ensure consistency in trans-Tasman clinical practice for people with CF.

The content draft for each chapter was then reviewed by all individuals involved in creating the chapter. Each chapter underwent several iterations until agreement between the members working on these drafts was reached. Completed chapters were then forwarded onto the dietitian steering group, and then onto the interdisciplinary expert committee for final ratification. These approved drafts were what went out to public consultation in November 2016.

T2.9 Peer Review

Throughout the guideline development process comments/feedback on all documents was also sought from dietitians not directly involved in this project through the Australian and New Zealand dietetic professional
associations (i.e. DAA and DNZ). Draft documents were also circulated for comments/feedback to dietitians working at major CF centres.

Prior to being released, the public consultation draft of the guideline was reviewed by members of the TSANZ and content experts as requested by the Clinical Care and Resources Subcommittee (CCRS). Two members of the CCRS committee also critiqued the quality of the final guideline using the AGREEII tool. Additionally, the names of four potential international clinical reviewers with expertise in nutritional aspects of CF have been provided to the NHMRC.

The guidelines were released for public consultation for a period of 30 days in November/December 2016. Feedback submissions were managed by TSANZ.

**T3.0 Incorporating Public Consultation Feedback & Finalising all Documents**

The dietitian steering group held a teleconference for each chapter of the guidelines with the chapter and section leader authors present where possible. Each comment received through public consultation was considered, and either accepted, not accepted or noted. A response for each decision is provided in the public consultation feedback table.

The chapter author or a member of the dietitian steering group then incorporated these changes into each chapter. The steering committee then checked the final version of the chapter against the public consultation feedback table to ensure all changes were addressed accordingly. Final formatting and editing checks were then performed. The lead methodological expert independently went through the entire guideline document at the very end to check for internal consistency and accuracy of statements.

**T4.0 Timeline**

<table>
<thead>
<tr>
<th>Month</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 2011</td>
<td>Reviewing the 2006 ‘Australasian Clinical Practice Guidelines for Nutrition in Cystic’ was briefly discussed at the CF dietitian interest group meeting held at the 9th Australian and New Zealand Cystic Fibrosis Conference in Melbourne. This meeting was led by Christie Graham (Australian convener) who identified a list of people who were interested in taking part. The need to also create supplementary evidence based patient resources as part of the guideline revision was identified.</td>
</tr>
<tr>
<td>June 2012</td>
<td>Expression of interests for dietitian CF guideline steering group circulated to whole DAA and DNZ memberships. All known dietitians working in CF care were also invited to participate via email.</td>
</tr>
</tbody>
</table>
| July 2012     | Meeting held at CFA headquarters Queensland, led by Nicole Saxby (new Australian CF convener):  
- Dietitian steering group voted in by Australian and New Zealand state and national CF conveners.  
- Nicole Saxby voted in to lead the guideline development process  
- Agreement to review guideline through TSANZ  
- Preliminary discussion of topics, including practice based questions  
- Topic areas roughly allocated to contributors and possible sub group leaders identified |
<p>| August – October 2012 | Draft guideline project proposal written by project directors, facilitators and section leaders. |
| September 2012 | Budget estimates submitted to DAA and DNZ for dietitian teleconference meeting |
| October 2012  | Draft project proposal sent to TSANZ, DAA, DNZ, DC, CFA and CFNZ for comment. |</p>
<table>
<thead>
<tr>
<th>Date Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 2012</td>
<td>Project proposal submitted to the TSANZ, approved without modification required. Face to face dietitian steering group meeting Sydney Children’s Hospital to discuss final topic allocations and proposed timeline.</td>
</tr>
<tr>
<td>December 2012 – January 2013</td>
<td>Recruitment of interdisciplinary steering group – through TSANZ and other appropriate professional organisations.</td>
</tr>
</tbody>
</table>
| December 2012 – March 2014 | Stage 1 topics completed  
  - Appetite Stimulants  
  - Minerals (Fe, Ca, Mg, Zn)  
  Full drafts completed, inclusive of review by dietitian steering group and interdisciplinary expert committee.                                   |
| August 2013               | Progress presented at a lunchtime workshop at the 10th Australian and New Zealand Cystic Fibrosis Conference in Auckland.                                                                                       |
| March 2014 – June 2015    | Stage 2 topics  
  - Complications  
    - Gastrointestinal (PERT, reflux, DIOS)  
    - Liver  
    - Bone  
    - CFRD  
  - Complementary therapies  
  - Essential fatty acids  
  - Vitamins A, D, E, K  
  - Nutrition assessment  
  Completed literature search, appraise articles, complete summaries for each evidence article and draft practice recommendations.                          |
| July – August 2015        | Project facilitators edited summaries and practice recommendations (stage 2) to ensure consistent formatting and style. Project facilitator then returned documents to sub-working groups for creation of draft publications. Sub group wrote first drafts of content (stage 2).  
  Review by dietitian steering group and interdisciplinary steering group. Consensus on practice points (stage 2) gained.                                                                       |
| September 2015 – June 2016 | Stage 3 topics (tentative)  
  - Special considerations – Pregnancy  
  - Special considerations – genetic modulators  
  - CF-Related diabetes  
  - Nutrition intervention  
  - Lung transplantation  
  Complete literature search, appraise articles, complete summaries for each evidence article and draft practice recommendations.                                                             |
| July-August 2016          | Project facilitator edited summaries and practice recommendations (stage 3) to ensure consistent formatting and style. Project facilitator to return documents to sub-working groups for creation of draft publications. Sub group wrote up drafts.          |
| October 2016              | Consensus on practice points (stage 2) gained from dietitian steering group and interdisciplinary expert committee.                                                                                       |
| Final drafts of all chapters sent out to interdisciplinary expert committee for approval prior to public consultation.                                                                        |
| December 2016             | Public consultation of complete nutrition guideline  
  AGREEII completed x independent reviewers.                                                                                                                                                               |
| January 2017              | Submitted guideline, administration report, technical report and summary of public consultation feedback to NHMRC.                                                                                           |
References


T5.0 Evidence Review

This section of the technical report outlines the following (where relevant) for each chapter:

- **The clinical questions to be addressed** (outlined as PICOs).
  - The clinical questions to be addressed in each chapter are outlined according one or more PICOs whereby the population, intervention, comparator(s) and outcome(s) where considered when formulating the question.
- **Search terms**
- **Inclusion and exclusion criteria used to select studies for critical appraisal**
- **Evidence tables**
  - Includes a complete reference for each study critiqued
  - Includes the NHMRC level of evidence, ADA quality ranking, study design, sample size, inclusion/exclusion criteria, intervention(s), outcome(s), results, conclusions, author limitations and appraiser limitations for each study
- **Evidence statement matrix**
  - Includes the NHMRC grade of evidence

Chapter 3 **Role of nutrition**
This chapter is a narrative of the role of nutrition in CF.
No clinical questions and PICOs were identified for this chapter.

Chapter 4 **Service delivery**
This chapter is a narrative of CF service delivery.
No clinical questions and PICOs were identified for this chapter.

Chapter 5 **Nutrition assessment**
This chapter is a narrative of the CF nutrition assessment process and considerations.
No clinical questions and PICOs were identified for this chapter.
Chapter 6 Nutrition Interventions

6.1 Undernutrition

PICOs

6.1.1 Compared to standard nutritional care, do behavioural interventions around food and mealtimes improve behaviours, diet variety, and weight or nutrition status in children with CF?
6.1.2 When should behavioural interventions around food and mealtimes be considered for children with CF?
6.1.3 Do appetite stimulants, megestrol acetate and cyproheptadine, improve nutritional status in CF?
6.1.4 Does the use of recombinant growth hormone improve nutritional status in pre-pubertal people with CF?
6.1.5 Is there any rationale for the use of commercial oral nutritional supplements over and above food or mealtime strategies to improve nutritional intake, weight or pulmonary function in CF?
6.1.6 Should enteral feeding be considered to improve nutrition outcomes for people with CF?
6.1.7 Should enteral feeding be considered to improve pulmonary status in people with CF?
6.1.8 When should enteral feeding be introduced for someone with CF?
6.1.9 What is the ideal enteral feeding regimen for someone with CF?
6.1.10 What are the risks associated with enteral feeding in CF compared to the general population?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:

Behavioural interventions:
- Cystic fibrosis, CF, mealtime, dinnertime, food, behavior/s, behaviour/s

Appetite Stimulants:
- Cystic fibrosis, CF, nutrition, diet, appetite stimulants, anabolic agents, anti-depressents, progestational agents, anabolic androgenic steroids, human growth hormone, growth hormone, recombinant human hormone, cyproheptadine, cyproheptadine hydrochloride, dronabinol, metesterol, megestrol acetate, megace OR mirazipine

Oral supplements:
- cystic fibrosis, CF, nutrition, diet, oral supplement/s, oral calorie supplement/s, commercial supplement/s, energy supplement/s, nutrition support

Enteral feeding:
- cystic fibrosis, CF, nutrition, diet, enteral nutrition, enteral, tube feeding, enteral tube feeding

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers

CLINICAL QUESTION
6.1.1 Do behavioural interventions around food and mealtimes improve behaviours, diet variety, and weight or nutrition status in children with CF?

Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammons A &amp; Feise B</td>
<td>NHMRC level I, ADA quality POSITIVE</td>
<td>Meta-analysis (N=230) (119 CF &amp; 111 controls), Age 18.6 months – 8.5 years</td>
<td>Aim: 1. To examine differences in family mealtimes between families with and without a child with CF. 2. Compare global measures of family functioning during mealtime with parent-child microbehaviours specific to feeding to determine if one class of mealtime behaviour is more strongly affected. 3. Are some of the behaviours, in particular meal length and family functioning, related to the child’s health status in the CF group.</td>
<td>Results: 1. Family mealtime differences. Across 4 studies, families with CF were found to have more difficult mealtimes than comparison families (d=-.42, 95% CI=-.68,-.15). Effect was consistent and all studies shared a common effect size (Q=1.03, df=3, p=.79). 2. Global and micro behaviours during mealtime. Global family functioning (n=3) - 90 children with CF vs 89 comparison. All 3 studies reported significant findings. Meta-analysis suggests that areas of family functioning are significantly more impaired in families with a CF child (d=-.68 CI=-.98,-.38). 3. Mealtime behaviours and children. - Weight = child health. - Length of meal + weight status.</td>
<td>Limitations: - Small number of studies. - Studies had small sample size. - Comparing data between studies can be less precise. - Variability restricted as 9 of 10 studies conducted by same research team using 3 independent samples. - Publication bias, possibly studies that are non-significant have not published thus not included. Conflicts of interest: - Nil reported or noted.</td>
</tr>
</tbody>
</table>
behaviours, interactions, family functioning

Conclusions:
• CF families have more difficult mealtimes and a higher level of impairment in family functioning.
• Family functioning appears to be related to weight status of CF child.
• Future interventions should include family functioning, particularly targeting affect management, interpersonal involvement and communication as well as micro behaviours.


<table>
<thead>
<tr>
<th>NHMRC level II</th>
<th>ADA quality</th>
<th>Randomized control trial (NCT00006169)</th>
<th>Aim to evaluate the efficacy of a behavioural nutrition education intervention (B+E), Be in Charge, and compare with nutrition education alone (NO).</th>
<th>Results:</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=79 Children with CF aged 4-12yrs</td>
<td></td>
<td>X9 sessions – parent (physiologist and dietitian), child (postdoctoral fellow or graduate student in psychology)</td>
<td></td>
<td>Children in B+E group had sig lower fat absorption than NO (p=0.02) pre vs post treatment</td>
<td>• Potential for some behavioural strategies to be included in both groups once they returned to standard care</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td></td>
<td>Nutrition education NO</td>
<td></td>
<td>Change in caloric intake pre and post treatment B+E&gt;NO (p&lt;0.001), % of EER B+E&gt; NO (p&lt;0.001)</td>
<td>• Recruitment rate low (44%) thus limiting to those families motivated and able to attend weekly treatment</td>
</tr>
<tr>
<td>• Age 4-12</td>
<td></td>
<td>Parent group: identical to both interventions – calorie content of meals, calorie goals, recommendations, graphs of intake compared with weekly goals</td>
<td></td>
<td>Weight increase B+E&gt;NO (p0.01)</td>
<td>• Even though randomised maintaining binding of participants and therapists difficult</td>
</tr>
<tr>
<td>• CF dx</td>
<td></td>
<td>Child group: fun activities to teach about high energy foods, practice meal, energy goals, trophies for attendance</td>
<td></td>
<td>BMI z score improved B+E &gt;NO (p=0.03)</td>
<td>• Randomisation allocation, sequence and concealment not met and potential for bias</td>
</tr>
<tr>
<td>• Pancreatic insufficient</td>
<td></td>
<td>Behavioural and nutrition B+E</td>
<td></td>
<td>Parent satisfaction:</td>
<td></td>
</tr>
<tr>
<td>• &lt;40th percentile for weight for age or weight for height</td>
<td></td>
<td></td>
<td></td>
<td>For approach used to increase child’s caloric intake, B+E was rated superior (p=0.005) however both groups rated well (&gt;6)</td>
<td></td>
</tr>
<tr>
<td>Exclusion:</td>
<td></td>
<td></td>
<td></td>
<td>2 year follow up:</td>
<td></td>
</tr>
<tr>
<td>• Medical condition affecting growth or diet</td>
<td></td>
<td></td>
<td></td>
<td>No statistical significance across 5 follow up assessment points for caloric intake, %EER, weight, BMI z score, height, height for age z score, FEV1</td>
<td></td>
</tr>
<tr>
<td>• Medications affecting growth or appetite</td>
<td></td>
<td></td>
<td></td>
<td>Conclusions:</td>
<td></td>
</tr>
<tr>
<td>• Significant developmental delay or mental health diagnosis</td>
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</tbody>
</table>
### Background


Behavioral and Nutritional Treatment of Preschool-Aged Children with CF: A Randomized Clinical Trial


**NHMRC level II**

**ADA quality POSITIVE**

<table>
<thead>
<tr>
<th>NHMRC level II</th>
<th>ADA quality</th>
<th>Randomised control trial (NCT00241969)</th>
<th>Inclusion criteria:</th>
<th>Exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=78 Children 4-6 years with CF and pancreatic insufficiency attending 7 accredited CF centres Jan 2006-Nov 2012</td>
<td>Confirmed CF</td>
<td>WAZ score greater than 1 using CDC</td>
<td>Current use of enteral or PN</td>
<td>Diagnosis of other conditions or use of medications known to affect growth</td>
</tr>
</tbody>
</table>

**Intervention:**

- **Behavioural (BEH) and control**
- In person or telehealth (phone delivery)
- 7 weekly sessions, 4 monthly sessions, 12 month follow up after end of programme (18 months from baseline)

**BEH**

- Individualized counselling targeting increasing energy and fat. Min 140% EER; 40% fat calories
- Meal by meal goals
- Parent training in behavioural child management skills. Dosage and timing of PERT monitored
- Regular meal schedule monitored
- Self-monitoring via diet diary

**Primary Outcomes:**

- Caloric intake
- EER BMI z score
- FEV1 measured pre and post treatment

**Results:**

**Energy:**

- **Post treatment:**
  - BEH>control (459cal/day SD 355 vs 58cal/day SD 248 p<0.001)
- **Follow up:**
  - BEH>control (545cal/day SD 505 vs 277cal/day SD 429; p=0.02)

**Weight:**

- No significant difference in WAZ post treatment or at follow up

**Height:**

- **Follow up only:**
  - BEH>Control (change 0.09 SD 0.26 vs -0.02 SD 0.32; p=0.49)

**Conclusions:**

- Yes answers this PICO as study shows that oral behaviour interventions, when delivered with nutritional interventions, resulted in a significant improvement in energy intake and height (WAZ score) in preschoolers aged 2-6 years with CF and PI.

**Limitations**

- Included well-nourished children
- 60% randomised – may limit generalisability to those willing and able to engage in weekly treatment
- Difference in diet collection 7DFR vs 3x24ffq noted in protocol
- Didn’t report on overall level of lung function (only respiratory adverse events)
- Dietitian who reviewed diet diaries for accuracy did not appear to be blinded
- No reasons given for data not completed
- Treatment group had significantly more digestive problems- not commented on
• Genetic potential for height as acceptable according to 2003 consensus conference guidelines
• Dietary intake exceeding 140% of av EER) as per 3 day diet recall
• Feedback Control:
  • Education generic – some food, routine and snack, vits and minerals, increased energy needs, also non nutritional sessions e.g. cleaning equipment, language and development, home safety, medications

Primary outcomes:
• Energy intake
• Weight and height


NHMRC level IV
ADA quality NEUTRAL

Cross sectional
N=8
5 year follow up of families who attended a previous behavioural nutrition programme reported in a previous study
Children with CF now mean 8.2 yrs. (SD 0.8) 62% (5/8) were male

Inclusion criteria:
• Parents of Children with Cystic Fibrosis who had attended behavioural nutrition education 5 yrs. previous

Exclusion:
• None listed

Aim to understand how families use strategies taught in a behaviour-nutrition intervention and identify the nutritional challenges with CF management families experience during the developmental transition from toddler to school age

Intervention:
• Previous involvement in a behavioural nutrition program
• Semi structure interview.

Primary outcome:
• Themes as identified by the review of the 8 transcripts of semi structured interviews

Results:
Parent recall of information from behavioural nutrition interventions
• Boosting calories through addable/spreads, high calorie food alternatives, Use high calorie beverages, Use snacks to increase daily calories

Behavioural recommendations
• Contingency management, Shift positive to negative attention, Flexible use of strategies

Ongoing challenges affecting CF management
• Parental stress, Picky eating, Behavioural non-compliance

New challenges that affect CF management
• New medical/psych diagnosis, Transfer of treatment responsibility, Transition to school

Protective factors
• Family factors, Child factors

Conclusions:

Limitations:
• Length of time after behavioural nutrition interventions 5yrs– routine care may have had some impact on parent recall and results
• Small sample size
Compared to standard nutritional care, do behavioral interventions around food and mealtimes improve behaviours, diet variety, and weight or nutrition status in children with CF?

**NHMRC Grade for recommendation:** Grade B

**Evidence statement:** There is some evidence to support the beneficial effect of behavioral modification techniques to help improve child behaviors during meal time and/or family functioning. Evidence that improved behaviors then results in increased energy intake and/or weight is conflicting. Providing parents with behavioral strategies and nutrition education has been shown to be more effective in

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<tbody>
<tr>
<td>NHMRC level III-2 ADA quality POSITIVE</td>
<td>N=67 children with CF Ages 4-12 Comparison sample =n=346 (matched from CFF registry 5:1)</td>
<td>Intervention: • 9 week nutrition intervention (behaviour plus nutrition education intervention) compared to routine care • Follow up for 2 years</td>
<td>Over 27 months, children in the Clinical Trial Group (the combined sample of the behaviour plus nutrition and the nutrition alone) demonstrated significantly less decline in BMI z-score (p&lt;0.05). • No statistically significant differences were found for decline in FEV1 between children in the Clinical Trial Group and the comparison Sample.</td>
<td>• Use of a comparison sample drawn from the CFF 4registry not randomised standard of care control group. • Potential for “standard of care not be uniform across centres • Potential differences in quality of data</td>
</tr>
<tr>
<td>Inclusion criteria: • Ages 4-12 years • dx CF by sweat test • pancreatic insufficient • &lt;40th percentile weight for age and sex of weight for height at the time of chart review</td>
<td>Primary outcome: • Change in body mass index z-score</td>
<td>Conclusions: • The key implication of these findings is that intensive behavioural and nutritional intervention is effective and needs to be adapted so that it can be broadly disseminated into clinical practice.</td>
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</table>
improving energy intake and growth of children than nutrition education alone. A limitation to this evidence base is that the vast majority of research comes from the same group in the USA.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>B Good</th>
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<tbody>
<tr>
<td>5 studies, various sample sizes.</td>
<td></td>
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<tr>
<td>• 1 level I study, meta-analysis positive quality</td>
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<tr>
<td>• 2 level II studies (n= 78, n=79), RCTs both positive quality</td>
<td></td>
</tr>
<tr>
<td>• 1 level III-2 comparative case control study (n=67 trial group), comparison sample (n=346), neutral quality</td>
<td></td>
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<tr>
<td>• 1 qualitative study (n= 8), neutral quality</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Studies reported on parent and child behaviors during meal time and/or overall family functioning</td>
<td></td>
</tr>
<tr>
<td>• Family functioning appears to be positively related to weight status and positive eating behaviors</td>
<td></td>
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<tr>
<td>3 Studies reported on energy intake and/or anthropometric measurements</td>
<td></td>
</tr>
<tr>
<td>• Mixed results for use of behavioral intervention and improved energy intake and positive changes in anthropometric measurements</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>C Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>The evidence is directly relevant to the clinical question.</td>
<td></td>
</tr>
<tr>
<td>• Potential benefits to energy intake and anthropometric measurements</td>
<td></td>
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<tr>
<td>• May require additional resourcing (e.g. psychology of family therapist support).</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies completed in paediatric population groups in the USA and are translatable to an Australian context.</td>
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<tr>
<td>Most data relates to children aged 1 to 12 years, may not be applicable to older adolescents.</td>
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</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>C Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many of these studies were undertaken in populations in whom newborn screening did not take place. Thus the early years journey in the study populations, age of diagnosis, time of treatment commencement and the severity of undernutrition is likely to be quite different from the current populations in Australia/New Zealand.</td>
<td></td>
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<tr>
<td>Dietitians and other practitioners may require additional training in behavioural modification techniques around food and mealtimes.</td>
<td></td>
</tr>
</tbody>
</table>
**Clinical Question**

6.1.2 When should behavioural interventions around food and mealtimes be considered for children with CF?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duff AJ, Wolfe SP, Dickson C, Conway SP, Brownlee KG. Feeding behaviour problems in children with cystic fibrosis in the UK: prevalence and comparison with health controls. J Pediatr Gastroenterol Nutr. 2003 Apr;36(4):443-7.</td>
<td>NHMRC level IV ADA quality POSITIVE</td>
<td>Cross sectional study Study A: parents of children aged 1-17yrs with CF attending clinic (n=108) Study B: CF patients From study A 1-12yrs (n=69) Control group (n=164) age 1-12yrs attending local schools and preschool nursery groups of similar demographics to CF population, no chronic health condition and full completion of questionnaire. Exclusion criteria: • Outside of age range 1-12yrs • Control group: Chronic health condition, • Incomplete completion of questionnaire</td>
<td>Aim to establish the prevalence and range of disruptive child behaviours (DCB) in patients with CF and the inappropriate parental responses (IPR) during mealtimes and compare with healthy children Intervention: • Study A+B: General information Questionnaire (GIQ) and Behavioural Paediatric Feeding Assessment scale (BPFAS) completed by CF parents • In CF group BPFAS was adapted and • Control group given modified GIQ Primary outcome: • Types and frequency of DCB and IPR</td>
<td>Results: • Significant differences in DCB and IPRs between CF and control groups for ages 5-8yrs (CF DCB frequency p&lt;0.001; CF DCB problems 0 P&lt;0.05; CF IPR Frequency p&lt;0.001; CF IPR problems p&lt;0.05) and 9-12yrs (CF DCB frequency p&lt;0.01; CF IPR freq p&lt;0.05; CF IPR problems p&lt;0.05) but not 1-4yrs Conclusions: • Behaviour problems are ongoing throughout different ages, need to continue past the early stages and make information developmentally pertinent. Behavioural strategies should be considered throughout all ages.</td>
<td>Limitations: • Differences in administration of questionnaire in control group vs CF • Some concerns raised about suitability of BPFAS for distinguishing normal vs abnormal feeding patterns in young children and adolescents • Slight difference in demographics in study B – CF families had a greater no. of single parents and non-paid employed parents than control. ? if this may put more stress on families, although when compared in study A – marital status and employment did not show effect • No details on clinical assessment of severity of disease for CF children. • Relies on questionnaires for data therefore is recall dependant on parent perceptions of problem (rather than an observational study).</td>
</tr>
<tr>
<td>Powers SW, Mitchell MJ, Patton SR, Byars KC, Jelalian E, Mulvihill MM, Hoveil MF, Stark LJ. Mealtime behaviours in families of infants and toddlers with cystic fibrosis.</td>
<td>NHMRC level III-3 ADA quality NEUTRAL</td>
<td>Aetiology - case control N=34 CF infants &amp; toddlers N=34 controls Inclusion criteria: • Not listed Exclusion criteria:</td>
<td>Aim to evaluate parent and child behaviours at mealtimes in infants and toddlers with CF Intervention: • Observational study • ≥3 taped typical family meals. Videotaped meals were coded using</td>
<td>Results: CF vs controls • Parent behaviours: Direct commands CF&gt;control (p&lt; 0.01) • Child behaviours – no sig differences • Child eating Bites CF&gt; controls (p&lt;0.01)</td>
<td>Limitations: • population not described in detail • no inclusion and limited exclusion criteria • CF &amp; control groups- don’t know who had previous dietetic/psychology input around meal time behaviour • Potential selection bias – interested parties • Don’t know health status and any</td>
</tr>
<tr>
<td>J Cyst Fibros. 2005 Sep;4(3):175-82.</td>
<td>Receiving behavioural or psychological interventions relating to eating or nutrition in CF the Dyadic Interaction Nomenclature for Eating by a blinded observer and scored separately by a second observer. Primary outcome: • Food related behaviours – parent and child, dietary intake (energy) Secondary outcome: • Anthropometric measures Frequency by meal half [all subjects] • Child behaviours: away from table 1st half&lt; 2nd half (p&lt;0.01), Food refusal – 1st half&lt; 2nd half (p&lt;0.050) • Child eating: Bites: 1st half&gt;2nd half (p&lt;0.05) Fast (&lt;16min) vs slow (&gt;16min) meals • Child eating: Fast eaters took more bites than slow eaters (p=0.001), Fast eaters took more sips than slow eaters p=0.003) • Child behaviours: Food refusal greater in fast eaters than slow (p=0.001) • CF parents used more physical prompts to encourage eating (p=0.009) and fed their child more (p&lt;0.02) Conclusions: • From infancy/toddlers – Intervention would assist parents in dealing with typical childhood mealtime behaviours in order to change sense of concern and maximise energy intake previous medical interventions of control group • Type of meal not described/ don’t know how well diet histories were completed, no mention of missing data • limited to certain SES • Short study timeframe • ? effect of videotaping on behaviours</td>
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<tr>
<td>Filigno SS, Brannon EE, Chamberlin LA, Sullivan SM, Barnett KA, Powers SW. Qualitative analysis of parent experiences with achieving cystic fibrosis nutrition recommendations. J Cyst Fibros. 2012 Mar;11(2):125-30. doi: 10.1016/j.jcf.2011.10.006. Epub 2011 Nov 22.</td>
<td>NHMRC level IV ADA quality NEUTRAL Cross sectional N=8 5 year follow up of families who attended a previous behavioural nutrition programme reported in a previous study Children with CF now mean 8.2 yrs. (SD 0.8) 62% (5/8) were male Aim to understand how families use strategies taught in a behaviour-nutrition intervention and identify the nutritional challenges with CF management families experience during the developmental transition from toddler to school age Intervention: • Previous involvement in a behavioural nutrition program • Semi structure interview. Results: Parent recall of information from behavioural nutrition interventions • Boosting calories through addable/spreads, high calorie food alternatives, Use high calorie beverages, Use snacks to increase daily calories Behavioural recommendations • Contingency management, Shift positive to negative attention, Flexible use of strategies Limitations: • Length of time after behavioural nutrition interventions 5yrs– routine care may have had some impact on parent recall and results • Small sample size</td>
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</table>
### Evidence Statement Matrix

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>Primary outcome:</th>
<th>Ongoing challenges affecting CF management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents of Children with Cystic Fibrosis who had attended behavioural nutrition education 5 yrs. previous</td>
<td>Themes as identified by the review of the 8 transcripts of semi structured interviews</td>
<td>Parental stress, Picky eating, Behavioural non-compliance</td>
</tr>
</tbody>
</table>

**Exclusion:** None listed

### Chapter 6  Q6.1.2 When should behavioural interventions around food and mealtimes be considered for children with CF?

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** Evidence suggests that behavioural modifications should be commenced early in life before typical childhood maladaptive eating behaviours become an ongoing issue. Early intervention may assist parents in dealing with problem mealt ime behaviours in order to change a sense of concern and maximize food intake. In addition, evidence suggests that these strategies should continue throughout all ages of childhood.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>Consistency</th>
<th>Clinical impact</th>
<th>Generalisability</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Satisfactory</td>
<td>B Good</td>
<td>C Satisfactory</td>
<td>C Satisfactory</td>
</tr>
</tbody>
</table>

- Three studies, small to medium sample sizes
  - One level III-2 study (n=68), positive quality
  - One level III-3 study (n=34), neutral quality
  - One level IV study (n=8), neutral quality

- Three studies show that disruptive mealt ime behaviours and inappropriate parental responses often start very early in life. One study showed that parents were still using behavioural management strategies learnt when their child was young years later.

- The evidence is suggestive that inappropriate mealt ime behaviours can commence early in childhood, and that parents often do not have the skills to deal with these behaviours
  - Starting behavioral modification interventions early is achievable and low risk.

- All studies completed in young children and children of primary school age, thus results are not transferrable to adolescents and adults.
Studies completed in USA are generally comparable to Australia and New Zealand CF populations.

<table>
<thead>
<tr>
<th>Applicability</th>
<th>Grade</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Good</td>
</tr>
</tbody>
</table>

Many of these studies were undertaken in populations in whom newborn screening did not take place. Thus the early years of the study populations, are likely to be quite different from the current populations in Australia/New Zealand.
**CLINICAL QUESTION**

6.1.3 Do appetite stimulants, megesterol acetate and cyproheptadine, improve nutritional status in CF?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results, conclusions &amp; comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinuck R, Dewar J, Baldwin DR, Hendron E. Appetite stimulants for people with cystic fibrosis. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD008190. DOI: 10.1002/14651858.CD008190.pub2.</td>
<td>NHMRC level I ADA quality Positive</td>
<td>Cochrane systematic Review Randomised and quasi-randomised controlled trials of appetite stimulants Adults &amp; children with CF</td>
<td>Intervention: • N/A Outcomes: • Comparison of appetite stimulants, compared to placebo or no treatment for at least one month</td>
<td>Results: • 3 trials (total of 47 recruited patients) comparing appetite stimulants (cyproheptadine hydrochloride and megesterol acetate) to placebo were included; the numbers of adults or children within each trial were not always reported. The risk of bias of the included trials was graded as moderate. • A meta-analysis of all three trials showed appetite stimulants produced a larger increase in weight z score at three months compared to placebo; - Mean difference 0.61 (95% confidence interval 0.29 to 0.93) (P &lt; 0.001) (n = 40) with no evidence of a difference in effect between two different appetite stimulants. • One of these trials also reported a significant weight increase with megesterol acetate compared to placebo at six months (n = 17). • The three trials reported no significant differences in forced expiratory volume at one second (per cent predicted) between the appetite stimulant groups and placebo at follow up, with durations ranging from two to nine months. • A meta-analysis of two trials showed a significantly higher proportion of patients reporting increased appetite, odds ratio 45.25 (95% confidence interval 3.57 to 573.33) (P = 0.003) (n = 23), but the frequency of reported side effects was undetermined Conclusions: • In the short term (six months) in adults and children, appetite stimulants improved only two of the outcomes in this review – weight for weight z score and appetite; and side effects were insufficiently reported to determine the full extent of their impact. • Whilst the data may suggest the potential use of appetite stimulants in treating anorexia in adults and children with cystic fibrosis, this is based upon moderate quality data from a small number of trials and so this therapy cannot be conclusively recommended based upon the findings in the review. • Clinicians need to be aware of the potential adverse effects of appetite stimulants and actively monitor any patients prescribed these medications accordingly. • Research is needed to determine meaningful surrogate measures for appetite and define what constitutes quality weight gain. Future trials of appetite stimulants should use a validated measure of symptoms including a disease-specific...</td>
</tr>
</tbody>
</table>
**Evidence Statement Matrix**

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>C Satisfactory</th>
<th>Evidence statement: As per the findings of a Cochrane review, there is some evidence from three small studies to suggest that appetite stimulants may improve weight and appetite for people with CF. However, there is inadequate evidence regarding adverse side effects and safety with longer term. As a result, the routine use of appetite stimulants is not recommended to improve nutrition status in CF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>B Good</td>
<td>Findings were generally consistent amongst the studies included in the systematic review:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Weight z-score significantly improved across all trials after 3 months of use</td>
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<tr>
<td></td>
<td></td>
<td>• Weight significantly improved after 6 months with megesterol acetate use in one study</td>
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<tr>
<td></td>
<td></td>
<td>• No significant impact on pulmonary outcomes (FEV, percent predicted)</td>
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<tr>
<td></td>
<td></td>
<td>• A statistically significant increase in the proportion of people with CF with an increased appetite</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>C Satisfactory</td>
<td>The evidence is directly relevant to the clinical question.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Potential benefits to nutritional status are highly relevant to people with CF.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• The lack of evidence regarding potential side effects and safety limits the overall assessment of clinical impact.</td>
</tr>
<tr>
<td>Generalisability</td>
<td>C Satisfactory</td>
<td>Most studies are conducted in countries with generally comparable populations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Includes both paediatric and adult population (note the breakdown in numbers between the paediatric and adult population weren’t always reported).</td>
</tr>
<tr>
<td>Applicability</td>
<td>C Satisfactory</td>
<td>Evidence somewhat applicable to the Australian CF population:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2 of the 3 studies from the US with a similar CF population to Australia</td>
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</table>

**NHMRC Grade for recommendation:** Grade C

**Evidence base**

1 Cochrane systematic review of the available evidence (Level 1 – positive quality)

- Includes 3 small randomized and quasi-randomised control trials
- N=47 participants across the 3 studies

**Consistency**

Findings were generally consistent amongst the studies included in the systematic review:

- Weight z-score significantly improved across all trials after 3 months of use
- Weight significantly improved after 6 months with megesterol acetate use in one study
- No significant impact on pulmonary outcomes (FEV, percent predicted)
- A statistically significant increase in the proportion of people with CF with an increased appetite

**Clinical impact**

The evidence is directly relevant to the clinical question.

- Potential benefits to nutritional status are highly relevant to people with CF.
- The lack of evidence regarding potential side effects and safety limits the overall assessment of clinical impact.

**Generalisability**

Most studies are conducted in countries with generally comparable populations.

- Includes both paediatric and adult population (note the breakdown in numbers between the paediatric and adult population weren’t always reported).

**Applicability**

Evidence somewhat applicable to the Australian CF population:

- 2 of the 3 studies from the US with a similar CF population to Australia

**Limitations:**

- Moderate quality data
- Small number of studies
### CLINICAL QUESTION

**6.1.4** Does the use of recombinant growth hormone improve nutritional status in pre-pubertal people with CF?

### Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results, conclusions &amp; comments</th>
</tr>
</thead>
</table>
| Thaker V, Haagensen AL, Carter B, Fedorowicz Z, Houston BW | NHMRC level I ADA quality Positive | Cochrane systematic Review Randomised and quasi-randomised controlled trials n=4 trials n=161 subjects Ages 7-23 years (mostly pre-pubertal) Adults & children with CF The evidence is current until 11 February 2015. | Intervention:  
• Use of man-made human growth hormone to improve lung function, growth and quality of life for people with CF.  
• Hormone treatment compared to no treatment in 3/4 trials  
• Hormone treatment compared to placebo in 1/4 trials  
Duration:  
• 3 trials = 12 months  
• 1 trial = 6 months  
Outcomes:  
• Anthropometry measures  
• Lung function  
• Muscle strength  
• Clinical condition  
• Quality of life | Results:  
• Modest improvement in height and weight over 6 to 12 months.  
• No consistent evidence in the improvement of lung function, muscle strength, clinical condition or quality of life after treatment.  
• No effects on glucose metabolism or the long-term risk of diabetes due to the treatment.  
Conclusion:  
• Unable to identify any clear benefit of therapy  
• More research from well-designed, large trials is needed.  
Limitations:  
• Unable to determine if trials were biased  
• Some concerns that outcomes based on personal judgement, like quality of life scores, might be affected because the volunteers in the three trials comparing treatment to no treatment would know which group they were in. |
### Evidence Statement Matrix

**Chapter 6 Q 6.1.4 Does the use of recombinant growth hormone improve nutritional status in pre-pubertal people with CF?**

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** As per the findings of a Cochrane review, there is some evidence from 4 studies to suggest that growth hormone may improve height, weight and lean tissue mass for the pre-pubertal CF population. However, the currently body of evidence only looks at short term use (6-12 months). Longer term randomised control trials are required prior to recommending the routine use of growth hormone for the CF population.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane systematic review of the available evidence (Level 1 – positive quality)</td>
<td></td>
</tr>
<tr>
<td>- Includes 4 randomized and quasi-randomised control trials</td>
<td></td>
</tr>
<tr>
<td>- N=161 participants across the 4 studies</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Findings were generally consistent amongst the studies included in the systematic review:</td>
<td></td>
</tr>
<tr>
<td>- Modest improvements in height, weight and lean tissue mass</td>
<td></td>
</tr>
<tr>
<td>- Improvement in lean tissue mass</td>
<td></td>
</tr>
<tr>
<td>- No consistent impact on lung function, muscle strength, clinical condition and/or quality of life</td>
<td></td>
</tr>
<tr>
<td>- No effect on glucose metabolism and doesn’t increase the chance of developing CFRD</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>The evidence is directly relevant to the clinical question</td>
<td></td>
</tr>
<tr>
<td>- Potential benefits to nutritional status are highly relevant to person with CF</td>
<td></td>
</tr>
<tr>
<td>- Little evidence to support an increase in quality of life</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most studies are conducted in countries with generally comparable populations.</td>
<td></td>
</tr>
<tr>
<td>- All studies included pre-pubertal people with CF (&lt;25 years of age)</td>
<td></td>
</tr>
<tr>
<td>- All participants had weight and height percentiles between the 10-25th percentile for age and gender</td>
<td></td>
</tr>
<tr>
<td>- Most subjects were clinically stable</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence somewhat applicable to the Australian context.</td>
<td></td>
</tr>
</tbody>
</table>
**CLINICAL QUESTION**
6.1.5 Is there any rationale for the use of commercial oral nutritional supplements over food or mealtime strategies to improve nutritional intake, weight or pulmonary function in CF?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>POUSTIE, V. J., RUSSELL, J. E., WATLING, R. M., ASHBY, D. &amp; SMYTH, R. L. 2006. Oral protein energy supplements for children with cystic fibrosis: CALICO multicentre randomised controlled trial. Bmj, 332, 632-6</td>
<td>NHMRC Level II ADA Qualtiy: Positive</td>
<td>Design: RCT Population: Children with CF ages 2 to 15 years, UK Multicentre (7 specialist paediatric CF centres and their associated shared care clinics and 7 smaller paediatric CF clinics) Number: n= 102 (treatment =50, control = 52)</td>
<td>Intervention: • Oral protein calorie supplementation in addition to normal diet. (Increase energy intake by 20%) • Routine dietetic advice • Control group- normal diet plus dietary counselling • 12 months, longest length study Outcomes: • change in body mass index centile over 1 year Secondary outcomes: • other nutritional parameters, • energy and macronutrient • lung function, eating behavior • activity levels</td>
<td>Results: • No significant differences seen in BMI centile or other anthropometric outcomes. • No differences between mean change from baseline to 12 months for dietary intake outcomes, except energy % EAR (P= 0.01) • BUT study concluded that as this didn't relate to an increase in weight, it was likely a product of overestimated diet data from food diaries and supplement consumption records from the ONS consuming population. Conclusions: • Long term use of oral protein energy supplements did not result in an improvement in nutritional status or clinical outcomes in children moderately malnourished. • Supplements should not be regarded as essential in children. • Dietary advice alone appears a satisfactory</td>
<td>Author limitations • Nil described Appraiser limitations • Compared a supplement to dietary advice alone – so participants not blinded • Potential for reporting bias • Generalisability: May not be appropriate to extrapolate children’s data to adults • Also may not be able to extrapolate to low lung fx group as those with FEV1 &lt;30% excluded. • Overall low risk of bias</td>
</tr>
<tr>
<td>FRANCIS, D. K., SMITH, J., SALJUQI, T. &amp; WATLING, R. M. 2015. Oral protein calorie</td>
<td>NHMRC Level I ADA Quality:</td>
<td>Systematic review of Randomised or quasi-randomised control trials (published only)</td>
<td>Intervention: • Oral calorie supplements Primary outcome:</td>
<td>Results: • Few statistical differences found between outcomes. • Change in total energy intake at</td>
<td>Author limitations • Two studies had high risk of bias for allocation concealment</td>
</tr>
</tbody>
</table>
**Smyth RL, Rayner O.**

**Oral calorie supplements for cystic fibrosis.** Cochrane Database of Systematic Reviews 2014, Issue 11.

<table>
<thead>
<tr>
<th>NHMRC Level</th>
<th>ADA Quality</th>
<th>Study Type</th>
<th>Number</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Positive</td>
<td>Systematic review of Randomised or quasi-randomised control trials (published or unpublished)</td>
<td>n=131 participants across 3 studies</td>
<td>identified 21 studies answering question – 3/21 met inclusion criteria as RCT, mostly malnourished children (Hanning 1993, Kalnin’s 2005, Poustie 2006)</td>
</tr>
</tbody>
</table>

**Inclusion criteria:**
- RCT or quasi-RCT comparing use of oral calorie supplements for

**Intervention:**
- Oral nutritional calorie supplements.
- Fortified milk or juice or simple energy sources, any amount for at least one month.
- How the intervention might work: by increasing total daily calorie intake on top of usual diet

**Primary outcome:**
- Daily calorie intake and/or improve nutritional status

**Results:**
- No major differences between people receiving supplements or just dietary advice for any nutritional or growth measurements (wt, ht, BMI, z score).
- There was no significant difference between groups but trend for the supplement group to have greater improvement at 3 months.
- This was not apparent at 12 months
- Changes in weight (kg) at three, six and twelve months respectively were: MD 0.32 (95% CI -0.09 to 0.72); MD 0.47 (95% CI 0.07 to 1.02); and MD 0.16 (-

**Appraiser limitations**
- Possibly excluded other lower grades of evidence which may help dietitians make nutritional decisions around oral supplements.
- 2/3 included studies only included children
- 2/3 studies have low risk of bias, quality of Kalnin’s 2005 study unclear
- Contains additional data and clarifications for Kalnin’s not included in published article (6 months data)
### Failure of conventional strategies to improve nutritional status in malnourished adolescents and adults with cystic fibrosis. *J Pediatr*, 147, 399-401

**NHMRC Level** II  
**ADA Quality:** Neutral  

**KALNINS, D., COREY, M., ELLIS, L., PENCHARZ, P. B., TULLIS, E. & DURIE, P. R. 2005.**  

Failure of conventional strategies to improve nutritional status in malnourished adolescents and adults with cystic fibrosis. *J Pediatr*, 147, 399-401

**Inclusion criteria:**  
- 10 years with <90% ideal body weight or a 5% reduction in percent IBW over a 3-month period.

**Exclusion:**  
- CFRD  
- Gastrostomy tube  
- CF liver disease  
- FEV1 <30% predicted  
- Oxygen dependence  
- Already receiving nutritional supplements  

**Intervention:**  
- High calorie drink to increase energy intake by 20% of predicted energy needs.  
- Control group: nutritional counseling to increase energy by 20% or predicted energy needs by eating high calorie foods.  
- 3 months follow up  

**Primary outcome:**  
- Caloric intake  
- Anthropometric

**Results:**  
- There was no significant change in energy intake or percent ideal body weight in either group.

**Conclusions:**  
- Conventional dietary practices do not appear to improve nutritional status in malnourished patients with CF.

**Author limitations:**  
- Nil listed  

**Appraiser limitations:**  
- Allocation/selection bias – inadequate used alternate allocation method  
- Not possible to blind dietitian or participants, all other investigators blinded  
- Interestingly there was almost 10 years between the abstract and journal article being published for this piece of work  
- Study had high percentage of females  
- Method of randomisation  
- Very small sample  
- Uses %IBW rather than BMI  
- Overall Mild risk of bias
<table>
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<tbody>
<tr>
<td><strong>NHMRC Level IV</strong></td>
</tr>
<tr>
<td><strong>ADA Quality: Neutral</strong></td>
</tr>
<tr>
<td>Observational cross sectional (from August 2009 to July 2011, 1 time point only)</td>
</tr>
<tr>
<td>N=47</td>
</tr>
<tr>
<td>Ages 2 to 19 years, Brazil. Children defined as ages 2 to 10 years Adolescents 10 to 19 years</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td>• Confirmed CF diagnosis</td>
</tr>
<tr>
<td>Exclusion:</td>
</tr>
<tr>
<td>• Adults who were not accompanied</td>
</tr>
<tr>
<td>• Breastfeeding</td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
</tr>
<tr>
<td>• Oral supplements</td>
</tr>
<tr>
<td>• dietetic prescription-supplements given before or after meals or before bedtime</td>
</tr>
<tr>
<td>• Not substituting the main meals</td>
</tr>
<tr>
<td><strong>Primary outcome:</strong></td>
</tr>
<tr>
<td>• Nutrition status measures</td>
</tr>
<tr>
<td><strong>Results:</strong></td>
</tr>
<tr>
<td>• Among those who use supplements there was lower rate of well-nourished patients</td>
</tr>
<tr>
<td>• CF patients without a deficit (well nourished) are more likely to be having supplements.</td>
</tr>
<tr>
<td>• Correlation between the use of nutritional supplements and nutritional status p=0.0098</td>
</tr>
<tr>
<td>• Malnourished patients are using less supplements and well-nourished patients are using more supplements</td>
</tr>
<tr>
<td>• Nutrition status was significantly associated with the different types of dietary supplements (p =0.0445), and frequency of supplementation (p=0.0255)</td>
</tr>
<tr>
<td>• For combined group (all participants) Caloric value of diet did not reach the 120-150% recommended energy intake recommended for CF</td>
</tr>
<tr>
<td><strong>Conclusions:</strong></td>
</tr>
<tr>
<td>• Nutritional support and clinical and nutritional follow up- can be an element of care used to reduce morbidity and mortality and frames of disease exacerbation.</td>
</tr>
<tr>
<td><strong>Limitations (authors):</strong> nil</td>
</tr>
<tr>
<td><strong>Limitations (appraisers):</strong></td>
</tr>
<tr>
<td>• Poor English translation made this article difficult to interpret</td>
</tr>
<tr>
<td>• More males (59.5%) than females in study</td>
</tr>
<tr>
<td>• Study contains a large percentage of late diagnosis (may affect generalisability to Australian/NZ health care context)</td>
</tr>
<tr>
<td>• Mild risk of bias as data collectors assumedly not blinded to nutrition status or sups use not possible given design).</td>
</tr>
<tr>
<td>• 24 hr recall not a reliable measure</td>
</tr>
<tr>
<td>• Unclear if results support conclusions as difficult to interpret.</td>
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<table>
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<tbody>
<tr>
<td><strong>NHMRC Level IV</strong></td>
</tr>
<tr>
<td><strong>ADA Quality: Neutral</strong></td>
</tr>
<tr>
<td>Retrospective Cross sectional survey (data taken between 1995-2000 from annual reviews)</td>
</tr>
<tr>
<td>N=80</td>
</tr>
<tr>
<td>Adults with CF various clinical status, UK study</td>
</tr>
<tr>
<td><strong>Intervention:</strong> N/A</td>
</tr>
<tr>
<td><strong>Primary outcome:</strong></td>
</tr>
<tr>
<td>• Energy and protein intakes</td>
</tr>
<tr>
<td><strong>Secondary outcomes:</strong></td>
</tr>
<tr>
<td>• Other nutritional parameters e.g. BMI, and clinical markers (e.g. FEV1, PS, CFRD)</td>
</tr>
<tr>
<td><strong>Results:</strong></td>
</tr>
<tr>
<td>• Mean energy and protein intakes approached recommended CF guidelines, but in 72% of assessments these values were not achieved.</td>
</tr>
<tr>
<td>• Oral supplementation increased energy and protein intake above recommended levels</td>
</tr>
<tr>
<td><strong>Author limitations:</strong></td>
</tr>
<tr>
<td>• Data collection methods (unweighed food dairy)</td>
</tr>
<tr>
<td>• Time to complete, patient willingness to return</td>
</tr>
<tr>
<td><strong>Appraiser limitations:</strong></td>
</tr>
<tr>
<td>• Cross sectional study design</td>
</tr>
<tr>
<td>• Unclear recruitment methods</td>
</tr>
<tr>
<td>HOLLANDER, F. M., VAN PIERRE, D. D., VAN DE ROOS, N. M., VAN DE GRAAF, E. A. &amp; IESTRA, J. A. 2014. Effects of nutritional status and dietetic interventions on survival in Cystic Fibrosis patients before and after lung transplantation. J Cyst Fibros, 13, 212-8</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Evidence Statement Matrix

**Chapter 6 Q 6.1.5 Is there any rationale for the use of commercial oral nutritional supplements over and above food or mealtime strategies to improve nutritional intake, weight or pulmonary function in CF?**

**NHMRC Grade for recommendation: Grade B**

**Evidence statement:** There is consistent evidence from studies of reasonable quality to suggest that oral nutrition supplements are unlikely to result in improved BMI outcomes, nutritional intake or pulmonary function in individuals with CF.
| Evidence base | B Good | 7 small – medium sized studies  
• 2 level I studies – both Cochrane reviews of RCTs or quasi-RCT’s,  
• 1 level II study (n=102) - RCT  
• 1 level III-1 (n=13)  
• 3 level IV studies – retrospective case series (n=75), two cross sectional studies (n=47 and n=94) |
| Consistency | B Good | Overall good consistency with most studies reporting a limited benefit regarding the use of oral nutrition support.  
• Two paediatric studies reported on BMI outcomes with only one of the two studies finding a positive correlation between supplementation & nutrition status.  
• Four combined paediatric and adult studies reporting no improvement in BMI.  
• Two studies looked at lung function and oral nutrition supplements. No statistically significant benefit was reported.  
• Three studies looked at nutritional intake while on oral nutrition supplements. Overall consistent findings with 2/3 studies reporting no improvement in total energy intake while on oral supplements. |
| Clinical impact | C Moderate | The evidence is directly relevant to the clinical question.  
• The likely lack of improvements in intake, BMI and lung function are relevant to people with CF and their decision making process around oral nutrition support. |
| Generalisability | C Satisfactory | Some studies are only in the paediatric population. Those looking at both the adult & paediatric population don’t extrapolate results by age. Most studies are conducted in countries with generally comparable populations.  
• Results are seen in people with CF with varying severity of lung disease (>30% FEV1), which is true of our population.  
• Inclusion/exclusion criteria are not outlined in most studies making it difficult to gauge a clinical picture of the study population. It is hence difficult to assume generalisability. |
| Applicability | B Good | The indications for oral nutrition support initiation and supplementation regimens used in the studies (though somewhat poorly described) generally appear to match current accepted practice in the Australian context (individualized supplement choice based on individual preference and tolerance between 1-3 supplements per day or as accepted in addition to normal high energy intake). |
## CLINICAL QUESTION

6.1.6 Should enteral feeding be considered to improve nutrition outcomes for people with CF?

### Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC), Quality (ADA), Relevance</th>
<th>Study Design and Sample</th>
<th>Aim, Intervention and Outcomes</th>
<th>Results and Author’s Conclusions</th>
<th>Appraiser’s Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST, C., BREARLEY, A., GAILLARD, P., REGELMANN, W., BILLINGS, J., DUNITZ, J., PHILLIPS, J., HOLME, B. &amp; SCHWARZENBERG, S. J. 2011. A pre-post retrospective study of patients with cystic fibrosis and gastrostomy tubes. <em>J Pediatr Gastroenterol Nutr</em>, 53, 453-8</td>
<td>NHMRC Level III-3, ADA Quality: Neutral</td>
<td>Retrospective Longitudinal open study with single group pre and post intervention N=46 Minnesota 1989-2007 boys, girls, women and men with CF</td>
<td>Intervention: • Placement of a gastrostomy tube Primary outcome: • Ht, wt, FEV1 National health &amp; nutrition survey ppFEV1. • Collected by experienced personnel. • Values collected 2 years before and 1, 2, 4 years post PEG. • Rate or Slope of deterioration of lung function before and after GT • Median BMI (for each time period) and change in BMI from baseline</td>
<td>Results: • GT placement improves BMI in patients with CF and is sustained for at least 4 years. • Second year after GT placement, the pBMI change was positive for 31 of the 39 pts (10/12 girls, 15/19 boys, 5/5 mean. Negative for 2/3 women) • Median change in pBMI of 6.3%. (13.3% at year 2 &amp; 8.9% at year 4). P&lt;0.0001 • Differed for gender. • BMI improves for men and male/female children but not adult women who see a decrease in median BMI.</td>
<td>Author limitations: • Retrospective study design • Includes data collected over several years (when changes in CF care occurred that may affect both pBMI and ppFEV1) • Confounding variables not accounted for (e.g. cannot demonstrate that improved BMI is solely the result of GT placement, or that subjects actually used their GT) • Single centre study (Minnesota USA), may not be generalizable to Aus/NZ CF population</td>
</tr>
<tr>
<td>EFRATI, O., MEI-ZAHAV, M., RIVLIN, J., KEREM, 2011. Nutritional supplementation (40-60% of recommended daily</td>
<td>NHMRC Level III-3</td>
<td>Retrospective Longitudinal open study with single group pre and post intervention</td>
<td>Intervention: • Nutritional supplementation (40-60% of recommended daily</td>
<td>Results: • Significant improvements in (at 1 year):</td>
<td>Author limitations: • Some variation in measurements from stadiometers etc inevitable • Number of women in the study low compared with men/children. • Blinding not discussed- likely data collectors are clinicians and not able to be blinded. • More baseline data needed- actual baseline FEV1 • Subgroup analysis were small • Generalisability concerns, single centre study • Nutritional status of patients at time of GT insertion not well defined • Details of GT tubes and types of feeding not available</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Title</td>
<td>Location</td>
<td>Study Design</td>
<td>Inclusion Criteria</td>
</tr>
<tr>
<td>---------</td>
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<td>---------------------</td>
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<tr>
<td>E., BLAU, H., BARAK, A., BUJANOVER, Y., AUGARTEN, A., COCHAVI, B., YAHAV, Y. &amp; MODAN-MOSES, D.</td>
<td>2006</td>
<td>Long term nutritional rehabilitation by gastrostomy in Israeli patients with cystic fibrosis: clinical outcome in advanced pulmonary disease</td>
<td>Israel – multicentre</td>
<td>Longitudinal open study with single group pre and post intervention. Retrospective case note review with comparison concurrently between groups. N=23 met criteria N=15 accepted N=6 declined Population: Leeds, UK 2004-2008</td>
<td>In patients that accepted ETF- all were provided 2 cal/ml formula at 20-60% energy intake overnight and free dietary intake during the day</td>
</tr>
<tr>
<td>WHITE, H., MORTON, A. M., CONWAY, S. P. &amp; PECKHAM, D. G.</td>
<td>2013</td>
<td>Enteral tube feeding in adults with cystic fibrosis; patient choice and impact on long term outcomes</td>
<td>Leeds, UK</td>
<td>Longitudinal open study with single group pre and post intervention. Retrospective case note review with comparison concurrently between groups. N=23 met criteria N=15 accepted N=6 declined Population: Leeds, UK 2004-2008</td>
<td>In patients that accepted ETF- all were provided 2 cal/ml formula at 20-60% energy intake overnight and free dietary intake during the day</td>
</tr>
</tbody>
</table>

**Appraiser limitations:**
- Small numbers of pts in subgroups precluded what would have been some useful sub analysis, unable to interpret growth patterns of individuals/subgroups
- Retrospective study design
- Generalisability concerns as study conducted in Israeli population
- Compliance reported by doctor
- FEV1 data not avail for pts<6yrs of age
- Specific genotype in this pop
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusions</th>
<th>Author limitations</th>
<th>Appraiser limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradley, G. M., Carson, K. A., Leonard, A. R., Mogayzel, P. J., Jr. &amp; Oliva-Hemker, M. 2012. Nutritional outcomes following gastrostomy in children with cystic fibrosis. Pediatr Pulmonol, 47, 743-8.</td>
<td>Retrospective cohort study, 2005 to 2010</td>
<td>N/A</td>
<td>Significant improvement in BMI - Baseline BMI Z score -1.19 subjects, -1.1 controls - At 6 months cases had a significant increase in BMI Z score to -0.29, p&lt;0.001 - At 1 year change in BMI Z less different (cases -0.41 vs controls -0.71, P=0.07)</td>
<td>Children with CF tube fed are more likely to achieve BMI &gt;50th percentile than matched children without tube feeding</td>
<td><strong>retrospective study design that does not allow for an exact comparison between the GT and non GT groups</strong></td>
<td><strong>Some controls treated with appetite stimulants and oral supplements (direct comparison not completed)</strong></td>
</tr>
<tr>
<td>Truby, H., Cowlishaw, P., O‘Neil, C. &amp; Wainwright, C. 2009.</td>
<td>Design: Retrospective case series (1999-2005)</td>
<td>Prior gastrostomy insertion &amp; overnight feeding</td>
<td>Subjects experienced a significant decline in both weight and height (%ile) for the 12 months prior to enteral</td>
<td></td>
<td><strong>No measure of intake or adherence to feeding regime</strong></td>
<td><strong>Controls supplementation is a confounder without nut intake data</strong></td>
</tr>
</tbody>
</table>

**Inclusion criteria:**
- Dx CF
- Gastrostomy placed between 1999 and 2005 at RCH Brisbane

**Exclusion:**
- None listed

**Primary outcome:**
- Body weight and BMI
- Clinical & pulmonary outcomes

**Data collected for 1 year prior and 2 year post insertion**

**feeding**
- Supplementing oral food and drink was tried in 93% of children prior to the use of overnight feeding which when instigated provided up between one third and one half of energy requirements with titration of PERT.
- Post PEG insertion, significant improvement in body weight and BMI (@12 months $t = -3.278$, $p = 0.01$), nutritional gains were less evident in 2nd year with no significant change in anthropometric indices

**Conclusions:**
- Significant improvement in some anthrop but not respiratory function in the first 12 months of feeding
- Plateau during the second year.
- Highlight the benefit of using height and weight Z scores rather than the measuring of the BMI in children

**Appraiser limitations:**
- Small numbers, low quality study design
- Practices may have changed since 2005
- Study does not explore other possible causes of improved BMI (may not be all attributable to gastrostomy placement)
- No compliance data
- Retrospective
- 2 pts had CFRD and 4 CFLD

---


**NHMRC Level IV**

**ADA Quality: Neutral**

**Retrospective case series**

- N=11 CF children
- Aged 6 months to 14 years at time of gastrostomy insertion

**Inclusion criteria:**
- Dx CF
- W/H% falls below 85% or severe stunting with a length below -2 standard deviation of the normal population

**Intervention:**
- N/A
- Prior gastrostomy insertion, overnight feeding

**Primary outcome:**
- BMI, height and percentage weight for height.
- Pulmonary function.
- Food intake as a % of the recommended daily allowances for children.
- Acceptance and problems with

**Results:**
- 5/10 subjects achieve a growth within 2 sd of the normal population within 12 months [indicates ability to achieve catch up growth]
- Although the diurnal oral intake of food decreased in all patients (median 10%, (1%; 35%), their total caloric intake improved by 37% (20%; 57%).
- Significant improvement in nutrition status-
- 7/11 subjects achieved wt for height of > 90%

**Author limitations:**
- Nil

**Appraiser limitations:**
- Questionnaires aren’t validated or described in any detail.
- Aims not clearly described
- Population not well described
- No discussions of methods
- No demographic data reported
- No limitations discussed by authors
- Small patient numbers
- Retrospective study design
- Subjects served as own controls
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusions</th>
<th>Author limitations</th>
<th>Appraiser limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>VANDELEUR, M., MASSIE, J. &amp; OLIVER, M. 2013. Gastrostomy in children with cystic fibrosis and portal hypertension. <em>J Pediatr Gastroenterol Nutr</em>, 57, 245-7</td>
<td>Retrospective case series [1991-2011]</td>
<td>Paediatric CF patients, Data on CFA database, Diagnosis of liver disease and portal hypertension</td>
<td>None listed</td>
<td>Gastrostomy placement was recommended by consensus of treatment physicians and followed published guidelines</td>
<td>Significant improvement in Weight for age Z score (0.002) and BMI z-score seen at 2 years (-0.05) (for children with CF liver disease and portal hypertension)</td>
<td>Gastrostomy feeding good and safe way to improve nutritional status, growth in CF. Full normalisation of growth pattern is not achieved despite catch-up. Gastrostomy tube feeding should perhaps be used earlier to optimise growth.</td>
<td>Very small numbers, Retrospective study design, No control group (each patient used as his/her own control), 20 year period of study time which may reflect changes in CF management</td>
<td>Selection of study subjects was subjective and down to clinical opinion, despite following the 1992 Ramsey guidelines</td>
</tr>
<tr>
<td>OLIVER, M. R., HEINE, R. G., NG, C. H., VOLDERS, E. &amp; OLINSKY, A. 2004. Factors affecting clinical outcome in gastrostomy-fed children with cystic fibrosis. <em>Pediatr Pulmonol</em>, 37, 324-328</td>
<td>Retrospective chart audits for all children 1989-1997</td>
<td>Royal children’s Melb Age range 3-20 years old.</td>
<td>None listed</td>
<td>Following gastrostomy feed protocol: At least 50% of energy via PEG, Overnight all but 2 patients on polymeric formula (but 8 changed to semi elemental over time due to GIT symptoms). Enzymes administered 50% pre, 50% post feed, unsatisfactory</td>
<td>Significant improvement in weight for age</td>
<td>Gastrostomy placement for poor nutrition in children with CFALD and portal hypertension is safe and contributes to improved nutritional and pulmonary outcome.</td>
<td>Uncontrolled, retrospective study design. Small numbers- thus lacked power for subgroup analysis.</td>
<td>Other co-morbidities or unplanned treatments not described. Adherence self reported rather than objectively measured by feed consumed or orders placed.</td>
</tr>
</tbody>
</table>
Inclusion criteria:
• Diagnosed CF
• Pancreatic insufficient, 
• Gastrostomy tube placed based on the CF nutrition consensus committees definition of nutritional failure (after diet counselling & oral supplements had failed after 3 month period)

Exclusion:
• Nil listed

Primary outcome:
• Weight for age standard deviation (WAZ score), FEV1 at least 3 monthly.
• Collected for 2 years before and 2 years after gastrostomy 
• GORD (classified by frequent vomiting/regurgitation, infrequent or nil),
• Adherence by self report- categorised as non-adherent if using PEG <2x wkly and reported this at least 50% of the visits.
• Sputum culture

Results:
• In the only study that included a control group, the intervention group significantly improved in z-score weight and z-score BMI after 6 and 12 months of enteral tube feeding.
• Apart from the study by Williams et al. who reported both absolute weight gain and z-score BMI, the other studies reported either percentiles, percentages or z-scores for weight variables.
• Also those studies that included both children and adults reported separate data for adults and children
• In 5 studies, a significant improvement in the weight variables was found after the start of enteral tube feeding, with follow-up periods lasting from 1 year to 2 years to 4 years
• Although, Truby et al. described

Conclusions:
• Advanced lung disease GORD and female gender associated with poor outcome after PEG.
• Feeding is more beneficial if initiated before advanced lung disease established.

### Table

<table>
<thead>
<tr>
<th><strong>Author</strong></th>
<th><strong>NHMRC Level</strong></th>
<th><strong>Case control study</strong></th>
<th><strong>Intervention</strong></th>
<th><strong>Results</strong></th>
<th><strong>Conclusions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHITE, H.,</strong>&lt;br&gt;<strong>POLLARD, K.,</strong>&lt;br&gt;<strong>ETHERINGTON, C.,</strong>&lt;br&gt;<strong>CLIFTON, I.,</strong>&lt;br&gt;<strong>MORTON, A. M.,</strong>&lt;br&gt;<strong>OWEN, D.,</strong>&lt;br&gt;<strong>CONWAY, S. P. &amp;</strong>&lt;br&gt;<strong>PECKHAM, D. G.</strong>&lt;br&gt;2009.</td>
<td>III-2</td>
<td>(with concurrent controls)&lt;br&gt;N=48 CF meeting inclusion&lt;br&gt;N=48 matched controls&lt;br&gt;Leeds, UK&lt;br&gt;1995-2005</td>
<td>Nutritional support per UK consensus guidelines. If ETF was initiated it was as adjunct to oral intake and administered overnight.</td>
<td>Enteral tube feeding resulted in a mean weight gain of 7.0% body weight at 1 year and 9.9% at 2 years after start of enteral tube feeding in those with CFRD, compared to 2.5% and 7.2% in controls with CF.</td>
<td><strong>•</strong> Enteral tube feeding is effective in improving nutritional status, especially in malnourished patients and to slow the decline of lung fx. <strong>•</strong> Patients who develop CFRD are significantly more likely to receive overnight enteral tube feed within the year of diagnosis than controls, highlighting a potential causal relationship that requires further investigation. <strong>•</strong> The impact of oral supplement and enteral feed composition, impaired glucose tolerance, adherence to treatment are all areas that may impact on diabetes outcome. <strong>•</strong> Future work is needed to clarify their effect on nutritional status and in particular the impact of nutritional repletion on glucose metabolism and body composition in the pre-diabetic phase.</td>
</tr>
</tbody>
</table>

**Inclusion criteria:**
- CFRD (OGTT at time of clinical stability and requiring insulin treatment)

**Exclusion:**
- Pancreatic sufficient
- Steroid induced CFRD
- Post organ transplant
- Gestational DM

**Primary outcome:**
- Wt, ht, BMI, FEV1, IV ABx.
- Lung tx and time of death.
- Prevalence of nutritional supplement intake and enteral tube feeding

**Author limitations:**
- Nil

**Appraiser limitations:**
- Study design can not deduce causative relationship
- No discussion of data collectors, blinding.
- Intervention is standard care nutrition support per UK guidelines but individual patient management would introduce some variability.
- Details of enteral feeding regimens not provided as not primary outcome measure
- Retrospective study design using historical matched controls
- 10 year study period – management of CF likely to have changed in this period thus there could be other factors resulting in improvements in nutritional status
**Chapter 6 Q 6.1.6 Should enteral feeding be considered to improve nutrition outcomes for people with CF?**

**NHMRC Grade for recommendation:** Grade B

**Evidence statement:** There is consistent evidence to indicate that enteral feeding improves markers of nutritional status such as weight, BMI and BMI z score in adults and children with CF. In most studies, the best outcomes appear to be achieved within the first 6-12 months of feeding. Improvements in weight were not necessarily exponential or sustained over time, appearing to plateau or decline at the 2, 3 or 4 year interval. The quality of the evidence base is poor, and future research would be enhanced in this areas should be by way of well-designed studies, multicenter in nature and minimising bias.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>D Poor</th>
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<tbody>
<tr>
<td>Evidence base</td>
<td>10 small studies</td>
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<tr>
<td></td>
<td>• 2 level III-2 studies – one comparative (n= 15) and one case control (n= 48), both with concurrent controls</td>
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<td>• 3 level III-3 studies- two retrospective cohort (n= 46, n= 40), one interrupted time series without a parallel control group</td>
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<tr>
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<td>• 5 level IV studies – three retrospective case series (n=14, n=11, n=7), one case series with pre/post-test (n=37), one systematic RV (n=17 studies)</td>
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<tr>
<th>Consistency</th>
<th>A Excellent</th>
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<tr>
<td>Consistency</td>
<td>Excellent consistency amongst studies looking at paediatric, children or combined paediatric &amp; adult data.</td>
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<td>• Various anthropometric markers were considered when looking at nutrition outcomes, including weight gain (% total body weight), BMI, weight for age z-score and BMI z-score.</td>
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<td>• Most studies reported an improvement in the anthropometric parameter studied, with the biggest improvements seen in the first 6-12 months.</td>
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<thead>
<tr>
<th>Clinical impact</th>
<th>A Excellent</th>
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<tr>
<td>Clinical impact</td>
<td>The evidence is directly relevant to the clinical question.</td>
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<td></td>
<td>• Potential benefits to nutritional status are highly relevant to people with CF.</td>
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<td></td>
<td>• The duration of the therapy required is achievable (most studies report on benefits within the first 6-12 months and follow for up to 4 years) and the benefits outweigh the risks.</td>
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<thead>
<tr>
<th>Generalisability</th>
<th>A Excellent</th>
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<tbody>
<tr>
<td>Generalisability</td>
<td>Evidence directly generalisable to target population</td>
</tr>
<tr>
<td></td>
<td>• Studies in both paediatric &amp; adult population</td>
</tr>
<tr>
<td></td>
<td>• Most studies are in Australia, UK and US giving comparable populations</td>
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<tr>
<td></td>
<td>• Study demographics with varying lung function, mostly pancreatic insufficient, either existing malnutrition or some level of nutritional failure or risk despite the implementation of nutritional therapies</td>
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<table>
<thead>
<tr>
<th>Applicability</th>
<th>A Excellent</th>
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<tbody>
<tr>
<td>Applicability</td>
<td>Evidence directly applicable to Australian healthcare context as resources required to achieve outcome in the studies e.g. staff time and expertise, EN supplies, feed type, equipment are all available in the Australian setting</td>
</tr>
<tr>
<td></td>
<td>• The indications for initiating enteral nutrition support and feeding regimens used in the studies matched current accepted practice.</td>
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<td></td>
<td>• Australian cultural factors would be similar in studied populations and Australian populations</td>
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</tbody>
</table>
CLINICAL QUESTION
6.1.7 Should enteral feeding be considered to improve pulmonary status in people with CF?

Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC), Quality (ADA), Relevance</th>
<th>Study Design and Sample</th>
<th>Aim, Intervention and Outcomes</th>
<th>Results and Author’s Conclusions</th>
<th>Appraiser’s Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST, C., BREARLEY, A., GAILLARD, P., REGELMANN, W., BILLINGS, J., DUNITZ, J., PHILLIPS, J., HOLME, B. &amp; SCHWARZENBERG, S. J. 2011. A pre-post retrospective study of patients with cystic fibrosis and gastrostomy tubes. J Pediatr Gastroenterol Nutr, 53, 453-8</td>
<td>NHMRC Level III-3 ADA Quality: Neutral</td>
<td>Retrospective Longitudinal open study with single group pre and post intervention N=46 Minnesota 1989-2007 boys, girls, women and men with CF</td>
<td>Intervention: • Placement of a gastrostomy tube Primary outcome: • Ht, wt, FEV1 National health &amp; nutrition survey ppFEV1. • Collected by experienced personnel. • Values collected 2 years before and 1, 2, 4 years post PEG. • Rate or Slope of deterioration of lung function before and after GT • Median BMI (for each time period) and change in BMI from baseline</td>
<td>Results: • There was significant improvement in the mean rate of FEV1 decline in men &amp; girls. A trend toward improvement in women and boys not significant. Changes not related to initial FEV1. Conclusions: • GT placement results in significant improvement in both BMI and FEV1 except in women • The change in lung Fx post PEG is not dependant on the lung Fx pre placement</td>
<td>Author limitations: • Retrospective study design • Includes data collected over several years (when changes in CF care occurred that may affect both pBMI and ppFEV1 • Confounding variables not accounted for (e.g. cannot demonstrate that improved BMI is solely the result of GT placement, or that subjects actually used their GT) • Single centre study (Minnesota USA), may not be generalizable to Aus/NZ CF population Appraiser limitations: • Some variation in measurements from stadiometers etc inevitable • Number of women in the study low compared with men/children. • Blinding not discussed- likely data collectors are clinicians and not able to be blinded. • More baseline data needed- actual baseline FEV1 • Subgroup analysis were small • Generalisability concerns, single centre study • Nutritional status of patients at time of GT insertion not well defined • Details of GT tubes and types of feeding not available</td>
</tr>
<tr>
<td>EFRATI, O., MEIZAHAV, M., RIVLIN, J., KEREM</td>
<td>NHMRC Level III-3</td>
<td>Retrospective Longitudinal open study with single group pre and post intervention</td>
<td>Intervention: • Nutritional supplementation (40-60% of recommended daily</td>
<td>Results: • Slower rate of respiratory decline (with trend towards</td>
<td>Author limitations: • Short follow-up period of up to 2 years, which is not sufficient to fully evaluate the</td>
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<tr>
<td><strong>ADA Quality:</strong> Neutral (1992 to 2001) N=21 Mild to moderately malnourished Children with CF (ages 8 months to 20 years), Israel – multicentre</td>
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<td><strong>Inclusion criteria:</strong> • Confirmed CF • Weight/height index consistently below 85% of ideal body • Weight, and/or weight loss for more than 3 consecutive months</td>
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<td><strong>Exclusion:</strong> • Lung transplantation, poor compliance • Discontinuation of supplementation</td>
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<tr>
<td><strong>Primary outcome:</strong> Nutritional status and pulmonary outcomes</td>
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<td><strong>Intervention:</strong> In patients that accepted ETF - all were provided 2 cal/ml formula at 20-60% energy intake overnight and free dietary intake during the day</td>
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<td><strong>Secondary outcome:</strong> • Wt, BMI, FEV1, FVC, CFRD, IV Abx at 1 year prior, baseline, and 1, 2 &amp; 3 years. • Looked at confounders including energy intake – overnight) via gastrostomy</td>
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<tr>
<td><strong>Results:</strong> • FEV1 had significant increase in first year of ETF 12.9% from baseline (p=0.01) and in those who opted not to tube feed FEV1 decreased 19.5% over 3 years. • No significant difference in IVABX between groups.</td>
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<tr>
<td><strong>Conclusions:</strong> • Trend towards improvement in pulmonary disease during the second year, and a significant improvement in weight, height and BMI z-scores • Decision to use aggressive nutritional support should be planned and individualised on a case-by-case basis.</td>
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<tr>
<td><strong>Author limitations:</strong> • Observational nature of the study prevents firm conclusions regarding correlation between lung fx stabilisation and nutrition or antibiotic treatment. • Mortality rates small and insufficient to draw conclusion. • Small sample size • Study design allows Self selection bias for ETF. • Wt and BMI may not be best measure of nutritional gain- body composition measures required. • Missing actual specific ETF intake, adherence and dietary intake data.</td>
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<tr>
<td><strong>Appraiser limitations:</strong> opportunistic sample with self-selection</td>
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<tr>
<td><strong>NHMRC Level III-2</strong> <strong>ADA Quality:</strong> Positive</td>
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<tr>
<td>Longitudinal open study with single group pre and post intervention. Retrospective case note review with comparison concurrently between groups. N=23 met criteria N=15 accepted N=6 declined Population: Leeds, UK 2004-2008</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong></td>
</tr>
<tr>
<td><strong>Intervention:</strong> In patients that accepted ETF- all were provided 2 cal/ml formula at 20-60% energy intake overnight and free dietary intake during the day</td>
</tr>
<tr>
<td><strong>Primary outcome:</strong> Clinician adherence to guideline recommendation on enteral feeding</td>
</tr>
<tr>
<td><strong>Secondary outcome:</strong> Wt, BMI, FEV1, FVC, CFRD, IV Abx at 1 year prior, baseline, and 1, 2 &amp; 3 years.</td>
</tr>
<tr>
<td><strong>Results:</strong> FEV1 had significant increase in first year of ETF 12.9% from baseline (p=0.01) and in those who opted not to tube feed FEV1 decreased 19.5% over 3 years. No significant difference in IVABX between groups.</td>
</tr>
<tr>
<td><strong>Conclusions:</strong> Supplemental tube feeding improves clinical outcomes when administered over 3 years resulting in significant wt gain, normal BMI and stabilisation of lung fx. It does not reduce IV A8x days.</td>
</tr>
<tr>
<td><strong>Author limitations:</strong> • Observational nature of the study prevents firm conclusions regarding correlation between lung Fx stabilisation and nutrition or antibiotic treatment. • Mortality rates small and insufficient to draw conclusion. • Small sample size • Study design allows Self selection bias for ETF. • Wt and BMI may not be best measure of nutritional gain- body composition measures required. • Missing actual specific ETF intake, adherence and dietary intake data.</td>
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<td><strong>Appraiser limitations:</strong> opportunistic sample with self-selection</td>
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<td>Inclusion criteria:</td>
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<td>Primary outcome:</td>
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<td>Author limitations:</td>
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<td>Appraiser limitations:</td>
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<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>N=14</td>
<td>N/A</td>
<td>No improvement in respiratory function in the first 12 months of feeding which then plateau during the second year.</td>
<td>Author limitations:</td>
</tr>
<tr>
<td>Exclusion:</td>
<td></td>
<td>Prior gastrostomy insertion &amp; overnight feeding</td>
<td>Conclusion:</td>
<td>Limitations of using weight, height and BMI measures in children and suggests using Z scores</td>
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<td></td>
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<td>Appraiser limitations:</td>
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<tr>
<td>ADA Quality: Neutral</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Inclusion/Exclusion Criteria</td>
<td>Intervention</td>
<td>Primary Outcome</td>
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<tr>
<td>Van Biervliet, S., De Waele, K., Van Winckel, M. &amp; Robberecht, E.</td>
<td>Retrospective case series</td>
<td>Children with CF with pancreatic insufficiency and mildly compromised lung function (FEV1 71% predicted), Australia - Brisbane</td>
<td>N/A</td>
<td>Body weight and BMI, Clinical &amp; pulmonary outcomes</td>
</tr>
<tr>
<td>Van de Leur, M., Massie, J. &amp; Oliver, M.</td>
<td>Retrospective case series [1991-2011]</td>
<td>Children with CF, liver disease and portal hypertension – Melbourne, Australia</td>
<td>N/A</td>
<td>BMI, height and percentage weight for height, Pulmonary function, Food intake as a % of the recommended daily allowances for children, Acceptance and problems with gastrostomy.</td>
</tr>
<tr>
<td>VANDELEUR, M., MASSIE, J. &amp; OLIVER, M.</td>
<td>Retrospective case series</td>
<td>N=7</td>
<td>N/A</td>
<td>Gastrostomy feeding good and safe way to improve nutritional status, growth in CF</td>
</tr>
</tbody>
</table>

**Open Respir Med J**, 3, 112-5

### Study Details

**Children with CF with pancreatic insufficiency and mildly compromised lung function (FEV1 71% predicted), Australia - Brisbane**

- **Inclusion criteria:**
  - Dx CF
  - Gastrostomy placed between 1999 and 2005 at RCH Brisbane.
- **Exclusion:**
  - None listed

**Primary outcome:**

- Body weight and BMI
- Clinical & pulmonary outcomes

**Data collected for 1 year prior and 2 year post insertion**

**Conclusions:**

- Significant improvement in some anthrop. but not respiratory function in the first 12 months of feeding
- Plateau during the second year.
- Highlight the benefit of using height and weight Z scores rather than the measuring of the BMI in children

**Appraiser limitations:**

- Small numbers, low quality study design
- Practices may have changed since 2005
- Study does not explore other possible causes of improved BMI (may not be all attributable to gastrostomy placement)
- No compliance data
- Retrospective
- 2 pts had CFRD and 4 CFLD
Diagnosis of liver disease and portal hypertension

Exclusion criteria:
• None listed

overnight feeding

Gastrostomy placement was recommended by consensus of treatment physicians and followed published guidelines

Primary outcome:
• Safety of PEG re stomal varices
• Anthropometry markers
• Pulmonary outcomes

Primary outcome:

Safety of PEG re stomal varices

Anthropometry markers

Pulmonary outcomes

Intervention:
• N/A

Following gastrostomy feed protocol:
• Overnight tube feeding providing 25-60% of recommended daily calories.
• Feeds ranged 1.5cal polymeric tube feed
• up to 2.6cal/ml modular elemental feed combined with polycose

Primary outcomes:
• Change in weight either absolute, weight for age, z score, percentage, %weight for height or ideal, BMI, %BMI, BMI z score.

Secondary outcomes:
• Change in caloric intake per day, FEV1

Results:
• Stabilisation in pulmonary function in the intervention group after 6 and 12 months providing enteral tube feeding was found in the studies of Bradley et al. Williams et al
• Two studies demonstrated a gradual decline in pulmonary function, respectively from 71% FEV1 Pred at baseline to 67% after 1 year and to 66% after 2 years of gastrostomy feeding and from 44% at baseline to 41% FEV1 pred after 1 year of gastrostomy feeding, and stabilizing at 41% FEV1 pred. after 2 years
• Best et al. found a significant reduction in the rate of pulmonary decline after the start of enteral tube feeding in girls, as well as in adult men (all pb0.05), while women showed a trend toward improvement
• For boys, no significant improvement in the decline of pulmonary function was found, but it should be noted that the initial rate of pulmonary function decline in boys was following the 1992 Ramsey guidelines


NHMRC Level IV

ADA Quality: Positive

Systematic Review – various study designs (enteral feeding studies mostly III-3 and IV)

N=17 articles total
N=7 were on enteral tube feeding

Inclusion criteria:
• Published articles 1st Jan 1997 to 30th April 2012,
• Original studies with 4 patients or more, with a nutritional intervention and describing at least weight as an outcome.

Exclusion:
• Animal studies
• Non English
• No abstract
• Not primary research
• Small sample.

Author limitations:
• Generalizability of results is limited by the lack of heterogeneity of the intervention groups across studies with respect to age, nutrition status, and intake, FEV1.
• Sample sizes varied widely and were generally small.
• Age ranges varied hugely and the impact of age on treatment efficacy is not clear.
• Study follow up ranged from 7 wks to 4 years.

Appraiser limitations:
• Nil
Evidence Statement Matrix

**Chapter 6 Q 6.1.7 Should enteral feeding be considered to improve pulmonary status in people with CF?**

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** [Grade C] There is inconsistent evidence from small, low quality studies to suggest that enteral feeding may improve pulmonary function in someone with CF. Overall, due to the heterogeneity of baseline lung function across studies and the likely progressive nature of lung function decline over study periods, the application of studied regimens could not be expected to generate a predictable outcome in our populations.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>D Poor</th>
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<tbody>
<tr>
<td>9 small studies:</td>
<td></td>
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<tr>
<td>- 1 level III-2 study – Interrupted time series (n= 17) with concurrent controls</td>
<td></td>
</tr>
<tr>
<td>- 3 level III-3 studies - retrospective cohort study (n= 20 cases &amp; controls), two interrupted time series without a parallel control groups (n= 21 &amp; n=46)</td>
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</tr>
<tr>
<td>- 5 level IV studies – three retrospective case series (n=14, n=11, n=7), one case series with pre/post test (n=37), one systematic RV (n=17 studies)</td>
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<thead>
<tr>
<th>Consistency</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, despite studies having similar designs, populations and outcome measures, the results are inconsistent across studies varying from significant improvement in lung function to significant decline.</td>
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<td>- 3 studies indicate increased FEV1</td>
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<td>- 2 studies found no change in FEV1</td>
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<tr>
<td>- 2 found a decline in FEV1</td>
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<tr>
<td>- 2 studies suggest minimal difference in IV antibiotic use and another suggests an increase in IV antibiotic days</td>
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<tr>
<th>Clinical impact</th>
<th>C Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>The evidence is directly relevant to the clinical question.</td>
<td></td>
</tr>
<tr>
<td>- Potential benefits to lung function are highly relevant to people with CF; the interventions required are achievable and relatively low risk. However given the variability in results across studies it is difficult to predict substantial clinic impact.</td>
<td></td>
</tr>
<tr>
<td>Generalisability</td>
<td>B Good</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td>Most studies are in children or adolescents only 3 include adults and results in children would not be transferrable to an adult population.</td>
</tr>
<tr>
<td></td>
<td>Most studies are in Australia &amp; US giving generally comparable populations</td>
</tr>
<tr>
<td></td>
<td>Results seen in people with CF with varying severity of lung disease- which is true of our populations</td>
</tr>
<tr>
<td></td>
<td>Given the intervention of enteral feeding most studies explain or imply their study population has existing undernutrition or a risk of developing undernutrition- this is relatable to our enteral fed populations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evidence directly applicable to Australian healthcare context as resources required to achieve outcome in the studies EG: staff time and expertise, EN supplies, feed type, equipment are all available in the Australian setting</td>
</tr>
<tr>
<td></td>
<td>The indications for EN initiation and feeding regimens used in the studies (though somewhat poorly described) generally appear to match current accepted practice in the Australia.</td>
</tr>
<tr>
<td></td>
<td>Cultural factors would be similar in studied populations and Australian populations given the bulk of studies are in Australia, US assumption can be made that attitudes to health and compliance would be similar in these settings.</td>
</tr>
</tbody>
</table>
CLINICAL QUESTION
6.1.4 When should enteral feeding be introduced for someone with CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.

CLINICAL QUESTION
6.1.5 What is the ideal enteral feeding regimen for someone with CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.

CLINICAL QUESTION
6.1.6 What are the risks associated with enteral feeding in CF compared to the general population?

Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST, C., BREARLEY, A., GAILLARD, P., REGEHMANN, W., BILLINGS, J., DUNITZ, J., PHILLIPS, J., HOLME, B. &amp; SCHWARZENBERG, S. J. 2011. A pre-post retrospective study of patients with cystic fibrosis and gastrostomy tubes. J Pediatr Gastroenterol Nutr, 53, 453-8</td>
<td>NHMRC Level III-3 ADA Quality: Neutral</td>
<td>Retrospective Longitudinal open study with single group pre and post intervention N=46 Minnesota 1989-2007 boys, girls, women and men with CF Inclusion criteria: • At least 5 FEV1 measurements and 1 BMI, • PEG, CF diagnosis, Exclusion:</td>
<td>Intervention: • Placement of a gastrostomy tube Primary outcome: • Ht, wt, FEV1 • National health &amp; nutrition survey ppFEV1. • Collected by experienced personnel. • Values collected 2 years before and 1, 2, 4 years post PEG. • Rate or Slope of deterioration of lung function before and after GT • Median BMI (for each time period) and change in BMI from baseline</td>
<td>Results: • No significant immediate positive or adverse consequences of GT placement on FEV1. • 2/21 patients had GORD req a PEJ, 3/21 had poor adherence and 2/21 had feed pump issues. Conclusions: • GT placement results in significant improvement in both BMI and FEV1 except in women • The change in lung Fx post PEG is not dependant on the lung Fx pre placement</td>
<td>Author limitations: • Retrospective study design • Includes data collected over several years (when changes in CF care occurred that may affect both pBMI and ppFEV1 • Confounding variables not accounted for (e.g. cannot demonstrate that improved BMI is solely the result of GT placement, or that subjects actually used their GT) • Single centre study (Minnesota USA), may not be generalizable to Aus/NZ CF population Appraiser limitations: • Some variation in measurements from stadiometers etc inevitable • Number of women in the study low compared with men/children.</td>
</tr>
<tr>
<td>Transplant</td>
<td>Other causes of malabsorption such as short gut</td>
<td>Transplant</td>
<td>Other causes of malabsorption such as short gut</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**References**


| & PECKHAM, D. G.  
2013.  
N=23 met criteria  
N=15 accepted  
N=6 declined  
Population: Leeds, UK  
2004-2008  
Inclusion criteria:  
• Confirmed CF,  
• Presence of BMI <19kg/m2, and/or 5% acute weight loss over a 2 month period  
• Failure of oral nutritional supplements to adequately improve nutritional status (CF Trust 2002 recommendations)  
Exclusion criteria:  
• Pancreatic sufficiency  
• Pregnancy  
• Lung transplant during the follow up period/  
Primary outcome:  
• Clinician adherence to guideline recommendation on enteral feeding  
Secondary outcome:  
• Wt, BMI, FEV1, FVC, CFRD, IV Abx at 1 year prior, baseline, and 1, 2 & 3 years.  
• Looked at confounders including CFRD, complications of ETF, mortality, compared relationship of low baseline lung fx to gains  
from 30-53% in the ETF group. (Possible that ETF may inadvertently effect the pathophysiology of CFRD by deposition of adipose)  
• Other complications were minimal  
• No major complications were observed. One patient (6%) had minor local infection.  
Conclusions:  
• Supplemental tube feeding improves clinical outcomes when administered over 3 years resulting in significant wt gain, normal BMI and stabilisation of lung fx. It does not reduce IV Abx days.  
• In contrast patients eligible for ETF who decline show deterioration in lung fx and failure to gain wt & achieve normal BMI status.  
|  
|  
| BRADLEY, G. M., CARSON, K. A., LEONARD, A. R., MOGAYZEL, P. J., JR. & OLIVA-HEMKER, M.  
2012.  
Nutritional outcomes following gastrostomy in children with cystic fibrosis. *Pediatr* | NHMRC Level III-3 | Retrospective cohort study, 2005 to 2010  
N=20 cases  
N=20 controls  
Mild to moderate malnourished CF children aged 2-20 years, USA | Intervention:  
• N/A  
• Prior gastrostomy insertion (overnight feeding, n=18 whole protein formula and 1 pt partially hydrolyzed, one elemental.  
• Meal time dose of pancreatic enzymes given at the beginning  
Results:  
• Between 6 months and 1 year, 3 patients were noted to have a GT site lesion and 1 patient complained of pain at the GT site; 80% of the patients developed no complications in this time frame.  
|  
Conclusion:  
|  
Appraiser limitations:  
• Opportunistic sample with self-selection (potential for bias)  
Author limitations:  
• retrospective study design that does not allow for an exact comparison between the GT and non GT groups  
• Short follow up period of 1 year (cannot fully evaluate changes in height, lung function, and frequency of pulmonary exacerbations)  
• Impact of GT on quality of life not assessed  
<p>|</p>
<table>
<thead>
<tr>
<th>Pulmonary, 47, 743-8.</th>
<th>Inclusion criteria:</th>
<th>Exclusion:</th>
<th>Primary outcome:</th>
<th>Appraiser limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CF Dx, at least 1 year post insertion of gastrostomy tube (GT) data</td>
<td>• GT placed for reasons other than nutritional supplementation and end of feeds, approximately 50% of caloric requirements provided through tube)</td>
<td></td>
<td>• Children with CF tube fed are more likely to achieve BMI &gt;50th percentile than matched children without tube feeding</td>
<td>• Some controls treated with appetite stimulants and oral supplements (direct comparison not completed)</td>
</tr>
<tr>
<td></td>
<td>• Each subject matched on age, sex, pancreatic status, BMI and lung function with a non-tube fed children with CF.</td>
<td></td>
<td></td>
<td>• No measure of intake or adherence to feeding regime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary outcome:</td>
<td></td>
<td>• Controls supplementation is a confounder without nut intake data</td>
</tr>
<tr>
<td></td>
<td>Data collected for 1 year prior and 2 year post insertion</td>
<td></td>
<td></td>
<td>• Small numbers, low quality study design</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Practices may have changed since 2005</td>
</tr>
<tr>
<td>TRUBY, H., COWLISHAW, P., O’NEIL, C. &amp; WAINWRIGHT, C.</td>
<td>Design: Retrospective case series (1999-2005)</td>
<td>Data collected for 1 year prior and 2 year post insertion</td>
<td>Results: Complications associated with the PEG:</td>
<td>Appraiser limitations:</td>
</tr>
<tr>
<td>2009.</td>
<td>N=14 Children with CF with pancreatic insufficiency and mildly compromised lung function (FEV1 71% predicted), Australia - Brisbane</td>
<td></td>
<td>• Mild – did not warrant the cessation of overnight feeding during the 3 year audit period [granulation tissue and the gastrostomy site, itchiness, redness and infection, and diarrhoea and reflux associated with feeding)</td>
<td>• Limitations of using weight, height and BMI measures in children and suggests using Z scores</td>
</tr>
<tr>
<td>The long term efficacy of gastrostomy feeding in children with cystic fibrosis on anthropometric markers of nutritional status and pulmonary function. Open Respir Med J, 3, 112-5</td>
<td>Inclusion criteria:</td>
<td></td>
<td>Conclusions:</td>
<td>• Small numbers, low quality study design</td>
</tr>
<tr>
<td></td>
<td>• Dx CF</td>
<td></td>
<td>• Significant improvement in some anthropometric but not respiratory function in the first 12 months of feeding</td>
<td>• Practices may have changed since 2005</td>
</tr>
<tr>
<td></td>
<td>• Gastrostomy placed between 1999 tand 2005 at RCH Brisbane.</td>
<td></td>
<td>• Plateau during the second year.</td>
<td>• Study does not explore other possible causes of improved BMI (may not be all attributable to gastrostomy placement)</td>
</tr>
<tr>
<td></td>
<td>Exclusion:</td>
<td></td>
<td>• Highlight the benefit of using height and weight Z scores rather than the measuring of the BMI in children</td>
<td>• No compliance data</td>
</tr>
<tr>
<td></td>
<td>• None listed</td>
<td></td>
<td></td>
<td>• Retrospective</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary outcome:</td>
<td></td>
<td>• 2 pts had CFRD and 4 CFLD</td>
</tr>
<tr>
<td></td>
<td>Data collected for 1 year prior and 2 year post insertion</td>
<td>• Body weight and BMI</td>
<td>Results: Complications: local irritation (n = 4), night sweating (n = 1) and bed-wetting (n = 1, may be related to larger volumes when 1kcal/ml feed given).</td>
<td>Author limitations:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clinical &amp; pulmonary outcomes</td>
<td></td>
<td>• Nil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Appraiser limitations:</td>
</tr>
<tr>
<td>VAN BIervliet, S., DE WAele, K., VAN WINckel, M. &amp; ROBBERECHT, E. 2004. Percutaneous endoscopic gastrostomy in cystic fibrosis: patient acceptance and effect</td>
<td>Design: Retrospective case series</td>
<td></td>
<td>• Complications: local irritation (n = 4), night sweating (n = 1) and bed-wetting (n = 1, may be related to larger volumes when 1kcal/ml feed given).</td>
<td>• Questionnaires aren’t validated or described in any detail.</td>
</tr>
<tr>
<td></td>
<td>N=11 CF children Aged 6 months to 14 years at time of gastrostomy insertion</td>
<td></td>
<td>• The gastrostomy was well accepted.</td>
<td>• Aims not clearly described</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria:</td>
<td></td>
<td>• Patients and parents were</td>
<td>• Population not well described</td>
</tr>
<tr>
<td></td>
<td>• Dx CF</td>
<td></td>
<td></td>
<td>• No discussions of methods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary outcome:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Inclusion criteria:
- Paediatric CF patients
- Data on CFA database
- Diagnosis of liver disease and portal hypertension

### Exclusion criteria:
- None listed

### Primary outcome:
- Safety of PEG re stomal varices
- Anthropometry markers
- Pulmonary outcomes


<table>
<thead>
<tr>
<th>NHMRC Level</th>
<th>ADA Quality</th>
<th>Study Type</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>Neutral</td>
<td>Retrospective case series [1991-2011]</td>
<td>N=7 Children with CF, liver disease and portal hypertension – Melbourne, Australia</td>
<td>None listed</td>
<td>N/A</td>
<td>Post gastrostomy insertion, overnight feeding</td>
<td>Complications associated with gastrostomy:</td>
<td>Gastrostomy feeding good and safe way to improve nutritional status, growth in CF</td>
</tr>
</tbody>
</table>

### Conclusions:
- Full normalisation of growth pattern is not achieved despite catch-up.
- Gastrostomy tube feeding should perhaps be used earlier to optimise growth.

### Author limitations:
- Very small numbers
- Retrospective study design
- No control group (each patient used as his/her own control)
- 20 year period of study time which may reflect changes in CF management

### Appraiser limitations:
- Selection of study subjects was subjective and down to clinical opinion, despite following the 1992 Ramsey guidelines

### Oliver, M. R., Heine, R. G., Ng, C. H., Volders, E. &

<table>
<thead>
<tr>
<th>NHMRC Level</th>
<th>Study Type</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>Results: Complications</th>
<th>Conclusions</th>
<th>Author limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>Retrospective chart audits for all children 1989-1997</td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
<td>11 patients (30%) reported mild complications</td>
<td>Gastrostomy placement for poor nutrition in children with CFALD and portal hypertension is safe and contributes to improved nutritional and pulmonary outcome.</td>
<td>Uncontrolled, retrospective study design. Small numbers- thus lacked power for...</td>
</tr>
</tbody>
</table>

### Conclusion:
Gastrostomy feeding is a good and safe way to improve nutritional status and growth in children with cystic fibrosis and portal hypertension. However, full normalisation of growth pattern is not achieved despite catch-up. Gastrostomy tube feeding may be used earlier to optimise growth.

### Author limitations:
- No demographic data reported
- No limitations discussed by authors
- Small patient numbers
- Retrospective study design
- Subjects served as own controls
### Olinsky, A. 2004.

<table>
<thead>
<tr>
<th>ADA Quality: Neutral</th>
<th>Case series with pre-test post test</th>
<th>N=37 Royal children’s Melb Age range 3-20 years old.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td></td>
<td>Diagnosed CF, Pancreatic insufficient, Gastrostomy tube placed based on the CF nutrition consensus committees definition of nutritional failure (after diet counselling &amp; oral supplements had failed after 3 month period)</td>
</tr>
<tr>
<td><strong>Exclusion:</strong></td>
<td></td>
<td>Nil listed</td>
</tr>
</tbody>
</table>

**Following gastrostomy feed protocol:**
- At least 50% of energy via PEG,
- Overnight all but 2 patients on polymeric formula (but 8 changed to semi elemental over time due to GIT symptoms).
- Enzymes administered 50% pre, 50% post feed, unsatisfactory weight gain resulted in further dietetics input and manipulation of regimen.

**Primary outcome:**
- Weight for age standard deviation (WAZ score), FEV1 at least 3 monthly.
- Collected for 2 years before and 2 years after gastrostomy
- GORD (classified by frequent vomiting/regurgitation, infrequent or nil),
- Adherence by self report-categorised as non-adherent if using PEG <2x wkly and reported this at least 50% of the visits.
- Sputum culture

**Stomal leakage**
- 6 (16%) had at least one episode of cellulitis at the stoma site, requiring antibiotic treatment.
- None had overt symptoms of pulmonary aspiration.
- No immediate procedure-related mortality after gastrostomy placement.
- 11 patients died during the study period- mortality was significantly associated with WAZ score and predicted FEV1 at time of gastrostomy.
- Female pts were 4x more likely to die though this did not reach statistical significance.

**Conclusions:**
- Advanced lung disease GORD and female gender associated with poor outcome after PEG.
- Feeding is more beneficial if initiated before advanced lung disease established.

### White, H., Pollard, K., Etherington, C., Clifton, I., Morton, A. M., Owen, D., Conway, S. P. &

<table>
<thead>
<tr>
<th>NHMRC Level III-2</th>
<th>Case control study (with concurrent controls)</th>
<th>N=48 CF meeting inclusion N=48 matched controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong></td>
<td>Nutritional support per UK consensus guidelines. If ETF was initiated it was as adjunct to oral intake and administered</td>
<td></td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td>In those who developed diabetes, the use of overnight tube feeds was 4 times more likely at the time of diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

### Appraiser limitations:
- Other co-morbidities or unplanned treatments not described.
- Adherence self reported rather than objectively measured by feed consumed or orders placed.
- Did not explore GI resolution changes from whole protein formula to semi/elemental formula
### Evidence Statement Matrix

**Chapter 6 Q 6.1.10 What are the risks associated with enteral feeding in CF compared to the general population?**

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** There is satisfactory, consistent evidence from low quality studies to suggest that enteral feeding in CF is safe, with no major complications or mortality reported in subjects. Studies describe a range of minor complications associated with enteral feeding in CF, the most common being stoma site issues or reflux.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 small studies:</td>
<td></td>
</tr>
<tr>
<td>• 2 level III-2 studies – one comparative (n= 15) and one case control (n= 48), both with concurrent controls</td>
<td></td>
</tr>
<tr>
<td>• 3 level III-3 studies - a retrospective cohort study (n= 20 cases &amp; controls), two interrupted time series without a parallel control groups (n= 21 &amp; n=46)</td>
<td></td>
</tr>
<tr>
<td>• 4 level IV studies – all retrospective case series (n=14, n=11, n=7), one case series with pre/post-test (n=37)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall consistent evidence between studies. Across all studies, there was no evidence of major complications or mortality reported. The main limitation to</td>
<td></td>
</tr>
</tbody>
</table>
Consistency is the heterogeneity of outcomes that studies looked at or looked for in their populations. This is related to differences in study aims and ability of retrospective data collection to target outcomes of interest.

- 2 studies suggested a link with CFRD
- 4 studies commented on an increased risk GIT issues (i.e. abdominal pain & reflux)
- 8 studies reported at least one subject with stoma issues (i.e. itchiness, redness, pain and milk stoma leakage).
- 2 studies found no pulmonary exacerbation or aspiration
- 1 study commented on Body image and acceptance
- 2 studies discussed a risk of poor adherence to enteral feeding
- Other identified risks included bed wetting, perhaps due to the larger feed volumes and feeding pump difficulties.

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>C Moderate</th>
<th>The evidence is directly relevant to the clinical question.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- The results are clinically important to the CF population as it allows them to weight up risks vs. benefits of enteral feeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Studies had reasonably long data collection periods of 6 months to 4 years, thus there would be sufficient time to pick up major complications of enteral feeding if they did exist.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>B Good</th>
<th>The evidence is directly generalisable to the target population however most studies are in the paediatric population and are not necessarily transferrable to the adult population.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- Most studies are in Australia &amp; US giving comparable populations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>A Excellent</th>
<th>The evidence is directly applicable to the Australian healthcare context as resources required to achieve outcome in the studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- The indications for EN initiation and feeding regimens used in the studies (though somewhat poorly described) generally appear to match current accepted practice in the Australian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cultural factors would be similar in studied populations and Australian populations given the bulk of studies are in Australia, US assumption can be made that attitudes to health and compliance would be similar in these settings.</td>
</tr>
</tbody>
</table>
6.2 Overnutrition

This section is a narrative outlining overnutrition in CF.
No clinical questions and PICOs were identified for this chapter.
Chapter 7 Macronutrients

7.1 Energy, Protein, Fat and Fibre

PICO

7.1.1 Are energy requirements elevated in the CF population compared to the general population?
7.1.2 Are protein requirements elevated in the CF population compared to the general population?
7.1.3 What is the evidence to support the routine recommendation of a high fat diet for people with CF?
7.1.4 What are the recommendations for fibre in people with CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:
- Energy
  - Cystic fibrosis, CF, Nutrition, Diet, energy, energy requirements, energy intake, resting metabolic rate, basal metabolic rate, total energy expenditure, growth
- Protein
  - Cystic fibrosis, CF, Nutrition, Diet, protein, amino acid/s
- Fat
  - Cystic fibrosis, CF, Nutrition, Diet, fat, fatty acid/s, lipid, lipid profile, lipid ratios, phospholipid/s, phospholipid fatty acids, medium chain triglycerides, MCT, linoleic acids, docosahexaenoic acid/s, eicosatrienoic acid/s, omega 6, omega 9, saturated, unsaturated
- Fibre
  - Cystic fibrosis, CF, nutrition, diet, fiber

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
**CLINICAL QUESTION**

7.1.1 Are energy requirements elevated for the CF population?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen JR, McCauley JC, Selby AM, Waters DL, Gruca MA, Baur LA, Van Asperen P, Gaskin KJ. Differences in resting energy expenditure between male and female children with cystic fibrosis. J Pediatr. 2003 Jan;142(1):15-9.</td>
<td>NHMRC level III-2 ADA quality NEUTRAL</td>
<td>Comparative (cross sectional cohorts) study with concurrent controls. Well-nourished CF outpatients: n=134 (males 68) Control group: n=100 (males 51) Inclusion criteria: - Children with confirmed CF aged 3-18.7 years Exclusion criteria: - Enteral feeds - Recent respiratory exacerbations (past month)</td>
<td>Intervention: - Indirect calorimetric measurements taken for 20 minutes in the morning post overnight fasting for all subjects with CF and matched controls. Primary outcome: - Resting energy expenditure (REE) Secondary outcomes: - Presence of clinical factors in children with CF – age, sex, lung function, bacterial colonisation, inhaled steroid use, liver disease, pancreatic insufficiency, genotype</td>
<td>Results: - REE for children with CF was increased, on average, 7.2 % compared to controls - Females 11% elevation (P&lt;0.001) - Males 4% elevation (P&lt;0.02) - REE (adjusted for fat free mass) was higher in children with a severe mutation (5495±47kJ) compared to a mild mutation (5176 ± 124 kJ, P &lt;0.2) CF MALES - REE positively associated with: - Fat free mass (88.3%) - Pancreatic insufficiency (2.3%) - Liver disease (0.6%) - REE negatively associated with: - Pulmonary function (0.6%) CF FEMALES - REE positively associated with: - Fat free mass (72%) - Pancreatic insufficiency (1.6%)</td>
<td>Appraisers limitations: - Nil noted</td>
</tr>
</tbody>
</table>

**Appraisers limitations:**
- Nil noted
| Barclay A1, Allen JR, Blyler E, Yap J, Gruca MA, Asperen PV, Cooper P, Gaskin KJ. | NHMRC level IV | Cross sectional study | Intervention: The following measures taken:  
- REE  
- Anthropometry (BMI, FFM, FM)  
- Pubertal staging.  
  - Prepubertal = Tanner stage I for both pubic hair and breast development.  
  - Premenarche = not having started mensturation  
  - Postmenarche = begun menstruation. | Results:  
- No difference between premenarche and postmenarche for FEV1 and shwachman score for CF group  
- Females with CF had a higher REE than controls (111.671.2% of predicted from controls P>0.001)  
- CF group had a mean increase in REE of 484kJ/24h compared with controls after adjustment for FFM and FM.  
- Significant effect of menarche on REE  
  - Decrease in the postmenarche -470kJ/24h compared with premenarche after adjustment for fat-free mass, fat mass and group (control or CF).  
Conclusion:  
- Females with CF had raised REE that appeared to be independent of menarche.  
- All females with CF and PI may need more intensive dietary management to maintain growth and nutritional status | Author Limitations:  
- Possible confounding effects of disease severity  
- Lack of effect seen in puberty may be due to small sample size of patients in the different tanner stages  
- Longitudinal design would have been more appropriate to measure rates of change in REE through puberty.  
Appraiser Limitations:  
- CF genotype not reported |
| --- | --- | --- | --- | --- |
| Béghin L, Gottrand F, Michaud L, Loeuille GA, Wiza-Derambure N, Sardet A, Guimber | NHMRC level IV | Pre and post design | Intervention:  
- Administration of 14 days home IVAT | Results:  
- TEE not affected by IVAT (7,014 ± 1,929 vs 7,081± 1,478kJ/d)  
- Weight significantly increased | Appraiser Limitations:  
- Nature of study design does not allow researchers to identify full causality to antibiotic treatment |
**D, Deschildre A, Turck D.**

Impact of Intravenous Antibiotic Therapy on Total Daily Energy Expenditure and Physical Activity in Cystic Fibrosis Children with Pseudomonas aeruginosa Pulmonary Exacerbation


**Inclusion criteria:**
- CF patients aged between 5-18yrs who were chronically colonized with pseudomonas (>6 months)
- Z score for weight above -2SD

**Exclusion criteria:**
- Cardiac insufficiency, cardiac rhythm abnormalities and/or treatment with beta blockers
- Oxygen therapy
- Lung transplantation.
- CF patients requiring hospitalization
- Treatment with corticosteroids
- Acute condition known to affect energy expenditure

<table>
<thead>
<tr>
<th>Outcome(s):</th>
<th>Changes in total energy expenditure (TEE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body composition analysis (skinfolds, bio-impedance, weight)</td>
<td></td>
</tr>
<tr>
<td>Energy intake (weekly diary dietitian reviewed)</td>
<td></td>
</tr>
<tr>
<td>Resting energy expenditure (indirect calorimetry)</td>
<td></td>
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<tr>
<td>Physical activity (diary)</td>
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</tr>
</tbody>
</table>

Each evaluation was carried out 3-7 days pre-intervention & 5-10 days post-intervention (at home and in research setting)

- 1.9% post IVAT (32.1 ± 7.5kg vs 32.7 ± 7.6kg, p<0.05)
- Non-significant increases in fat and fat free mass
- Energy intake significantly increased by 4.6% (10,797 ± 3,039kJ vs 11,320 ± 3,307kJ; p<0.05)
- REE decreased by 4.1% (5,295 ± 909 versus 5,093 ± 837kJ/day)
- 9.3% increase in physical activity assessed by activity diary converted to metabolic equivalents tasks (METS) (37.0±3.1 versus 40.7 ± 4.5 MET; p<0.05)

**Conclusion:**
- Improvement in nutritional status after home IV antibiotic therapy is not related to a decrease in total energy expenditure (TEE), but probably an increase in energy intake and a decrease of resting energy expenditure (REE) after therapy.

---

**Bines JE1, Truby HD, Armstrong DS, Phelan PD, Grimwood K.**

Energy metabolism in infants with cystic fibrosis.

**J Pediatr. 2002 May;140(5):527-33.**

**Inclusion criteria:**
- Newly diagnosed subjects with CF aged <20 weeks living in Victoria (AUS)
- Healthy controls aged

**Intervention:**
- Nil (observational)
- CF Infants assessed during initial hospitalisation after dx made, 2.6 - 19.7 weeks
- Controls studied at ages 3 - 13 weeks

**Outcomes:**
- Anthropometrical measures -

**Results:**
- Anthropometry:
  - No significant differences between birth wt or length at birth between CF infants and controls
  - PI strongly associated with poor wt & length gains in CF
- Energy expenditure:
  - CF infants vs. control REE, TEE or MEI not significantly

**Author limitations:**
- No established predictive equations to accurately estimate basal metabolic rate in infants with CF or healthy infant

**Appraiser limitations:**
- Out of date methods for assessing pancreatic insufficiency
- Unable to determine why only some CF infants were included in the study
Prospective Study  
N=17 (10 boys & 7 girls)  
Inclusion criteria:  
- Patients >6 years with CF  
- Admitted to the hospital with exacerbation of CF (meeting at least 5 criteria recommended by Ramsey)  
Exclusion criteria:  
- Oxygen dependent  
- CFRD or cardiovascular  

Primary interventions  
- Indirect calorimetry and body composition (by bioelectric impedance analysis) analysis  
- IV antibiotic course  

Secondary Interventions  
- Anthropometry, Spirometry, standard laboratory test  

Primary Outcomes  
- Measured REE (Weir equation)  
- Estimated REE by calorimeter (Harris Benedict equation)  

Results:  
- REE expressed as kcal/day and kcal/kg fat free mass reduced with antibiotic therapy (not significant)  
- Baseline REE:  
  - 1453±251 kcal/d  
  - 50±11 kcal/kg FFM  
  - Post antibiotics REE:  
    - 1391±273 kcal/d  
    - 46.1±9 kcal/kg FFM  


NHMRC level III-3  
ADA quality NEUTRAL  

Author limitations:  
- Small sample size  

Appraiser limitations:  
- Inclusion criteria not clear  
- No power calculations for sample size  
- Only subjects with poor nutrition status studied (not true reflection of population)
<table>
<thead>
<tr>
<th>Davie PS, Erskine JM, Hambidge KM, Accurso FJ. Longitudinal investigation of energy expenditure in infants with cystic fibrosis. Eur J Clin Nutr. 2002</th>
<th><strong>Heart Failure</strong></th>
<th><strong>Secondary Outcomes</strong></th>
<th><strong>Secondary Outcomes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pneumothorax or haemoptysis</td>
<td>• FEV1, complete blood count, inflammatory markers including ESR, and C-Reactive protein</td>
<td>• % difference between measured and estimated REE (ie % predicted) showed significant difference (p=0.002);</td>
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<tr>
<td></td>
<td></td>
<td>- Baseline = +12.8±2.8</td>
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<tr>
<td></td>
<td></td>
<td>- Post-antibiotics +10.0±2.1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Anthropometry (wt, Ht, BMI, weight/height) no significant difference seen (p≥ 0.05)</td>
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<tr>
<td></td>
<td></td>
<td>• Significant difference b/w inflammatory markers and FEV1, before and after antibiotics: ESR p=0.01, CRP p=0.01, neutrophil count p=0.03, FEV1 p=0.03</td>
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<tr>
<td></td>
<td></td>
<td>Conclusion:</td>
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<tr>
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<td></td>
<td>• Infective exacerbation increases REE (% predicted) in young subjects with CF.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Indirect calorimetry may prove useful in the diagnosis of infective exacerbations and in monitoring the effect of antibiotic therapy.</td>
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<tr>
<td></td>
<td></td>
<td>• Estimated calorimetry measurements expressed in relation to fat free mass suggest that infective exacerbations are among the causes of increased REE in young patients with CF.</td>
<td></td>
</tr>
<tr>
<td>NHMRC level III-3</td>
<td>Longitudinal study</td>
<td><strong>Intervention(s):</strong></td>
<td><strong>Results:</strong></td>
</tr>
<tr>
<td>ADA quality NEUTRAL</td>
<td>N = 12 (8 female)</td>
<td>• Studied at 2, 6 &amp; 12 months to determine TEE and lean body mass using DLW</td>
<td><strong>Author limitations:</strong></td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria:</td>
<td>• Dietary intake measured over 72 hrs (pre and post wt for breastfed and bottle fed infants).</td>
<td>• Small sample size</td>
</tr>
<tr>
<td></td>
<td>• Infants diagnosed with CF on newborn screening</td>
<td></td>
<td><strong>Appraiser limitations:</strong></td>
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<td></td>
<td></td>
<td></td>
<td>• Uses of historical controls</td>
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<td></td>
<td></td>
<td></td>
<td>• Control group not adequately described</td>
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<td></td>
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<td>• Limitations with accuracy of weighed food records</td>
</tr>
</tbody>
</table>
**Inclusion criteria:**
- Confirmed CF
- Receiving care for CF at centre
- >5yrs age

**Exclusion criteria:** Nil stated

**Intervention:**
- Nil (observational)

**Primary outcomes**
Correlation between disease severity (as evaluated by the Shwachman-Kulczycki (SK) score) and the following:
- REE
- FEV1

**Results:**
- Mean SK score = 75.3 +/- 15.7 (range 28-95)
- Mean REE = 109.1% of predicted vs. 96.5% predicted in 16 healthy subjects (P = 0.002)
- Significant correlation between SK score and the following:
  - REE (P = 0.001)
  - FEV1 (P < 0.001)
- Significant correlation between:
  - REE and FEV1 (P = 0.034).

**Conclusion:**
- Correlations between the SK score, REE and FEV1 demonstrate a close connection between disease severity, caloric requirement and lung damage.
- The correlations confirm the clinical value of the SK score, which is easy to assess in a clinical setting.

**Author limitations:**
- Nil noted

**Appraiser limitations:**
- Small sample size
- Opportunistic sample
- SK is a subjective measure of disease severity

---

**Exclusion criteria:**
- Small for gestational age
- Meconium ileus

**Outcomes:**
- TEE and lean body mass using DLW at 2, 6 & 12 months

**Conclusion:**
- Energy expenditure in infants with CF is comparable to healthy controls at 2/12 age.
- TEE is increased by 6/12 of age and this continues through to the first year of life.
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<tbody>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td><strong>N=12 CF subjects (+ 13 healthy age, gender, developmentally matched controls)</strong></td>
<td><strong>Intervention:</strong></td>
<td><strong>Results:</strong></td>
<td><strong>Inclusion criteria:</strong></td>
<td></td>
</tr>
<tr>
<td>• Confirmed CF</td>
<td>• 6wk exercise program and either fat or carbohydrate supplement</td>
<td>• Mean REE was not sig different between CF and controls (p= 0.17)</td>
<td><strong>Challenges with HR measurement equipment</strong></td>
<td></td>
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<tr>
<td>• Aged 9-21yrs</td>
<td>The following measures were taken:</td>
<td>• Mean ECA was different in CF vs controls (p=.02)</td>
<td><strong>Daily activity levels not collected so unsure if the difference in ECA was due to fact that CF patients had less activity or intrinsic metabolic difference from controls</strong></td>
<td></td>
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</tr>
<tr>
<td>• Clinically stable</td>
<td>• REE</td>
<td>• No significant differences in EE after intervention of energy supplementary powder added to food</td>
<td><strong>Diet supplement adherence not reported</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Attends Washington Unit CF centre</td>
<td>• Baseline FVC and FEV1 after a snack</td>
<td><strong>Mostly well patients included</strong></td>
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<tr>
<td>• Must be able to do CPET (maximal cardiopulmonary exercise testing)</td>
<td>• ECG, vCO2, Vo2, resp quotient (RQ) EE/m (weir equation) measured during 5 step activity programme (sitting, standing, walking)</td>
<td><strong>Measurements for controls taken once vs. 3x for CF subjects</strong></td>
<td></td>
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</tr>
<tr>
<td>• FEV1 consistently &gt; 50% for 2yrs prior to enrolment</td>
<td>• Max CPET - cycle ergometers increasing resistance to V02 max – measured V02, VCO2, Ve (endtidal O2 (ETo2, end tidal Co2) and HR by ECG</td>
<td><strong>Unclear response rate (as percent of total clinic population)</strong></td>
<td></td>
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<tr>
<td>• No CFRD or CFLD</td>
<td>TDEE and ECA</td>
<td><strong>Inclusion and exclusion criteria not</strong></td>
<td></td>
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</tr>
<tr>
<td>• No pulmonary exacerbation</td>
<td><strong>Outcome(s)</strong></td>
<td><strong>Included in the study population</strong></td>
<td><strong>Prospective longitudinal study</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Exclusion criteria:</strong> Nil stated</td>
<td><strong>Total daily energy expenditure (TDEE)</strong></td>
<td><strong>Prospective longitudinal study N=86</strong></td>
<td><strong>Measurement of REE and body composition (3 measurements in 2 years)</strong></td>
<td><strong>Unclear response rate (as percent of total clinic population)</strong></td>
<td></td>
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</tbody>
</table>


**Intervention:**
- Measurement of REE and body composition (3 measurements in 2 years)

**Results:**
- REE didn’t change with time allowing for FFM, PI or severe mutations

**Appraiser limitations:**
- Unclear response rate (as percent of total clinic population)
- Inclusion and exclusion criteria not
<table>
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<tr>
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<tbody>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td><strong>Outcome(s):</strong></td>
<td><strong>FEV1 and liver disease were not significant predictors of REE.</strong></td>
<td><strong>REE is elevated in patients with CF with PI and severe mutations.</strong></td>
<td></td>
</tr>
<tr>
<td>• 5 - 18 years</td>
<td>Longitudinal changes in REE</td>
<td>% predicted REE compared with control data was;</td>
<td>The elevation of % predicted REE was greater in females than males &amp; persisted for 2yrs and during pubertal maturation, independent of pulmonary and liver disease.</td>
<td></td>
</tr>
<tr>
<td>• Generally well at time of assessment</td>
<td>The following were also measured:</td>
<td>- Higher (P = .002) in CF females (109.5%)</td>
<td>Results highlight need for a high-energy diet throughout childhood and adolescence, particularly in female patients with PI.</td>
<td></td>
</tr>
<tr>
<td>• No enteral feeds or TPN</td>
<td>• Anthropometry &amp; body composition</td>
<td>- Lower in CF males (104%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No recent infections past month</td>
<td>- Ht. &amp; wt. converted to SDS using US (NCHS) reference tables</td>
<td>- Persisted with time.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> Nil stated</td>
<td>- Skin folds (biceps, triceps, suprailiac, subscapular)</td>
<td>Post-menarchal CF females;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- TBN &amp; FFM</td>
<td>- REE adjusted for FFM was 366 kJ/d lower than in pre-menarchal females but still 112% predicted</td>
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</table>

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</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td><strong>Intervention:</strong></td>
<td>Mean energy intake of CF subjects</td>
<td><strong>Not controlled for genotype characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>• CF patients</td>
<td>• Measurement of REE with indirect calorimetry</td>
<td>- = 127+/-.21% on average (range 100-161%)</td>
<td><strong>Physical activity estimates and dietary intake estimates have limitations</strong></td>
<td></td>
</tr>
<tr>
<td>• Non oxygen dependent</td>
<td>The following measures also taken:</td>
<td>- Was in excess of the EER - 141% higher when compared with TEE.</td>
<td><strong>Appraiser limitations:</strong></td>
<td></td>
</tr>
<tr>
<td>• &lt;15 years</td>
<td>• Anthro (wt., ht.,)</td>
<td>Total energy intake comprised</td>
<td><strong>Small sample size</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> Nil specified</td>
<td>• Body composition (skinfolds, FFM)</td>
<td>16% protein, 55% CHO and 29% fat</td>
<td><strong>Stool samples not taken to assess losses in CF patients</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Author limitations:**
- No control group
- Methods to assess TBN not described

**Appraiser limitations:**
- Small sample size
- Stool samples not taken to assess losses in CF patients
- Lung function not assessed – disease severity
| Mc Closkey M, Redmond AO, Mc Cabe C, Pyper S, Westerterp KR, Elborn SJ. | NHMRC level III-3 | Comparative study without concurrent controls | Aim to measure energy intake (EI) & total energy expenditure (TEE) in CF patients when they are clinically stable & during exacerbation. | Results:  
REE was higher at the start of an exacerbation  
- 8.3 (0.9) MJ/d) than the end of IV Ab 7.1 (1.2) MJ/d)  
(P <0.05)  
No significant difference in TEE during stable period compared to exacerbation;  
- 10.53 (2.39) MJ/day | Author limitations:  
Small sample size limiting degree to which data can be interpreted. | Biochemical markers  
• Hair Zn levels  
• Dietary intake (24hr food recall)  
• Physical activity levels (questionnaire)  
Primary outcome:  
• REE  
REE no significant difference between groups.  
• REE values were similar to estimates of FAO/WHO equations in both groups.  
- 105% in CF and 103% controls  
• REE was associated with nutritional status as measured by W/H (r=-0.46) and triceps skinfold (r=-0.54) in both groups  
• REM and FFM were strongly associated (r=0.85) in the entire group  
• TEE was highly correlated to FFM by deuterium (r=0.79) and energy intake (r=0.48)  
Conclusions:  
• Energy requirements for CF children are similar to those for normal health children.  
• Their food intake (particularly energy) was higher than their requirements, emphasising the need to reassess nutritional recommendations for these patients to avoid overweight and obesity.  
Conclusions:  
Energy requirements for CF children are similar to those for normal health children.  
Their food intake (particularly energy) was higher than their requirements, emphasising the need to reassess nutritional recommendations for these patients to avoid overweight and obesity. |
between 15-40 years

- Confirmed CF
- Moderate respiratory disease (FEV1 30-70%)

Exclusion:
- Nil stated

Measure of TEE (24hr heart rate and doubly labeled water)

Primary outcomes:
- REE
- TEE

compared to 8.77 (1.59) MJ/day using doubly isotopically labeled water

- No difference in EI during exacerbation compared to stable period;
  - 11.19 (2.31) MJ/day compared to 11.77 (2.30) MJ/day
- Resting heart rate was higher at the start of an exacerbation;
  - 85 (5) beats/min and decreased by the end of the exacerbation 81 (6) beats/min (P<0.05)
- Correlation between TEE and EI using 24 h HR methodology, \( r^2 = 0.6 \) (P=0.03)
- No correlation between TEE and EI using DLE

Conclusions:
- No difference in TEE & EI when pts unwell (hospital admission) compared to when stable (home) despite an increase in REE in hospital.
- EI is maintained throughout.


Case series post-test

N = 38
(CF patients aged 9-35yrs)

Inclusion criteria:
- Clinically stable CF pts.
- Confirmed CF diagnosis
- Regular clinic attendance

Aim: To investigate the relation between Resting Energy Expenditure (REE) and disease severity in clinically stable CF pts without pulmonary exacerbation; also to investigate whether REE may serve as an indicator of disease severity.

Intervention:
- Measure of REE (indirect calorimetry - fasting)

Results:
- Increased REE expressed as a percentage of predicted (REE%) was seen in PI CF pts (113.3±2.5%) compared to PS CF pts (98±2.5%) & healthy subjects
- Elevated REE% in the PI group wasn’t affected by gender and showed correlation with the clinical status of the pts (r=-

Author limitations:
- Small sample size of PS patients compared with PI

Appraiser limitations:
- Overall small sample size
**Exclusion criteria:**
- Pulmonary exacerbation, verified on the basis of physical examination, CRP, leukocyte and neutrophil counts.
- Gastrostomy tube feeds or parenteral nutrition.
- PFTs (FEV1, FVC, PEFR)
- Chest x-ray
- Sputum culture
- Bloods – leukocytes, neutrophils, CRP & ferritin

**Primary outcomes:**
- REE, PFT, Chest Xray

**Secondary outcomes:**
- Sputum cultures
- Leukocytes, neutrophil counts, CRP, ferritin, Shwachman scores (SS)

**Conclusions:**
- Percent predicted REE is an objective indicator of disease severity, progression & energy requirements in the assessment of CF pts.
- Strong negative correlation between REE% and pulmonary function as well as clinical status in PI group.
- REE is increased in CF pts with PI compared with PS.
- Exocrine pancreatic function determines REE% rather than clinical status which is also affected by pancreatic function.

**Results:**
- REE as % predicted values were significantly higher in CF subjects:
  - WHO equation
    - CF = 109+/12%
    - Controls = 100+/-10%
    - p 0.02
  - Schofield equation
    - CF = 110+/-11%
    - Controls = 100+/-10%
    - p 0.008
- FFM (p=0.0001) and FM (p=0.016) positively associated

**Author limitations:**
- Control group not was not representative of population as indicated by lower growth and nutritional z-scores.
- Small sample size

**Appraiser limitations:**
- Nil

---

<table>
<thead>
<tr>
<th>Stallings VA, Tomeszko JL, Schall JI, Mascarenhas MR, Stettler N, Scanlin TF, Zemel BS.</th>
<th>NHMRC level IV</th>
<th>ADA quality POSTIVE</th>
<th>Cross sectional study</th>
<th>Intervention:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent development and energy expenditure in females with cystic fibrosis.</td>
<td>N=16 (CF) N=38 (controls)</td>
<td>Measurement of the following:</td>
<td>REE as % predicted values were significantly higher in CF subjects;</td>
<td>WHO equation</td>
<td></td>
</tr>
<tr>
<td>Clin Nutr. 2005 Oct;24(5):737-45.</td>
<td></td>
<td>- REE</td>
<td>- 109+/12% Controls = 100+/-10% p 0.02</td>
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<tr>
<td></td>
<td></td>
<td>- Anthro (wt. and ht.)</td>
<td>- Schofield equation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Body composition (skinfolds &amp; FFM)</td>
<td>- CF = 110+/-11% Controls = 100+/-10% p 0.008</td>
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<tr>
<td></td>
<td></td>
<td>- PFTs</td>
<td>- FFM (p=0.0001) and FM (p=0.016) positively associated</td>
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</tbody>
</table>
Control sample of similar age and menarcheal status with no known medical illness.

Exclusion Criteria:
- Incomplete data

with REE.
- REE was negatively associated with menarcheal age after adjusting for FFM and FM in females with CF had significantly greater REE ($p=0.017$) by 110 kcal/d. (explains 55% variance)
- CF females:
  - FFM was a significant positive predictor ($p=0.011$)
  - Menarcheal age a negative predictor ($p=0.04$). With each advancing year of menarcheal age REE declined by 36 kcal/d)
- Control group:
  - FFM ($p=0.002$) and FM ($p=0.03$) a predictor of REE

Conclusion:
- Height and muscle stores were reduced and REE elevated in subjects with CF.
- Poorer growth and nutritional status and delayed menarche in CF were associated with poorer pulmonary function in CF and were likely related to the cumulative effect of energy imbalance on growth and body composition.
**Evidence statement:** Within the inclusion period for this review, there was no evidence to guide energy requirements for the entire CF population. The evidence from observational studies refers mostly to infants, children and young people <21 years. Until further evidence is available, it is recommended that health professionals continue to be guided by consensus guidelines when recommending energy targets for people with CF.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>Satisfactory</th>
</tr>
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<tbody>
<tr>
<td>A combination of level III and IV studies were included for review.</td>
<td></td>
</tr>
<tr>
<td>4 Level III-2 studies</td>
<td></td>
</tr>
<tr>
<td>- Children: n=15, n=134; positive quality</td>
<td></td>
</tr>
<tr>
<td>- Children &amp; adults: n=12; positive quality</td>
<td></td>
</tr>
<tr>
<td>- Adults: n=21; neutral study</td>
<td></td>
</tr>
<tr>
<td>5 Level III-3 studies</td>
<td></td>
</tr>
<tr>
<td>- Infants: n=46; neutral quality</td>
<td></td>
</tr>
<tr>
<td>- Children: n=17, n=15, n=12; neutral quality</td>
<td></td>
</tr>
<tr>
<td>- Adults: n=11; neutral quality</td>
<td></td>
</tr>
<tr>
<td>5 Level IV</td>
<td></td>
</tr>
<tr>
<td>- Children: n=16, n=56, n=86; neutral quality</td>
<td></td>
</tr>
<tr>
<td>- Children &amp; adults: n=16; positive quality and n=38; neutral quality</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall lack of consistency in study methodology and outcome measures.</td>
<td></td>
</tr>
<tr>
<td>Each study looked at one (or more) of the following on REE:</td>
<td></td>
</tr>
<tr>
<td>- Disease progression, pulmonary function, fat free mass (FFM), pancreatic status, gender, age, pubertal status and exercise</td>
<td></td>
</tr>
<tr>
<td>Also lack of consistency in findings with somewhat conflicting results in the following areas:</td>
<td></td>
</tr>
<tr>
<td>- Correlation between REE and FFM, pancreatic function and pulmonary function</td>
<td></td>
</tr>
<tr>
<td>- Change in REE with acute respiratory exacerbations</td>
<td></td>
</tr>
<tr>
<td>- Impact of gender and puberty on REE</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to conflicting results, the clinical impact is difficult to assess. Despite some evidence of altered REE for people with CF, guidance is lacking in regards to the practical application of these findings</td>
<td></td>
</tr>
<tr>
<td>- Individual variation in energy requirements aren’t accounted for</td>
<td></td>
</tr>
<tr>
<td>- Unable to use results to guide best practice when estimating energy requirements and setting energy targets for people with CF</td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL QUESTION
7.1.2 Are protein requirements elevated for the CF population?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.

CLINICAL QUESTION
7.1.3 Is there evidence to support a high fat diet for the CF population?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.

The formulated recommended and NHMRC evidence grade was based on the extensive literature to support the high fat diet in CF, pre 2002.

Evidence Statement Matrix

<table>
<thead>
<tr>
<th>Chapter 7 Q7.1.3 What is the evidence to support the routine recommendation of a high fat diet for people with CF?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHMRC Grade for recommendation:</strong> <strong>Grade D</strong></td>
</tr>
<tr>
<td><strong>Evidence statement:</strong> There were no new studies included in this systematic literature review (2002-2016) to make changes to the existing recommendation for fat intake in CF. The <em>Australasian CF Guidelines (2006)</em> recommended an unrestricted diet, containing adequate fat to meet energy requirements. Target 100g/day if over five years of age based on the premise that a diet high in fat is less bulky and more achievable than a diet that is low in fat. Studies published since 2002 focused on the lipid profile and supplementation of essential fatty acids in people with CF.</td>
</tr>
</tbody>
</table>

CLINICAL QUESTION
7.1.4 What are the fibre requirements for people with CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.
7.2 Essential fatty acids

PICO

7.2.1 Does dietary supplementation with omega-3 essential fatty acids improve health outcomes in people with CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:

- Omega 3 essential fatty acids
  - Cystic fibrosis, CF, omega-3 essential fatty acids, omega 3, omega 3 polyunsaturated fatty acids, essential fatty acids, serum phospholipids, omega 6, fatty acid ratio, fish oils, essential fatty acid deficiency, linoleic acid, linolenic acid

Inclusion & exclusion criteria:

Inclusion criteria:

- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:

- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers

Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
</table>
| De Vizia B., Raia V., Spano C., Pavlidis C., Coruzzo A., Alessio M.. | NHMRC level III-3 ADA quality NEGATIVE | Comparative study without concurrent controls/case-control study with historical controls. | Intervention:
  - Enteric coated capsules containing either 0.5g or 1g of fish oil concentrate.
  - 1g capsule contained: 400mg EPA, 200mg DHA + 10mg of vitamin E. | Results:
  1. Fatty acid content of erythrocyte membrane phospholipids:
    - Significant rise in DHA levels after 4 | Author limitations:
    - Nil
  Appraiser limitations:
    - Adherence levels not measured |
<table>
<thead>
<tr>
<th>N=30 (CF children and adults; mean age 12.4 years, ranging from 0-24 years)</th>
<th>Patients were also encouraged to consume a fish-rich diet. Therefore – mean daily intake of EPA and DHA = 1.28g EPA and 0.93g DHA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=20 (controls)</td>
<td></td>
</tr>
</tbody>
</table>

**Inclusion criteria:**
- PI
- PsA

**Exclusion criteria:**
- High serum creatinine
- Oral contraceptives
- Coagulation issues
- Low platelet count
- Daily use of steroids or NSAIDs

**Outcome:**
- Erythrocyte/RBC fatty acid analysis
- FEV1 (>5 years)
- Nutritional status
- Lipids
- Inflammatory markers (WCC, CRP, IgG, IgA, IgM, α-1 antitrypsin)
- Antibiotic use

Data collected at baseline, 4, 8 months.

- Levels of EPA were increased after 4 months (p<0.05) but not after 8 months.
- No significant changes in other omega 3 fatty acids.
- Significant reduction in AA between baseline and 8 months in intervention group (p<0.05).

2. **FEV1:**
- Significant, increase at 8 months (p<0.05)

3. **Nutritional status:**
- Significant increase in height at 4 and 8 months (p<0.05) and increase in weight at 4 months only (p<0.05), weight returning to baseline at 8 months.

4. **Lipids:**
- Significant reduction in trigs at 4 months only (p<0.05).
- No change to cholesterol.

5. **Inflammatory markers:**
- Significant reduction in IgG at 8 months and reduction in α-1 antitrypsin at 4 and 8 months.

6. **Antibiotics:**
- Significantly lower use of antibiotics (total days) compared to preceding 8 months (p<0.05)

**Conclusions:**
- Study showed anti-inflammatory effects of EPA+DHA supplementation with reduction in AA levels which in turn may lead to decreased levels of pro-inflammatory eicosanoids.

- Bias in patient selection
- No concurrent controls
- No power calculation
- Use of 2 different supplementation doses with no information on which patients received which dose
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>NHMRC level</th>
<th>ADA quality</th>
<th>Case series</th>
<th>Primary Intervention</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Author limitations</th>
</tr>
</thead>
</table>
| Jumpsen J.A., Brown N.E., Thomson A.B.R., Paul Man S.F., Goh Y.K., Ma D., Clandinin M.T. | IV | NEUTRAL | N=4 (CF adults; mean age 36.5, age range 18-43 years) | • 70mg/kg/day DHA for 6 weeks (200mg DHA per capsule) 45% DHA.  
• Average dose = (64.6kg average weight) = 4522mg/day DHA | • FEV1 - No significant change  
• Plasma DHA levels  
  - Total, PE and PC plasma phospholipid levels showed a significant increase in DHA pre vs post (p<0.05)  
  - Plasma AA levels  
  - PE and PC plasma phospholipid levels showed a significant decrease in AA pre vs post (p<0.05).  
  - Not sig. for total levels.  
• RBC DHA levels  
  - Total, PE and PC RBC phospholipid levels showed no significant increase in DHA pre vs post.  
• RBC AA levels:  
  - Not significant decrease in AA for any of total, PE or PC.  
• Intestinal DHA levels  
  - Total intestinal phospholipid levels the increase was not significant for DHA; however was significant for both minor classes of phospholipids (PE and PC) (p<0.05).  
• Intestinal AA levels  
  - Not significant decrease in AA for any of total, PE or PC. | • Pro-inflammatory neutrophils LTB-4  
• LFTs  
• Dietary DHA intake | • Nil |
| Inclusion criteria: | Exclusion criteria: | Compliance by phone and capsule count. | | Capsules also contained the following fatty acids:  
  - Saturated fatty acids (myristic, palmitic and stearic)  
  - Very small percentage of omega 3 EPA and α-linolenic <0.05%). | | | Appraiser limitations: |
| • Delta F508  
• Clinically stable  
• Mild lung disease (FEV1 51-79%)  
• BMI > 18  
• Taking minimum vit E dose 80IU for at least 3 months. | • Nil stated | | | | |  |
| Primary Outcomes: | | | | | | |
| • FEV1  
• Plasma, red blood cell and intestinal (baseline + 6 weeks) levels of DHA | | | | | | |

Conclusions:  
• Dietary supplementation with DHA over a six week period can achieve positive
| Oliver C., Watson H.  
Omega-3 fatty acids for cystic fibrosis.  
Cochrane Database Systematic Rev.  
2013. Issue 11. | NHMRC level I  
ADA quality POSITIVE | Cochrane systematic review of level II studies.  
Randomised controlled trials (RCTs), quasi-randomised trials, and cross-over trials  
**Selection criteria:**  
RCTs in CF subjects comparing omega-3 fatty acid supplements with placebo.  
4 studies with total of 91 participants were included based on selection criteria.  
**Participants:**  
12-43 participants  
Children and adults  
Age range up to 41 years  
Most PI  
**Length of duration:**  
6 weeks -6 months | **Aim:**  
To determine whether there is evidence that omega-3 polyunsaturated fatty acid supplementation reduces morbidity and mortality and to identify any adverse events associated with supplementation.  
**Intervention:**  
- Dietary supplementation of omega-3 essential fatty acids of any dosage, frequency and duration compared with placebo in people with CF. The supplements contain omega-3 fatty acids in the form of EPA or DHA or both.  
- Dose in studies included ranged from 0.2g EPA and 0.1g DHA to 3.2g EPA and 2.2g DHA  
- 2 studies compared omega-3 fatty acids to olive oil for six weeks  
- 1 study compared a liquid dietary supplement containing omega-3 fatty acids to one without for six months  
- One study compared omega-3 fatty acids and omega-6 fatty acids to a control (capsules with customized fatty acid blends) for three months (Keen) h/e omega-6 group not included in analysis as not part of Cochrane question.  
**Primary outcomes:**  
- Number of respiratory exacerbations including:  
  - Hospitalizations  
  - antibiotic courses  
- Adverse events and dropouts | **Significant results:**  
- 1 short-term study comparing omega-3 to placebo reported a significant improvement in lung function and Shwachman score and a reduction in sputum volume in the omega-3 group.  
- 1 study (43 participants) demonstrated a significant increase in serum phospholipid essential fatty acid content and a significant drop in the n-6/n-3 fatty acid ratio following omega-3 fatty acid supplementation compared to controls.  
- The longer-term study (17 participants) demonstrated a significant increase in essential fatty acid content in neutrophil membranes and a significant decrease in the leukotriene B4 to leukotriene B5 ratio in participants taking omega-3 supplements compared to placebo.  
**Conclusions:**  
- Regular omega-3 supplements may provide some benefits for people with cystic fibrosis with relatively few adverse effects, although evidence is insufficient to draw firm conclusions or recommend routine use of these supplements in people with cystic fibrosis.  
- This review has highlighted the lack of data for many outcomes meaningful to people with or making treatment decisions about cystic fibrosis. A large,  
| **Limitations:**  
- Level of bias unclear  
- Small sample sizes meaning data potentially skewed and therefore not generalisable to entire CF population |
<table>
<thead>
<tr>
<th>Evidence Statement Matrix</th>
</tr>
</thead>
</table>

**Chapter 7 Q7.2.1 Does dietary supplementation with omega-3 essential fatty acids improve health outcomes in people with CF?**

**NHMRC Grade for recommendation: Grade C**

**Evidence statement:** There is some evidence to suggest that dietary supplementation with omega-3 fatty acids may improve health outcomes for people with CF; this evidence relates only to ‘biochemical’ health outcomes and not to ‘clinical’ or ‘therapeutic’ health outcomes. There is insufficient evidence to recommend routine omega-3 fatty acid supplementation for improving health outcomes in either children or adults with CF and there is no evidence to recommend routine omega-3 fatty acid supplementation for improving health outcomes in infants with CF. There is insufficient evidence to suggest that any one particular type of omega-3 fatty acid or a mix of omega-3 fatty acids is superior for improving health outcomes in people with CF.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 studies included:</td>
<td></td>
</tr>
<tr>
<td>• 1 level 1 randomised control study, n= 20 children and young adults</td>
<td></td>
</tr>
<tr>
<td>• 1 level III-3 study (n= quality)</td>
<td></td>
</tr>
<tr>
<td>• 1 level IV study (n= quality)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies looked at a variety of outcomes and were therefore difficult to compare for consistency.</td>
<td></td>
</tr>
<tr>
<td>• Fatty acid content of membrane phospholipids - findings consistently demonstrate increased omega-3 content of membrane phospholipids post omega-3 supplementation</td>
<td></td>
</tr>
<tr>
<td>Clinical impact</td>
<td>D Poor</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------</td>
</tr>
<tr>
<td>Difficult to ascertain the clinical impact due to the following:</td>
<td></td>
</tr>
<tr>
<td>- Dose and duration required to achieve the effect is inconclusive</td>
<td></td>
</tr>
<tr>
<td>- Size of the effect was unable to be measured due to underpowered sample sizes</td>
<td></td>
</tr>
<tr>
<td>- Many studies failed to report on adverse events</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Given the heterogeneous nature of CF and the fact that overall the studies address this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega-3 supplements are available on the Australian and New Zealand market however compliance may be an issue in the CF population.</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 8 Fat Soluble Vitamins

8.1 Vitamin A

PICO

8.1.1 How should vitamin A be assessed for people with CF?
8.1.2 What is the role for routine supplementation of vitamin A in people with CF and pancreatic insufficiency?
8.1.3 What vitamin A supplementation dose should be prescribed to treat vitamin A deficiency in people with CF?
8.1.4 What is the safe upper limit for vitamin A supplementation in people with CF?
8.1.5 How often should we measure / monitor vitamin A levels in people with CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:

- Vitamin A
  - Cystic fibrosis, vitamin A, retinol, retinal, deficiency, subclinical deficiency, supplementation, toxicity

Inclusion & exclusion criteria:

Inclusion criteria:

- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:

- Studies that didn't specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers

CLINICAL QUESTION

8.1.1 How should vitamin A be assessed for people with CF?

Evidence Table

There were no studies available within the search strategy and criteria that addressed this PICO.
**CLINICAL QUESTION**

**8.1.2** What is the role for routine supplementation of vitamin A in people with CF and pancreatic insufficiency?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
</table>
- Nil – observational  
Following measurements recorded:  
- Serum retinol and α-tocopherol levels were Vitamin A and E supplementation (prescribed only if reduced serum levels were found)  
  - Water miscible vitamin preparation at dose of 1500 IU/day of Vitamin A and 78IU of Vitamin E, and if both levels low a combined dose of Vit A 2210 IU & E 102 IU/day  
- Serum fat soluble vitamin levels  
- Anthropometry  
- Dietary intake  
- Pancreatic function  
- Assessment of lung disease  
T1 = within 2 months of enrolment/ diagnosis  
T2 = 12 months of age  
Outcomes:  
- Serum retinol and α-tocopherol levels  
- Assessment of lung disease  
- Anthropometry; weight, length, TSF  
- Dietary intake MJ/kg  
- Pancreatic function | Results:  
Anthropometry:  
- At T1, CF infants already showed abnormalities in weight, length, weight for length ratio and body composition. Serum retinol and α-tocopherol:  
- At T1, 20 infants (51%) had serum retinol levels below the normal reference range 0.7 (0.3) umol/L, including 5 both low serum retinol and α-tocopherol concentrations.  
- Dietary energy intake was related to serum retinol concentration at T1 (r² = 0.27; P<0.001).  
- Serum retinol levels (umol/L) increased significantly from T1 to T2 =0.69 (0.59, 0.79) and 1.23 (1.11, 1.36) respectively (P<0.001) umol/L  
- T2 mean serum retinol levels had increased significantly. Biochemical vitamin A deficiency had been corrected in all but one patient.  
- No significant relationship between serum retinol levels and pancreatic status or growth at T1.  
- No significant relationship between serum retinol concentrations and CF genotype, pancreatic status or mode of presentation.  
- Evidence of lung disease as suggested by  
Appraiser’s limitations:  
- Not reported if fasting for tests - unlikely in infants.  
- No objective measures of inflammation  
- No control group  
- No lipid ratio for vitamin E  
- Supplemented if any deficiency detected but didn’t state how often ax for deficiency  
- Compliance to taking supplements not measured or commented on  
- Were there enough subjects enrolled in study to get meaningful results (no statistical power)?  
- Did not comment on intake of dietary Vitamin E (and bottle vs breast fed infant) and impact on serum levels.  
- Only measured serum vitamins at baseline and 1 year after  
- How was the food diary executed, if not weighed data then higher degree of error |
Nil stated

Assessment of lung disease:
- At T1 and T2 number of subjects with pulmonary infection was similar. (31% and 44% respectively)
- Some evidence of mild progressive lung disease in older subjects who systematically were more likely to have respiratory symptoms, lower Brasfield scores and increased airway inflammation.
- No association between serum retinol and α-tocopherol levels at T1 and the development of lung disease, determined by the presence of respiratory symptoms, Brasfield scores and pulmonary inflammatory markers at T2.

Conclusion:
- No evidence found to implicate the deficiency of Vitamin A and E with the early development of CF lung disease, including airway inflammation, during infancy

Wood LG, Fitzgerald DA, Lee AK, Garg ML.
Improved antioxidant and fatty acid status of patients with cystic fibrosis after antioxidant supplementation is linked to improved lung

<table>
<thead>
<tr>
<th>NHMRC level: Level II Intervention</th>
<th>Double blind randomised control trial</th>
<th>Primary Intervention(s):</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood LG, Fitzgerald DA, Lee AK, Garg ML. Improved antioxidant and fatty acid status of patients with cystic fibrosis after antioxidant supplementation is linked to improved lung</td>
<td>N=46 children with CF Group A Low dose supp (n=24) Group B High dose supp (n=22)</td>
<td>4 wk run-in period during which they received a low-dose supplement [10 mg vitamin E (as RRR-tocopherol) and 500 ug vitamin A (as retinyl palmitate) in oil]. This meant that in addition to their dietary intakes of vitamins A and E, Note all vitamin and mineral supplements ceased other than trial supplements Group A, continued to receive low-dose supplement ie served as a control group</td>
<td>No sig differences bw groups any outcome parameter at baseline Antioxidant defences improved in group B but not in group A (plasma concentrations of vitamin E, B carotene, and selenium and in GSHPx activity were observed in group B. No significant difference between groups in the mean change in plasma 8-iso-PGF2α concentrations. No significant differences between groups</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Appraiser’s Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No inclusion criteria</td>
</tr>
<tr>
<td>No information on numbers excluded</td>
</tr>
<tr>
<td>4 wk run in still given Vit E supps for ethical reasons.</td>
</tr>
<tr>
<td>Generalisability - Patient’s relatively mild lung disease and children. Otherwise F508 and pancreatic status similar to usual populations</td>
</tr>
<tr>
<td>Didn’t report reference ranges (except low Vit E) ie were baseline levels post washout normal or not?</td>
</tr>
</tbody>
</table>
Inclusion criteria:
- CF diagnosis confirmed by elevated sweat chloride
- Age < 5 y (Unable to perform reproducible spirometry)
- Abnormal vitamin E concentration (< 8 mol/L) at baseline (Karr et al 1997).

Exclusion criteria:
- Age < 5 y (Unable to perform reproducible spirometry)
- Abnormal vitamin E concentration (< 8 mol/L) at baseline (Karr et al 1997).

Group B, received a high-dose supplement [200 mg vitamin E (as RRR-_-tocopherol), 300 mg vitamin C (as sodium ascorbate), 25 mg B-carotene (all-trans isomer), 90ug Se (as selenomethionine), and 500 ug vitamin A (as retinyl palmitate) in oil], for 8 wks.

Supps taken with BF with usual dose PERT. Compliance measured with diary cards recording daily intake and counting of pills.

Primary Outcomes:
- Diet intake - 3d food record
- Plasma A,E and B carotene by HPLC methods
- Isoprostanates
- Plasma fatty acids
- Glutathione peroxidase enzyme
- Superoxide dismutase enzyme assay

in changes in % FEV1, % FVC, quality of well-being or in change in cell counts.

- No significant differences between groups in the change in nutrient intake during (note gp B higher zinc intake at baseline) or in the change in fatty acid concentrations.

- Within group B, the change in B-carotene concentrations correlated with the change in percentage of FVC (r = 0.586, P = 0.005)

- The correlations between the change in vitamin E concentrations and the change in % FEV1 (r = 0.363, P = 0.106) and the change in % FVC (r = 0.148, P = 0.523) were not sig.

- In group B, the change in total plasma fatty acid concentrations correlated with the change in %FEV1 (r = 0.583, P = 0.006) and with the change in 8-iso-PGF2 concentrations (r = 0.538, P = 0.010)

Secondary Outcome:
- Compliance similar between groups.
- No difference bw gps in diet intake.
- Vit Eu mol/L Baseline GpA 18.8+-1.5; GpB 16.5+-1.1 Change in Gp A -1.9+-0.9 and in Gp B 10.6+-1.5 P<0.001

Conclusions:
- Improved plasma B-carotene, selenium, and fatty acid status are linked to improved lung function, despite the fact that increased fatty acid concentrations are also linked to increased oxidative stress.

- Although antioxidant defences improved with high doses of antioxidants, there was no corresponding decrease in oxidative stress (as measured by 8-iso-PGF2_...
Plasma fatty acid concentrations were found to have the strongest influence on plasma 8-iso-PGF2α concentrations, suggesting that a high fat intake contributes to oxidative stress. However, a correlation between increased plasma fatty acid concentrations and improved lung function suggests that high fat diets have clinical benefit.


<table>
<thead>
<tr>
<th>Case series (aetiology) - predominantly descriptive study</th>
<th>Inclusion criteria:</th>
<th>Intervention(s):</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=35 Age: 12.1 ± 8.8 (2-40)</td>
<td>• Nil listed only that met criteria for Dx of CF (repeated elevated sweat chloride concentrations and typical clinical manifestations in all patients)</td>
<td>• Nil – observation</td>
<td>• Mean FE-1 for 35 pts: 256.9 ± 445.2 ug/g (median: 24.1 ug/g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annual fat soluble vitamins A, D, E (retinol, 25-OH-vitamin D and alpha-tocopherol)</td>
<td>• Significant difference b/w PI vs PS pts: -24 pts with PI mean 19.9 ± 15.8 ug/g (median 18.7 ug/g) and 11 pts with PS had mean of 773.9 ± 494.4 ug/g (median: 728.9 ug/g p&lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FE-1</td>
<td>• All 24 patients with exocrine pancreatic insufficiency had FE-1 values lower than 60µg/g.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily vitamin supplementation</td>
<td>• Fat Sol Vit Levels</td>
</tr>
</tbody>
</table>
|                                                          |                     | - Standard multivitamin preparation (e.g. Biovit, Nycomed) - 20ml dose (double dose), containing per millilitre: 50ug vitamin A, 0.75ug vit D, and 0.6mg vit E plus water soluble vitamins | • At Dx and follow up for 17 pts: all mean values for fat soluble vitamins were in normal range except Vit E for PI-
|                                                          |                     | - OR their ordinary dose plus cod liver oil (the recommend 5ml of oil contains 500µg vitamin A, 10µg Vitamin D and 10mg Vitamin E) | • 55% (5/9) in this group had low vit E at diagnosis with mean value 7.0 ± 6.6 mg/L (medium 3.6mg/L) and were all corrected at follow up (9.8 ±2.7 mg/L (median 10.8mg/L)) |
|                                                          |                     | - PLUS Vitamin E supplement (Ido-E, Pharmacia & Upjohn) of 50-200mg daily | • One pt with Vit E deficiency at diagnosis also had deficiency of Vit A and Vit D-
|                                                          |                     | | • 2 pts with PS had low Vitamin levels: 1 pt both Vit A & Vit E deficiency corrected at follow up and 1 pt Vit D deficiency also corrected |
|                                                          |                     | | • Mean values for fat soluble Vitamins at diagnosis |

**Appraiser's Limitations:**
- Were serum levels measured when stable?
- Other treatments not mentioned (other than IV AB's)
- Did not measure selection bias possible (no comment on how selected pts, was it all newly Dx b/w 1992-2001)
- Ordinary dose of fat soluble vitamin not stated
- Didn't say how the dose of fat soluble vitamins was adjusted over years (for PI pts with low vitamin E and other pts))
- Did not ask pts if they were started on vitamin A, & D and cod liver oil prior to diagnosis
- Reported received double dose or ordinary dose plus cod liver oil but didn’t specify which participants received which.
- Compliance to taking vitamins not assessed nor to PERT
- Small sample size (no statistical power calculation)
- Why did they only have serum fat soluble vitamin levels for 17/35 pts at diagnosis (were some already corrected?)
follow up for 35 pts did not differ significantly b/w PI and PS (p>0.05) and all in normal range: Serum Vitamin E -for PI 9.1 ± 2.7 (3.4- 12.0 and PS 9.8 ± 4.2 (5.2-18.9)

- No correlation b/w pancreatic exocrine function measured by FE-1 and fat soluble vitamin profiles neither at Dx nor at follow up (r=0.292, p< 0.100)
- At follow up with all apparently supplemented highest range in PS patients was 18.9mg/l and PI 12.9mg/L (Mean PI 9.1+-2.7 range 3.4-12.9); PS 9.8+-4.2 (5.2-18.9)

Conclusions:
- No correlation b/w faecal elastase-1 levels and fat soluble vitamin status.
- Values of fat-soluble vitamins were mostly in the normal range in both PS and PI. This may be an indication of appropriate PERT and vitamin supplementation both before and after diagnosis and may reflect good patient compliance.
- Official recommended supplementation of vitamin A & D in Norway during infancy and childhood may explain why so few pts had vitamin deficiencies at diagnosis.

Author’s Limitations:
- Common use of Vitamin A, D and cod liver oil supplementation in infants and children.

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| Lezo A, Biasi F, Massarenti P, Calabrese R, Poli G, Santini B, Bignamini E. Oxidative stress in stable cystic fibrosis patients: Do we need higher antioxidant | NHMRC level IV Aetiology | Cross-sectional study N=70 Stable CF children ages 1 to 18 years Inclusion criteria: Stable CF 1-18 years | Intervention: Observational review of clinical parameters plus a prospective 3 day diet history Observational review of the following: Vit supplementation Antioxidant status: plasma selenium ug/l, ascorbic acid, retinol ug/l + alpha tocopherol mg/l (HLPC), red blood cell total and reduced glutathione (GSH) GSH-umol/gHb, selenium | Results: Primary outcome: Chromolipids (HNE-L) and (MDA-L) significantly higher than reference ranges for health population, only 4.8% and 1/6 of CF pts in reference range HNE-L and MDA-L were elevated in the majority of patients despite normal plasma vitamin E, A and C. HNE-L and MDA-L increased with age | Appraiser’s Limitations: Potential biases – no details on subjects were selected and no inclusion or exclusion criteria: only 36/70 subjects were pancreatic insufficient, slightly more females (32M/38F) Confusing reporting vitamin supplementation (e.g. swaps between median and mean) |
Exclusion:
• None listed

Primary outcome:
• Oxidative stress markers:
  - Chromolipids [Lipid-adducts 4-hydroxynonenal (HNE-L) and malonaldehyde (MDA-L)]

Secondary outcomes:
• Energy and nutrient intakes
• Anthropometry: wt (kg, centile, z score); ht (cm, centile, z score); BMI
• Resp fn test FEV1

PI showed significantly higher plasma chromolipids (MDA-L 0.92UF/mg PI pts vs 0.68 non-PI, p=0.002) and (HNE-L 1.77UF/mg PI vs 1.22UF/mg, p=0.004) despite no differences in plasma vitamins.

Plasma antioxidants were inversely correlated with age that exerts an independent significant effect in reducing vitamin E C but not sig for A ie

Mean vitamin A and E intakes were aligned above recommendations for CF,

Oxidative stress (Cromolipid HNE-l and MDA-l) were significantly higher than healthy pop local reference range (LRR) HNE-l and MDA- normal in 4.8% and 1.6% only

3DFR – E intake met recommendations

Using Bielsalski categorisation:
  - Suboptimal Vit E (67.1%) (still in normal local reference ranges)
  - Deficient Vit E (21.5% vs 7.2 using local ref ranges) – all patients showed higher oxidative stress (plasma chromolipids) than those with optimal levels

Age related to clusters: patients with optimal Vit E levels were significantly younger (p<0.05)

Optimal 4.6yrs (1.9-7.9) vs Supoptimal 8.8yrs (1.1-19) vs Deficient 7.0 (1.1-18)

Plasma antioxidants were inversely correlated with age that exerts an independent significant effect in reducing vit E (ps=-0.25, p=0.034)

Plasma oxidative stress markers HNE-l, MDA-l, Ratio plasma cholesterol showed increasing trend with lower antioxidant Vitamin Concentrations

Author’s limitations:
• Limited number of oxidative stress markers measured eg airway markers of oxidative stress could provide further information
• Not all specific p values provided
• Vit E (HNE-L/chol ps=-0.11, p=0.384; MDA-L/chol ps=-0.24, p=0.058),
  - Assumed higher levels of Vit E (12.9-18.9mg/l) provide better protection against lipid peroxidation
• Plasma antioxidants inversely correlated with age Vit E (ps=-0.25, p=0.034),
• Plasma chromolipids increased significantly with age -MDA-L/cholesterol ps=0.36, p=0.003, HNE-L/cholesterol ps=0.33, p=0.004
• Aging accounted for 10% MDA-L and 12% HNE-L of the increase in the plasma chromolipids
• Inverse relationship between plasma concentrations of both chromolipids and antioxidant status -Not sig for Vit E – hne-lhd/chol (ps -0.11 p=0.384)
• PI vs PS: similar plasma vit levels Vit E (PS 9.1 (3.0-18) vs PI 9.4 (1.4-15) p=0.455 and GSH/GSSG ratio in plasma
• Plasma chromolipids were significantly higher in PI vs PS MDA-L/cholesterol PI 0.92 (0.29-3.78) vs Ps 0.68 (0.46-2.63) p=0.002; HNE-L/cholesterol PI 1.77 (0.49-3.20) vs PS 1.22 (0.75-2.67) p=0.004

Conclusions:
• Majority of CF pts showed elevated oxidative stress markers in stable clinical conditions and plasma antioxidant in normal range
• Aging led to progressive increase in plasma oxidative stress markers and decrease in plasma antioxidant vitamins inverse correlation between plasma vitamin levels and oxidative stress markers (consistent with Vit C)
• PI patients showed higher oxidative stress markers without significant differences in
Retrospective cross sectional  
N=530 CF children & adolescents  
Inclusion criteria:  
• All children attending CF centres during time period of 2007-2010  
Exclusion criteria:  
• Nil stated  
Primary Intervention(s):  
• Nil – observation  
Following measures taken:  
• Vit A levels using protein precipitation with high performance liquid chromatography (HPLC) and ultraviolet detection (in house method)  
• Vitamin E, D(25 OHD) and PT (for vitamin K)  
Primary Outcomes:  
• Fat soluble vitamin deficiency rates  
Results:  
• Deficiency of one or more fat-soluble vitamins was present in 240/530 children (45%)  
• 301 /470 (64%) took fat-soluble vitamin supplementation.  
• No overt signs of deficiency, such as peripheral neuropathy and spinocerebellar degeneration with ataxia (vitamin E)  
• Serum vit E levels were abnormal in 201/523 children. (38%)  
• 105 children (20%) had low vit E.  
• Mean vit E was 19umol/L±9.  
• 35% of PI were deficient and 3% of PS deficient. (Vit A 10% and 0% respectively)  
• PI 19umol/L+9 vs PS 22umol/L+6, p<0.01 Vit E levels assoc with pancreatic status  
• Prevalence 2007-2010 decreased 15.54% to 13.89% (Vit A increased from 11.17% to 13.13%)  
• Vitamin E supplements were taken by 266/470 children (57%). - Median vitamin E supplement dose was 150 ug/day (75–150ug/d).  
Conclusion:  
• Vit A,D,E deficiency in small minority of children. Fat sol vit testing important in all to identify def in PI patients who may not be compliant to supps and/or inadequate supplementation, and in PS patients who may be progressing to PI.  
• Approx 1/3 PI patients were deficient in plasma vitamins.  
• Suggests the need for a careful definition of vitamin needs in CF that may need to consider oxidative status. Consider the need for Vit C monitoring and supplementation  
| Appraiser’s Limitations:  
• No details re how CF or PI diagnosed  
• Different reference ranges used between laboratories indicating "deficiency"  
• 85% patients 'recruited' patients with vit levels. Characteristics of the 15% without levels not known. No reasons given for loss.  
• No regression analysis with vit supp - variable likely to impact results.  
• No method info at time of tests re whether patients acute/non acute (ie exacerbation dec vit A levels); fasting non fasting etc?  
• No CRP level done to help determine inflammation  
• Doesn't report if any with CFLD  
• Many confounders that may affect levels such as diet, type of supplementation, compliance not measured.  
• Nil adherence measure  
Author Limitations:  
• Prevalence rates influenced by recruitment no  
• No control group of healthy same age range.  
• Vitamin ref ranges differed between labs |

**NHMRC level:** IV  
**ADA quality:** NEUTRAL

<table>
<thead>
<tr>
<th>NHMRC level: IV (Aetiology)</th>
<th>ADA quality: NEUTRAL</th>
<th><strong>Intervention:</strong></th>
<th><strong>Results:</strong></th>
<th><strong>Appraiser’s limitations:</strong></th>
</tr>
</thead>
</table>
| Retrospective arm: n=102; 465 (3 years)  
Mean age 11.1 +/-6.4 years (1.5-27)  
Prospective arm n=62 (43 PI patients and 19 PS patients) | | | | |
| | | Retrospective  
Patient records retrospectively studied over 3 years and mean serum Vitamin A (and E) for each patient calculated  
3 groups - FEV1 >80%; 60-80% and <60%  
(Bloods routine care q 4-12m)  
Further, Vitamin A (and E) levels were measured prospectively over a 2 year period at the onset of IV ABs and 1 month post-discharge | Retrospective arm of study  
Average Vit E level was 0.7±0.28mg/dL  
Negative correlation bw number PE and vitamin serum levels - E levels (r=-0.444, P<0.001), even when levels within the normal range. This indicates that the number of respiratory exacerbations increased as the mean values of serum vitamin E decreased.  
Sig negative correlation when analysed in both PS and PI groups separately.  
No significant differences seen between groups with good (FEV1>80%), moderate (FEV160-80%) or poor lung function (<60%) for Vitamin E p=0.237 but sig diff for vitamin A as well as no of PE bw these groups. p<0.001 | - Prospective arm: PS pts older (mean 13.26 vs 10.17 years PI)  
- Cofounders for Vitamin A Vitamin A measured during exacerbations (false low due to acute phase response)  
- Prospective study  
- Poor study design – testing done during acute phase response  
- Part one of study - unclear when levels tested ie reports part of routine care every 6-12m but were they acutely unwell at the time  
- Small sample size may have resulted in Vitamin E increase post PE not reaching sig.  
- appraiser  
- No reports of diet intake  
- No info re compliance with supplements  
- No info re mean supp intake  
- No info whether PS patients taking supps as guidelines PI specific  
- No info re inflammatory status  
- No methodology for vit levels ie fasting  
- No measure of RBP or B carotene  
- No measure of cholesterol/lipid ratio |
| | | | | |
| | | Prospective  
Vitamin levels onset PE and 1/12 post over 2 years. Only PE requiring IV Abx. | Prospective arm of study  
At onset of exacerbation, vitamin E levels were reduced in the PI patients - vit E 0.67±0.13mg/dL increasing to 0.85±0.35 after recovery, P<0.001)  
Similar seen in the PS patients (vit E 0.82mg/DL increasing to 0.98 after recovery, P<0.07) | | |
| Inclusion criteria:  
- Confirmed Dx CF  
- Dx PS made by normal 3-day fecal fat collection and/or normal fecal elastase. | Ref ranges reported; Vit A 25-200ug/dL and Vitamin E 0.5-2mg/dL | | |
| Exclusion criteria:  
- None listed | | | |

Vit E (?non compliance or in need of higher supp does?) Only small number of PS deficient in vit E. A lower limit of normal of Bumol/L for vitamin E may be more appropriate than 12umol since complications are commonly seen once vitamin E levels are <5umol/L.  
- Recommend all patients (PI and PS) have annual levels. Based on def of some fat sol vits in PS patients. These PS patients may be progressing to PI.
### Conclusions:
- Reduced serum levels of vitamin A and E even in the normal range are associated with an increased rate of pulmonary exacerbations in CF.
- Authors propose increase the target serum levels to at least 35μg/dL for Vitamin A and 0.9μmol/dL Vitamin E. Unclear if maintaining levels > than these will decrease no. of PE. ie higher levels of serum vitamin A and E may lower risk for PE.
- Vitamin deficiency may play a role in predisposition to PE in both PI and PS patients.
- Further studies are required to confirm the necessity of supplementation of vitamins A and E to PS patients.

### Author's Limitations:
- Nil stated


**Relationship between Fat-soluble Vitamin Supplementation and Blood Concentrations in Adolescent and Adult patients**

<table>
<thead>
<tr>
<th>NHMRC level: IV</th>
<th>ADA quality: NEUTRAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case series:</td>
<td>N=243 (n=177 eligible)</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td></td>
</tr>
<tr>
<td>All patients seen at the CF centre were eligible</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td></td>
</tr>
<tr>
<td>Those without fat soluble vitamin concentration data</td>
<td></td>
</tr>
</tbody>
</table>

| Primary Intervention(s): |
| Nil-observation. |
| Following measures taken: |
| Prescribed or reported fat soluble vitamin supplement |
| Serum fat soluble vitamin concentrations |
| CFTR gene mutation |
| Age, sex, race, BMI, and PI |

| Primary Outcomes: |
| Serum levels of retinol and retinyl palmitate (vitamin A) |
| - Suboptimal concentrations were defined as vitamin A, serum retinol <0.3 mg/L (1.05 μmol/L) |
| Serum levels of α-tocopherol and β/γ-tocopherol (vitamin E) |

| Results: |
| Baseline vitamin E supplement was 218.38 ± 224.11 IU in 2008 and 351.58 ± 295.99 IU in 2012. |
| Vit E serum levels 2008 8.93±4.46 to 2012 8.15±3.87mg/L |
| 24% of patients had suboptimal serum vitamin E levels at baseline. |
| Vitamin E supplement, on average, increased by 12.2% annually (P < .0001) in contrast to the α-tocopherol and β/γ-tocopherol level, which did not change significantly over the past 5 years (P = .26 and P = .96). |
| High vit E serum tocopherol >18mg/L (42μmol/L) found in a few patients but no symptoms of hypervitaminosis E were documented in medical records |

| Appraiser's Limitations |
| No info re where reference ranges obtained from |
| No reference ranges for retinol palmitate or By tocopherol |
| Did not report data for tertile intake. Only reported % suboptimal levels at baseline (ie 2008). |
| Did not report ref rec intakes - i.e how did intakes compare with rec? |
| Prescribed OR reported fat sol vit use data collected. These are both very different |
| No 'control' group or reference comparisons |
| No methodology re how fat sol vitamins measured ie usual protocol. |
| Were subjects fasting?
Suboptimal concentrations were defined as vitamin E, serum α-tocopherol <5 mg/L (12 μmol/L).

- No significant association between the level of vitamin intake and the corresponding concentration of the serum fat-soluble vitamin was found in any type of the vitamins studied.
- No significant association between type of CFTR gene mutation and the concentration of other serum fat-soluble vitamins, including retinol, retinyl palmitate, α-tocopherol, β/γ-tocopherol, α-tocopherol, and β/γ-tocopherol.

Conclusions:
- The results from this study have demonstrated that a substantial increase in fat-soluble vitamin supplementation in adults with CF over the past 5 years was not associated with a significant increase in serum concentrations of these vitamins.
- Despite a near doubling of reported fat-soluble vitamin supplementation over the past 5 years, the changes of these vitamins’ serum concentrations were not clinically significant.
- Potential reasons include suboptimal dosages, low adherence or ongoing issues with malabsorption.

Author’s Limitations:
- Retrospective study
- Did not assess the adherence to fat-soluble vitamins or fat-soluble vitamin intakes from dietary sources given the limitation of our study design.
- Only included adolescents and adults, and findings may not be applicable to other age groups
- Lack of comparative data for serum concentrations of fat-soluble vitamins from a control group.


<table>
<thead>
<tr>
<th>NHMRC level</th>
<th>Intervention:</th>
<th>Results:</th>
<th>Appraiser’s Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>II (Intervention)</td>
<td>ML1 (100ml liquid multi) once a day for 3 months OR 100ml placebo with a wash-out period of 3 months (placebo identical taste and macronutrient composition)</td>
<td>Plasma vitamin E and A levels increased during ML1 when compared to placebo. Vitamin E had increased with 16.9± 11.6 μmol/l (from 11.7±7.4 μmol/l to 28.6±12.8 μmol/l), while in the placebo group vitamin E levels had dropped 2.3±7.9 μmol/l (from 13.2±5.9 μmol/l to 11.0±6.1 μmol/l).</td>
<td>Compliance data not recorded/collected</td>
</tr>
<tr>
<td>ADA quality NEGATIVE</td>
<td>Nutritional assessment – weight, height, BMI and skinfold thickness (4 sites)</td>
<td>PFTs – performed after salbutamol</td>
<td>Small pt numbers for an RCT</td>
</tr>
</tbody>
</table>

Patient stable and had no IV Abs for 2

Inclusion criteria
- Children aged 9 to 18 years with stable clinical condition (i.e. no need for oral or IV antibiotic treatment other than chemoprophylaxis) in the two months prior to testing
- Absence of musculoskeletal disorders
- FEV1 > 70% predicted.

Exclusion:
- None listed

Peripheral muscle strength – hand-held dynamometer used to measure isometric muscle force in 6 groups
Exercise testing – cycle ergometer and the Wingate anaerobic test
Lab analysis – fasting state, prior to exercise, venous blood sample, including retinol and vitamin E α-tocopherol HPLC methods
Malondialdehyde (MDA)

This difference in change between intervention and placebo period is significant (P<0.001).
Increase in Vit E correlated with increased pulmonary function p=0.04 (Reported in discussion only)
Plasma MDA levels decreased during placebo but marginally increased during ML1 p=0.15 ie ‘pro oxidant effect’
No significant difference in vitamin A levels in groups at the end of 3 months
No significant difference in nutritional parameters, BMI, FFM and skinfolds between groups at end of 3 months
FEV1, FVC and anaerobic and aerobic test – significant difference towards the placebo group.
No beneficial effects on either pulmonary function or muscle performance in CF patients given a micronutrient supplement vs placebo

Conclusions:
- Micronutrient mixture was not superior to placebo with respect to changes in pulmonary function or muscle performance in pediatric CF patients, despite a significant increase in plasma vitamin E concentrations (increase seen in vitamin A serum levels not significantly increased).
- Need studies of single antioxidant nutrients and to determine optimal supplementation levels required to normalise parameters of oxidative stress.

Brei C, Simon a, Krawinkel MB, Naehrlich L.
NHMRC level: IV
Descriptive study (Observational)
Primary Intervention(s):
- Nil – observational study

Results:
- Total Vitamin A intake (RE/d) from food & supplements was 315 ±182% of D-A-CH

Appraiser’s limitations:
- No information given on algorithms or guidelines used to individually dose
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<td>Met diagnostic criteria for CF</td>
<td>• Vitamin A intake from food &amp; supplements (as retinol equivalents) and compared to age and gender based D-A-CH intake recommendations and UL RDI’s</td>
<td>N=32 CF paediatric (&gt;4yrs) and adults</td>
<td></td>
</tr>
<tr>
<td>&gt;4 years</td>
<td>Compared to age-based supplementation recommendations for CF pts from Australia, US, UK, Germany, Europe</td>
<td>Vitamin A deficiency defined as serum retinol concentration &lt; 20 ug/dl</td>
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<td>PI</td>
<td>Vit A supplementation doses</td>
<td>Outcomes: Fat soluble vitamin supplementation doses.</td>
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<td>Mild – moderate lung disease (FEV1 &gt; 40%)</td>
<td>Nutrition status (anthropometry)</td>
<td>Serum biochemistry: Retinol binding protein (RBP)</td>
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**Outcomes:**

- Fat soluble vitamin supplementation doses.
- Serum biochemistry:
  - Retinol binding protein (RBP)
  - Retino:RBP
  - Zinc
  - CRP
  - IgG and LFTs
- Deficiency defined as RBP<15mg/l and ratio of retinol:RBP <0.8 squared

**Recommendations with 65% from supplements**

- Total vitamin A intake exceeded the UL of D-A-CH recommendations in 69 % of subjects
- Prescribed Vitamin A supplement dose range was 0-20,000 IU/day (medium 5500 IU)
- Vitamin A supplements provided as retinol equivalents/day (mean ±SD) 2425 ± 1181 ug (429-6000)
- 25% did not receive any vitamin A supplement and 25% of these pts had a Vitamin A intake > UL ( and had higher Vit A food intake, better lung function, younger age and better Nut’s status and were healthier subjects)
- 41% of supplemented patients, the supplementation dose alone exceeded the UL. The same was true for 9% of subjects with regard to food intake alone.
- CF recommendations for supplementation was met in 28% of all subjects
  - 50% of pts met prescribed Vit A dose of US (Borowitz 02) & German (Stern 2011) recommendations for 4-8 year olds (rec dose is 4000-10,000 IU/day)
  - 25% of > 8 year olds (rec dose of 10,000 IU/day)
- All pts had serum retinol levels in normal range: > 20 ug/dl and <72 ug/dl despite highly variable total intake (95th percentile of NHANES reference range)
- Mean serum retinol range was 38.6 ± 0.2 ug/L (22.1-59.1 ug/dl)
- Significant differences in serum retinol levels found b/w children & adolescents (< 11 yrs : 33.6 ± 6.6 ug/dl : 11-18 yrs 41.2 ug/dl)

**Author’s limitations:**

- Small number of subjects in study
- Exclusion criteria - bias to stable, PI, > 4 yrs. Healthier subjects
- Only analysed serum retinol (and not retinyl ester levels or liver biopsy
- No local comparison data for serum retinol therefore used NHANES reference range
- 4 day food records may not accurately reflect long term consumption
- All pts had serum retinol levels in normal range: > 20 ug/dl and <72 ug/dl despite highly variable total intake (95th percentile of NHANES reference range)
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- Significant differences in serum retinol levels found b/w children & adolescents (< 11 yrs : 33.6 ± 6.6 ug/dl : 11-18 yrs 41.2 ug/dl)
- Did not discuss if any multivitamin’s included in routine care
- Previous low serum levels were not reported
- Did not say how the food records were executed, can be unreliable unless weighed data & not clear if food records were only done once
- Only measured compliance to taking vitamin sups at one point (food record)
- Unclear when the blood test was done in relation to food records fasting?
- No control group

**Vitamin A based on serum levels**

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**Outcomes:**

- Fat soluble vitamin supplementation doses.
- Serum biochemistry:
  - Retinol binding protein (RBP)
  - Retino:RBP
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- Deficiency defined as RBP<15mg/l and ratio of retinol:RBP <0.8 squared

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- Prescribed Vitamin A supplement dose range was 0-20,000 IU/day (medium 5500 IU)
- Vitamin A supplements provided as retinol equivalents/day (mean ±SD) 2425 ± 1181 ug (429-6000)
- 25% did not receive any vitamin A supplement and 25% of these pts had a Vitamin A intake > UL ( and had higher Vit A food intake, better lung function, younger age and better Nut’s status and were healthier subjects)
- 41% of supplemented patients, the supplementation dose alone exceeded the UL. The same was true for 9% of subjects with regard to food intake alone.
- CF recommendations for supplementation was met in 28% of all subjects
  - 50% of pts met prescribed Vit A dose of US (Borowitz 02) & German (Stern 2011) recommendations for 4-8 year olds (rec dose is 4000-10,000 IU/day)
  - 25% of > 8 year olds (rec dose of 10,000 IU/day)
- All pts had serum retinol levels in normal range: > 20 ug/dl and <72 ug/dl despite highly variable total intake (95th percentile of NHANES reference range)
- Mean serum retinol range was 38.6 ± 0.2 ug/L (22.1-59.1 ug/dl)
- Significant differences in serum retinol levels found b/w children & adolescents (< 11 yrs : 33.6 ± 6.6 ug/dl : 11-18 yrs 41.2 ug/dl)

**Author’s limitations:**

- Small number of subjects in study
- Exclusion criteria - bias to stable, PI, > 4 yrs. Healthier subjects
- Only analysed serum retinol (and not retinyl ester levels or liver biopsy
- No local comparison data for serum retinol therefore used NHANES reference range
- 4 day food records may not accurately reflect long term consumption
- All pts had serum retinol levels in normal range: > 20 ug/dl and <72 ug/dl despite highly variable total intake (95th percentile of NHANES reference range)
- Mean serum retinol range was 38.6 ± 0.2 ug/L (22.1-59.1 ug/dl)
- Significant differences in serum retinol levels found b/w children & adolescents (< 11 yrs : 33.6 ± 6.6 ug/dl : 11-18 yrs 41.2 ug/dl)
±7.9 µg/dl with p=0.019 and no significant difference found b/w the age groups with (> 18 yrs 40.2 ± 12.2 µg/dl) No gender diffs.
- Serum RBP was 29.9 ± 8.1 mg/l and > 15mg/l in all pts
- Correlation b/w serum retinol and RBP was significant (r=0.79; p< 0.0001)
- Ratio of serum retinol:RBP was 0.99 ± 0.14 and <0.08 in one pt
- 2 patients suffered from liver cirrhosis and 19% had at least an elevation of AST or ALT.
- Zinc deficiency was detected in one patient.
- No correlation b/w FEV1% and serum retinol concentrations (r=0.27, p=0.14)
- Serum retinol levels were significant lower in pts with elevated IgG (chronic inflammation) compare to normal IgG (29.6 ± 3.9 µg/dl vs 40.0 ± µg/dl; p=0.017) but NO association b/w retinol and CRP levels < 0.5 versus > 0.5mg/l.

**Conclusion:**
- Individualized vitamin A supplement (of 0-20,000 IU/day) based on annual serum retinol levels can prevent Vitamin A deficiency and high serum retinol levels but it may lead to Vitamin A intake above the recommended upper intake limit.
- Clinicians should aim for minimum Vit A supplement dosage to achieve sufficient serum retinol levels to prevent deficiency and avoiding hypervitaminosis.

<table>
<thead>
<tr>
<th>Graham-Maar RC, Schall JI, Stettler N, Zemel BS, Stallings VA.</th>
<th>NHMRC level: IV (Aetiology)</th>
<th>Cross sectional study design</th>
<th>Primary Intervention(s): Nil – observational</th>
<th>Results:</th>
<th>Appraiser’s limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=73 children with CF</td>
<td>The following measures taken in study: CF 7 day diet record: Mean daily vit A intake was 816+-336 ug RAE providing 165+-69%</td>
<td></td>
<td></td>
<td>Generally for reasonable healthy PI Cf patients over 6yrs age-12yrs</td>
<td></td>
</tr>
</tbody>
</table>
| | | | | Does not do any stats if there was any

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>Exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=742 children from NHANES</td>
<td>Poor lung function &lt;40%</td>
</tr>
<tr>
<td>8-11.9 year old CF children with PI</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Reference population NHANES children 8-11.9 years old</td>
<td>CFRD</td>
</tr>
<tr>
<td>Brand and dose</td>
<td>B.cepsacia, growth impairing medical conditions or growth altering medications</td>
</tr>
</tbody>
</table>

### Primary Outcomes:
- Total energy intake (% EER in CF)
- Physical activity
- Retinol intake (%RDA and UL)
- Vitamin supplements (as ug RAE)
- Serum retinol
- Anthropometric
- FEV1 in CF

### RDA:
- Diet intake of vit A NS different to NHANES 8-8.9yr p=0.15 and 9-11.9yrs p=0.52
- The mean daily supplement Vitamin A intake for CF was 2234 +/- 1574 ug RAE, 83% +/- 17% was preformed retinol. This was significantly higher than supplement intake of the NHANES subjects (p<0.0001)
- Diet and supp intake CF 3050(1660) range 2663-3438RAE vs NHANES 2136(1221); range 1924-2349)
- 78% of CF had total dietary and supplemental preformed retinol intakes exceeding the UL for healthy subjects without CF.
- 21% supp vit A intakes exceeding CF rec and 49% had diet and supp intakes exceeding supplement recommendations for CF patients.
- Mean serum retinol concentrations for CF was significantly higher than the NHANES subjects (52 +/- 13ug/dL; range 26 to 98) p<0.001 vs (37 +/- 10ug/dL; range 17-63ug/dL)
- 47% of CF had a serum retinol concentration above the NHANES 95th %ile - (51.3ug/dL).
- NHANES had 5% above 95th %.
- Only one CF with serum retinol below NHANES 5th percentile (26.7ug/dL). 5% NHANES below 5th percentile
- Adjustment for lower BMI in CF subjects did not change results.

### Conclusion:
- This sample of preadolescent CF children with PI had vit A intakes and serum retinol concentrations higher than representative sample.
Vitamin A deficiency was not observed suggests that children with CF cared for under the current practice recommendations may be ingesting more than is required to prevent deficiency.

- May be at risk for chronic hypervitaminosis A.
- Combination of food and supplements provided a high vitamin A intake in this group of preadolescents with CF and PI.
- Associated high serum retinol concentrations suggest that this intake may be more than necessary to prevent deficiency and may pose a risk of vitamin A toxicity.
- Overlapping signs of chronic hypervitaminosis A and longstanding CF, namely hepatic fibrosis, cirrhosis, osteoporosis anorexia and weight loss make vitamin A toxicity particularly concerning to this population.

CF children should be carefully monitored for excess vitamin A.

Recommendations:
- Minimum vitamin A supplementation necessary to maintain normal serum retinol concentrations
- Dietary supplement industry provide labels that state the content of vitamin A as micrograms RAE, the proportion of retinoid and carotenoid components and the fat or water solubility of their products

<table>
<thead>
<tr>
<th>Maqbool A, Graham-Maar RC, Schall JI, Zemel BS, Stallings VA.</th>
<th>Vitamin A intake and elevated</th>
<th>NHMRC level</th>
<th>Cross sectional with historic controls</th>
<th>Intervention: Nil – observational</th>
<th>Results: Serum retinol</th>
<th>Appraiser’s limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA quality</td>
<td>NEUTRAL</td>
<td>N=78 (CF patients 8-25 years)</td>
<td>Following measures taken: Dietary intake of vitamin A from food and supplements RAE</td>
<td>Median (range) serum retinol was 80 μg/dL (33 to 208) in subjects with CF</td>
<td>58% (CF/PI) were above the NHANES reference range (30 to 72 μg/dL)</td>
<td>Use of historical controls, Small sample size, Vitamin A intake - 3 day food record - need longer term study, No measure of CRP/inflammation</td>
</tr>
</tbody>
</table>
### Serum Retinol Levels in Children and Young Adults with Cystic Fibrosis

**J. Cystic Fibrosis, 2008 Mar;7(2):137-41.**

**Inclusion criteria:**
- Confirmed dx of CF and PI
- FEV1 > 40% predicted

**Exclusion:**
- FEV1 <40% predicted
- Other major medical illnesses that affect growth

**Outcomes:**
- Vitamin A status - serum retinol ug/dL measured by HPLC
- Retinal levels compared to NHANES ref 5th to 95th centile - age equivalent
- Correlation between vitamin A intake and vitamin A status (serum retinol levels)
- Correlation serum retinol and FEV1

**Intake**
- Total vitamin A intake from diet and supplements was high (608±431% RDA or 3972±2359ug RAE/day, mean and SD).
- Total preformed retinol intake was 564 ± 409% RDA with 86% of subjects exceeding UL and 73% exceeding CF foundation recommendations
- 67% vitamin A intake from supplements and 58% used water miscible pre formed vit A supps.
- 27 types of supplements used and 11% used >1 supplement.
- Serum retinol was not correlated with vitamin A intake, age or gender, and was inversely correlated with weight and height z scores (r=−0.28, pb0.05) in the subjects with CF.
- Not associated with FEV1

**Conclusion:**
- Serum retinol level not associated with FEV1, age, gender or vitamin A intake
- Both vitamin A intake and serum retinol were elevated in subjects with CF and PI, corroborating recent evidence of elevated serum retinol in preadolescent children with CF.
- These findings indicate the need for further study of dosing and monitoring care practices of vitamin A, to ensure adequacy and to avoid toxicity.

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<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>N</th>
<th>Intervention</th>
<th>Results</th>
<th>Appraiser’s Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivas-Crespo MF, González Jiménez D, Acuña Quirós MD, Sojo Aguirre A, Heredia</td>
<td>Cross-sectional study</td>
<td>N=98 (Young CF patients ages 6.8-22.3 years)</td>
<td>Intake 978±346µg daily preformed retinol and dose adjusted aiming for normal ref range of serum retinol (didn’t state what normal reference range is)</td>
<td>Intake 978±346µg daily preformed retinol - Mean serum retinol 56.6±18.4 mg/dL - Average retinol intake - 6.8-11 years = 32.1±12 µg/kg wt/d</td>
<td>Cross-sectional study design (could be improved with longitudinal study) - FEV1 measured at one time point only - No info on type of supplements or...</td>
</tr>
</tbody>
</table>
Inclusion criteria:
- CF dx attending clinic regularly who were able to perform reproducible spirometry
- Clinically stable
- Serum retinol >20g/dL
- Able to produce reproducible spirometry

Exclusion criteria:
- Pulmonary exacerbations
- Vitamin A deficiency or other risk factors for retinol toxicity (protein malnutrition, liver disease, hyperlipidaemia, alcohol intake, pregnancy, or voriconazol treatment)

Primary outcome:
- Serum retinol and z score serum retinol ug (measured HPLC)
- FEV1% vs Serum retinol across age groups

Secondary outcomes:
- Other clinical characteristics

- >11 years = 20.2±9.5 µg/kg wt/d
- Serum retinol (56.6±18.4 ug/dL) was >2.5th percentile of healthy people in the whole group, although 31 patients were situated above the 97.5th percentile - 54.4ug/dL <12 years 7.2ug/dL 12-19years and 89.1ug/dL >20years (higher value:110 ug/dL).
- When serum retinol above normal range (NHANES) then FEV1 greater 93.6±14.0 vs those who were within normal range FEV1 = 85.0±17.6 %predicted .p<0.05
- Data of (FEV1) were widely scattered (87.7%±16.9%). Similarly in the 78 PI and 11 PS patients. The proportion in PS and PI groups not different but retinol levels were higher in PS than PI p<0.05
- Retinol above ref range higher in children than adults
- The z score of SR correlated positively with FEV1 (r=0.364; P=0.000), after adjusting data for sex, age, body mass index, and pancreatic function.
- The odds ratio for a FEV1 >80% is 3.78 in patients with SR above the 97.5th percentile, versus only 0.26 in those within the normal range.
- Correlation more marked in those with mod high FEV1
- SR determined 13.6% variability FEV1 (11% PI and 34.6% PS subgroups)
- SR higher in PS than in PI (87.4±19 vs 55.5±18.3 µg/dL)
- No cases of retinol toxicity at serum retinol >110µg/dL
- All lower than NAOL (IOM) ie far below reported toxic range
- No undesirable clinical effects

Conclusions:
- No info on how retinol intake is assessed
- Process of selection and how defined each of the exclusion criteria isn’t always clear so may be some selection bias
- Don’t report supplementation protocol

Author’s limitations:
- Nil stated
Lung function of young patients with CF correlates directly with SR, this being especially noteworthy in those with a moderately high retinol level (up to 110 mg/dL). This subgroup maintains the best respiratory function (FEV1 >80% in >90% of them). This moderate rise in retinol does not cause any signs of toxicity and is far from its toxic level.

The aim of maintaining SR level within the normal limits must be revised to achieve better health care.

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<tbody>
<tr>
<td>NHMRC level: IV</td>
<td>Aetiology</td>
<td>Cross sectional study with historical control</td>
<td>Intervention: Nil</td>
<td></td>
</tr>
<tr>
<td>ADA quality : NEUTRAL</td>
<td></td>
<td></td>
<td>Routine Vit A supplementation as per routine clinic procedure</td>
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<td></td>
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<td></td>
<td>- PI patients mostly supplemented for the first year of life; serum testing performed at least annually (3-6 monthly if low serum levels or following change to supp) and supplements given if Vitamin A &lt;0.7umol/L (as per clinic, not part of study)</td>
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<tr>
<td></td>
<td>N=41 Paediatric CF patients ages 4 to 18 years</td>
<td>Inclusion criteria:</td>
<td>Outcome(s):</td>
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<tr>
<td></td>
<td></td>
<td>- Confirmed CF status in infancy</td>
<td>Recorded scotopic and photopic flash electroretinograms (ERGs) and results grouped according to PI or PS</td>
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<td></td>
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<td>- PI confirmed by 5 day fecal fat measurement</td>
<td>Serum vitamin status</td>
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<td></td>
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<td>- Serum Vitamin A, B carotene and RBP measured same day as the ERG</td>
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<td>- Measured HPLC</td>
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<td></td>
<td>Exclusion:</td>
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<td></td>
<td>Not stated</td>
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<td></td>
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<td></td>
<td>No significant difference in ERGs, amplitudes or implicit times between PI and PS groups</td>
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<tr>
<td></td>
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<td>No significant difference in (mean ±SD) serum retinol (PI 1.51 ± 0.27 umol/l; PS 1.36 ± 0.41 umol/l), b-carotene (PI 0.26 ± 0.16 umol/l; PS0.18 ± 0.04 lmol/l) or RBP (PI 24.57 ± 5.30 mg/l; PS 21.67 ± 7.81 mg/l) between the PI and PS groups(P&gt;0.2)</td>
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<td>No significant difference within the PI group between supplemented (n = 15) and unsupplemented (n = 14) individuals in (1) vitamin A levels (unpaired t-test, P =0.22; supplemented mean 1.57 ± 0.27(SD)umol/l; and unsupplemented mean 1.44 ± 0.25 (SD)umol/l), (2) Carotene levels (unpaired t-test, P = 0.31; supplemented mean 0.29 ± 0.16 (SD)umol/l; and unsupplemented mean 0.19 ± 0.14 (SD)umol/l), and (3) RBP levels (unpaired t-test, P = 0.14; supplemented mean 26.27 ± 6.50 (SD)mg/l; and unsupplemented mean 23.00 ± 3.49 (SD)mg/l).</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Vitamin A and B carotene and RBP levels</td>
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<td></td>
<td>Appraiser’s limitations:</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>No description of how subjects were recruited, assume opportunistic sample = potential bias</td>
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<td></td>
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<td>No descriptive characteristics of PI and PS groups – are they comparable?</td>
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<tr>
<td></td>
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<td>Small sample size - possibly not powered enough to detect diff in clinical outcomes between groups.</td>
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<td></td>
<td>Diet intake of these nutrients not recorded</td>
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<td></td>
<td></td>
<td></td>
<td>Conducted no association/correlation stats between vit status and ERG</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Author’s Limitations:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nil stated</td>
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</tr>
</tbody>
</table>
Vitamin A levels in patients with CF are influenced by the inflammatory response. Journal of Cystic fibrosis. 2004 Aug;3(3):143-9.

| Greer RM, Buntain HM, Lewindon PJ, Wainwright CE, Potter JM, Wong JC, Francis PW, Batch JA, Bell SC. |
|---|---|---|---|
| NHMRC level: III-2 (Aetiology) | ADA quality: NEUTRAL | Retrospective cohort with concurrent controls | | |
| CF n=138 (children & adults) Controls n=138 | Inclusion criteria: | Intervention(s): | Results: | |
| Not specified (refers to previous study) | • Nil specific – normal clinical care - Daily vitamin A prescription 1650-5000IU vitamin A /day (4 patients had 50,000IUtwice weekly) | • Vit A levels lower in CF vs controls (p<0.001) | • CRP was higher in CF with low Vit A |
| Exclusion criteria: | • Serum vitamin A | • When broken into age groups sig lower in adolescents (p<0.001) and adults (p<0.003) but not children (p=0.08) vs controls. | • Pts with PSA did not have different Vit A levels |
| • Not specified | • Bone mineral density - lumbar spine | • No significant differences in gender (p=0.03) | • Low Vit A correlated with low FEV1 (p=0.001); weight z-score (p=0.002); Lumbar spine BMD (p=0.009); higher CRP (p<0.001) |
| • Vitamin E & D | • CRP | • CF increase in Low vit A levels with age 30.8% children; 44.5% adolescents; 55.6% adults | • Lumbar Spine BMD lower in male CF with low Vit A levels vs those with normal levels (p=0.009) but no difference in females with CF with low vs normal Vit A levels (p=0.88) |
| • Anthropometric indices | • Anths | | | |
| • Lung function | • Pseudomonas infection(PSA) | |
| • Number of hospital admissions, pulmonary exacerbations and number of days in hospital in previous 12 months | • Presence of CFLD | |
| | | | |

Conclusions:
• Similarity of ERGs across the PI and PS CF pt populations allows similar levels of retinal function in the two groups.

Appraiser’s Limitations:
• Compliancy with vitamin supplements and enzymes not measured
• Any other supps used?
• Diet intake of vit A?

Author’s Limitations:
• Serum retinol binding protein not measured (this would give more info regarding inflammatory status and liver function)
• Adherence to PERT and/or vitamin A supplementation not assessed
CRP higher in CF vs controls \( (p=0.04) \); correlated with age in CF \( (p=0.0001) \) but not in controls \( (rs=0.06; \ p=0.45) \). CRP was negatively correlated with Vit A in CF \( (rs=-0.37, \ p<0.0001) \), but not control \( (rs=-0.01; \ p=0.9) \) and correlated in CF subjects with FEV1 \( (RS=-0.42, \ p<0.0001) \).

High CRP was a risk factor for low serum Vit A in CF \( (OR \ 6.39, \ CI \ 2.93-13.90) \).

No controls with High CRP had a low Vit A level.

**Conclusion:**

Serum vit A levels are inversely proportional to CRP in CF – implication that decreased serum retinol associated with inflammation is not caused by nutritional vitamin A deficiency.

Nutritional deficiency must be differentiated from low serum retinol associated with the inflammatory response.

Low serum vitamin A levels in CF may be due to nutritional vit A deficiency or inflammation or from a combination of both.

Further studies and clarification are needed as to the role of the liver in Vit A storage and transport, and the importance of Serum Vit A in the pathophysiology of lung disease in CF.

**Woestenenk JW, Broos N, Stellato RK, Arets HG, van der Ent CK, Houwen RH.**

Vitamin A intake and serum retinol levels in children

<table>
<thead>
<tr>
<th>NHMRC level:</th>
<th>Aetiology cross sectional</th>
<th>Primary Interventions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV (Aetiology)</td>
<td>N=221 (children &amp; adolescents with CF)</td>
<td>• Nil – observational</td>
</tr>
</tbody>
</table>

**Inclusion criteria:**

**Primary Interventions:**

- Nil – observational

**Following measures taken:**

- Vitamin A intake: (dietary vitamin A intake measured by 3d diet diary plus prescribed supplementation)

**Results:**

- Mean total vitamin A intake in the different age groups was between 1169 and 1546 mg RAE, providing 187-419% RDA, and was relatively stable

- >1yr of age, mean prescribed supplementation in every year of age was lower than both the European, and the

**Appraiser’s Limitations:**

- No info re Dx of PI
- No BMI or energy intake calculations to standardise the dietary and supp intake of A
- Did not measure/report energy intake as means of assessing likely under or over reporting vitamin A intake
Data obtained 2007-2013
At least one measure of vitamin A intake (dietary intake and prescribed supplementation) and a measure of serum retinol level
Receiving pancreatic enzyme replacement therapy at the time of reporting

Exclusion criteria:
Transplant patients

Vitamin A total intake was compared with Dutch nutritional recommendations %RDA and %TUL. Also % of both the European and North-American CF-specific vitamin A recommendations - LL and UL. Serum retinol levels compared with healthy NHANES values.

Association vit A intake and retinol levels - based on categorisation of children for every year of age above or below 50th centile of NHANES
Secondary Intervention(s): Assess if serum Vit E related to serum retinol levels

Primary Outcomes:
- Relationship between vitamin A intake and serum retinol
- Vit A intake expressed as (ug RAE). Total Vit A intake as %RDA and %TUL. Prescribed supplementation as %LL and UL
- Relationship between vitamin E and serum retinol levels

North-American, CF-specific vit A recommendations.
In most age groups, mean total vitamin A intake was at the lower limit of the European CF-specific recommendation and far below both the upper limit of the European-, and the North-American recommendation
No differences in vitamin A intake between patients above and below 50th%ile, exception was at age 16;
- No differences in total vitamin A intake among the categories p <0.0888
- No association vitamin A intake and serum retinol levels (95% CI −0.04 to 0.01%), p =0.245
- Median serum retinol levels were within the references values of the NHANES at all ages
- Serum retinol def in 2% measurements (17 measures in 11 children)
- Toxic levels in 0.3% measures (3 measures in 3 children)
- Total vit A intake in those with deficiency 293% RDA and in those with toxic values 224 ie no relationship supp and retinol levels
- No assoc CFA and retinol levels (95% CI = 39.98-55.83%, p =0.890)

Conclusion:
- Current rec's for vit A supp in CF children not met but serum retinol was normal.
- Seems that current vitamin A specific rec's are no longer appropriate and a reduction in vit A supp should be considered.

Author’s Limitations:
- Single centre study
- Food records may lead to altered diet and under or over reporting
- Did not measure adherence of vitamin supplementation
- Did not measure water miscible vs other vit supp which may affect intake
- Did not assess intake of other vit supplements which may contain vit A
- Did not assess dietary intake of Vit A supplemented foods
### Evidence Statement Matrix

#### Chapter Q8.1.2 What is the role for routine supplementation of vitamin A in people with CF and pancreatic insufficiency?

**NHMRC Grade for recommendation:** Grade D

**Evidence statement:** The evidence is unclear regarding the need for routine versus individualised supplementation of vitamin A in people with CF. Whilst some studies suggest that routine supplementation is required, others suggest that not all people with CF and pancreatic insufficiency require supplements and that supplementation should be individualised based on serum levels. There is no evidence to suggest a need to change from current practice.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>Grade</th>
<th>Evidence basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children n=46 children, positive quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children &amp; adolescents n=22, negative quality</td>
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<td></td>
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<tr>
<td><strong>Level III</strong></td>
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<tr>
<td>Infants n=39; positive quality</td>
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</tr>
<tr>
<td>Children &amp; Adults: n=138; neutral quality</td>
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<tr>
<td><strong>Level IV</strong></td>
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<tr>
<td>Infants n=39; positive quality</td>
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<tr>
<td>Children n=73, n=70, n=41, n=556</td>
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<tr>
<td>Children &amp; Adults: n=32, n=78, n=98, n=221, n=102</td>
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<tr>
<td>Adults: n=43</td>
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<tr>
<td><strong>β-carotene</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children n=46 CF children; positive quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children n=17 children &amp; adults; positive study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Consistency**

**D Poor**

Difficulties in assessing the need for routine versus individualised supplementation of vitamin A due to lack of consistency between studies with the following:

- Definitions used to define vitamin A status (inconsistent reported prevalence of vitamin A deficiency and excess)
- Methods of assessment and reporting of dietary vitamin A intake, serum vitamin A reference ranges, supplementation formulation & doses
- Comparison study populations

Most studies unable to assess causation and can only provide suggestive or inferential evidence only.
Some consistency in the following:
- Australian studies do not suggest excessive intakes of vitamin A with current recommended levels of supplementation.
- No association between serum levels of vitamin A and intake

Insufficient evidence to suggest routine supplementation with β-carotene.
- Studies consistently report deficiency of β-carotene and improvement of β-carotene levels with supplementation. However there is limited and unclear evidence re the effects of β-carotene supplementation on clinical outcomes and they are likely reflective of the total antioxidant mixture rather than β-carotene in isolation.

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence unclear regarding the association between improved retinol levels with supplementation and clinically important outcomes i.e. pulmonary status.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most evidence is from children and adults, without CF-liver disease and with mild-moderate lung disease.</td>
<td></td>
</tr>
</tbody>
</table>
- Over 60% of studies included both pancreatic insufficient and pancreatic sufficient patients.
- Only 2 studies included infants.
- Only 5 studies with Australian populations.
  - High reported intakes of vitamin A have generally been reported in studies from the US.
  - Vitamin A sources (dietary & supplements) and methods of assessment not always generalisable to Australian context. |

<table>
<thead>
<tr>
<th>Applicability</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only one CF-specific multivitamin supplement is available in Australia/NZ and its formulation/composition has not changed since the 2006 guidelines.</td>
<td></td>
</tr>
</tbody>
</table>
- Significant differences in food sources of vitamin A between countries.
- No excessive vitamin A intakes reported in Australia/NZ studies.
- β-carotene is not available as an individual prescription supplement in Australia/NZ and the available CF-specific multivitamin has only a low percentage as β-carotene.
- Limited options for increasing Vitamin A supplementation where there is risk of toxicity from preformed retinol. |
CLINICAL QUESTION
8.1.4 What is the safe upper limit for vitamin A supplementation for people with CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.

CLINICAL QUESTION
8.1.5 How often should we measure / monitor vitamin A levels in people with?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.
8.2 Vitamin D

PICO

8.2.1 Is vitamin D status associated with measures of respiratory health (lung function, pulmonary exacerbations, markers of inflammation) in people with CF?
8.2.2 Is there an ideal serum 25-hydroxyvitamin D to aim for in people with CF?
8.2.3 Is the time of year, specifically the season, important when measuring and interpreting an individual’s serum vitamin D level?
8.2.4 Should supplemental vitamin D be given to people with pancreatic sufficient cystic fibrosis as part of routine care?
8.2.5 What doses of vitamin D are needed to prevent deficiency in people with CF?
8.2.6 What doses of vitamin D are needed to correct deficiency in people with CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:
- Vitamin D
  - Cystic fibrosis, CF, nutrition, diet, deficiency, subclinical deficiency, supplementation, vitamin D, vitamin D2, vitamin D3, cholecalciferol, hydroxycholecalciferol, calcifediol, ergocalciferol, calcidiol, vitamin D/blood/25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, 1-α-hydroxyvitamin D, 1-alpha-hydroxyvitamin D, calcitriol, alfalcacidal, paricalcitol, toxicity

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
**CLINICAL QUESTION**

8.2.1 Is vitamin D status associated with measures of respiratory health (lung function, pulmonary exacerbations, markers of inflammation) in people with CF?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grossmann RE, Zughaier SM, Liu S, Lyles RH, Tangpricha V. Impact of vitamin D supplementation on markers of inflammation in adults with cystic fibrosis hospitalized for a pulmonary exacerbation. European Journal of Clinical Nutrition. 2012; 66(9):1072-4.</td>
<td>NHMRC level II ADA quality NEUTRAL</td>
<td>Double blind, placebo controlled RCT N=30 CF adults (15 in each arm)</td>
<td>Intervention: • A one off dose of 250 000IU of cholecalciferol or placebo Primary outcome: • Changes in inflammatory cytokines (serum IL-1B, IL-10, IL-18 – binding protein and plasma IL-6, IL-8 and TNF-α and plasma LL-37 (antimicrobial peptide)</td>
<td>Results: Vitamin D group • 50.4% reduction in TNF-α at 12 weeks (p&lt;0.01) • 64.5% reduction in IL-6 which was not significant (P=0.09). No significant reduction in any other inflammatory cytokines measured. Conclusions: • Vitamin D may help regulate inflammation in CF</td>
<td>Limitations: • Small sample may not have been powered adequately to detect smaller changes in inflammatory cytokines; other factors can impact on inflammatory outcomes; systemic markers of inflammation are only surrogates for possible changes in the respiratory tract</td>
</tr>
<tr>
<td>Grossmann RE, Zughaier SM, Kumari M, Seydaftan S, Lyles RH, Liu S, et al.</td>
<td>NHMRC level II ADA quality NEUTRAL</td>
<td>Double blind, placebo controlled RCT N=30 CF adults (15 in each arm)</td>
<td>Intervention: • A one off dose of 250 000IU of cholecalciferol or placebo Primary outcome: • Change in serum 25(OH)D, PTH and calcium</td>
<td>Results: Vitamin D status – serum 25(OH)D increased significantly from a mean of 30.6+/−3.2ng/ml to 58.1+/−3.5ng/ml (p&lt;0.0001) at one week and 36.7+/−2.6ng/ml by 12 weeks (p=0.06). Unchanged in the placebo group.</td>
<td>Limitations: • Small sample size • No record of medications and therapies used following the intervention, • Didn’t account for vitamin D status at baseline (some were sufficient)</td>
</tr>
</tbody>
</table>
### Pilot study of vitamin D supplementation in adults with cystic fibrosis pulmonary exacerbation: A randomized, controlled trial.


- **Inclusion criteria:**
  - 75ng/ml in the past year
  - <2000IU of supplemental vitamin D, current respiratory exacerbation (determined by pulmonologist)

- **Exclusion criteria:**
  - History of disorders affecting vitamin D status or calcium/phosphate metabolism, previous organ transplant, currently pregnant or planning to be pregnant

- **Secondary outcomes:**
  - Mortality, hospital free days, IV antibiotic free days, lung function – FEV1

- **Results:**
  - Hospital free days, 6 months post intervention – increased in vit D group (p=0.036)
  - IV antibiotic free days, 6 months post intervention – trend toward more in Vit D group (p=0.073)
  - Lung function – 9 of 10 versus 4 of 8 in the placebo group returned to 95% or more of their baseline FEV1 at 3 months post intervention (p = 0.12)

- **Conclusions:**
  - A single dose of 250,000IU cholecalciferol was associated with a trend toward improved clinical outcomes in hospitalised CF adults and it is safe and feasible


- **NHMRC level IV**
- **ADA quality NEUTRAL**
- **Inclusion criteria:**
  - Attending clinic as part of the Mid-Atlantic Research Study Group
  - CF dx confirmed by sweat test and/or genetic testing
  - > 6 years of age
  - 25(OH)D level not drawn during an exacerbation as judged by their CF clinician
  - Able to perform spirometry
  - Spirometry performed within 2 months of vit D level and not during a period of exacerbation

- **Intervention:** N/A

- **Primary outcome:**
  - 25OHD level
  - Lung function tests

- **Results:**
  - There was a significant correlation between vit D and pulmonary function.
    - FEV1 % predicted (r=0.20, p<0.0001) and FVC % predicted (r=0.13, p=0.0019) for the whole group.
    - This relationship was strongest for those homozygous F508: (p=0.015) for FEV1 %predicted and (p=0.029) for FVC %predicted and for males (p=0.015) for FEV1 %predicted.

- **Conclusions:**
  - Serum 25OHD levels are sig associated with pulmonary function in CF. the association was strongest for those homozygous F508 and males. Further studies needed to establish causality.

- **Limitations:**
  - Didn’t quantify activity levels or sunlight exposure, supplemental vitamin D (doses and duration), complete genotyping.
  - Retrospective study.
  - Used different labs for vit D measurements.
<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Design</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Conclusions</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Simoneau T; Bazzaz O; Sawicki GS; Gordon C. Vitamin D status in children with cystic fibrosis. Associations with inflammation and bacterial colonization. Annals Of The American Thoracic Society 2014. 11 (2): 205-10. | NHMRC level IV ADA quality NEUTRAL | Retrospective cross sectional (chart review) | N=148 Children with CF under 12 years of age attending a Boston CF clinic | Exclusion criteria:  
- None | Intervention: N/A | Primary outcome:  
- Vitamin D levels. | Results:  
- No correlation between inflammatory markers (IgG, IgE, CRP) and vit D.  
- No sig difference in FEV1 or BMI between deficient, insufficient and sufficient. | Conclusions:  
- In this population vitamin D insufficiency is associated with a history of pseudomonas colonization but not with classic markers of systemic inflammation. | Limitations:  
- Adherence of prescribed supplementation  
- Adherence to PERT  
- Small sample size  
- Retrospective design. |
| Vanstone MB; Egan ME; Zhang JH; Carpenter TO. Association between serum 25-hydroxyvitamin D level and pulmonary exacerbations in cystic fibrosis. Pediatric | NHMRC level IV ADA quality NEUTRAL | Retrospective cross sectional (chart review) | N=53 Patients with CF between 5 and 22 years of age attending a New Haven based CF centre | Exclusion criteria:  
- Transferred to adult care or moved clinic during study period | Intervention: N/A | Primary outcome:  
- Pulmonary function tests (averaged all tests done over the year).  
- Vit D levels.  
- Pulmonary exacerbations (identified as initiation or increase of antibiotic use based on reported symptoms or an Akron Pulmonary Exacerbation threshold of ≥5). | Results:  
- This group had 83% of the exacerbations. Those with vit D levels <50nmol/L had 20% (n=6) and those <30nmol/L had 10.3% (n=2) and those with >75nmol/L had 26% (n=14).  
- 25OHD and gender were each independent determinants of the number of pulmonary exacerbations (p<0.01).  
- There was no effect of 25OHD on pulmonary function tests  
- There was one additional hospitalization for every 10ng/mL decrease in 25OHD but it was not significant. | Limitations:  
- Low vit D levels may be a marker of disease severity and may not be causal  
- Chart review  
- Patients who have poorer compliance with medications, including vit D may have worse health and more pulmonary exacerbations, sicker patients may have less sun exposure or eat less (including vit D rich foods). |
<table>
<thead>
<tr>
<th>Pulmonology, 2015;50(5)</th>
<th>Conclusions:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The annual number of pulmonary exacerbations in paediatric CF patients is significantly associated with 25OHD levels and gender. Maintaining vit D sufficiency may lead to decreased incidence of hospitalizations.</td>
<td>• The rate of exacerbations for the deficient vitamin D group, aged 15-18 years was 13.1 per 10 patient years, significantly higher than 4.3 per 10 patient years for the insufficient (p=0.041) and sufficient vitamin D groups (p=0.035), which were not significantly different.</td>
<td>• There were no differences between vitamin D groups in pulmonary function or incidence of first pseudomonas infection.</td>
</tr>
</tbody>
</table>

**McCauley et al.**


**NHMRC level** III-2  
**ADA quality** NEUTRAL

| Retrospective cohort | Intervention: N/A | Primary outcome:  
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>N=130 Children with CF from a Minnesota based clinic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Inclusion criteria: | Vitamin D levels  
| • CF diagnosed by sweat test  
| • 2 known CF mutations on different chromosomes  
| • At least one 25- OHD measurements and one lung function during the study period  
| • 6 and 18 years of age  
| • Between 2000 and 2012 | Numbers of pulmonary exacerbations (defined as hospitalisations)  
| | Incidence of first pseudomonas infection  
| | % predicted lung function |

**Note – children were grouped into sufficient (≥30µg/L), insufficient (20-29µg/L), and deficient (<20µg/L).**

**Conclusions:**  
• 25OHD level less than or equal to 20µg/L in children with CF is associated with a 3 time higher rate of pulmonary exacerbations than those sufficient in vitamin D. In addition, in adolescents with CF, a higher vitamin D level was associated with a higher FEV1.

**Limitations:**  
• Retrospective  
• Single centre  
• No consensus definition of exacerbation  
• Could only count exacerbations requiring admission and not ones managed as an outpatient (underestimated rates of exacerbations)  
• Small sample meant could not adjust for other confounders

**Pinckova et al.**

**Inverse relation between vitamin D and serum total immunoglobulin G in the**

**NHMRC level** IV  
**ADA quality** NEUTRAL

| Cross sectional study | Intervention:  
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>N=898 Children and adults with CF from 7 centres in Scandinavia (Denmark, Norway and Sweden)</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td></td>
</tr>
<tr>
<td>• Clinically stable condition</td>
<td></td>
</tr>
</tbody>
</table>
| | 7 day food record  
| | Blood sample  
| | Lung function |

**Primary outcome:**  
• Vitamin D intake through diet via 7 day food record and

**Results:**  
• Significant positive correlation between FEV1 and 25(OH)D (p=0.025).  
• Significant negative association between serum IgG levels and serum 25OHD (p<0.001), supplemental vit D/kg of bodyweight (p<0.001) and total vit D/kg intake (p<0.002).

**Limitations:**  
• Food records used were not validated to measure vit D.
**Evidence Statement Matrix**

**Chapter 8 Q8.2.1 Is vitamin D status associated with measures of respiratory health (lung function, pulmonary exacerbations, markers of inflammation) in people with CF?**

**NHMRC Grade for recommendation: Grade D**

**Evidence statement** There is an increasing interest in the potential association between vitamin D status and markers of pulmonary function. However within the area of CF, the evidence base remains small with significant limitations and the findings are inconsistent. Further research is required to establish if vitamin D status is a contributing factor to the clinical course of lung disease in CF rather than an association.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 papers representing 6 studies – all of neutral quality</td>
<td></td>
</tr>
<tr>
<td>One level II study - double blind, placebo controlled RCT (n=15 adults with CF and 15 controls)</td>
<td></td>
</tr>
<tr>
<td>One level III study - retrospective cohort (n=130 children)</td>
<td></td>
</tr>
<tr>
<td>Four level IV studies - retrospective cross sectional studies (n=898 children and adults; n =597 children and adults; n=148 children; n=53 children)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung function (FEV1) &amp; vitamin D (5 studies). Inconsistent findings</td>
<td></td>
</tr>
<tr>
<td>2 level IV studies found a significant positive association between FEV1 and vitamin D status while the other 3 (2 level IV and 1 level III-2) found no significant association.</td>
<td></td>
</tr>
<tr>
<td>Markers of Inflammation &amp; vitamin D (3 studies). Inconsistent findings</td>
<td></td>
</tr>
<tr>
<td>1 level II study showed a significant reduction in TNFα but not in other inflammatory cytokines after giving a one off high dose of vitamin D</td>
<td></td>
</tr>
<tr>
<td>1 level IV study showed no association between vitamin D and IgG, IgE and CRP</td>
<td></td>
</tr>
</tbody>
</table>
1 level 1V study found a significant reduction in IgG with higher vitamin D levels
Pulmonary Exacerbations and vitamin D (2 studies)

- Both low level and small in number have looked at vitamin D status and pulmonary exacerbations, no conclusions can be drawn from this.
- One level IV study showed that vitamin D status was an independent determinant of the number of pulmonary exacerbations
- One level IV study showed that the rate of pulmonary exacerbations in those deficient in vitamin D between the ages 15-18yrs was significantly higher than those who were insufficient or sufficient within that age group

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevance of the evidence to the clinical question is poor.</td>
<td></td>
</tr>
<tr>
<td>- FEV1 % predicted most commonly assessed measure</td>
<td></td>
</tr>
<tr>
<td>- Findings are very inconsistent</td>
<td></td>
</tr>
<tr>
<td>- No evidence to support a causal link as the influence of other confounding variables was not assessed in most of the studies</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>The studies to date have been based in children and adults with CF from CF care centres worldwide which are comparable to Australasian CF centres.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>The findings of the studies to date would be relevant to Australasian CF populations</td>
<td></td>
</tr>
</tbody>
</table>
**CLINICAL QUESTION**

**8.2.2** Is there an ideal serum 25-hydroxyvitamin D to aim for in people with CF?

Evidence Table

There were no studies available within the search strategy and criteria that addressed this PICO.

**CLINICAL QUESTION**

**8.2.3** Is the time of year, specifically the season, important when measuring and interpreting an individual's serum vitamin D level?

Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robberecht E, Vandewalle S, Wehlou C, Kaufman JM, De Schepper J.</td>
<td>NHMRC level III-3 ADA quality NEGATIVE</td>
<td>Case control study</td>
<td>Intervention: N/A</td>
<td>Results: Both CF patients and controls had sig higher median vit D levels (474 values for CF patients during the months with high UVB exposure. There was no significant difference between the 2 groups.</td>
<td>Appraiser’s limitations: Did not discuss method of collection of vitamin D from healthy controls. Did not quantify with precision with amount of vit D taken orally Author’s limitations: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=141 Patients with CF older than one year of age attending a CF centre in Belgium and 160 controls</td>
<td>Inclusion criteria: None Exclusion: Transplanted patients</td>
<td>Primary outcome: Serum vit D levels (collected over 4 consecutive years) compared with healthy peers and weighed against annual UVB exposure.</td>
<td></td>
</tr>
<tr>
<td>Malay-Rana et al. Fat-soluble vitamin deficiency in children and adolescents with cystic</td>
<td>NHMRC level IV ADA quality NEUTRAL</td>
<td>Retrospective cross sectional (chart review)</td>
<td>Intervention: N/A</td>
<td>Results: Low vit D levels were sig lower in patients with pancreatic insufficiency than sufficiency (28% versus 3%) (p&lt;0.01) and sig higher in summer (p&gt;0.01).</td>
<td>Author’s limitations: Vitamin reference ranges differed between labs Retrospective Did not measure adherence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=556 Children with CF attending one of three CF clinics in NSW, Australia</td>
<td>Inclusion criteria:</td>
<td>Primary outcome: Prevalence of fat soluble vit deficiencies.</td>
<td>Appraiser’s limitations:</td>
</tr>
<tr>
<td>Study</td>
<td>Author(s)</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Study Design</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td></td>
<td>Neville et al.</td>
<td>Vitamin D in infants with cystic fibrosis diagnosed by newborn screening.</td>
<td>Journal of Paediatrics and Child Health. 2009. 45(1-2): 36-41</td>
<td></td>
<td>Retrospective cross sectional (chart review)</td>
</tr>
<tr>
<td>Medical Journal. 2015; 108: 3</td>
<td>Simoneau T; Bazzaz 0; Sawicki GS; Gordon C. Vitamin D status in children with cystic fibrosis. Associations with inflammation and bacterial colonization. Annals Of The American Thoracic Society 2014; 11 (2): 205-10.</td>
<td>Ahmareen O., Pentony M., Healy F., Zaid A. A one-year retrospective review of vitamin D level, bone profile, liver function tests and body mass index in children with cystic fibrosis in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
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</tbody>
</table>
| • <1 year of age  
• Patients with fewer than three 25(OH)D measurements during the 2 year study period  
• Patients with levels done less than 6 months apart or greater than 18 months apart | • Fat soluble vitamin levels measured between Jan 2009 and Dec 2011  
Exclusion: None | • Attended clinic between Jan 2012-Jan 2013  
Exclusion: Incomplete data |
| Intention: N/A  
Primary outcome: Vitamin D levels. | Intervention: N/A  
Primary outcome: Vitamin D levels. | Intervention: N/A  
Primary outcome: Change in vit D levels over the study period |
| Results: • Vit D levels did not differ by season.  
• Supplemental vit D data was available on 131/148. Median dose was 800IU (0-3600IU). | Results: • 69/89 (77.5%) of children were vit D deficient defined as <75nmol/L. No correlation between vit D and LFT, lung function, genotype, age, BMI z scores or seasons. | Results: • 69/89 (77.5%) of children were vit D deficient defined as <75nmol/L. No correlation between vit D and LFT, lung function, genotype, age, BMI z scores or seasons. |
| Conclusions: • Vit D insufficiency is common among young children with CF, even in those who are PS. Vit D levels did not differ by season. | Conclusions: • Attributed poor response to non-compliance. Healthy Irish population showed 47% deficiency compared with 77.5% in this cohort (didn't mention if they too used 75nmol/l as a cut off). No | Conclusions: • Attributed poor response to non-compliance. Healthy Irish population showed 47% deficiency compared with 77.5% in this cohort (didn't mention if they too used 75nmol/l as a cut off). No |
| Appraiser’s Limitations: • Limited applicability as only looked at children less than 12 years  
• Cross sectional study therefore can’t establish causality | Appraiser’s Limitations: • Set deficiency at below 75nmol/L.  
• Did not show stats on seasons  
• Did not assess intake of vit D from CF multivitamins  
• Didn’t provide statistics on vit D levels/change in vit D levels. Very limited statistics presented. | Appraiser’s Limitations: • Set deficiency at below 75nmol/L.  
• Did not show stats on seasons  
• Did not assess intake of vit D from CF multivitamins  
• Didn’t provide statistics on vit D levels/change in vit D levels. Very limited statistics presented. |
| Author’s Limitations:  
• Adherence of prescribed supplementation/PERT  
• Small sample size  
• Retrospective design. | Author’s Limitations:  
Notes: Deficiency <20ng/ml Insufficiency 20>29.9ng/ml | Author’s Limitations:  
Notes: Deficiency <20ng/ml Insufficiency 20>29.9ng/ml |

Notes: Normal vit D levels were defined as between 30-80ng/ml
<table>
<thead>
<tr>
<th>Study</th>
<th>NHMRC level</th>
<th>ADA quality</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Children’s University Hospital. International Journal on Disability and Human Development. 2015; 14 (1): 31-36</td>
<td>IV</td>
<td>NEUTRAL</td>
<td>Retrospective cross sectional (chart review)</td>
<td>N/A</td>
<td>25OHD level, lung function tests</td>
<td>• Levels of 25OHD drawn in spring or summer were significantly higher than those drawn in fall or winter.</td>
<td>• No data on adherence to supplements. Days of hospital admissions.</td>
</tr>
<tr>
<td>Sexauer WP et al. Vitamin D deficiency is associated with pulmonary dysfunction in cystic fibrosis. J Cyst Fibros. 2015; 14(4):497-506.</td>
<td>IV</td>
<td>NEUTRAL</td>
<td>Retrospective cross sectional (chart review)</td>
<td>N/A</td>
<td>25OHD level at annual review assessment.</td>
<td>• Vit D sig lower in the “winter” months (Oct-March) compared with April – Sept (p&lt;0.001). 75% of low levels were measured in the “winter”.</td>
<td>• Problem with definition of abnormal being &lt;25nmol/L. • No formal assessment of vit D intake from supplements (or food) in PS or PI patients.</td>
</tr>
<tr>
<td>Chavasse RJ, Francis J, Balfour-Lynn I, Rosenthal M, Bush A. Serum vitamin D levels</td>
<td>IV</td>
<td>NEUTRAL</td>
<td>Retrospective cross sectional (chart review)</td>
<td>N/A</td>
<td>25OHD levels at annual review assessment.</td>
<td>• Levels were compared to other fat soluble vitamin levels, bone and</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>liver biochemical parameters, pulmonary function, growth, and date of testing. Subgroup analysis for pancreatic status and liver disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>between 1 and 18 years of age; confirmed CF through sweat +/- genetic testing; attended annual clinic during the study period of August 1999 – April 2001</td>
<td>• No difference between PS and PI (age, gender, season of testing matched) OR in those with liver disease and those without (age, gender, season of testing matched).</td>
</tr>
<tr>
<td>Exclusion: None</td>
<td>Conclusions: May be more useful to measure 25OHD in winter but not practical. No consensus for optimal level of 25OHD. Lower levels in adolescents may be a precursor to low levels in adulthood and did not seem to be related to poor compliance with supplements</td>
</tr>
</tbody>
</table>

**Evidence statement matrix**

**Chapter 8 Q8.2.3 Is the time of year, specifically the season, important when measuring and interpreting an individual’s serum vitamin D level?**

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** There is satisfactory evidence (from cross sectional studies) that vitamin D levels drawn in months of lower UVB exposure, regardless of latitude, are lower than those drawn in months of higher UVB exposure. Therefore the time of year is an important factor when interpreting an individual’s serum vitamin D level. From this it could be extrapolated that achieving an adequate vitamin D status through the whole year is best achieved by measuring serum vitamin D at the end of winter and adjusting dosing regimens accordingly.

<table>
<thead>
<tr>
<th>Evidence Base</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 studies included in the body of evidence</td>
<td></td>
</tr>
<tr>
<td>• One level III study (case control); n=141 CF patients &gt;1yr of age; negative quality</td>
<td></td>
</tr>
<tr>
<td>• Seven level IV studies (retrospective cross sectional studies)</td>
<td></td>
</tr>
<tr>
<td>• 1 study; n=89 CF children; negative quality</td>
<td></td>
</tr>
<tr>
<td>• 6 studies; neutral quality</td>
<td></td>
</tr>
<tr>
<td>o n=556, n=129, n=148, n=290 children</td>
<td></td>
</tr>
<tr>
<td>o n=597 adults and children</td>
<td></td>
</tr>
<tr>
<td>o n=58 newborns</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>The majority of studies, including the two largest studies (&gt; 1000 people with CF), demonstrated that vitamin D levels drawn in months of higher UVB exposure are significantly greater than those in months of lower UVB exposure.</td>
<td></td>
</tr>
<tr>
<td>• Studies that showed no difference were smaller and potentially not powered adequately to show a seasonal difference.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically relevant as the results provide guidance as to:</td>
<td></td>
</tr>
<tr>
<td>• The best time of year to check vitamin D levels</td>
<td></td>
</tr>
<tr>
<td>• What to do in terms of supplementation based on your findings</td>
<td></td>
</tr>
<tr>
<td>Generalisability</td>
<td>B Good</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------</td>
</tr>
<tr>
<td>Studies acknowledged that an individual’s total UVB exposure is dependent on how far they live from the equator - The further away you are the less exposure you receive.</td>
<td></td>
</tr>
<tr>
<td>Studies acknowledged that UVB rays are stronger during the spring and summer months regardless of where you live.</td>
<td></td>
</tr>
<tr>
<td>Despite the studies above being conducted in countries outside of Australasia, the findings can be generalised to apply to most countries.</td>
<td></td>
</tr>
<tr>
<td>Mostly in children with only one study including adults</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application of findings i.e. testing vitamin D at the end of winter would be limited by several factors:</td>
<td></td>
</tr>
<tr>
<td>• Variation in vitamin D measurements between laboratories means that use of one central laboratory is best practice, but may not be feasible for all individuals</td>
<td></td>
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<tr>
<td>• Individuals often have bloods checked opportunistically e.g. as an inpatient or while under sedation for a procedure.</td>
<td></td>
</tr>
<tr>
<td>• CF clinics usually manage individuals from a large geographical region, including those from rural locations who may be unable to attend CF clinic at the end of winter for a blood test.</td>
<td></td>
</tr>
</tbody>
</table>
**CLINICAL QUESTION**

8.2.4 Should supplemental vitamin D be given to people with CF who are pancreatic sufficient as part of routine care?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chavasse RJ, Francis J, Balfour-Lynn I, Rosenthal M, Bush A. Serum vitamin D levels in children with cystic fibrosis. Pediatric Pulmonology. 2004; 38(2):119-22.</td>
<td>NHMRC level IV ADA quality NEUTRAL</td>
<td>Retrospective cross sectional (chart review) 290 Children with CF attending a London based CF clinic Inclusion criteria: between 1 and 18 years of age; confirmed CF through sweat +/- genetic testing; attended annual clinic during the study period of August 1999 – April 2001 Exclusion: None</td>
<td>Intervention: N/A Primary outcome: 25OHD levels at annual review assessment. Levels were compared to other fat soluble vitamin levels, bone and liver biochemical parameters, pulmonary function, growth, and date of testing. Subgroup analysis for pancreatic status and liver disease.</td>
<td>Results:  • PI patients routinely prescribed 800-1200IU vit D a day. PS not routinely prescribed.  • 1% of patients had levels &lt;15nmol/L, 6% less than 25nmol/L and (14% less than 40nmol/L). Significantly lower levels in adolescents (age&gt;13) compared with children less than 5 or between 5-12 years (p&lt;0.001)  • No correlation between pulmonary function, weight or height Z scores.  • No difference between PS and PI or in those with liver disease and those without liver disease (age, gender and season of testing matched).</td>
<td>Conclusions: No consensus for optimal level of 25OHD. Lower levels in adolescents may be a precursor to low levels in adulthood and did not seem to be related to poor compliance with supplements or disease severity. Appraiser’s Limitations:  • Problem with definition of abnormal being &lt;25nmol/L.  • No formal assessment of vit D intake from supplements (or food) in PS or PI patients. Appraiser’s Limitations: None</td>
</tr>
<tr>
<td>Sexauer WP et al. Vitamin D deficiency is associated with pulmonary dysfunction in cystic fibrosis. J</td>
<td>NHMRC level IV ADA quality NEUTRAL</td>
<td>Retrospective cross sectional (chart review) 597 Adults and children with CF attending a clinic in a Mid -Atlantic state of America (a total of 9 CF centres)</td>
<td>Intervention: N/A Primary outcome:  • 25OHD level, lung function tests</td>
<td>Results:  • Mean 25OHD level was 29.6 +/- 12.8 ng/ml.  • Pediatric patients, females and pancreatic sufficient patients had significantly higher 25OHD levels than adult, males and pancreatic insufficient respectively.</td>
<td>Limitations:  • Didn’t quantify activity levels or sunlight exposure, supplemental vitamin D (doses and duration), complete genotyping.  • Retrospective study.  • Used different labs for vit D</td>
</tr>
</tbody>
</table>
Inclusion criteria: Attending clinic as part of the Mid-Atlantic Research Study Group; CF dx confirmed by sweat test and/or genetic testing; > 6 years of age; 25(OH)D level not drawn during an exacerbation as judged by their CF clinician; able to perform spirometry; spirometry performed within 2 months of vit D level and not during a period of exacerbation

Exclusion criteria: organ transplant; spirometry performed only during an exacerbation

- Patients with CFRD, liver disease and mucoid pseudomonas had significantly lower 25OHD than those without these conditions.
- Those taking vit D supplements did not have significantly different vit D levels than those who didn’t.
- There was a significant correlation between vit D and pulmonary function.
- FEV1 % predicted ($r=0.20$, $p<0.0001$) and FVC % predicted ($r=0.13$, $p=0.0019$) for the whole group.
- This relationship was strongest for those homozygous F508: ($p=0.015$) for FEV1 %predicted and ($p=0.029$) for FVC %predicted and for males ($p=0.015$) for FEV1 %predicted.

Conclusions: Serum 25OHD levels are sig associated with pulmonary function in CF. the association was strongest for those homozygous F508 and males. Further studies needed to establish causality.


<table>
<thead>
<tr>
<th>NHMRC level</th>
<th>ADA quality</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Results</th>
<th>Appraiser’s Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-3</td>
<td>NEUTRAL</td>
<td>Retrospective cohort</td>
<td>360 Adults with CF attending Toronto based CF clinic</td>
<td>Baseline serum vitamin D were monitored and adjusted as needed (400-1000IU cholecalciferol). 25OHD levels were re-measured 3 months after intervention.</td>
<td>69% had 25OHD &lt;50nmol/L at baseline and 82% had 25OHD &gt;50nmol/L after intervention. Serum 25OHD levels increased significant yin 92% of subjects post intervention ($p&lt;0.0001$). Largest increase was seen in those with baseline levels &lt;25nmol/L. Mean cholecalciferol supplementation also increased after intervention from a median of 800IU to 1800IU ($p&lt;0.001$). After dividing the patients into those &lt;25nmol/L, 25-50nmol/L and &gt;50nmol/L there was a significant difference between groups with</td>
<td>None</td>
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<tr>
<td></td>
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<td>Exclusion: Post lung transplant</td>
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<td></td>
<td>Retrospective study design. Exact date of intervention not recorded. No record of sun exposure or sunscreen use.</td>
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</table>

Author’s Limitations:
<table>
<thead>
<tr>
<th>Authors</th>
<th>NHMRC</th>
<th>Study Design</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansing et al.</td>
<td>IV</td>
<td>Retrospective cross sectional (chart review)</td>
<td>129 Children with CF from a Utah based clinic</td>
<td>N/A</td>
<td>No patient had vitamin D toxicity despite receiving higher doses than suggested in the 2012 US revised vit D guidelines. Mean supplemental dosing was 1650IU for 1-&lt;5yrs, 3170IU for those 5-&lt;10 and 3463 for those &gt; 10 yrs. (guidelines say 800-1000IU/day for 1-10yrs and 800-2000IU/day for 10yrs and above.</td>
<td>May require supplement doses well above the CFF recommendations. No sig risk of toxicity in doing this. Risk factors for low vit D are older age and seasonality. Diligence in vit D monitoring and dosing can improve serum 25OHD levels.</td>
</tr>
<tr>
<td>Simoneau T; Bazzaz O; Sawicki</td>
<td>IV</td>
<td>Retrospective cross sectional (chart review)</td>
<td></td>
<td>N/A</td>
<td>Mean serum 25OHD levels were</td>
<td>Adherence of prescribed</td>
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**Notes:** Normal vit D levels were defined as between 30-80ng/ml
<table>
<thead>
<tr>
<th>GS; Gordon C.</th>
<th>Ada quality: NEUTRAL</th>
<th>Primary outcome: Vitamin D levels.</th>
<th>ADA quality: NEUTRAL</th>
<th>Primary outcome: Vitamin D levels.</th>
<th>Ada quality: NEUTRAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D status in children with cystic fibrosis. Associations with inflammation and bacterial colonization. Annals Of The American Thoracic Society. 2014. 11 (2): 205-10.</td>
<td>148 Children with CF under 12 years of age attending a Boston CF clinic</td>
<td>32.4ng/ml, 7% were deficient - &lt;20ng/ml. 36% were vit D insufficient (20&gt;29.9ng/ml). 50% of PS patients were either deficient or insufficient. 41% of PI patients were deficient or insufficient, there was no significant difference in mean serum levels between the two groups. PSA was more sig more common in those deficient/insufficient compared with sufficient (p=0.018). No sig difference in FEV1 or BMI between deficient, insufficient and sufficient. Supplemental vit D data was available on 131/148. Median dose was 800IU (0-3600IU).</td>
<td>Retrospective cross sectional (chart review)</td>
<td>11/33 infants who were tested for vit D levels were deficient (&lt;25nmol/L). Vit D level was not related to pancreatic function. Vit D was lower in months with lower UV radiation but this was not significant. With routine vitabdeck those with initial deficiency were sufficient at 2 yrs of age.</td>
<td>Retrospective cross sectional (chart review)</td>
</tr>
<tr>
<td>Neville et al. Vitamin D in infants with cystic fibrosis diagnosed by newborn screening. Journal of Paediatrics and Child Health. 2009. 45(1-2): 36-41</td>
<td>58 Infants with CF from an Australian based CF clinic (Victoria)</td>
<td>32.4ng/ml, 7% were deficient - &lt;20ng/ml. 36% were vit D insufficient (20&gt;29.9ng/ml). 50% of PS patients were either deficient or insufficient. 41% of PI patients were deficient or insufficient, there was no significant difference in mean serum levels between the two groups. PSA was more sig more common in those deficient/insufficient compared with sufficient (p=0.018). No sig difference in FEV1 or BMI between deficient, insufficient and sufficient. Supplemental vit D data was available on 131/148. Median dose was 800IU (0-3600IU).</td>
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<td>11/33 infants who were tested for vit D levels were deficient (&lt;25nmol/L). Vit D level was not related to pancreatic function. Vit D was lower in months with lower UV radiation but this was not significant. With routine vitabdeck those with initial deficiency were sufficient at 2 yrs of age.</td>
<td>Retrospective cross sectional (chart review)</td>
</tr>
<tr>
<td>Inclusion criteria: Fat soluble vitamin levels measured between Jan 2009 and Dec 2011</td>
<td></td>
<td></td>
<td>Inclusion criteria: Patients 0-3 months of age diagnosed with CF through newborn screening program between 2001-2006</td>
<td>Inclusion criteria: Patients 0-3 months of age diagnosed with CF through newborn screening program between 2001-2006</td>
<td>Inclusion criteria: Patients 0-3 months of age diagnosed with CF through newborn screening program between 2001-2006</td>
</tr>
<tr>
<td>Exclusion criteria: None</td>
<td></td>
<td></td>
<td>Exclusion: Patients diagnosed following neonatal presentation with meconium ileus; diagnosis over 3 months of age</td>
<td>Exclusion: Patients diagnosed following neonatal presentation with meconium ileus; diagnosis over 3 months of age</td>
<td>Exclusion: Patients diagnosed following neonatal presentation with meconium ileus; diagnosis over 3 months of age</td>
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<td></td>
</tr>
<tr>
<td>Conclusions: Vitamin D deficiency is common in infants newly diagnosed with CF by newborn screening and is not related to pancreatic status and not predicted by low vitamin E status. Routine supplementation of vitamin D (vitabdeck) results in normalisation of levels in most cases.</td>
<td>Conclusions: Vitamin D deficiency is common in infants newly diagnosed with CF by newborn screening and is not related to pancreatic status and not predicted by low vitamin E status. Routine supplementation of vitamin D (vitabdeck) results in normalisation of levels in most cases.</td>
<td>Conclusions: Vitamin D deficiency is common in infants newly diagnosed with CF by newborn screening and is not related to pancreatic status and not predicted by low vitamin E status. Routine supplementation of vitamin D (vitabdeck) results in normalisation of levels in most cases.</td>
<td>Appraiser's limitations: Small sample</td>
<td>Appraiser's limitations: Small sample</td>
<td>Appraiser's limitations: Small sample</td>
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<tr>
<td>Appraiser's limitations:</td>
<td>Appraiser's limitations:</td>
<td>Appraiser's limitations:</td>
<td>Author's limitations:</td>
<td>Author's limitations:</td>
<td>Author's limitations:</td>
</tr>
<tr>
<td>• Adherence to PERT</td>
<td>• No record of supplementation protocol/compliance.</td>
<td>• Caucasian sample not representative of Australian CF population.</td>
<td>• Reference ranges are based on historical data, few reference ranges include levels measured in infants.</td>
<td>• Lack of control group.</td>
<td>• Does not take into account maternal sun exposure/vit D status, food/supplement intake of vitamin D, physical activity, comorbidities, environmental conditions</td>
</tr>
</tbody>
</table>
| **Norton et al.**  
**Prevalence of Inadequate Vitamin D status and Associated Factors in Children With Cystic Fibrosis. Nutr Clin Pract, 2015; 30: 111-116** | **NHMRC level IV** | **ADA quality NEUTRAL** | Retrospective cross sectional (chart review)  
Children with CF from a Canadian based CF clinic - 77 in 2010 and 77 in 2011  
Inclusion criteria: confirmed CF diagnosis by two positive sweat tests and genetic testing; consented; had a measured 25(OH)D level during study period (2010 and 2011)  
Exclusion: Lung transplant | **Intervention:** If vit D levels were <60nmol/l then an additional 1000IU/d of cholecalciferol or if levels were between 60>75nmol/L then they were given 400IU/d.  
**Primary outcome:** prevalence of inadequate 25(OH)D levels  
**Secondary outcomes:** Clinical measure associated with vit D levels | **Results:**  
- 26% of patients were deficient in 2010 and 23% in 2011. Out of the 20 that were identified as deficient in 2010 and started on additional supplementation, there was a sig increase in mean 25(OH)D levels (p = 0.03) and 50% were sufficient in 2011. Age was sig negatively associated with 25(OH)D levels in both years (p=0.002) and FEV1 was sig positively associated with 25(OH)D levels in 2011 (p=0.03) but not in 2010. CF related hospital admissions were sig associated with a higher prevalence of inadequate 25(OH)D levels in 2011 (p=0.02) but not in 2010. Total BMD in 2010 was sig positively associated with 25(OH)D levels (p=0.044). Not association between BMI percentile, pancreatic status, steroid use, CFRD or location of residence.  
**Conclusion:** This protocol did not achieve optimal vit D status in 25% of the population. Increasing age had the strongest association with 25(OH)D. | **Appraiser’s limitations:**  
• Provided information on supplemental doses of vit D given but not on baseline dose.  
• No measure of compliance.  
**Author’s limitations:**  
• Seasonal variation not accounted for  
• Did not measure vit D intake from the diet  
• Short period of follow up (only 2 consecutive years)  
**Notes:** Adequacy was set at 75nmol/l |
| **Malay-Rana et al.**  
**Fat-soluble vitamin deficiency in children and adolescents with cystic fibrosis. Journal of Clinical Pathology 2014;** | **NHMRC level IV** | **ADA quality NEUTRAL** | Retrospective cross sectional (chart review)  
556 Children with CF attending one of three CF clinics in NSW, Australia  
Inclusion criteria: Attended one of these clinics between 2007 and 2010 | **Intervention:** N/A  
**Primary outcome:**  
- Prevalence of fat soluble vit deficiencies.  
- Low vit D levels were sig lower in patients with pancreatic insufficiency than sufficiency (28% versus 3%) (p<0.01) and sig higher in summer (p>0.01). Prevalence of vit D deficiency was a mean of 16.96% from 2007-2010. | **Results:**  
- Low vit D levels were sig lower in patients with pancreatic insufficiency than sufficiency (28% versus 3%) (p<0.01) and sig higher in summer (p>0.01). Prevalence of vit D deficiency was a mean of 16.96% from 2007-2010. | **Author’s limitations:**  
• Vitamin reference ranges differed between labs  
• Retrospective  
• Did not measure adherence  
**Appraiser’s limitations:**  
• Did not define what they used as a
Evidence statement matrix

**Chapter 8 Q8.2.4 Should supplemental vitamin D be given to all people with pancreatic sufficient cystic fibrosis as part of routine care?**

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** There have been numerous studies, mostly level IV (retrospective chart reviews) that have looked to describe vitamin D deficiency and sufficiency in people with CF (both pancreatic sufficient and insufficient). These studies have been conducted in different geographical locations, usually with small numbers of pancreatic sufficient people and poorly controlled for known risk factors for low serum vitamin D (including the time of year of testing). Therefore, the literature does not provide a good evidence base to answer whether routine vitamin D supplementation should be given to all people with CF. It should be noted however that regardless of study design and country of origin, these studies have shown that it is a common finding for pancreatic sufficient people with CF to be deficient in vitamin D.

<table>
<thead>
<tr>
<th>Evidence Base</th>
<th>C Satisfactory</th>
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</thead>
<tbody>
<tr>
<td>8 studies included in the body of evidence</td>
<td></td>
</tr>
<tr>
<td>• One level III retrospective cohort study; n=360 adults; neutral</td>
<td></td>
</tr>
<tr>
<td>• 7 level IV cross sectional chart reviews; all of neutral quality</td>
<td></td>
</tr>
<tr>
<td>• n=58 infants</td>
<td></td>
</tr>
<tr>
<td>• n=556, n=290, n=129, n=148, n=77 children</td>
<td></td>
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<tr>
<td>• n=297 children and adults</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>D Poor</th>
</tr>
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<tbody>
<tr>
<td>Inconsistent findings relating to pancreatic status and serum vitamin D levels.</td>
<td></td>
</tr>
<tr>
<td>• Some report the percentage of pancreatic sufficient and pancreatic insufficient people who fall below set vitamin D level</td>
<td></td>
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<tr>
<td>• Cut off vitamin D level varies between studies</td>
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<tr>
<td>• No universally accepted definition of vitamin D deficiency</td>
<td></td>
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<tr>
<td>• Some studies report mean or median vitamin D levels.</td>
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<tr>
<td>• The number of pancreatic sufficient people is usually low and not always adequately powered to detect a difference.</td>
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<tr>
<td>• All but one study did not match for other potential confounders e.g. season of testing, gender and age.</td>
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</tr>
<tr>
<td>Of the eight studies reviewed:</td>
<td></td>
</tr>
<tr>
<td>• 5 studies found no significant difference in vitamin D status between pancreatic sufficient and insufficient patients</td>
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</tbody>
</table>
| • 3 studies found a significant difference in vitamin D status between pancreatic sufficient and insufficient patients (1 showing that mean serum levels were significantly lower in pancreatic insufficient patients and 2 showing that those who were pancreatic insufficient were
significantly more likely to be deficient (based on a cut off of 25nmol/L).

| Clinical Impact | C Satisfactory | The finding that pancreatic sufficient individuals are at risk of vitamin D deficiency is important in guiding clinical practise:
|                 |               | • Highlights that annual screening is important for everyone
|                 |               | • There may be a potential role in routine supplementation for all people with CF

| Generalisability | C Satisfactory | Studies mostly conducted in children
|                 |               | • Each clinic likely differed in their approach to routine supplementation of those with pancreatic sufficiency
|                 |               | • Individuals from different countries were likely to have received varying amount of UVB exposure as well as different amounts of vitamin D from food (some countries having mandatory fortification and others not).
|                 |               | • Overall somewhat generalizable to the Australian community

| Applicability    | B Good        | It is feasible to expect that all individuals with CF and not just those who are pancreatic insufficient, undergo annual serum vitamin D testing and supplementation as needed |
CLINICAL QUESTION
8.2.5 What doses of vitamin D are needed to prevent deficiency in people with CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.

CLINICAL QUESTION
8.2.6 What doses of vitamin D are needed to correct deficiency in people with CF?

Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shepherd et al. Single high-dose oral vitamin D3 (stoss) therapy – A solution to vitamin D deficiency in children with cystic fibrosis? Journal of cystic fibrosis. 2013;12(2):177-82</td>
<td>NHMRC level III-2 ADA quality NEUTRAL</td>
<td>Retrospective cross sectional (chart review) Children with CF attending an Australian based CF clinic (Sydney) Number: 142 patient’s charts were reviewed. Of these 38 received stoss and 37 served as controls. Inclusion criteria: All children attending CF clinic between 2007-2011 Exclusion: None</td>
<td>Intervention: • Either stoss (one off dose of 100,000-600,000IU cholecalciferol given orally – depending on age and vit D level) followed by daily cholecalciferol supplemented as per routine care or routine care alone which was 400IU/day cholecalciferol if &lt;1yr and 800IU/day if &gt;1yr. Primary outcome: • Change in serum 25OHD, calcium, mg, po, alb, ALP levels</td>
<td>Results: 56% of children had vit D level &lt;75nmol/L. Stoss treated group had a significant and sustained increase in 25OHD levels measured at 1,3,6 and 12 months post treatment compared with controls. At 12 months post intervention, the mean difference in vitamin D levels from baseline between the stoss and control group was significant (15nmol/L versus 5nmol/L, p=0.038). Conclusions: Stoss therapy effectively achieves and maintains levels of 25OHD greater than 75nmol/L over 12 months. There was no evidence of vit D toxicity. Limitations: lack of placebo control group, potential seasonal bias of baseline and 12 months tests, did not control for vit D maintenance therapy or dietary advice given to each group</td>
<td>Appraiser’s Limitations: None Author’s limitations: • lack of placebo control group • Potential seasonal bias of baseline and 12 months tests • Did not control for vit D maintenance therapy or dietary advice given to each group Notes: Deficiency defined as &lt;75nmol/l</td>
</tr>
</tbody>
</table>
**Evidence statement matrix**

**Chapter 8 Q 8.2.6 What doses of vitamin D are needed to correct deficiency in individuals with CF?**

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** Whilst there is good evidence in the use of high dose cholecalciferol to correct deficiency in people with CF, there is limited benefit in its application to the Australian and NZ setting given our knowledge of potential toxicity in some people who may be unable to convert excess cholecalciferol to its inactive form. There is a lack of evidence on conventional, daily doses of vitamin D needed to correct vitamin D deficiency. In the absence of CF specific doses needed to correct deficiency, guidance should be taken from the general Australian and NZ population recommendations as well as recommendations from other CF specific guidelines.
| Evidence Base | B Good | 2 studies looked at a set dosing protocol and measured subsequent serum vitamin D levels.  
• 1 level II intervention, positive quality (50,000IU vitamin D) study; n=30 adolescents and adults  
• 1 level III intervention, neutral quality (100,000-600,000IU); n=38 children  

Other studies have reported the general practice of their clinic in terms of supplementation and then described mean vitamin D levels. These studies were not included as they lacked an assessment of individual doses and adherence. |
<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>B Good</td>
<td>Consistent findings that high dose cholecalciferol can significantly raise serum vitamin D levels in individuals with CF.</td>
</tr>
</tbody>
</table>
| Clinical Impact | D Poor | There is benefit in using high dose cholecalciferol to correct vitamin D deficiency in people with CF.  
Given the risk versus benefit of using high dose supplementation (due to potential toxicity), the potential benefit from applying this protocol is poor. |
| Generalisability | B Good | The findings of these studies can be applied to the Australian and New Zealand setting |
| Applicability | D Poor | Evidence of an autosomal recessive mutation which can affect the conversion of excess cholecalciferol to its inactive form therefore increasing the risk of hypercalcaemia.  
• Some hospitals have advised against the use of high dose treatment i.e. 50,000IU  
• There is a lack of studies that are based on the more conventional, daily dosing of vitamin D which would be more applicable to Australian and NZ CF centres. |
8.3 Vitamin E

PICOs

8.3.1 How should vitamin E status be assessed for people with CF?
8.3.2 What is the role for supplementation of vitamin E supplementation in people with CF?
8.3.3 What is the safe upper limit for vitamin E supplementation in people with CF?
8.3.4 How often should we measure/monitor vitamin E levels in people with CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:
Vitamin E
  • Cystic fibrosis, CF, nutrition, diet, vitamin E, alpha*tocopherol, deficiency, subclinical deficiency, supplementation, toxicity

Inclusion & exclusion criteria:

Inclusion criteria:
• Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
• Systematic reviews

Exclusion criteria:
• Studies that didn’t specifically address the PICO
• Case reports
• Guidelines and consensus documents
• Review papers

CLINICAL QUESTION
8.3.1 How should vitamin E status be assessed for people with CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.
### Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
</table>
- Nil – observational  
Following measurements recorded:  
- Serum retinol and α-tocopherol levels were Vitamin A and E supplementation (prescribed only if reduced serum levels were found)  
- Water miscible vitamin preparation at dose of 1500 IU/day of Vitamin A and 780 IU of Vitamin E, and if both levels low a combined dose of Vit A 2210 IU & E 102 IU/day  
- Serum fat soluble vitamin levels  
- Anthropometry  
- Dietary intake  
- Pancreatic function  
- Assessment of lung disease | Results: Anthropometry:  
- At T1, CF infants already showed abnormalities in weight, length, weight for length ratio and body composition. Serum retinol and α-tocopherol:  
- At T1, 20 infants (51%) had serum retinol levels below the normal reference range 0.7 (0.3) umol/L, including 5 both low serum retinol and α-tocopherol concentrations.  
- Dietary energy intake was related to serum retinol concentration at dose of 1500 IU/day of Vitamin A and 780 IU of Vitamin E, and if both levels low a combined dose of Vit A 2210 IU & E 102 IU/day  
- Serum retinol levels (umol/L) increased significantly from T1 to T2 =0.69 (0.59, 0.79)and 1.23 (1.11, 1.36) respectively (P<0.001).  
- T2 mean serum retinol levels had increased significantly. Biochemical vitamin A deficiency had been corrected in all but one patient.  
- No significant relationship between serum retinol levels and pancreatic status or growth at T1.  
- No significant relationship between serum retinol concentrations and CF genotype, pancreatic status or mode of presentation.  
- Evidence of lung disease as suggested by respiratory symptoms, radiographic scores, infection or increased inflammatory | Appraiser’s limitations:  
- Not reported if fasting for tests - unlikely in infants.  
- No objective measures of inflammation)  
- No control group  
- No lipid ratio for vitamin E  
- Supplemented if any deficiency detected but didn’t state how often ax for deficiency  
- Compliance to taking supplements not measured or commented on  
- Were there enough subjects enrolled in study to get meaningful results (no statistical power)?  
- Did not comment on intake of dietary Vitamin E (and bottle vs breast fed infant) and impact on serum levels.  
- Only measured serum vitamins at baseline and 1 year after  
- How was the food diary executed, if not weighed data then higher degree of error |
**Anthropometry; weight, length, TSF**
**Dietary intake MJ/kg**
**Pancreatic function** markers in BL fluid was not associated with serum retinol levels.

Assessment of lung disease:
- At T1 and T2 number of subjects with pulmonary infection was similar. (31% and 44% respectively)
- Some evidence of mild progressive lung disease in older subjects who systematically were more likely to have respiratory symptoms, lower Brasfield scores and increased airway inflammation.
- No association between serum retinol and α-tocopherol levels at T1 and the development of lung disease, determined by the presence of respiratory symptoms, Brasfield scores and pulmonary inflammatory markers at T2.

**Conclusion:**
- No evidenced found to implicate the deficiency of Vitamin A and E with the early development of CF lung disease, including airway inflammation, during infancy

---

**Dorlochter, L, Aksnes, L, Fluge, G.**

<table>
<thead>
<tr>
<th>NHMRC level</th>
<th>Case series (aetiology)- predominantly descriptive study</th>
<th>Inclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>N=35 Age: 12.1 ± 8.8 (2-40)</td>
<td>Nil listed only that met criteria for Dx of CF (repeated elevated sweat chloride concentrations and typical clinical manifestations in all patients)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Intervention(s):</th>
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<tbody>
<tr>
<td>Nil – observation</td>
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</tbody>
</table>

The following measures noted:
- Annual fat soluble vitamins A, D, E (retinol, 25-OH-vitamin D and alpha-tocopherol)
- FE-1
- Daily vitamin supplementation
  - Standard multivitamin preparation (e.g. Biovit, Nycomed) - 20ml dose (double dose), containing per millilitre: 50ug vitamin A, 0.75ug vit D, and 0.6mg vit E plus water soluble vitamins

<table>
<thead>
<tr>
<th>Results:</th>
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<tbody>
<tr>
<td>FE-1</td>
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<tr>
<td>Mean FE-1 for 35 pts: 256.9 ± 445.2 ug/g (median: 24.1 ug/g)</td>
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<tr>
<td>Significant difference b/w PI vs PS pts: -24 pts with PI mean 19.9 ± 15.8 ug/g (median 18.7 ug/g) and 11 pts with PS had mean of 773.9 ± 494.4 ug/g (median: 728.9 ug/g p&lt; 0.01)</td>
</tr>
<tr>
<td>All 24 patients with exocrine pancreatic insufficiency had FE-1 values lower than 60µg/g.</td>
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</table>

**Fat Sol Vit Levels**
- At Dx and follow up for 17 pts: all mean values for fat soluble vitamins were in 

**Appraiser’s Limitations:**
- Were serum levels measured when stable? 
- Other treatments not mentioned (other than IV AB’s) 
- Did not measure selection bias possible (no comment on how selected pts, was it all newly Dx b/w 1992-2001) 
- Ordinary dose of fat soluble vitamin not stated 
- Didn’t say how the dose of fat soluble vitamins was adjusted over years (for PI pts with low vitamin E and other pts)) 
- Did not ask pts if they were started on
Exclusion criteria:
• Nil stated

OR their ordinary dose plus cod liver oil (the recommend 5ml of oil contains 500µg vitamin A, 10µg Vitamin D and 10mg Vitamin E)
- PLUS Vitamin E supplement (Ido-E, Pharmacia & Upjohn) of 50-200mg daily

Outcomes:
• FE-1 value
• Fat soluble vitamin profiles- serum retinol, 25-OH-vitamin D and alpha-tocopherol
- All exocrine pancreatic insufficient patients had low levels FE-1 and are treated with enzymes.

normal range except Vit E for PI
- 55% (5/9) in this group had low vit E at diagnosis with mean value 7.0 ± 6.6 mg/L (medium 3.6mg/L) and were all corrected at follow up (9.8 ±2.7 mg/L ( median 10.8mg/L)
- One pt with Vit E deficiency at diagnosis also had deficiency of Vit A and Vit D
  - 2 pts with PS had low Vitamin levels: 1 pt both Vit A & Vit E deficiency corrected at follow up and 1 pt Vit D deficiency also corrected
- Mean values for fat soluble Vitamins at follow up for 35 pts did not differ significantly b/w PI and PS (p>0.05) and all in normal range: Serum Vitamin E -for PI 9.1 ± 2.7 (3.4-12.0 and PS 9.8 ± 4.2 (5.2-18.9)
- No correlation b/w pancreatic exocrine function measured by FE-1 and fat soluble vitamin profiles neither at Dx nor at follow up (r=0.292, p< 0.100)
- At follow up with all apparently supplemented highest range in PS patients was 18.9mg/l and PI 12.9mg/L (Mean PI 9.1+2.7 range 3.4-12.9); PS 9.8+4.2 (5.2-18.9)

Conclusions:
• No correlation b/w faecal elastase-1 levels and fat soluble vitamin status.
• Values of fat-soluble vitamins were mostly in the normal range in both PS and PI. This may be an indication of appropriate PERT and vitamin supplementation both before and after diagnosis and may reflect good patient compliance.
• Official recommended supplementation of vitamin A & D in Norway during infancy and vitamin A, & D and cod liver oil prior to diagnosis
• Reported received double dose or ordinary dose plus cod liver oil but didn’t specify which participants received which.
• Compliance to taking vitamins not assessed nor to PERT
• Small sample size (no statistical power calculation)
• Why did they only have serum fat soluble vitamin levels for 17/35 pts at diagnosis (were some already diagnosed going into study?)

Author’s Limitations:
• Common use of Vitamin A, D and cod liver oil supplementation in infants and children.
- ADEK supplement (Scandipharm) – 1 tablet 9000IU Vitamin A and 40IU vitamin E; Patients <3yrs 1ml ADEK liquid/d 1500IU Vitamin A and 40IU vitamin E  
Retrospective:  
- Patient records retrospectively studied over 3 years and mean serum Vitamin A (and E) for each patient calculated  
- 3 groups - FEV1 >80%; 60-80% and <60% (Bloods routine care q 4-12m)  
- Further, Vitamin A (and E) levels were measured prospectively over a 2 year period at the onset of IV AEs and 1 month post-discharge  
Prospective  
- Vitamin levels onset PE and 1/12 post over 2 years. Only PE requiring IV Abx.  
Primary outcome:  
- Vitamin levels A and E by HPLC  
Ref ranges reported; Vit A 25-200ug/dL and Vitamin E 0.5-2mg/dL | Results:  
Retrospective arm of study  
- Average Vit E level was 0.7±0.28mg/dL  
- Negative correlation bw number PE and vitamin serum levels - E levels (r=−0.444, P<0.001), even when levels within the normal range. This indicates that the number of respiratory exacerbations increased as the mean values of serum vitamin E decreased.  
- Sig negative correlation when analysed in both PS and PI groups separately.  
- No significant differences seen between groups with good (FEV1>80%), moderate (FEV160-80%) or poor lung function (<60%) for Vitamin E p=0.237 but sig diff for vitamin A as well as no of PE bw these groups. p<0.001  
Prospective arm of study  
- At onset of exacerbation, vitamin E levels were reduced in the PI patients - vit E 0.67±0.13mg/dL, increasing to 0.85±0.35 after recovery, P<0.001  
- Similar seen in the PS patients (vit E 0.82mg/dL increasing to 0.98 after recovery, P<0.07)  
Conclusions:  
- Reduced serum levels of vitamin A and E even in the normal range are associated with an increased rate of pulmonary exacerbations in CF.  
- Authors propose increase the target serum levels to at least 35ug/dL for Vitamin A and 0.9ml/dL Vitamin E. Unclear if maintaining levels > than these will decrease no. of PE. | Appraiser’s limitations:  
- Prospective arm: PS pts older (mean 13.26 vs 10.17 years PI)  
- Cofounders for Vitamin A Vitamin A measured during exacerbations (false low due to acute phase response)  
- Retrospective study  
- Poor study design – testing done during acute phase response  
- Part one of study - unclear when levels tested ie reports part of routine care every 6-12m but were they acutely unwell at the time  
- Small sample size may have resulted in Vitamin E increase post PE not reaching sig.  
- appraiser  
- No reports of diet intake  
- No info re compliance with supplements  
- No info re supp intake  
- No info whether PS patients taking supps as guidelines PI specific  
- No info re inflammatory status  
- No methodology for vit levels ie fasting  
- No measure of RBP or B carotene  
- No measure of cholesterol/lipid ratio for vit E.  
Author’s Limitations:  
- Nil stated |
<table>
<thead>
<tr>
<th>Hollander F, de Roos N, Dopheide J, Hoekstra T, Teding van Berhout F.</th>
<th>Cross sectional study-aetiology study N=93 Adult CF patients</th>
<th>Nil – observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross sectional study-aetiology study</td>
<td>Nil – observational</td>
<td>Following measures taken:</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>Nil – observational</td>
<td>Assessment of dietary supplement intake for fat soluble vitamins, minerals, fish oil &amp; creatine (telephone survey)</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Nil – observational</td>
<td>Serum vitamin D &amp; E levels (non-fasting) – medical notes audit</td>
</tr>
<tr>
<td>Outcomes:</td>
<td>Nil – observational</td>
<td>Nutrition status (anthropometry markers)</td>
</tr>
<tr>
<td>Intervention(s):</td>
<td>Nil – observational</td>
<td>Intake of fat soluble vitamins (only from CF specific vitamins and multivitamin &amp; mineral supplements (not food)</td>
</tr>
<tr>
<td>Results:</td>
<td>Overall 74 pts (80%) reported the use of vitamin &amp; mineral supplements</td>
<td>Serum tocopherol and vitamin D levels (no cholesterol ratio)</td>
</tr>
<tr>
<td></td>
<td>Fat soluble vitamins used by 43% of PS and 81% of PI patients</td>
<td>Comparison of supplement intake with guidelines</td>
</tr>
<tr>
<td></td>
<td>Vitamin E supplemented in 63% of PI pts (most frequently used single supplement)</td>
<td>Serum vitamin E levels available for 39 PI patients and 28 (72%) on Vit E supplements.</td>
</tr>
<tr>
<td></td>
<td>Multivitamins frequently used (42% of PI vs 29% PS)</td>
<td>- Serum levels ranged from 2.41 umol/L, mean of 20.4 umol/L</td>
</tr>
<tr>
<td></td>
<td>Mean daily dose of Vitamin E= 100mg/day (range 5 - 600mg)</td>
<td>- Low serum Vit E levels found in 15% of PI patients who had levels measured (6/39) and half of these were not on Vit E supplements</td>
</tr>
<tr>
<td></td>
<td>59% of PI patients on Vitamin E met the recommendations for supplementation dosage</td>
<td>No association found between intake from supplements and serum levels (p = 0.60)</td>
</tr>
<tr>
<td></td>
<td>Comparison of supplement intake with guidelines</td>
<td>Author Conclusions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High % of PI patients use fat-soluble</td>
</tr>
</tbody>
</table>

**Author Conclusions:**

- High % of PI patients use fat-soluble

**Appraiser’s limitations:**

- No data on FEV1 and other medical conditions; genotype, CFRD, liver disease, end stage
- No data reported for PS patients
- 16% did not consent to participate (higher age non responders).
- 49% of PI patients without serum E levels - no characteristics of this group provided
- Don’t know supplement intake of those who are deficient
- Patient report of vitamin intake to
- Vitamin E levels non fasting and no lipid ratio
- No measure of inflammation; disease acuity which may affect serum levels of E
- No measure of PUFA intake which may affect levels
- Serum levels may not been tested at time when on same supplement intake.
- Non fasting bloods

**Author’s Limitations:**

- Supplement intake was self-reported data only and not measured

<table>
<thead>
<tr>
<th>NHMRC level IV (Aetiology)</th>
<th>Cross sectional study with reference control group</th>
<th>Intervention(s):</th>
<th>Results:</th>
<th>Appraiser’s Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA quality NEUTRAL</td>
<td>N=69 CF children (7-10yrs) N=222 reference population (NHANES 1988-1994)</td>
<td>Nil – observational</td>
<td>CF subjects had:</td>
<td>No info regarding recruitment</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria:</td>
<td>Outcomes:</td>
<td>Higher serum a-tocopherol:cholesterol ratios (median [5th-95th percentile], 8.2 [4.6-14.5] vs 4.6 [3.7-6.1] mg/g, P &lt;0.0001)</td>
<td>All patient high CFA, good nutrition status, high FEV1 and limited age range so not generalisable to high moderate and severe CF or &lt; 7yrs and &gt;10yrs All PI</td>
</tr>
<tr>
<td></td>
<td>• CF and PI</td>
<td>• Fasting serum α-tocopherol, cholesterol and α-tocopherol:cholesterol ratio</td>
<td>Higher α-tocopherol levels:</td>
<td>No info how diet ax</td>
</tr>
<tr>
<td></td>
<td>• Aged 7-10 yrs</td>
<td>• Intake vitamin E (and cholesterol, fat, PUFA total energy, EER% and %RDA Vit E)</td>
<td>• [600-1988] vs 786 [581-1133] g/dL, P &lt;0.0001</td>
<td>Adherence to supplementation not measured</td>
</tr>
<tr>
<td></td>
<td>• Mild to moderate lung Dx</td>
<td>• Z scores ht, wt, BMI; FEV1; CFA %</td>
<td>Lower cholesterol levels:</td>
<td>No stats methods reported for associations.</td>
</tr>
<tr>
<td></td>
<td>• On PERT and vitamin supplementation</td>
<td>Exclusion criteria:</td>
<td>• 139 [97-184] vs 169 [134-215] mg/dL, P&lt;0.0001</td>
<td>No diet or supplement intake methodology</td>
</tr>
<tr>
<td></td>
<td>• Nil reported</td>
<td></td>
<td>• 4% low and 48% high serum a-tocopherol levels</td>
<td>Only PI patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 4% low and 83% high a-tocopherol:cholesterol ratio</td>
<td>Recruitment not described and likely recruitment bias</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>• 4-13% had low vit E:chol ratio depending on cut off used</td>
<td>No definition of mild to moderate lung Dx given for inclusion criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Vit E intake higher from supplements than diet sources</td>
<td>Fasting times for blood test differ- 12 hrs for CF and 4hrs for reference pop</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Most supp doses within rec doses from CFF(Ramsey et al 1992) 100-200IU/d</td>
<td>No details on protocol for supplementation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Cholesterol levels (on basis of NCEP)</td>
<td>Author’s Limitations:</td>
</tr>
<tr>
<td></td>
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<td>- 87% CF normal</td>
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<td></td>
<td>- 12% borderline high</td>
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Koscik RL, Farrell PM, Kosorok MR, Zaremba KM, Laxova A, Lai HC, Douglas JA, Rock MJ, Splaingard ML. Cognitive Function of Children with Cystic Fibrosis: Deleterious Effect of Early NHMRC level: III-2 (Aetiology) ADA quality POSITIVE Retrospective cohort study (cohort originally from RCT) N=89 CF children & adolescents Inclusion criteria: • Registered participants in the Wisconsin Cystic Fibrosis Neonatal Screening Project. – subject recruited who met the following criteria 1) Intervention(s): • Nil – observational study with standard CF care Note: Once diagnosed, all patients treated with same protocol • Nutrition therapy included PER, increased caloric intake 120-150% RDA, fatty acid supplements (linoleate levels <26%) and water miscible multivitamin supplements. • Doses for vitamin E 50IU/d infants; 200IU/d 1-10yrs; 200IU/d>10yrs Results: • Lower Cognitive scores in those with low a-T <300 at diagnosis in 3 out of 4 cognitive outcomes (global cognitive skills index p=0.006; verbal p=0.03; Non verbal p=0.1) • Patients in control group with low levels at diagnosis (a-T<300ug/dl) lower CSI scores vs a-T sufficient control subjects and both deficient and sufficient a-T subsets. Vitamin E • Overall 49% of patients had a-T levels <300ug/dl at diagnosis but only 8 and 3% were low at 3 and 6 months after Tx. Appraiser’s Limitations: • No details in the paper of how Ax Vitamin E (and A) ie fasting • No measures of lipid ratio with Vit E (and no measures of RBP for A) • No measures of inflammatory markers • No details re how Ax vit E levels • No lipid ratio • No measure of CRP at time of testing Author’s Limitations: • Lower % of non-white population in

| No diff in diet or supp intake of Vit E between low/normal and high vitamin E status groups |
| No assoc’n vit E status and age, sex, pulmonary status, CFA%, growth, nut status, cholesterol, fat or energy intake. |
| Supp intake of E = 224mg (0-630mg) |
| Diet intake E = 6mg/d (4-20mg) |
| Vit E supp rec’s 149-298mg (100-200IU/d) |

Author Conclusions: • Most children with CF on typical CF vit E supplementation (ie standard care) may have normal or high vit E status and only few low. • Risks and benefits of high levels are not known. • Vit E supp should be based on dose and response studies. Few children had low vit E levels on typical CF supp but 48-83% high. • Deficiency in CF may be missed if ‘healthy’ ref ranges used ie 13% def using 5.4mg/g cut of vs 4% using NHANES. • Unavailable indicators peroxide induced haemolysis and neurological findings • Small sample size thus unable to detect possible associations with vit E status.

**Exclusion criteria:**
- As per exclusion criteria from previous study

**Outcomes:**
- Test of Cognitive skills (TCS/2) - global score and 3 subscale scores (verbal, non-verbal and memory). Normative Scores for TSC/2 mean 100, SD 16- aged based std scores
- a-T and retinol at time of diagnosis and a-T also at time of CSI Ax.
- Vitamin E status - a-T - characterised into 4 groups based on RCT group; screened (S) or control (C) and plasma a-T levels at diagnosis.

The categories include:
1. Control patients with an a-T level <300 mg/dL at diagnosis (C<300E);
2. Control patients with an a-T level >300 mg/dL (C>300E)
3. Screened patients with an a-T level <300 mg/dL (S<300E); and
4. Screened patients with an a-T level >300 mg/dL (S>300E)

- No patient low vit E at Dx was low after 6m on evaluation and Tx protocol.

Vitamin A
- 34% low at diagnosis and none with retinol levels 20ug/dl at 6m.

**Conclusions:**
- Prevention of prolonged malnutrition by early diagnosis and nutrition therapy, particularly minimising duration of vitamin E deficiency, is associated with better cognitive function.
- Demonstrated better nutrition outcomes and potential cognitive benefits with better nutrition achieved through early diagnosis and diet preventative therapy with PERT and fat sol vitamins

**Results:**
- After adjusting for covariates, CSI in the C<300E group was significantly lower than each of the other groups
- Patients in this group also had the lowest mean head circumference z-scores at diagnosis.
- Head circumference scores obtained at diagnosis were significantly correlated with

**Appraiser’s Limitations:**
- Retrospective study design
- Later diagnosis in Australia unlikely as we have had newborn screening in place since early 1990s – relates to generalisability


Preventing early, prolonged vitamin E deficiency: An opportunity for better cognitive

**NHMRC level:** Aetiology III-2
**ADA quality:** POSITIVE

**Retrospective data analysis from the Cognitive study**
(Note: Secondary analysis of Wisconsin Cystic Fibrosis Neonatal Screening Project 1985-1994 - RCT)

N=71 Infants with CF and without MI n=37 screened / n=34 control

**Inclusion criteria:**
- Full fevers; 7 years of age before August 2002, 3) currently receiving care at centre, 4) parents consented to child’s participation

**Intervention(s):**
- Test of Cognitive skills (TCS/2) - global score and 3 subscale scores (verbal, non verbal and memory)
  - Normative Scores for TSC/2 mean 100, SD 16- aged based std scores

Routine nutritional care at the time:
- Vitamin E supplementation:
  - 50IU/day for infants
  - 100IU/day for children 1-10

**Results:**
- The highest proportion of CSI scores >84 occurred in the C<300E group (41%).
  - Patients in this group also had the lowest mean head circumference z-scores at diagnosis.
### Outcomes via Early Diagnosis through Neonatal Screening

*J Pediatric*. 2005; 147 (3 suppl):S51-S56

- Patients enrolled in the WCFNSP

**Exclusion Criteria:**
- MI

**Study evolved from the outcomes of the Wisconsin CF Neonatal Screening Project randomized clinical trial (RCT)** - showing that head circumference differences in those identified early with NBS vs. those with later diagnosis. WCFNSP bw 1985 and 1994

**Control group > no. with PI and < with F508**

- Years
  - 200IU/day for those >10 years

**Other variables measured:**
- Genotype, pancreatic status, SES and family variables (inc education status), anthropometry and plasma vitamin A
- Nutritional measures were also summarized as dichotomous variables, with cutoff levels indicating evidence of malnutrition: <10th percentile for height, weight, and head circumference; and retinol of <20mg/dL for vitamin A status

**Primary Outcomes:**
- Cognitive skills index (CSI)
- Vitamin E status (in 4 categories)

The categories include:
1. Control (C) patients with an a-T level <300 mg/dL at diagnosis (C<300E)
2. Control (C) patients with an a-T level >300 mg/dL (>300E)
3. Screened (S) patients with an a-T level <300 mg/dL (S<300E)
4. Screened (S) patients with an a-T level >300 mg/dL (S>300E)

**Vitamin E deficiency at diagnosis was defined as plasma alpha tocopherol (a-T) below 300 ug/dL (<300E)**

**Vitamin E & PI**
- The control group has a significantly higher % of children who have vitamin E levels less than the cut-off level for severe deficiency.
- The duration of deficiency, approximated by using age of diagnosis, is significantly longer for the control group.

**A & E Summary**
- More children show biochemical evidence of vitamin E deficiency than vitamin A deficiency at diagnosis, although the cut-off level for vitamin A deficiency represents a higher level of nutrition than that used for vitamin E.

**Conclusions:**
- Prolonged a-T deficiency in infancy is associated with lower subsequent cognitive performance.
- Diagnosis via NBS may benefit the cognitive development of children with CF, particularly in those prone to vitamin E deficiency during infancy.
- Vitamin E deficiency tends to occur earlier than other fat soluble vitamin deficiencies.
  - The group/a-T effect, links vitamin E deficiency in infancy with later cognitive outcomes, and is consistent with other observations showing a link between vitamin E deficiency and physiologic functions sensitive to antioxidant deficiency

---

<table>
<thead>
<tr>
<th>Lezo A, Biasi F, Massarenti P, Calabrese R, Poli</th>
<th>NHMRC level IV</th>
<th>Cross-sectional study</th>
<th>N=70</th>
<th>Intervention:</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Observational review of clinical parameters plus a prospective 3 day</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Results:</th>
<th>Primary outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chromolipids (HNE-L) and (MDA-L)</td>
</tr>
</tbody>
</table>

**Appraiser’s Limitations:**
- Potential biases – no details on subjects were selected and no
G, Santini B, Bignamini E. Oxidative stress in stable cystic fibrosis patients: Do we need higher antioxidant levels? J Cystic Fibrosis 2013; (1): 35-41

<table>
<thead>
<tr>
<th>ADA quality</th>
<th>Stable CF children ages 1 to 18 years</th>
<th>diet history</th>
<th>significantly higher than reference ranges for health population, only 4.8% and 1/6 of CF pts in reference range</th>
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</thead>
<tbody>
<tr>
<td>NEUTRAL</td>
<td>Stabile CF 1-18 years</td>
<td>Inclusion criteria:</td>
<td>HNE-L and MDA-L were elevated in the majority of patients despite normal plasma vitamin E, A and C.</td>
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<tr>
<td></td>
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<td>• Stable CF 1-18 years</td>
<td>HNE-L and MDA-L increased with age (10% MDA-L accounted for by age, 12% HNE-L), while plasma vitamins decreased.</td>
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<tr>
<td></td>
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<td>Exclusion:</td>
<td>PI showed significantly higher plasma chromolipids (MDA-L 0.92UF/mg PI pts vs 0.68 non-PI, p&lt;0.002) and (HNE-L 1.77UF/mg PI vs 1.22UF/mg, p=0.004) despite no differences in plasma vitamins.</td>
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<td>• None listed</td>
<td>Plasma antioxidants were inversely correlated with age that exerts an independent significant effect in reducing vitamin E C but not sig for A ie</td>
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<td>Observational review of the following:</td>
<td>Mean vitamin A and E intakes were aligned above recommendations for CF,</td>
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<tr>
<td></td>
<td></td>
<td>• Vit supplementation</td>
<td>Oxidative stress (Cromolipid HNE-L and MDA-L) were significantly higher than healthy pop local reference range (LRR) HNE-L and MDA- normal in 4.8% and 1.6% only</td>
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<tr>
<td></td>
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<td>• Antioxidant status: plasma selenium ug/l, ascorbic acid, retinol ug/l + alpha tocopherol mg/l (HLPC), redblood cell total and reduced glutathione (GSH) GSH-umol/gHb, selenium dependent glutathione-peroxidase (GSH-PxSe) GSH-PxSe-U/gHb</td>
<td>3DFR – E intake met recommendations</td>
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<td>• Plasmal lipids (Lipid-adducts 4-hydroxynonenal (HNE-L) and malonaldehyde (MDA-L))</td>
<td>Using Bielsalski categorisation:</td>
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<td>Secondary outcomes:</td>
<td>- Suboptimal Vit E (67.1%) (still in normal local reference ranges)</td>
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<td></td>
<td>• Energy and nutrient intakes</td>
<td>- Deficient Vit E (21.5% vs 7.2 using local ref ranges) – all patients showed higher oxidative stress (plasma chromolipids) than those with optimal levels</td>
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<td></td>
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<td>• Anthropometry: wt (kg, centile, z score); ht (cm, centile, z score): BMI</td>
<td>Age related to clusters: patients with optimal Vit E levels were significantly younger (p&lt;0.05)</td>
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<tr>
<td></td>
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<td>• Resp fn test FEV1</td>
<td>Optimal 4.6yrs (1.9-7.9) vs Supoptimal 8.8yrs (1.1-19) vs Deficient 7.0 (1.1-18)</td>
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<tr>
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<td>Plasma antioxidants were inversely correlated with age that exerts an</td>
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<td></td>
<td>inclusion or exclusion criteria: only 36/70 subjects were pancreatic insufficient, slightly more females (32M/38F)</td>
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<td>Confusing reporting vitamin supplementation (e.g. swaps between median and mean)</td>
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<td></td>
<td></td>
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<td>Not all specific p values provided</td>
</tr>
</tbody>
</table>

Author’s limitations:
- Limited number of oxidative stress markers measured eg airway markers of oxidative stress could provide further information
independent significant effect in reducing vit E (ps=-0.25, p=0.034)

- Plasma oxidative stress markers HNE-I, MDA-I, Ratio plasma cholesterol showed increasing trend with lower antioxidant Vitamin Concentrations
- Vit E (HNE-I/Chol ps=-0.11, p=0.384; MDA-L/chol ps=-0.24, p=0.058),
  - Assumed higher levels of Vit E (12.9-18.9mg/l) provide better protection against lipid peroxidation
- Plasma antioxidants inversely correlated with age Vit E (ps=-0.25, p=0.034),
- Plasma chromolipids increased significantly with age -MDA-I/cholesterol ps=0.36, p=0.003, HNE-L/cholesterol ps=0.33, p=0.004
- Aging accounted for 10% MDA-I and 12% HNE-L of the increase in the plasma chromolipids
- Inverse relationship between plasma concentrations of both chromolipids and antioxidant status -Not sig for Vit E – hne-lhd/chol (ps -0.11 p=0.384)
- PI vs PS: similar plasma vit levels Vit E (PS 9.1 (3.0-18) vs PI 9.4 (1.4-15) p=0.455 and GSH/GSSG ratio in plasma
- Plasma chromolipids were significantly higher in PI vs PS MDA-I/cholesterol PI 0.92 (0.29-3.78) vs Ps 0.68 (0.46-2.63) p=0.002; HNE-L/cholesterol PI 1.77 (0.49-3.20) vs PS 1.22 (0.75-2.67) p=0.004

Conclusions:
- Majority of CF pts showed elevated oxidative stress markers in stable clinical conditions and plasma antioxidant in normal range
- Aging led to progressive increase in plasma oxidative stress markers and decrease in
plasma antioxidant vitamins inverse correlation between plasma vitamin levels and oxidative stress markers (consistent with Vit C)

- PI patients showed higher oxidative stress markers without significant differences in plasma vitamins.
- Suggests the need for a careful definition of vitamin needs in CF that may need to consider oxidative status. Consider the need for Vit C monitoring and supplementation.

Rana M, Wong-See D, Katz T, et al.

NHMRC level: IV
ADA quality: NEUTRAL

Retrospective cross sectional
N=530 CF children & adolescents

Inclusion criteria:
- All children attending CF centres during time period of 2007-2010

Exclusion criteria:
- Nil stated

Primary Intervention(s):
- Nil – observation

Following measures taken:
- Vit A levels using protein precipitation with high performance liquid chromatography (HPLC) and ultraviolet detection (in house method)
- Vitamin E, D(25 OHD) and PT (for vitamin K)

Primary Outcomes:
- Fat soluble vitamin deficiency rates

Results:
- Deficiency of one or more fat-soluble vitamins was present in 240/530 children (45%)
- 301 /470 (64%) took fat-soluble vitamin supplementation.
- No overt signs of deficiency, such as peripheral neuropathy and spinocerebellar degeneration with ataxia (vitamin E)
- Serum vit E levels were abnormal in 201/523 children. (38%)
- 105 children (20%) had low vit E.
- Mean vit E was 19umol/L±9.
- 35% of PI were deficient and 3% of PS deficient. (Vit A 10% and 0% respectively)
- PI 19umol/L+9 vs PS 22umol/L+6, p<0.01 Vit E levels assoc with pancreatic status
- Prevalence 2007-2010 decreased 15.54% to 13.89% (Vit A increased from 11.17% to 13.13%)
- Vitamin E supplements were taken by 266/470 children (57%).
- Median vitamin E supplement dose was 150 ug/day (75–150ug/d).

Conclusion:
- Vit A,D,E deficiency in small minority of children. Fat sol vit testing important in all to identify def in PI patients who may not

Appraiser’s Limitations:
- No details re how CF or PI diagnosed
- Different reference ranges used between laboratories indicating “deficiency”
- 85% patients ‘recruited’ patients with vit levels. Characteristics of the 15% without levels not known. No reasons given for loss.
- No regression analysis with vit supp - variable likely to impact results.
- No method info at time of tests re whether patients acute/non acute (ie exacerbation dec vit A levels); fasting non fasting etc?
- No CRP level done to help determine inflammation
- Doesn’t report if any with CFLD
- Many confounders that may affect levels such as diet, type of supplementation, compliance not measured.
- Nil adherence measure

Author Limitations:
- Prevalence rates influenced by recruitment no
- No control group of healthy same age range.
| Sagel SD, Sontag MK, Anthony MM, Emmett P, Papas KA. Effects of an antioxidant-rich multivitamin supplement in Cystic Fibrosis. Journal of Cystic Fibrosis. 2011;10(1):31-6. | NHMRC level: IV (Intervention) | Pre test and post test intervention study N=14 (note n=17 recruited) (CF patients aged 10-23) ADA quality: POSITIVE | Primary Intervention(s): 2 AquADEK softgels capsules a day 300IU α tocopherol; 160mg other mixed tocopherols (contains 18,167IU vitamin A in each capsule with enzymes immediately prior to breakfast for 12 weeks 92% B carotene and 8% palmitate 6 week visit and 12 week visit Discontinue other supplemental doses of vitamins Fasting bloods at least 8hrs | Results: Compliance: >90% in 11/14 pts 58 adverse events – not serious or not due to formulation Baseline sig differences between PI vs PS patients y (PI<1 vs PS 1.25 P<0.05) and α tocopherol (PI 9.6 vs PS 12.2 P<0.05, Supplementation: Entire cohort Increased: y tocopherol (P<0.05) PI - No sig change: - y tocopherol baseline< 1.0 (<1.0-1.1); 6 weeks 1.2 (<1.0-2.0); 12 weeks <1.0 (<1.0-1.8) (p<0.09), α tocopherol baseline 9.6 (6.5-11.1); 6 weeks 10.9 (9.5-14.8); 12 weeks 11.2 (8.5-11.3) (P=0.58) End of study: PI pts sig lower than PS pts for α tocopheral: PI 11.2;8.5-13.3 vs PS 16.4; 13.3-24.4 p<0.05 y tocopherol significantly increased in from baseline for PS and PI subjects (pooled data); p<0.05. | Appraiser’s Limitations: Data not collected by consistent people eg one person withdrawn by a nurse unfamiliar with the study OR no process to check with a study person before withdrawing Self-report data used to measure compliance Potential recruitment bias Author Limitations: Not controlled Not powered to detect significant changes in lung function and clinical outcomes |
• Had oral Aquadeks or another source of B carotene or CoQ10 in 2months prior to study
• Participated in another interventional clinical trial within 30day of study.

Secondary outcome:
• Anthropometry measures
• Spirometry: FEV1; FVC; FEF 25-75)
• Adherence
• Repeat urine for 8 isoprostane level at visit 3 only; 8-isoprostanes (elisa DL 2.7pg/ml)
• # pts with vitamin A toxicity
• medication changes & hospitalisations
• Adverse symptoms possibly related to formulation eg GIT or Neurological

Clinical outcomes:
• Entire cohort:
  - Improved weight percentile (+2.4% IRQ: -0.05-4.5%; p=0.03);  FEV1 (+3.8% IRQ -2.0-9.1% p=0.04)
  - NO significant changes in BMI centile (p=0.17); Urine 8-isoprostane levels (p=0.28)
  - Changes in tocopherols, did not correlate with changes in weight, BMI or FEV1

Author Conclusions:
• Antioxidant rich multivit supplement increased circulating antioxidant levels and decreased PIVKA-II concentrations whilst maintaining Vit A levels in normal range in PI and PS subjects
• 30% GIT symptoms that may be related to formulation. Modest improvements in weight and pulmonary function and B carotene levels were weakly associated with better growth parameters. Need for higher antioxidant vit supplementation in PI vs PS pts was indicated by PI having lower antioxidant plasma levels and that micronutrients and antioxidant deficiencies were observed almost exclusively in PI Subjects

| Siwamogsatham, O, Dong W, Binongo JN, Chowdhury R, Alvarez JA, Feinman SJ, Enders J, Tangpricha V. | NHMRC level: IV | N=243 (n=177 eligible) CF adolescents and adults | Case series | Primary Intervention(s):
• Nil- observation. Following measures taken:
• Prescribed or reported fat soluble vitamin supplement
• Serum fat soluble vitamin concentrations
• CFTR gene mutation
• Age, sex, race, BMI, and PI | Results:
• Baseline vitamin E supplement was 218.38 ± 224.11 IU in 2008 and 351.58 ± 295.99 IU in 2012.
• Vit E serum levels 2008 8.93+-4.46 to 2012 8.15+-3.87mg/L
• 24% of patients had suboptimal serum vitamin E levels at baseline.
• Vitamin E supplement, on average, increased by 12.2% annually (P < .0001) in | Appraiser’s Limitations
• No info re where reference ranges obtained from
• No reference ranges for retinol palmitate or tocopherol
• Did not report data for tertile intake. Only reported % suboptimal levels at baseline (ie 2008).
• Did not report ref rec intakes - i.e how did intakes compare with rec? | Aetiology
• ADA quality: NEUTRAL
Inclusion criteria:
• All patients seen at the CF centre were eligible

CF adolescents and adults

Relationship

| Siwamogsatham, O, Dong W, Binongo JN, Chowdhury R, Alvarez JA, Feinman SJ, Enders J, Tangpricha V. | NHMRC level: IV | N=243 (n=177 eligible) CF adolescents and adults | Case series | Primary Intervention(s):
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Inclusion criteria:
• All patients seen at the CF centre were eligible

CF adolescents and adults

Relationship
between Fat-soluble Vitamin Supplementation and Blood Concentrations in Adolescent and Adult patients with CF. Nutrition in Clinical Practice, 2014. 29 (4): 491-497

Exclusion criteria:
• Those without fat soluble vitamin concentration data

Primary Outcomes:
• Serum levels of retinol and retinyl palmitate (vitamin A)
  - Suboptimal concentrations were defined as vitamin A, serum retinol <0.3 mg/L (1.05 μmol/L)
• Serum levels of α-tocopherol and β/γ-tocopherol (vitamin E)
  - Suboptimal concentrations were defined as vitamin E, serum α-tocopherol <5 mg/L (12 μmol/L)

contrast to the α-tocopherol and β/γ-tocopherol level, which did not change significantly over the past 5 years (P = .26 and P = .96).
• High vit E serum tocopherol >18mg/L (42μmol/L) found in a few patients but no symptoms of hypervitaminosis E were documented in medical records
• No significant association between the level of vitamin intake and the corresponding concentration of the serum fat-soluble vitamin was found in any type of the vitamins studied.
• No significant association between type of CFTR gene mutation and the concentration of other serum fat-soluble vitamins, including retinol, retinyl palmitate, α-tocopherol, β/γ-tocopherol,

Conclusions:
• The results from this study have demonstrated that a substantial increase in fat-soluble vitamin supplementation in adults with CF over the past 5 years was not associated with a significant increase in serum concentrations of these vitamins.
• Despite a near doubling of reported fat-soluble vitamin supplementation over the past 5 years, the changes of these vitamins' serum concentrations were not clinically sig.
• Potential reasons include suboptimal dosages, low
• Adherence or ongoing issues with malabsorption.

Woestenenk JW, Broos N, Stellato RK, Arets HG, van der Ent CK,

NHMRC level: III-2 (Aetiology) Retrospective Cohort Study N=232 CF children aged 0-17 years

Intervention:
• Nil – observational

Following measures taken:

Results:
Primary Outcomes:
• Mean intake n=218 varied from 55-150mg α-tocopherol/day from diet

Author’s Limitations:
• Retrospective study
• Did not assess the adherence to fat-soluble vitamins or fat-soluble vitamin intakes from dietary sources given the limitation of our study design.
• Only included adolescents and adults, and findings - may not be applicable to other age groups
• Lack of comparative data for serum concentrations of fat-soluble vitamins from a control group.

Appraiser’s Limitations:
• No description of population characteristics
• Less measures for FEV1, CFA and IgG
**Houwen RH.**
Vitamin E intake, α-tocopherol levels and pulmonary function in children and adolescents with cystic fibrosis. British Journal of Nutrition. 2015; 113 (7), 1096-1101

<table>
<thead>
<tr>
<th>ADA quality:</th>
<th>POSITIVE</th>
</tr>
</thead>
</table>
| Inclusion criteria: | • Dutch children (born between 1989 and 2013) with proven CF (positive sweat test and/or the presence of two CF mutations as well as clinical signs of CF) who received medical care at the CF Centre.  
• At least one measurement of vitamin E intake (dietary intake plus prescribed supplementation) or serum α-tocopherol levels and who were receiving PERT. |
| Exclusion criteria: | • None listed |

| Primary outcomes: | • Vitamin E intake (mg/d)  
• Serum α-tocopherol levels ug/dl and umol/l (measure of vitamin E status) HPLC |
| Note: | • Prescribed supplement intake expressed as % of lower level and upper level of European and US CF specific vit E recommendations.  
• Supplement levels compared with NHANES 2005-6 (age equiv healthy controls) |

| Secondary outcomes: | • Long term effects of vitamin E on pulmonary outcomes  
• CFA - 72hr fat test  
• IgG g/l  
• PFx- FEV1 |

Results stratified to age groups  
Associations bw serum α-T and PFx and intake - categorised on serum α-T level <50th centile or >50th or between 2.5th and 97.5th centile of NHANES  
+supplementation (Vitamin E intake higher with supps than dietary sources)  
• CF patients failed to meet the CF-specific vitamin E  
• Median serum α-tocopherol levels were normal in all age groups  
• Supranormal serum levels (i.e. ≥97.5%) found in 12% of the cohort  
• Median serum α-T varied between 18-25umol/l (775 - 1079ug/dl) and all above the 50th NHANES centile.  
• No diff in vitamin E intake bw those < and those >50th NHANES centiles or between those in the 2.5-97.5 centiles and those > 97.5th centile.  

The European and North American lower level of the CF-specific vitamin E supplementation recommendations were only met in adolescents aged 15 years and older and in children less than 1 year of age. In all age groups, the prescribed supplementation was far below the upper limits of both the European and North American Recommendations.

**Author’s Limitations:**  
• Method used for assessing serum vitamin E status (a-tocopherol vs a-tocopherol:total lipid ratio), however references Cyamon 1988, Feranchak 1999, sokol 1989 which apparently show little difference between the two methods  
• Single study centre – results not generalizable  
• Limitations associated with use of food record method (i.e. over and under reporting)  
• Patient adherence not measured  

| Secondary outcomes: | • Longitudinally, there was no significant association of serum α-tocopherol levels with total vitamin E intake (95% CI 0.01, 0.00; P=0.224), the CFA (95% CI 0.07, 0.81; P=0.103) or serum IgG levels (95% CI 0.95, 1.36; P=0.738).  
• No clear effect of vitamin E intake or the coefficient of fat absorption on serum a-T  
• FEV1% pred. was longitudinally inversely associated with age (P<0.001) and serum IgG (P<0.003), but it was not related to serum a-tocopherol levels.  
• Trend toward higher a-T and lower FEV1 than a-T and intake. Some patients may not have all measures  
• Supplement intake as prescribed - not actual intake. No measures of compliance.  
• No info re intake of other antioxidants which may impact FEV1  
• No CRP (IgG only measure for inflammation- ie chronic inflammation measure)  

• Supplement intake as prescribed - not actual intake. No measures of compliance.  
• No info re intake of other antioxidants which may impact FEV1  
• No CRP (IgG only measure for inflammation- ie chronic inflammation measure)
### Conclusion:
- Vitamin E intake was lower than recommended (both European and North American recommendations), but serum α-tocopherol deficiency was rare.
- No evidence that higher serum α-tocopherol levels had protective effects on PF.
- Adjustment of the recommendations to the real-life intake of these patients may be considered.

### Oudshoorn JH1, Klijn PH, Hofman Z, Voorbij HA, van der Ent CK, Berger R, Houwen RH.

<table>
<thead>
<tr>
<th>NHMRC level II (Intervention)</th>
<th>ADA quality NEGATIVE</th>
<th>A double-blind, randomized, placebo controlled, cross-over trial</th>
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<tbody>
<tr>
<td>22 paediatric CF pts with moderately mild lung disease (ages 9.8 to 18.9 years, mean 13.3 years), USA</td>
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</table>

**Inclusion criteria**
- Children aged 9 to 18 years with stable clinical condition (i.e. no need for oral or IV antibiotic treatment other than chemoprophylaxis in the two months prior to testing)
- Absence of musculoskeletal disorders
- FEV1>70% predicted.

**Exclusion:**
- None listed

**Intervention:**
- ML1 (100ml liquid multi) once a day for 3 months OR 100ml placebo with a wash-out period of 3 months (placebo identical taste and macronutrient composition)

**Primary outcome:**
- Nutritional assessment – weight, height, BMI and skinfold thickness (4 sites)
- PFTs – performed after salbutamol
- Peripheral muscle strength – hand-held dynamometer used to measure isometric muscle force in 6 groups
- Exercise testing – cycle ergometer and the Wingate anaerobic test
- Lab analysis – fasting state, prior to exercise, venous blood sample, including retinol and vitamin E αtocopherol HPLC methods
- Malondialdehyde (MDA)

**Results:**
At the end of 3 months intervention period:
- Plasma vitamin E and A levels increased during ML1 when compared to placebo.
- Vitamin E had increased with 16.9±11.6 μmol/l (from 11.7±7.4 μmol/l to 28.6±12.8 μmol/l), while in the placebo group vitamin E levels had dropped 2.3±7.9 μmol/l (from 13.2±5.9 μmol/l to 11.0±6.1 μmol/l).
- This difference in change between intervention and placebo period is significant (P<0.001).
- Increase in Vit E correlated with increased pulmonary function p=0.04 (Reported in discussion only)
- Plasma MDA levels decreased during placebo but marginally increased during ML1 p=0.15 ie ‘pro oxidant effect’
- No significant difference in vitamin A levels in groups at the end of 3 months
- No significant difference in nutritional parameters, BMI, FFM and skinfolds between groups at end of 3 months
- FEV1, FVC and anaerobic and aerobic test – significant difference towards the placebo group
- No beneficial effects on either pulmonary function or muscle performance in CF patients given a micronutrient supplement

**Appraiser’s Limitations:**
- Compliance data not recorded/collection
- Small pt numbers for an RCT
- No information on randomisation or blinding methods used – states double blind randomised placebo controlled cross over trial in the abstract but nowhere else
- Patients stable and had no IV Abs for 2 months prior to testing
- Originally 29 patients but 7 excluded due to small stature, anxiety, complications, physical injury etc – not necessarily representative of CF population
- Muscle strength etc the outcome, not symptoms of deficiency/excess
- Short length of study (3 months)
- Patient characteristics - No info CFLD or Pancreatic status?
- No info Inflammatory status eg CRP
- No info re characteristics of drop outs
- Other vitamin intake from diet not recorded
- Were they taking other vitamin supplements?

**Author’s Limitations:**
### Conclusions:
- Micronutrient mixture was not superior to placebo with respect to changes in pulmonary function or muscle performance in pediatric CF patients, despite a significant increase in plasma vitamin E concentrations (increase seen in vitamin A serum levels not significantly increased).
- Need studies of single antioxidant nutrients and to determine optimal supplementation levels required to normalise parameters of oxidative stress.

### Appraiser’s Limitations:
- No inclusion criteria
- No information on numbers excluded
- 4 wk run in still given Vlt E supps for ethical reasons.
- Generalisability - Patient’s relatively mild lung disease and children. Otherwise F508 and pancreatic status similar to usual populations
- Didn’t report reference ranges (except low Vit E) ie were baseline levels post washout normal or not?
- No sub group analysis for PI vs PS
- Non fasting bloods
- No diet control for fat intake at BG at time of supp intake
- Same # P bw groups but less on PERT in gp B ie not all PI on PERT? This may dec likelihood of effect in Gp B as supp less well absorbed?
- High dose supp same amt retinyl palmitate as low does (ie only B caroten changes)
- What supplementation were pts on pre washout and what were levels? ie

### Wood LG, Fitzgerald DA, Lee AK, Garg ML.

<table>
<thead>
<tr>
<th>NHMRC level:</th>
<th>Double blind randomised control trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td>N=46 children with CF</td>
<td></td>
</tr>
<tr>
<td>Group A Low dose supp (n=24)</td>
<td></td>
</tr>
<tr>
<td>Group B High dose supp (n=22)</td>
<td></td>
</tr>
</tbody>
</table>

### Inclusion criteria:
- CF diagnosis confirmed by elevated sweat chloride

### Exclusion criteria:
- Age < 5 y (Unable to perform reproducible spirometry)
- Abnormal vitamin E concentration (< 8 _mol/L) at baseline (Karr et al 1997).

### Primary Intervention(s):
- 4 wk run-in period during which they received a low-dose supplement [10 mg vitamin E (as RRR--tocopherol) and 500 ug vitamin A (as retinyl palmitate) in oil]. This meant that in addition to their dietary intakes of vitamins A and E, *Note all vitamin and mineral supplements ceased other than trial supplements*
- Group A, continued to receive low-dose supplement ie served as a control group
- Group B, received a high-dose supplement [200 mg vitamin E (as RRR- tocopherol), 300 mg vitamin C (as sodium ascorbate), 25 mg B-carotene (all-trans isomer), 90ug Se (as selenomethionine), and 500 ug vitamin A (as retinyl palmitate) in oil], for 8 wks.

### Results:
- No sig differences bw groups any outcome parameter at baseline
- Antioxidant defences improved in group B but not in group A (plasma concentrations of vitamin E, B carotene, and selenium and in GSHPx activity were observed in group B.
- No significant difference between groups in the mean change in plasma 8-iso-PGF2α concentrations.
- No significant differences between groups in changes in % FEV1, % FVC, quality of well-being or in change in cell counts.
- No significant differences between groups in the change in nutrient intake during (note gp B higher zinc intake at baseline) or in the change in fatty acid concentrations.
- Within group B, the change in B-carotene concentrations correlated with the change in percentage of FVC (r = 0.586, P = 0.005)
- The correlations between the change in vitamin E concentrations and the change in % FEV1 (r = 0.363, P = 0.106) and the change in % FVC (r = 0.148, P = 0.523) were not sig.
Supps taken with BF with usual dose PERT. Compliance measured with diary cards recording daily intake and counting of pills.
Non fasting - ref that unlikely to be affected by postprandial effects

Primary Outcomes:
- Diet intake - 3d food record
- Plasma A,E and B carotene by HPLC methods
- Isoprostanes
- Plasma fatty acids
- Glutathione peroxidase enzyme
- Superoxide dismutase enzyme assay

In group B, the change in total plasma fatty acid concentrations correlated with the change in %FEV1 \(r = 0.583, P = 0.006\) and with the change in 8-iso-PGF2_ 
concentrations \(r = 0.538, P = 0.010\)

Secondary Outcome:
- Compliance similar between groups.
- No difference bw gps in diet intake.
- Vit Eumol/l Baseline GpA 18.8+-1.5; GpB 16.5+-1.1 Change in Gp A -1.9+-0.9 and in Gp B 10.6+-1.5 P<0.001

Conclusions:
- Improved plasma B-carotene, selenium, and fatty acid status are linked to improved lung function, despite the fact that increased fatty acid concentrations are also linked to increased oxidative stress.
- Although antioxidant defences improved with high doses of antioxidants, there was no corresponding decrease in oxidative stress (as measured by 8-iso-PGF2_ concentrations). Plasma fatty acid concentrations were found to have the strongest influence on plasma 8-iso-PGF2_ concentrations, suggesting that a high fat intake contributes to oxidative stress. However, a correlation between increased plasma fatty acid concentrations and improved lung function suggests that high fat diets have clinical benefit.

Author’s limitations:
- No control of diet intake. ie low fat intake at BF may account for low B carotene levels post supplementation
- Diet analysis programs have no intake data on Vit E and Se
- Increase in vit C levels post suppl in both groups despite no diff in diet intake - unclear but may have masked potential effects of antioxidant suppl in G[ A.
- Peripheral blood markers less sensitive than direct lung measures (lung lining fluid) ie poor reflection of antioxidant defences in the lung.
- Ox stress may have been stabilised by low dose suppl such that high dose suppl could not increase levels isoprostanes further
**Q 8.3.2 What is the role for supplementation of vitamin E supplementation in people with CF?**

**Evidence statement:** The evidence suggests the need for routine supplementation of vitamin E in all pancreatic insufficient people with CF. There is inadequate evidence to establish recommendations for supplement dose.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 studies included in body of evidence:</td>
<td></td>
</tr>
<tr>
<td>• 2 level II studies</td>
<td></td>
</tr>
<tr>
<td>• Children: n=46; positive quality</td>
<td></td>
</tr>
<tr>
<td>• Children &amp; adolescents: n=22; negative quality</td>
<td></td>
</tr>
<tr>
<td>• 3 level III studies; positive quality</td>
<td></td>
</tr>
<tr>
<td>• Infants: n=39, n=71</td>
<td></td>
</tr>
<tr>
<td>• Children: n=232</td>
<td></td>
</tr>
<tr>
<td>• 8 level IV studies; neutral quality</td>
<td></td>
</tr>
<tr>
<td>• Infants, children &amp; adults: n=35</td>
<td></td>
</tr>
<tr>
<td>• Children: n=69, n=70, n=556</td>
<td></td>
</tr>
<tr>
<td>• Children &amp; adults: n=102, n=10</td>
<td></td>
</tr>
<tr>
<td>• Adults: n=93, n=43</td>
<td></td>
</tr>
<tr>
<td>• 1 level IV study; positive quality</td>
<td></td>
</tr>
<tr>
<td>• Children &amp; adults: n=17</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies mostly consistent in suggesting need for routine supplementation of vitamin E however variability between studies in the following areas:</td>
<td></td>
</tr>
<tr>
<td>• Definition of vitamin E adequacy (no clear reference range or target for supplementation)</td>
<td></td>
</tr>
<tr>
<td>• Dietary intake of vitamin E</td>
<td></td>
</tr>
<tr>
<td>• Association between vitamin E intake and α-tocopherol levels.</td>
<td></td>
</tr>
<tr>
<td>Most studies supplemented at levels within CF consensus guideline recommended ranges with inconsistent evidence of efficacy of these doses on serum levels and clinical outcomes.</td>
<td></td>
</tr>
</tbody>
</table>
Most studies suggest that supplement intake below CF recommended guidelines is most likely inadequate. There is limited and unclear evidence regarding need for routine supplementation in pancreatic sufficient patients.

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation likely to impact CF population:</td>
<td></td>
</tr>
<tr>
<td>• Vitamin E supplementation is effective in increasing serum levels of α-tocopherol.</td>
<td></td>
</tr>
<tr>
<td>• Vitamin E deficiency is still common though there is some limited evidence of high levels though not in Australian/NZ populations.</td>
<td></td>
</tr>
<tr>
<td>• Limited and unclear evidence correlating improved vitamin E levels post supplementation and important clinical outcomes such as pulmonary function, improved oxidative stress and cognitive status.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most evidence from children and adults with no CF-related liver disease and mild-moderate lung disease.</td>
<td></td>
</tr>
<tr>
<td>• Only 3 studies with infants</td>
<td></td>
</tr>
<tr>
<td>• Over 70% of studies included both pancreatic insufficient and insufficient patients.</td>
<td></td>
</tr>
<tr>
<td>• Evidence not generalisable to those with more severe lung disease.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Only 3 studies with Australian populations</td>
<td></td>
</tr>
<tr>
<td>• Only one CF-specific multivitamin available in Australia/NZ and its composition has not changed since last guidelines.</td>
<td></td>
</tr>
<tr>
<td>• Greater variability in choice of supplement formulations in settings outside of Australia/NZ however with vitamin E content similar to the formulation available in Australia.</td>
<td></td>
</tr>
<tr>
<td>• No high vitamin E intakes have been shown in Australian/NZ studies</td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL QUESTION
8.3.3 What is the safe upper limit for vitamin E supplementation in people with CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.

CLINICAL QUESTION
8.3.4 How often should we measure/monitor vitamin E levels in CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.
8.4 Vitamin K

PICO

8.4.1 How should vitamin K status be assessed for people with CF?
8.4.2 Should vitamin K supplementation be recommended for all people with CF and pancreatic insufficiency?
8.4.3 How often should vitamin K status be assessed in people with CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:

Vitamin K

- Cystic fibrosis, CF, nutrition diet, vitamin K, prothrombin, blood coagulation, cystic fibrosis related liver disease, deficiency, subclinical deficiency, supplementation

Inclusion & exclusion criteria:

Inclusion criteria:

- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:

- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers

CLINICAL QUESTION

8.4.1 How should vitamin K status be assessed for people with CF?

Evidence Table

There were no studies available within the search strategy and criteria that addressed this PICO.
**CLINICAL QUESTION**
8.4.2 Should vitamin K supplementation be recommended for all people with CF and pancreatic insufficiency?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dougherty KA, Schall JI, Stallings VA. Suboptimal vitamin K status despite supplementation in children and young adults with cystic fibrosis. 2010 Am J Clin Nutr. 92(3):660-7</td>
<td>Cross-sectional study (with concurrent healthy controls) / Aetiology</td>
<td>Intervention: N/A</td>
<td>Results: [%observer - CF group (n=97)</td>
<td>Appraiser’s limitations:</td>
</tr>
<tr>
<td>NHMRC level: IV (Aetiology) ADA quality: POSITIVE</td>
<td>CF n=97 (aged 8-25 years) Healthy controls n=140</td>
<td>Outcomes:</td>
<td>27% sufficient (n=26)</td>
<td></td>
</tr>
<tr>
<td>Recruited from the Reference Project on Skeletal Development in Children recruited from the CHOP primary care practices and surrounding community over 6 years (Nov 2001-July 2007).</td>
<td>CF and healthy subjects were grouped according to vitamin K status based on serum %ucOC (n=97):</td>
<td>• Vitamin K status</td>
<td>55% insufficient (n=53)</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>• Sufficient &lt;20%</td>
<td>• 19% deficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Confirmed CF (sweat test and/or genotype)</td>
<td>• Insufficient 20–50%</td>
<td>PIVKA-II - CF Group (n=60)</td>
<td>50% deficient (n=30)</td>
<td></td>
</tr>
<tr>
<td>• PI (72 CFA or trypsin)</td>
<td>• Deficient &gt;50%.</td>
<td>50% sufficient (n=30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mild-to-moderate lung disease (&gt;40%)</td>
<td>CF subjects also divided into 2 vitamin K status groups based on plasma PIVKA-II (n=60):</td>
<td>Supplemental vitamin K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>• Sufficient ≤ 2 ng/mL</td>
<td>0 (0, 86), 300 (150, 380), and 1729 (1371, 10,000) ug/d, respectively (low compared with high and middle compared with high; both P&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF:</td>
<td>• Deficient &gt;2 ng/mL</td>
<td>Vitamin K supplementation negatively associated with %ucOC (r = -0.55, P&lt;0.0001) and PIVKA-II (r = -0.30, P&lt;0.05).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• FEV1 &lt;40% or major medical illnesses known to affect growth or nutritional status</td>
<td>CF subjects also divided into 3 groups according to reported daily vitamin K supplementation:</td>
<td>PIVKA-II measures</td>
<td>67%, 58%, 29% of subjects with CF in the low, middle, and high supplemental intake groups, respectively, were vitamin K deficient (low compared with high; P&lt;0.03).</td>
<td></td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>• &lt;150 ug/d (low)</td>
<td>• For subjects with CF in the low, middle, and high supplemental intake groups, PIVKA-II was 4 (1, 42), 3 (0, 13), and 2 (1, 4) ug/L, respectively (low compared with high; P&lt; 0.01).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Any disease or genetic syndrome</td>
<td>- Multivitamin supplements or no supplement daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 150–999 ug/d (mid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- CF-specific vitamin daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ≥1000 ug/d (high)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Mephyton (commonly taken as 5000 lg twice per week, or 1429 lg/d)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Appraiser’s limitations:**
- Only children and young adults with FEV1 >40%
- No power calculation
- Not stated how long vit k supplementation was prior to study
- No PIVKA-II measures in healthy controls
- 69/70 completed diet intake records. No reasons reported.

**Author’s limitations:**
- Incomplete food composition databases - dietary vitamin k levels may be underestimated.
<table>
<thead>
<tr>
<th>Use of medication known to affect growth, nutritional status, bone health</th>
<th>%ucOC measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>59%, 70%, and 38% were insufficient (middle compared with high; P&lt;0.01) and 37%, 18%, and 5% were deficient (low compared with high; P&lt;0.01).</td>
<td></td>
</tr>
<tr>
<td>59%, 70%, and 38% were insufficient (middle compared with high; P&lt;0.01) and 37%, 18%, and 5% were deficient (low compared with high; P&lt;0.01).</td>
<td></td>
</tr>
<tr>
<td>Weight or height above the 97th percentile for age and sex</td>
<td>There was no association between the supplemental vitamin K intake group and growth, pulmonary status, or dietary vitamin K intake.</td>
</tr>
<tr>
<td>Overall, subjects with CF had higher %ucOC (35% (3%, 76%)), which indicated poorer vitamin K status compared with healthy subjects (P&lt;0.0001).</td>
<td></td>
</tr>
<tr>
<td>Subjects with CF had higher %ucOC in the low [45% (10%, 76%)] and middle [41% (3%, 66%)] but not in the high [16% (4%, 72%)] supplemental intake groups compared with healthy subjects (both P&lt; 0.05).</td>
<td></td>
</tr>
<tr>
<td>59% of subjects had a dietary (not supplemented) vitamin K intake below the adequate intake for age and sex of healthy children</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td>Conclusion:</td>
</tr>
<tr>
<td>Age negatively associated with %ucOC (r =-0.30, P= 0.003) and positively associated with supp (r=0.30, P&lt; 0.001).</td>
<td>Vitamin K status often suboptimal despite routine supplementation.</td>
</tr>
<tr>
<td>Girls had 6.8% lower %ucOC than boys (P&lt;0.05)</td>
<td>Only subjects taking high-dose vitamin K (≥1000ug/d) achieved a vit k status similar to healthy subjects.</td>
</tr>
<tr>
<td>59% of subjects had a dietary (not supplemented) vitamin K intake below the adequate intake for age and sex of healthy children</td>
<td>Only vitamin K supp dose predicted vitamin K status.</td>
</tr>
<tr>
<td>Data suggest that higher doses of vitamin</td>
<td>Data suggest that higher doses of vitamin</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>N=32 (CF infants, children &amp; adults aged 7months to 25 years) N=18 controls (healthy subjects)</td>
<td>Inclusion criteria:  - Confirmed CF - sweat test/genotype  - Controls: Attended outpatient clinics to rule out a disorder.</td>
</tr>
<tr>
<td>Exclusion criteria:  - Not reported</td>
<td>- Vit k deficiency may occur (Evidence of low serum k and PIVKA-II in CF w/o vit k supp)  - PT inadequate to detect deficiency  - Routine supplementation requirement in</td>
</tr>
<tr>
<td>Study Title</td>
<td>NHMRC level</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Van Hoorn JH, Hendriks JJ, Vermeer C, Forget PP</td>
<td>IV (Diagnostic)</td>
</tr>
<tr>
<td>NHMRC level: IV (Diagnostic) ADA quality NEGATIVE</td>
<td>Diagnostic test (short report/Cross sectional) N=39</td>
</tr>
<tr>
<td>4 groups</td>
<td>CF + no vitamin K supp,</td>
</tr>
<tr>
<td>N=19 healthy</td>
<td>CF + low vitamin K sup</td>
</tr>
<tr>
<td>N=10 CF + No Vit k</td>
<td>CF + high vitamin K supp</td>
</tr>
<tr>
<td>N=6 CF low dose vit k (&lt;0.25mg/d)</td>
<td>Outcomes:</td>
</tr>
<tr>
<td>N=4 CF high dose vit k (&gt;1mg/d)</td>
<td>• Serum PIVKA-II</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>• Serum bone formation markers:</td>
</tr>
<tr>
<td>• CF</td>
<td>• Osteocalcin (OC, total OC (t-OC)</td>
</tr>
<tr>
<td>• PI</td>
<td>• undercarboxylated OC (u-OC)</td>
</tr>
<tr>
<td>• Normal LFTs</td>
<td>• carboxylated OC (c-OC))</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>• bone alkaline phosphatase (BAP)</td>
</tr>
<tr>
<td>• Not stated</td>
<td>• Bone resorption marker serum N-terminal collagen type 1 (NTX)</td>
</tr>
<tr>
<td></td>
<td>• urinary deoxypyridinoline (DPD)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drury D, Grey VL, Ferland G,</th>
<th>II</th>
<th>RCT (Dose ranging)</th>
<th>Intervention:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHMRC level: II</td>
<td>Randomized to receive either</td>
<td>Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Appraiser’s limitations:</td>
<td>No info re disease severity or status</td>
<td></td>
</tr>
</tbody>
</table>

**Intervention**
- Number: N= 14 CF
  - 1mg supplement n=7
  - 5mg supplement n=7
- CF children; ages 8 to 18 years
- Inclusion criteria:
  - Pancreatic insufficient
- Exclusion criteria:
  - Pancreatic sufficient
  - Known liver disease (diagnosed by ultrasound, liver function tests and/or hepatomegaly)
  - Receiving supplemental therapeutic vitamin K to treat coagulopathies.
- 1 mg/day Vitamin K OR
- 5 mg/day Vitamin K
- Duration: 1 month.
- The injectable formulation of vitamin K1 – phytonadione was diluted to 1 mg/ml and given orally.

**Primary outcome:**
- Undercarboxylated osteocalcin (%Glu-OC) - Success of the intervention defined as a %Glu-OC of <21%.

**Secondary outcome:**
- Measured serum k but did not state was an outcome of interest in methods

**Intervention:**
- All (14/14) %Glu-OC levels were elevated, (> 21%).
- 50% (7/14) vitamin K levels were suboptimal (<0.3 nmol/L) with 43% (6/14) of all vit K levels undetectable (<0.03 nmol/L).
- Significantly reduced overall %Glu-OC from median of 46.8 to 29.1% (p<0.0003). 3/13 (23%) %Glu-OC levels decreased into normal —one in 5 mg/day group and two in 1 mg/day group.
- Serum vitamin K levels improved significantly (p<0.001).
  - All subjects who were below the optimal range (0.3 nmol/L) rose into the normal range with supplementation.
- There was no trend towards a difference between the 5 mg/day vitamin K1 and the 1 mg/day in terms of change in %Glu-OC or in the change in serum vitamin K. (Note no raw values or p values provided)

**Conclusions:**
- "There was a highly significant improvement in vitamin K status, as assessed by the %Glu-OC, but in both the 1 mg/day and the 5 mg/day supplemented groups, the majority of patients remained in the suboptimal range. Our results suggest that higher doses of vitamin K1 than presently recommended, given over a one month period, improve vitamin K status."
- "The 5 mg/day dose did not appear to offer an advantage over the 1 mg/day

**Author’s limitations:**
- Possibly inadequate intensity and duration of intervention
- Not representative of adult CF
- Didn’t report method of diagnosis of CF or PI
- No details where or how recruited
- No info re method of randomisation.
- No allocation concealment
- No information re Abx use (concomitant or hx)
- No Ax compliance
- Not powered to detect difference between doses.
- No healthy control group
- No diet Ax of Vit K intake
- Not all conclusions supported by results
- Levels of supplementation higher than available in Aus
- No variability data provided. i.e. CI or IQR

<table>
<thead>
<tr>
<th>NHMRC level: IV (Intervention)</th>
<th>Pre test and post test intervention study</th>
<th>Primary Intervention(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=14 (note n=17 recruited)</td>
<td>N=14 (note n=17 recruited) (CF patients aged 10-23)</td>
<td>2 AquADEK softgels capsules a day 300IU α tocopherol; 160mg other mixed tocopherols) (contains 18,167IU vitamin A in each capsule with enzymes immediately prior to breakfast for 12 weeks 92% B carotene and 8% palmitate</td>
</tr>
<tr>
<td>ADA quality: POSITIVE</td>
<td></td>
<td>6 week visit and 12 week visit Discontinue other supplemental doses of vitamins Fasting bloods at least 8hrs</td>
</tr>
</tbody>
</table>

Exclusion criteria:
- Pregnant/lactating
- Significant liver disease (defined as portal HT, cirrhosis or liver enzymes >2x normal)
- Had oral Aquadeks or another source of B carotene or CoQ10 in 2months prior to study
- Had oral Aquadeks or another source of B carotene or CoQ10 in 2months prior to study
- Participated in another interventional clinical trial within 30 days prior to screening

Inclusion criteria:
- Confirmed CF (no details given)
- >10yrs
- Weight >30kg
- FEV1 > 35% predicted
- Stable pulmonary disease as defined by both clinical impression and no hospitalisations in the 30 days prior to screening

Primary outcome:
- Serum vitamin level – laboratory reference ranges
- Vit E – normal ranges (α tocopherol 3.8-20.3 ug/ml); γ tocopherol (0.4-4.0 ug/ml) Vit A retinol (19-77ug/dl) B carotene (0.04-0.85 ug/ml) Lower limits of detection for B carotene 0.03ug/ml

Secondary outcome
- Anthropometry measures
- Spirometry: FEV1; FVC; FEF 25-75%
- Adherence
- Repeat urine for 8 isoprostanate level at visit 3 only; 8-

Results:
- Compliance: >90% in 11/14 pts
- 58 adverse events – not serious or not due to formulation
- Baseline sig differences between PI vs PS patients γ (PI<1 vs PS 1.25 p<0.05) and α tocopherol (PI 9.6 vs PS 12.2 P<0.05,

Supplementation:
- Entire cohort Increased:
  - γ tocopherol (P<0.05)
  - PI: No sig change:
    - γ tocopherol baseline< 1.0 (<1.0-1.1); 6 weeks 1.2 (<1.0-2.0); 12 weeks <1.0 (<1.0-1.8) (p<0.09));
    - α tocopherol baseline 9.6 (6.5-11.1); 6 weeks 10.9 (9.5-14.8); 12 weeks 11.2 (8.5-11.3) (P=0.58)
- End of study:
  - PI pts sig lower than PS pts for α tocopheral: PI 11.2;8.5-13.3 vs PS 16.4; 13.3-24.4 p<0.05)
  - γ tocopherol significantly increased in from baseline for PS and PI subjects (pooled data); p<0.05.

Clinical outcomes:
- Entire cohort:
  - Improved weight percentile (+2.4% IRQ: -0.05-4.5%; p=0.03); FEV1 (+3.8% IRQ -2.0-9.1% p=0.04)
  - NO significant changes in BMI centile (p=0.17); Urine 8-isoprostanate levels (p=0.28)

Appraiser’s Limitations
- Data not collected by consistent people eg one person withdrawn by a nurse unfamiliar with the study OR no process to check with a study person before withdrawing
- Self-report data used to measure compliance
- Potential recruitment bias

Author Limitations:
- Not controlled
- Not powered to detect significant changes in lung function and clinical outcomes
Conway SP, Wolfe SP, Brownlee KG, White H, Oldroyd B, Truscott JG, Harvey JM, Shearer MJ.

<table>
<thead>
<tr>
<th>NHMRC level:</th>
<th>IV Aetiology Cross sectional study</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA quality:</td>
<td>NEUTRAL</td>
</tr>
</tbody>
</table>

Aetiological Cross sectional observational study (with case series-no controls) or Diagnostic study
Children ≥ 5 years Age median (95% CI) 10.95 (9.95 - 12.21) Paediatric CF unit

**Inclusion criteria:**
- Nil stated

**Exclusion criteria:**
- Nil stated

**Intervention:** N/A

**Outcomes:**
- Vitamin K1
- PIVKA-II prothrombin produced in vitamin K absence
- Total OC, undercarboxylated OC (Glu-OC), and carboxylated osteocalcin (Gla-OC) (Also reported %Glu-OC)
- Bone-specific alkaline phosphatase (BSAP) and procollagen I carboxy-terminal propeptide (PICP) (bone formation markers).
- N-telopeptide and free pyridinoline and deoxypyridinoline (bone breakdown products) were

**Results:**
- 65/93 children (70%) - suboptimal vitamin K status, on the basis of low serum vitamin K1 levels, increased PIVKA-II, or both abnormalities.
- 54/93 undetectable ≤0.05ng/ml or suboptimal (≤0.15ng/ml) serum vit k.
- 39/93 increased PIVKA-II (>0.3AU/ml) (28/39 also low vit k)
- 15 on vit k supplements:
  - 4 high vitamin K
  - 2 normal vitamin K
  - 2 low vitamin K
  - 7 undetectable vitamin K
- 78 not on supplements
  - 48 low vitamin K
- Vitamin K1 levels showed a significant but weak negative correlation with;

**Author Conclusions:**
- Antioxidant rich multivit supplement increased circulating antioxidant levels and decreased PIVKA-II concentrations whilst maintaining Vit A levels in normal range in PI and PS subjects
- 30% GIT symptoms that may be related to formulation. Modest improvements in weight and pulmonary function and B carotene levels were weakly associated with better growth parameters. Need for higher antioxidant vit supplementation in PI vs PS pts was indicated by PI having lower antioxidant plasma levels and that micronutrients and antiboxidant deficiencies were observed almost exclusively in PI Subjects

**Appraiser’s limitations:**
- Most results combined for supp and non supp patients (Small number results reported for PIVKA-II and Vit K for each group)
- Selection of patients unclear
- Inclusion & exclusion criteria not specifically stated
- No concurrent control group
- Statistics - univariate analysis only.
- Data not available for all included patients
- Table of results combine supp and non supp patients-can't differentiate.
- Not stated if outcome assessors blinded
- Compliance not measured for those on supplements
measured in urine samples.
• Bone mineral density (BMD) and bone mineral content (BMC) were measured at the lumbar spine (L2-L4) and for the total body - GE Lunar Prodigy densitometer.

- uc-OC levels ($r=0.32$, $P=0.01$)
- %uc-OC ($r=0.25$, $P<0.05$)
  Showed no significant correlation with any marker of bone turnover or measurement of bone mineral status.
• PIVKA-II - no correlation with any parameters

**Bone turnover markers**
- Total OC & uc-OC levels were correlated positively significantly with bone turnover markers, in particular BSAP and PICP.
- %uc-OC correlated less strongly with bone formation markers (BSAP $r=0.20$, $p=0.05$) and (PCIP $r=0.28$, $p=0.007$) and not correlated with bone resorption markers.
- Bone formation and resorption markers showed a significant negative correlation with measurements of bone mineral density and content.
- There were no significant correlations between carboxylated or undercarboxylated OC levels and bone density measurements.

**Conclusions:**
- Vitamin K1 deficiency is common among children with CF.
- Routine supplements should be considered.
- Vitamin K deficiency may be associated with an uncoupling of the balance between bone resorption and bone formation (based on sig neg correlation Vit K with uc-OC which were associated with levels of bone turnover markers).
- A cause-effect relationship between vitamin K deficiency and low bone mass has not been proved (study showed no correlation bw Glu-OC, Gla-OC or vit K and BMD or BMC).

**Author's Limitations:**
- Suboptimal vitamin D status with only 13 patients $>30$ug/L. High levels of Glu-OC may reflect vit D and vit K deficiency.
- Vit D and Ca supplements can increase the percentage of Gla-OC among those with low BMD.
- Other potential influences on bone metabolism, including serum pro-inflammatory cytokine levels, respiratory exacerbation rates, calcium intake, corticosteroid use, activity levels and general nutritional status were not analysed in this study.
- Lack of comparative data for Glu-OC and Gla-OC levels from a control group healthy children of same age range.
- Not a validated measure of total OC however used BSAP and PICP and alternative well validated markers of bone formation.
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>NHMRC level</td>
<td>IV (Aetiology)</td>
</tr>
<tr>
<td>Study type</td>
<td>Cross sectional observational study</td>
</tr>
<tr>
<td>ADA quality</td>
<td>POSITIVE</td>
</tr>
<tr>
<td>Sample size</td>
<td>N=32</td>
</tr>
<tr>
<td>CF children 8.4–12.1 years</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>• Children 8-12 years attending CF clinic</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>• Children too unwell for whole body plethysmography (not reported in this study) due to their respiratory status</td>
</tr>
<tr>
<td>Intervention:</td>
<td>N/A</td>
</tr>
<tr>
<td>Outcomes:</td>
<td>• Whole body (WB) and lumbar spine (LS) (DXA scan -Lunar Prodigy)</td>
</tr>
<tr>
<td></td>
<td>• Markers of bone formation Plasma osteocalcin (N-Mid osteocalcin)</td>
</tr>
<tr>
<td></td>
<td>• N-terminal pro-peptide of type 1 collagen (P1NP)</td>
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<tr>
<td></td>
<td>• Indirect measure of vitamin K status</td>
</tr>
<tr>
<td></td>
<td>• Undercarboxylated osteocalcin (uc-OC).</td>
</tr>
<tr>
<td></td>
<td>• PTH and 25-OH vitamin D</td>
</tr>
<tr>
<td>Samples were obtained in a non-fasting state.</td>
<td></td>
</tr>
<tr>
<td>Plasma total OC (t-OC) and uc-OC were analysed by onestep ELISA. Uc-OC was measured using the same assay following a hydroxyapatite binding stage - modified method (Gundberg)</td>
<td></td>
</tr>
<tr>
<td>Results:</td>
<td>• % uc-OC ranged from 22 to 62%</td>
</tr>
<tr>
<td></td>
<td>• % uc-OC (Mean(SD))</td>
</tr>
<tr>
<td></td>
<td>- N=24 pre pubertal 35% (8.7)</td>
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<tr>
<td></td>
<td>- n=4 pubertal 45% (11)</td>
</tr>
<tr>
<td></td>
<td>• Plasma osteocalcin (ng/ml) (Mean(SD))</td>
</tr>
<tr>
<td></td>
<td>- N=24 pre pubertal 98.6 (29.7)</td>
</tr>
<tr>
<td></td>
<td>- n=4 pubertal 129.2 (40.7)</td>
</tr>
<tr>
<td></td>
<td>• P1NP mcg/l (Mean(SD))</td>
</tr>
<tr>
<td></td>
<td>- N=24 pre pubertal 401 (148)</td>
</tr>
<tr>
<td></td>
<td>- n=4 pubertal 449 (54)</td>
</tr>
<tr>
<td>Bone mass/content</td>
<td>• WBBMD and WBBMC normal.</td>
</tr>
<tr>
<td></td>
<td>• LS BMD scores ≤1.0 in 20% Size adjusted bone mass normal.</td>
</tr>
<tr>
<td></td>
<td>• LS bone mass was predicted by % uc-OC but not other markers (0.4% decrease in size-adjusted LSBMC (p=0.05); 0.04 SD decrease in LSBMAD (p=0.04) per 1% increase in uc-OC).</td>
</tr>
<tr>
<td></td>
<td>Mean Vit D normal (&gt;50)</td>
</tr>
<tr>
<td>Conclusions:</td>
<td>• Markers suggest sub-optimal vitamin K status and low bone formation were present despite normal size-adjusted bone mass.</td>
</tr>
<tr>
<td></td>
<td>• The association between LSBMC and % uc-OC is consistent with the hypothesis that sub-optimal vitamin K status is a risk factor for CF bone disease. This should ideally be investigated in an intervention trial.&quot;</td>
</tr>
</tbody>
</table>

**Appraiser’s limitations:****
- Excluded those not able to do plethysmography - i.e. those more severe respiratory
- Representative of young children only (8-12yrs)
- 13% sample no blood results - reasons and characteristics of patients not reported.
- No concurrent healthy control group. (Aetiology study) and no reference std (Diagnostic study)
- No "cut off values" for main outcomes such as P1NP and uc-OC%.
- No info on diet intake.
- Statistics - reported mean and SD but used non parametric tests for associations
- No power calculation - small convenience sample

**Author’s Limitations:**
- No established normal reference range for %uc-OC
- Assay variation limits comparison of different studies

<table>
<thead>
<tr>
<th>NHMRC level</th>
<th>Step 1 IV (Aetiology)</th>
<th>Step 1</th>
<th>Cross sectional observational (Aetiology) i.e. compared CF group with healthy control pre supplementation</th>
<th>Intervention:</th>
<th>Intervention:</th>
<th>Results:</th>
<th>Appraiser’s limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Step 2- IV (Intervention - case series with pre-test and post-test outcomes)</td>
<td></td>
<td>Open label prospective intervention Pre/Post Case series CF N=20 (children 6-17 years) CF N=25 (children 8-17 years)</td>
<td>1 year of vitamin K supplementation administered orally in a single weekly dose of 10 mg.</td>
<td>Outcomes:</td>
<td>BMD</td>
<td>No information re control group selection.</td>
</tr>
<tr>
<td></td>
<td>ADA quality POSITIVE</td>
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<td></td>
<td>10 CF BMD z-score ≤2.5 (n=5) or between −1 and −2.5 (n=5).</td>
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<td>No difference BMD CF pre and post supp (p=0.935)</td>
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<td>- i.e. 50% had osteopenia /osteoporosis</td>
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<td></td>
<td>BMD CF positively correlated with:</td>
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<td>- BMI pre (r=0.45, p=0.045) and post (r=0.56 p=0.009)</td>
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<td>- FEV1 pre (r=0.7, p&lt;0.001) and post (r=0.66, p=0.001)</td>
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<td>- SK score pre (r=0.67, p=0.001) and post(r=0.67, p&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

Inclusion criteria:
- Clinically stable for at least 6 months.
- No acute infection, not currently taking antibiotics or not taken them for at least 3 weeks prior to the blood samples being taken.
- Not currently taking or had ever taken oral or IV corticosteroids.

Exclusion criteria:
- Not stated in methods.

Intervention:
- Levels of vitamin K, 25(OH)D, BAP, Glu-OC, PICP and PINP were significantly lower CF A1 vs. control (p=0.021, p<0.001, p=0.002, p=0.012, p<0.001, respectively),
- Glu-OC, PTH and Ca/Cr values were higher (p<0.001, p=0.005, p=0.017, respectively)

Vit K (ng/ml)
- Pre-supplementation control vs. CF 0.277 (0.140, 0.631) vs. 0.140 (0.059, 0.590); p=0.021
- Sig lower in CF vs control

Glu-OC (ng/ml)
- Pre supp control vs. CF 4.00 (3.38, 6.52) vs. 8.08 (4.25, 10.77) p=0.017
- Post supp control vs. CF 1.25 (0.53, 2.14) p<0.001; CF pre vs. post supp <0.001
- Vitamin K intake independent predictor of Glu-OC (p<0.001); Glu-OC (p=0.013); PICP (p=0.001); PINP (p<0.001)

Conclusions:
- CF patients had impaired bone formation.
- Vitamin K supplementation may have a beneficial role in bone health in CF

Appraiser’s limitations:
- No information re control group selection.
- No info on how normal daily activity ax nor who ax Tanner staging.
- No control comparison for BMD (only Vit K)
- Compliance with supplementation not measured
- No reference values/cut off values except for BMD.
- Statistics - Role of vit k in bone turnover markers - multivariate analysis. However didn’t do correlation for vit k intake and BMD
- Small sample of 20

Author’s limitations:
- Unable to measure vit k levels post supplementation (studied indirectly via Glu-OC)
- Low levels of Vit D which may have obscured effects of vit k supp.
<table>
<thead>
<tr>
<th>Grey V, Atkinson S, Drury D, Casey L, Ferland G, Gundberg C, Lands LC.</th>
<th>NHMRC level IV Aetiology</th>
<th>Cross sectional design</th>
<th>Intervention: N/A</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of low bone mass and deficiencies of vitamins D and K in paediatric patients with cystic fibrosis from 3 Canadian centres. Pediatrics. 2008 Nov;122(5):1014-20.</td>
<td>ADA quality POSITIVE</td>
<td>N=81 Children ≥8years (12.6±2.9)</td>
<td>Whole-body bone mineral content (WBBMC) and lumbar spine (L1–L4) bone mineral density (LSBMD) by DEXA (Hologic and Lunar Prodigy)</td>
<td>Vitamin D (25-OHD)nmol/L (n=75) - 95% suboptimal levels 42.00 ± 20.70</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>Vit D (25-OHD), parathyroid hormone (PTH), Vitamin K, osteocalcin (total and undercarboxylated), carboxyterminal propeptide type 1 procollagen (PICP), protein induced by vitamin K absence factor II (PIVKA-II), INR</td>
<td>PIVKA-II (ng/mL) n= 75 - 10.60 ± 24.10</td>
<td>Adequacy levels of vit k status - Vit K &gt;0.29nmol/L - PIVKA-II &lt;2.0ng/ml - %Glu-OC &lt;20%</td>
<td>GLU-OC n=78 - 35.50±14.40</td>
</tr>
<tr>
<td>• Clinically stable for at least 3months</td>
<td></td>
<td>Notes re methods:</td>
<td>Sig negative correlation seen between serum vit k and Glu-OC levels (r=-0,46, p&lt;0.1)</td>
<td></td>
</tr>
<tr>
<td>• PI (assessed by faecal fat measurements at the time of diagnosis)</td>
<td></td>
<td>• Completed a FFQ to Ax calcium, D and K intake including supplements</td>
<td>INR 76 1.09±0.12 (INR) levels were normal for all but 9 patients. Only 12% INR&gt;1.2 (Ref 0.9 - 1.2)</td>
<td></td>
</tr>
<tr>
<td>• Majority had not taken systemic steroids.</td>
<td></td>
<td></td>
<td>Dietary intakes of calcium, vitamin D, and vitamin K based on an FFQ met or exceeded the recommended values for age of the dietary reference intakes for most children.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Adequacy levels of vit k status</td>
<td></td>
<td>Vitamin K (ug/d) intake: - 295 ± 184 DRI 8-18yrs - 55–75)</td>
<td></td>
</tr>
<tr>
<td>• Nil stated</td>
<td>• Vit K &gt;0.29nmol/L</td>
<td>- 6% patients intake &lt;DRI</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• PIVKA-II &lt;2.0ng/ml</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>• %Glu-OC &lt;20%</td>
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</tbody>
</table>

**Notes re methods:**
- Completed a FFQ to Ax calcium, D and K intake including supplements
- Bloods fasting

**Results:**
- Vitamin D (25-OHD)nmol/L (n=75) - 95% suboptimal levels 42.00 ± 20.70
- Vitamin K (nmol/L) n=78 - 0.51 ± 0.93 Vitamin K values were <0.29 nmol/L in 65% of patients, - 30% had undetectable levels (<0.03nmol/L)
- PIVKA-II (ng/mL) n= 75 - 10.60 ± 24.10
- GLU-OC n=78 - 35.50±14.40
- By using GLU-OC <20% and PIVKA-II <2ng/mL as the indicator of adequate vitamin K status, 82% of the patients had suboptimal vitamin K.
- Sig negative correlation seen between serum vit k and Glu-OC levels (r=-0,46, p<0.1)
- INR 76 1.09±0.12 (INR) levels were normal for all but 9 patients. Only 12% INR>1.2 (Ref 0.9 - 1.2)
- Dietary intakes of calcium, vitamin D, and vitamin K based on an FFQ met or exceeded the recommended values for age of the dietary reference intakes for most children.
- Vitamin K (ug/d) intake:
  - 295 ± 184 DRI 8-18yrs - 55–75
  - 6% patients intake <DRI
  - 94% >75ug/d
  - 40% >300ug/d CF rec

**Appraiser’s limitations:**
- Lack of info on % with CFLD
- No correlation b/w dietary vitamin k and vit k status.
- Applicable to paediatrics only
- No info on range of lung disease severity
- Statistics methods - limited discussion that is relevant to the vit K questions

**Author’s limitations:**
- Minimal but noted lack of vit k supplement preparations
• DEXA N=77 WB and n=76 LS
  - Low WBBMC and LSBMD for gender and chronological age detected in 29 (38%) and 20 (28%) of patients respectively.
• Bone biomarkers
  - Mean values for the bone formation marker osteocalcin were lower than reference values for all female patients and almost all but 1 male patient during puberty.
  - The bone formation marker PICP was also below normal in all stages of puberty in both girls and boys.
• Age, Tanner stage, height z score, BMI, and 25-OHD were predictors of WBBMC z scores, whereas age, height z score, and BMI were predictors of LSBMD z scores.
• Calcium intake had an effect on the bone formation marker osteocalcin, whereas GLU-OC had an effect on the formation markers PICP and osteocalcin and the resorption marker deoxypyridoline-creatinine ratio.

Conclusions:
• State of suppressed bone formation and elevated bone resorption in a large proportion of the patients.
• Despite widespread supplementation with vitamins D and K, suboptimal biochemical status.
• Results point to the importance of monitoring vitamin status and bone health even in relatively healthy patients.
• Suboptimal status of vitamins D and K may be key causative factors of the low bone status for age.
**Evidence Statement Matrix**

**Q 8.4.2 Should vitamin K supplementation be recommended for all people with CF and pancreatic insufficiency?**

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** The evidence suggests that vitamin K supplementation is required for all people with CF and pancreatic insufficiency. There is insufficient high quality evidence available to recommend an optimal dose. Given the recent evidence suggesting the importance of vitamin K in bone health, it is recommended where possible, that practitioners follow the recommendations of the most recent guidelines. In practice this will require an increase in vitamin K supplementation doses that are routinely provided and currently available in Australia.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>D Poor</th>
</tr>
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<tbody>
<tr>
<td>Nine studies included in evidence base:</td>
<td></td>
</tr>
<tr>
<td>• 1 level II intervention study; neutral quality n=14; children</td>
<td></td>
</tr>
<tr>
<td>• 1 level III-3 diagnostic case-control study; neutral quality; n=32; infants, children &amp; young adults</td>
<td></td>
</tr>
<tr>
<td>• 7 level IV studies</td>
<td></td>
</tr>
<tr>
<td>• 1 prospective, non-randomised trial; positive quality; n=17; children</td>
<td></td>
</tr>
<tr>
<td>• 1 diagnostic study; negative quality; n=20; children</td>
<td></td>
</tr>
<tr>
<td>• 5 aetiology studies; 4 positive quality; n=97; children &amp; adults; n=81, 32, 20; children; 1 neutral quality; n=106; children</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>B Good</th>
</tr>
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<tbody>
<tr>
<td>Generally studies consistently report the following:</td>
<td></td>
</tr>
<tr>
<td>• Suboptimal levels of vitamin K as assessed by PIVKA-II and uc-OC%</td>
<td></td>
</tr>
<tr>
<td>• Increased likelihood of inadequate vitamin K status with low level supplementation (&lt;500ug/d)</td>
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<tr>
<td>Overall studies are consistent in showing lower levels of bone formation markers in CF compared with healthy controls.</td>
<td></td>
</tr>
<tr>
<td>• Inconsistent as to the effect of vitamin K supplementation on bone turnover markers.</td>
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<tr>
<td>Evidence consistently shows no association between vitamin K status and bone mineral density.</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence suggests the following:</td>
<td></td>
</tr>
<tr>
<td>• Adequate vitamin K supplementation will decrease the incidence of subclinical vitamin K deficiency.</td>
<td></td>
</tr>
<tr>
<td>• Subclinical deficiency of vitamin K may negatively impact the bone health of people with CF.</td>
<td></td>
</tr>
<tr>
<td>• Vitamin K supplementation appears to be safe at doses significantly higher than current supplementation practices in Australia</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most evidence is from children and adults, mostly without CF-related liver disease, with pancreatic insufficiency, mild to moderate lung disease and variable nutritional status. The evidence can generally be applied across a heterogeneous CF population, however is less generalisable to infants and to people with CF and pancreatic sufficient or with CF-related liver disease.</td>
<td></td>
</tr>
</tbody>
</table>
| Applicability | C Satisfactory | The only CF fat soluble multivitamin available in Australia (VitABDECK) provides 150ug per capsule of Vitamin K  
- Less than supplementation doses associated with more optimal vitamin K status  
- Vitamin K as an individual supplement is not readily available in most clinics.  
- The need for an additional vitamin K supplement would incur an additional cost and add to patient treatment burden. |
CLINICAL QUESTION
8.4.3 How often should vitamin K status be assessed in CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.
Chapter 9 Minerals

9.1 Iron

PICO

9.1.1 How should iron status be assessed in people with CF?
9.1.2 How should iron deficiency be treated in people with CF?
9.1.3 Is iron supplementation contraindicated in people with CF who are chronically colonised with pseudomonas aeruginosa?

Search strategy: See T2.4 Systematic Search Strategy

Search terms: Iron

- Cystic fibrosis, CF, nutrition, diet, iron, soluble transferring receptor, soluble transferrin, transferrin, ferritin, iron deficiency, iron studies, pseudomonas aeruginosa, pseudomonas, inflammation, inflammatory markers, infection, soluble transferrin

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
**CLINICAL QUESTION**

9.1.1 How should iron status be assessed in CF?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
</table>
• Blood test for soluble transferrin receptor (sTFR), Ferritin, Transferrin, Iron, CRP, Hb, Mean Cell Volume (MCV), Total Iron Binding Capacity (TIBC)  
Outcomes:  
• Subjects classified as iron deficient (ID) based on; ferritin levels, transferrin saturation and sTFR  
The following was examined:  
• Impact of CRP on biochemical values  
• The relationship between biochemical parameters and ID diagnosed by transferrin saturation, sTFR and ferritin  
• Relationship between CRP and each of transferrin saturation, sTFR and ferritin | Results:  
• Iron deficiency diagnosed in the following proportion of subjects:  
  - 69% based on transferrin saturation  
  - 11% based on ferritin  
  - 29% based on sTFR  
  
  • CRP was elevated in 64% of subjects  
  • Significant correlation between CRP & ferritin (r=0.38, P=0.0001), CRP & transferrin saturation (r=-0.54, P<0.0001), CRP & sTFR (p<0.0001)  
  
  • Correlation between ferritin and other parameters improved significantly when patients with CRP < 10mg/L only included:  
    - sTFR (r=-0.56, P=0.02), MCV (r=0.49, P=0.02), %Transferrin saturation (r=0.74, P<0.001) but not Hb (r=0.02, P=0.89)  
  
  • Significant difference between CRP values in iron-deficient and iron replete subjects as determined by either transferrin saturation or sTFR  
  
  • When corrected for CRP levels no improvement seen in the following correlations:  
    - % transferrin saturation and: Hb (r=0.60, P<0.0001) and MCV (r=0.5, P<0.0001) OR  
    - sTFR and Hb (r=-0.47, P<0.0001), MCV (r=0.54, P<0.0001) and % Transferrin saturation (r=-0.45, P<0.0001) | Authors limitations:  
• sTFR assays may have different reference ranges between laboratories  
• Bone marrow biopsy is gold standard for diagnosis of iron deficiency (note this isn’t practical)  
• sTFR is adversely affected by some disorders (of erythropoiesis)  
Appraiser’s limitations:  
• CF population not described in any detail  
• No description of factors which may impact blood tests i.e. were subjects symptomatic or well at time of test, lung function, weight loss, iron supplements etc.  
• Lack of information on tests (other than bone marrow biopsy) to diagnose iron deficiency or assess iron status (i.e. transferrin saturation & ferritin) and validity of these tests with references to support this  
• No reference given for cut off ranges in the lab tests  
• Not all results reported after correcting for CRP levels  
• No blinding of investigators
**Conclusion:**
- Ferritin is not a good test in CF patients because of the presence of inflammation.
- Transferrin saturation overestimates and ferritin underestimates iron deficiency in this population due to over half of the population having elevated CRP levels.
- sTFR may be the most useful test for the assessment of iron deficiency in CF. This is because it’s not affected by the acute phase response.


<table>
<thead>
<tr>
<th>Authors limitations:</th>
<th>Appraisers limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unsure if sTFR takes into account haemolysis or increased ineffective erythropoiesis that can increase sTFR.</td>
<td>• Although potential confounding information collected on bleeding, menstruation, liver disease, GIT disease, blood transfusions, iron supplements etc., none of these were included in results or discussion</td>
</tr>
<tr>
<td>• Further studies needed to assess if iron therapy is useful in people with CF.</td>
<td>• Further studies required to confirm the specificity and sensitivity of sTFR measurement in this population</td>
</tr>
</tbody>
</table>

**Diagnostic accuracy study**

<table>
<thead>
<tr>
<th>Intervention:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood test for soluble transferrin receptor (sTFR), Ferritin, Transferrin saturation (TS), Iron, CRP, Hb, Mean Cell Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Total Iron Binding Capacity (TIBC), White blood cells, neutrophils, platelets and Erythrocyte Sedimentation Rate (ESR)</td>
<td>30% of unwell group had low serum iron vs 78% of well group</td>
</tr>
<tr>
<td>Full history taken of anemia, bleeding menstruation, liver disease, GI disease, blood transfusions, symptoms in past week of cough, breathlessness, increase in volume or change in colour of sputum, absenteeism from work, decreased exercise tolerance and fever, all meds.</td>
<td>Difference in sTFR between the 2 groups was not significant (p&gt;0.05)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes:</th>
<th>CRP Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency (ID) based on; ferritin levels &lt;12ug/l), transferrin saturation (TS) (&lt;15%) and sTFR (&gt;1.74mg/l)</td>
<td><strong>Unwell group:</strong> elevated in 98% of patients and correlated significantly with sTFR (r=0.42); TS (r=-0.56) but not ferritin (r=0.22)</td>
</tr>
<tr>
<td>The following was also examined:</td>
<td><strong>Well group:</strong> elevated in 2% of patients and no significant correlations with sTFR (r=0.08), TS (r=-0.19) or ferritin (r=0.01)</td>
</tr>
<tr>
<td>Relationship between biochemical parameters and ID diagnosed by transferrin saturation, sTFR and ferritin</td>
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<tr>
<td>Relationship between CRP and each of transferrin saturation, sTFR and ferritin</td>
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<td>• Although potential confounding information collected on bleeding, menstruation, liver disease, GIT disease, blood transfusions, iron supplements etc., none of these were included in results or discussion</td>
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<td>• Further studies needed to assess if iron therapy is useful in people with CF.</td>
<td>• Further studies required to confirm the specificity and sensitivity of sTFR measurement in this population</td>
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</tbody>
</table>
Evidence Statement Matrix

<table>
<thead>
<tr>
<th>Evidence statement:</th>
<th>Soluble transferrin receptor (sTfR) is unaffected by the acute phase response and may be a useful biomarker to measure when assessing iron status for people with CF. However, the overall body of evidence to guide practice for assessing iron status in CF is insufficient. Further research or expert consensus is required. Until further evidence is available, it is suggested that iron status in CF be assessed as per recommendations for the general population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHMRC Grade for recommendation:</td>
<td>Grade C</td>
</tr>
<tr>
<td>Evidence base</td>
<td>C Satisfactory</td>
</tr>
<tr>
<td>Two diagnostic studies</td>
<td>One level III-2 study (n=70 adolescent and adult CF patients; ADA neutral)</td>
</tr>
<tr>
<td>One level III-2 study (n=127 adult CF patients; ADA positive)</td>
<td></td>
</tr>
<tr>
<td>Consistency</td>
<td>C Satisfactory</td>
</tr>
<tr>
<td>Both studies concluded that soluble transferrin receptor (sTfR) was a useful biomarker to help assess iron status in CF as it is not affected by the acute phase response with inflammation.</td>
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</tr>
<tr>
<td>Inconsistency between the studies regarding the use of serum ferritin in diagnosing iron deficiency in CF.</td>
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<tr>
<td>Study 1 found no correlation between serum ferritin and CRP</td>
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<tr>
<td>Study 2 found a significant correlation between ferritin and CRP</td>
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</tr>
<tr>
<td>Clinical impact</td>
<td>B Good</td>
</tr>
<tr>
<td>Relevance of the evidence to the clinical question is satisfactory.</td>
<td></td>
</tr>
<tr>
<td>Generalisability</td>
<td>B Good</td>
</tr>
<tr>
<td>------------------</td>
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<tr>
<td>Applicability</td>
<td>B Good</td>
</tr>
</tbody>
</table>
### CLINICAL QUESTION

9.1.2 How should iron deficiency be treated in people with CF?

**Evidence Table**

There were no studies available within the search strategy and criteria that addressed this PICO.

### CLINICAL QUESTION

9.1.3 Is iron supplementation safe for people with CF and colonised pseudomonas aeruginosa (PA)?

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gifford AH, Alexandru DM, Li Z, Dorman DB, Moulton LAS, Price KE, Hampton TH, Sogin ML, Zuckerman JB, Parker HW, Stanton BA, O'Toole GA</td>
<td>NHMRC level II, ADA quality POSITIVE</td>
<td>Randomized double blind placebo controlled crossover trial N = 22 adults with CF</td>
<td>Intervention: 325mg ferrous sulphate per day vs placebo for 6 weeks (30 day washout between each arm)</td>
<td>Results: Ferrous sulphate increased haemoglobin by 0.04 (p=0.81) Ferrous sulphate increased transferrin saturation by 10.6 (26.8%) (p=0.02) Ferrous sulphate increased serum iron by 9.9 (22.3%) (p=0.03) Use of ferrous sulphate did not affect sputum iron variation (p=0.16) Ferrous sulphate was not associated with triggering a CF pulmonary exacerbation score (using Akron PES instrument) (p=0.29)</td>
<td>Author limitations: Finding regarding ferrous sulphate not improving haemoglobin may have been affected by the following: - Not reaching target enrolment numbers - Supplement not absorbed as efficiently as others - Serum iron may not have been increased sufficiently to affect haemoglobin - Gastric acid suppression used in CF may have affected uptake of iron - Vitamin C not used to enhance supplement absorption - Anaemia may have been to mild reflecting a potential ceiling effect - Under-dosed supplement - Underpowered study and therefore can’t definitively conclude that iron supplementation is not associated with CF pulmonary exacerbation or sputum iron content</td>
</tr>
</tbody>
</table>

**Inclusion criteria:**
- Serum transferrin saturation ≤21% and haemoglobin 5.5 g.dl (men) or <13.6 g/dl (women)
- History of ≥1 pseudomonas (PA) positive sputum culture

**Exclusion criteria:**
- Use of iron containing vitamins
- History of an iron overload condition or cirrhosis
- Pregnancy or breastfeeding
- Recent visible

**Author limitations:**
- Finding regarding ferrous sulphate not improving haemoglobin may have been affected by the following:
  - Not reaching target enrolment numbers
  - Supplement not absorbed as efficiently as others
  - Serum iron may not have been increased sufficiently to affect haemoglobin
  - Gastric acid suppression used in CF may have affected uptake of iron
  - Vitamin C not used to enhance supplement absorption
  - Anaemia may have been to mild reflecting a potential ceiling effect
  - Under-dosed supplement
  - Underpowered study and therefore can’t definitively conclude that iron supplementation is not associated with CF pulmonary exacerbation or sputum iron content
**Chapter Q9.1.3 Is iron supplementation contraindicated in people with CF who are chronically colonised with Pseudomonas Aeruginosa (PA)?**

**NHMRC Grade for recommendation: Grade D**

**Evidence statement:** There is insufficient evidence from clinical trials to suggest that iron supplementation is contraindicated in adults and children with CF who are chronically colonised with Pseudomonas aeruginosa (PA). When indicated, an iron supplement should be prescribed for adults and children with CF who are chronically colonised with PA.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>Consistency</th>
<th>Clinical impact</th>
<th>Generalisability</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>D Poor</td>
<td>N/A</td>
<td>No adverse effect on sputum microbiome or pulmonary exacerbation score but the study was underpowered to detect a significant difference</td>
<td>B Good</td>
<td>Applicable to the Australia CF population</td>
</tr>
</tbody>
</table>

One randomized double blind placebo controlled crossover trial to answer this PICO.
- Level II study (n=22 CF adults; ADA positive)
9.2 Magnesium

**PICO**

9.2.1 Does supplementing magnesium above the RDI improve nutrition and/or respiratory outcomes in people with CF?

**Search strategy:** See T2.4 Systematic Search Strategy

**Search terms:**
- Magnesium
  - Cystic fibrosis, CF, nutrition, Diet, magnesium

**Inclusion & exclusion criteria:**

**Inclusion criteria:**
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

**Exclusion criteria:**
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers

**CLINICAL QUESTION**

9.1.2 Does magnesium supplementation above the RDI improve nutrition and/or respiratory outcomes for people with CF?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Gontijo-Amoral C, Guimaraes EV, Camargos P. Oral magnesium | NHMRC level II ADA quality | Double-blind, randomized placebo controlled cross-over study | Intervention:
- 8 week supplementation with 300mg (5-12mg/kg) magnesium or placebo with 4wk wash out between | Results:
- Significant increase in urinary Mg (mg/d) after supplementation (p<0.001)
- 11 ± 7.8% predicted increase in MIP with | Appraisers limitations:
- Only relatively well/clinically stable patients with mean FEV1 75% were studied |
**Evidence Statement Matrix**

**Chapter 9 Q9.2.1 Does supplementing magnesium above the recommended dietary intake (RDI) improve nutrition and/or respiratory outcomes in people with CF?**

**NHMRC Grade for recommendation: Grade D**

**Evidence statement:** There is insufficient evidence to support the suggestion that magnesium supplementation improves respiratory outcomes in CF. No studies have looked at magnesium supplementation and nutrition outcomes in CF.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>D Poor</th>
<th>One study only – double blind, randomized placebo controlled cross-over study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>N/A</td>
<td>-</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>C Satisfactory</td>
<td>Relevance of the evidence to the clinical question is satisfactory.</td>
</tr>
<tr>
<td>Generalisability</td>
<td>D Poor</td>
<td>Paediatric patients only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Majority of population was pancreatic sufficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean FEV1 75% predicted which is much lower than the Australian paediatric population.</td>
</tr>
<tr>
<td>Applicability</td>
<td>D Poor</td>
<td>Population group studied not applicable to the Australian and NZ context</td>
</tr>
</tbody>
</table>
9.3 Calcium

Refer to Chapter 13 Bone Health for all relevant calcium content.

9.4 Sodium

PICO

9.4.1 How do environmental factors and exercise impact sodium requirements for people with CF compared to those without?

9.4.2 What is the recommended daily sodium requirements for people with CF compared to those without?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:
- Sodium
  - Cystic fibrosis, CF, nutrition, diet, salt, sodium, sodium chloride

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
### CLINICAL QUESTION

**9.4.1** What is the impact of environmental factors and exercise on sodium requirements for the CF population?

### Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
</table>
| KRIEMLER, SUSI; WILK, BOGUSLAW; SCHURER, WILLEMEN; WILSON, WILLIAM M.; BAR-OR, ODED | NHMRC level II ADA quality POSITIVE | Double blinded cross over study (intervention) N= 11 children and adolescents with CF 5 male, 6 female Age: 10.9-19.5 yrs Exclusion criteria: • O2 desaturation induced by moderate exercise | Intervention: • 4 bouts of 20min cycling at moderate intensity, interspersed with 25 min rest periods, at 35 ± 1°C, 48-50% humidity • Different beverage assigned at each session - Unflavoured water (W) - Flavoured water (FW) - 30mmol/L NaCl beverage (Na30) - 50mmol/L NaCl beverage (Na50) | Results: • No significant drink effect on body fluid balance, core temp, HR, a serum electrolyte with W, FW or Na30 • Serum osmolality, Na & Cl decreased significantly throughout the sessions • NaSO drink induced a higher fluid intake (p=0.08) and there was a 3 fold decrease in the negative fluid balance NaSO vs W (p<0.08) • Participants greatly underestimated fluid intake and became dehydrated when exercising in the heat, even when flavour, CHO and 30mmol/L NaCl were added. • When given a 50mmol/L CHO flavoured solution, fluid intake increased sufficiently to prevent dehydration. • Concentrations of Na and Cl in the sweat of subjects were 3-4 times as high as healthy children | Author limitations: • Small sample size • Several children declined having their blood collected. • Only 19 out of a possible 39 sweat samples could be harvested.  
Appraisers limitations: • Limited age group (only paediatric and adolescent population) • Doesn’t provide high level evidence to inform any recommendations about Na+ requirements for children when exercising  
Conflict of interest: • Drink mixtures provided by Gatorade science institute |
| **Brown MB, McCarty A, Millard-Stafford M.** | NHMRC level III  
ADA quality POSITIVE | **Case Control Study** | **Intervention:**  
Control group (no CF) n = 8 (2F)  
Salty sweaters (no CF) n=7 (2F)  
CF group n= 6 (2F)  
All aged 18-40yrs  
Inclusion criteria (controls):  
• Young adults (18-40yrs)  
• Recreationally active  
• Not known to have CF  
Additional inclusion criteria (salty sweaters):  
• >70mmol/L Na concentration in sweat  
PRIOR to exercise intervention:  
• Standardised meal/fluid /exercise protocol prior to testing to ensure consistent Na+ intake.  
POST exercise intervention:  
• Carbo-electrolyte replacement beverage 20mM Na (Gatorade)  
**Outcome (primary):**  
• Rating of perceived thirst before during & after exercise  
• Volume of beverage voluntarily ingested following exercise  
• Sweat sodium concentration & urine analysis  
**Outcome (secondary measures):**  
• First test session – Vo2 max, respiratory exchange ratio RER, HR & perceived exertion  
• Weight, DEXA, 3 day food record prior to next test session.  
**Results:**  
• Perceived thirst was not affected by high Na+ sweat during exercise.  
• Hypovolemia likely providing a compensatory stimulus to trigger thirst rather than hyper osmolality in individuals with CF.  
• In recovery, those subjects with CF drank 40% less fluid compared to non CF subjects despite similarly high perceived thirst ratings.  
• Serum Na+ & Cl- were low & continued to fall until 2 hrs post exercise.  
**Conclusions:**  
• For people with CF, fluid replacement following prolonged exercise should not consist solely of hypotonic fluids  
• Drinking beyond thirst should not be encouraged.  
• Further research required to identify optimal fluid & electrolyte replacement strategies for the CF population who can obtain health related benefits from moderate – vigorous exercise  
**Appraisers limitations:**  
• Small sample size  |
| **Guimarães EV, Schettino GCM, Camargos PAM,** | NHMRC level IV | **Case Series**  
N=20  
**Intervention:**  
• 1-3g salt daily (added to breast milk, formula or solids from 4-6 months)  
**Results:**  
• Hyponatraemia at dx: 19/20 patients (95%)  
**Author limitations:**  
• Unable to identify impact of age on serum sodium concentration |
### Evidence Statement Matrix

**Q9.4.1 How do environmental factors and exercise impact on sodium requirements for people with CF compared to those without CF?**

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** There is insufficient evidence available to determine how environmental factor and exercise impact on sodium requirements for people with CF. The available evidence is from small, underpowered studies and is unable to be used to recommend sodium supplementation for the CF population.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>Evidence base</th>
<th>Consistency</th>
<th>Evidence base</th>
<th>Consistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazilian Study</td>
<td>Poor</td>
<td>• CF patients from any region in state of Minaj (Brazil) between Nov 04 – Aug 05</td>
<td>Correlation between serum sodium and the following over time:</td>
<td>Diet (p = 0.008)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Newly diagnosed via NBS</td>
<td>• Temperature &amp; Humidity</td>
<td>Climate/temp (p = 0.005)</td>
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<tr>
<td></td>
<td></td>
<td>Exclusion:</td>
<td>• Pa &amp; Sa</td>
<td>Note:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Diagnosed via NBS but not referred to this centre (n=5)</td>
<td>• Diet</td>
<td>Mean f/u duration of 14.3 ± 5.2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Age</td>
<td>Conclusion:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Note hyponatremia was defined as a serum sodium level of</td>
<td>Infants with CF who are exclusively breastfed or formula fed and living in a high temp environment are ↑ risk hyponatraemia</td>
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<tr>
<td></td>
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<td>&lt;135 mEq/L and severe hyponatremia as</td>
<td>• Urine sodium &amp; fractional excretion of urine sodium can detect sodium depletion early.</td>
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<td>&lt;120 mEq/L</td>
<td>• Hyponatraemia is a late event during depletion of body sodium (not sensitive)</td>
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<td>Variations to serum Na affected by:</td>
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<td></td>
<td></td>
<td></td>
<td>• Diet (p = 0.008)</td>
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<td>• Climate/temp (p = 0.005)</td>
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<td>Note:</td>
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<td>Infants with CF who are exclusively breastfed or formula fed and living in a high temp environment are ↑ risk hyponatraemia</td>
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<td>• Urine sodium &amp; fractional excretion of urine sodium can detect sodium depletion early.</td>
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<td>• Hyponatraemia is a late event during depletion of body sodium (not sensitive)</td>
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<td>Variations to serum Na affected by:</td>
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<td>• Climate/temp (p = 0.005)</td>
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<td>• Urine sodium &amp; fractional excretion of urine sodium can detect sodium depletion early.</td>
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<td>• Hyponatraemia is a late event during depletion of body sodium (not sensitive)</td>
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<td>Variations to serum Na affected by:</td>
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<td>Appraisers limitations:</td>
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<td>Unable to be applied to general CF population:</td>
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<td></td>
<td>• Infants only</td>
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<td></td>
<td>• All PI</td>
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<td>• Small numbers</td>
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<td>• 1-3g is a large variation and not specified how dose was decided</td>
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<td>• Specific climate in Brazil (warm, humid)</td>
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<td>• No report (no measure) on tolerance, compliance, of salt supplementation + actual intake as other signs/symptoms of depletion</td>
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<tr>
<td>Clinical impact</td>
<td>Satisfactory</td>
<td>The clinical impact is difficult to assess with small and underpowered studies. Safety of high dose sodium supplementation was not assessed.</td>
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</table>
| Generalisability| Satisfactory | • Each study looked at a different age group; infants (0-12 months), children & adolescents (11-20 years) and adults (18 years +).  
• Numbers in each study were small.  
• No study included young children aged 1-10 years. |
| Applicability   | Good         | Climate difference exists between the studies based on location or geography. Not always applicable to the Australian context |
### CLINICAL QUESTION

#### 9.4.2 What is the recommended daily sodium requirement for people with CF?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
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</table>
  - Newly diagnosed CF infants via NBS (and a positive sweat chloride)  
  - All required PERT (low faecal pancreatic elastase < 120ug/g stool).  
Exclusion criteria:  
  - Short bowel syndrome (requiring TPN) | Intervention:  
  Sodium chloride solution 1mmol/ml supplement given, dose 1-2mmol/kg body weight per day.  
Sodium chloride supplement was maintained, increased or reduced according to whether infants had a UNa:Cr ratio within, below or above the target range.  
Sodium chloride solution 1mmol/ml supplement given, dose 1-2mmol/kg body weight per day.  
Outcome:  
  - Sodium supplementation requirements | Results:  
  - All 10 infants required sodium supplementation to achieve urine sodium concentrations >10mmol/l and UNa:Cr ratio > 17 mmol/l.  
  - Mean (range) recommended sodium chloride supplementation:  
    - 0–3 months = 1.9 (1.2–2.6) mmol/kg/d  
    - 3–6 months = 1.8 (0.7–3.6) mmol/kg/d  
    - 6–9 months = 1.9 (0.8–3.0) mmol/kg/d  
    - 9–12 months = 0.8 (0.2–1.5) mmol/kg/d  
  - Requirements decreased at 9-12months as infants took more salt containing solid foods in their diet.  
  - One infant developed mild transient hypernatraemia from extra Na in a reflux medication | Comments:  
  - Hyponatraemia is an insensitive and late sign of sodium depletion  
  - Urine Na:Cr ratio correlates with FENa (compensates for the urinary flow rate)  
  - Salt intake from solids & other Na sources should be assessed  
  - Urine Na should be checked before considering energy supplements.  
  - Further research required |
|                                   |                                  |                                                                  |                                                                                                             |                                                                                         |                                                                          | Author limitations:  
  - No control group without Na supplementation  
  - Small sample size  
  - Choice of target limits for FENa (used to base Na supplementation) was based on limited published data | Appraisers limitations:  
  - Only PI infants                                                                 |
### Chapter 9 Q9.4.2 What is the recommended daily sodium requirement for people with CF compared to those without CF?

**NHMRC Grade for recommendation:** Grade D

**Evidence statement:** There are no randomised control trials and insufficient evidence available to provide specific sodium supplementation doses for people with CF. The evidence refers only to infants; there is no evidence to guide sodium supplementation for the broader paediatric and adult CF population.

| Evidence base | D Poor | One small observational case study  
| Consistency | N/A | Level IV study (n=10 infants, ADA negative) |
| Clinical impact | D Poor | The findings are unlikely to alter current clinical practice. |
| Generalisability | D Poor | CF infants only. Small study size. No pancreatic sufficient patients included in the study |
| Applicability | B Good | The study was conducted in a country with an established health-care system similar to that of Australia |
9.5 Zinc

PICOs

9.5.1 How should Zinc status be assessed for people with CF?
9.5.2 What are the recommendations for zinc supplementation in people with CF?
9.5.3 What is the safe upper limit for zinc supplementation in CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:
- Zinc
  - Cystic fibrosis, CF, nutrition, diet, zinc

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
**CLINICAL QUESTION**

9.5.1 How should zinc status be assessed for people with CF?

**Evidence Table**

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<tr>
<td>Akanli L, Lowenthal D, Gjonaj S, Dozor A. <em>Plasma and Red Blood Cell Zinc in Cystic Fibrosis</em> Pediatr Pulmonol. 2003 Jan;35(1):2-7</td>
<td>NHMRC Level Aetiology IV ADA quality NEUTRAL</td>
<td>Cross sectional N = 53.</td>
<td>Primary Intervention(s): • Non fasting blood samples for plasma and RBC Zn levels</td>
<td>Results: • 16/51 (31%) had low RBC Zn levels compared to 4/40 (10%) with low plasma Zn concentrations (P&lt;0.01) • 13/38 (34%) in whom both values were obtained had low RBC Zn concentrations compared to 4/38 (11%) with low plasma Zn levels (P&lt;0.022) • Neither low RBC nor plasma Zn levels correlated with nutritional status or lung function • No difference in either mean RBC Zn or mean plasma Zn concentrations compared with control means between 2 nutritional status groups</td>
<td>Author limitations: • Samples were not obtained from the study’s own normal control group.</td>
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<td>Secondary Intervention(s): • Relationship of Zn levels to weight (%ideal wt) and FEV1 (%predicted value) • Weight, height, ideal weight for height, intake of Zn in vitamin</td>
<td>Conclusions: • 1/3 CF group had low RBC Zn levels • Plasma Zn concentrations may not reflect overall Zn status. • Deficiency did not appear to be related to nutritional status or lung function. • The significance of low RBC Zn in CF remains unknown</td>
<td>Appraiser limitations: • No information re supplement intake doses • No Ax of diet intake</td>
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<td>Primary Outcomes: • Plasma and RBC Zn levels (non-fasting)</td>
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<td>Secondary Outcomes: • Albumin levels, Hb, mean corpuscular red cell volume (MCV)</td>
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<td>Zinc deficiency defined as: • 2SD below the normal means</td>
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<td>Exclusion criteria: • Known liver dysfunction • Renal failure • Malignancies • Collagen vascular disease • Taking medications known to effect Zn status (eg OCA’s or corticosteroids)</td>
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<td>Inclusion criteria: • Confirmed Dx of CF • Clinically stable for at least 2 weeks • PI • PERT adherence</td>
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<td>CF patients divided into 2 Groups based on nutrition status. • Group 1 normal status &gt;90% ideal weight for height • Group 2 impending or nutritional failure</td>
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<td></td>
<td>Healthy volunteers</td>
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<td>Control group: • Healthy volunteers</td>
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## Evidence Statement Matrix

### Chapter 9 Q9.5.1 How should zinc status be assessed in people with CF?

**Evidence statement:** [Grade D] There are no diagnostic studies addressing this question. Plasma zinc is the most common measure used to assess zinc status.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>D Poor</th>
<th>Only one study includes two measures of assessing zinc status.</th>
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<tbody>
<tr>
<td></td>
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<td>• Level IV cross sectional</td>
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<td>• n=53 people, neutral quality</td>
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<td>Consistency</td>
<td>N/A</td>
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<tr>
<td>Clinical impact</td>
<td>D Poor</td>
<td>Not a diagnostic study so unlikely to change clinical practice.</td>
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<tr>
<td>Generalisability</td>
<td>C Satisfactory</td>
<td>Includes diverse age group, all pancreatic insufficient.</td>
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<tr>
<td>Applicability</td>
<td>D Poor</td>
<td>Red blood cell zinc test not routinely performed in practice. Limited evidence of its use in people with CF.</td>
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</table>
**CLINICAL QUESTION**

9.5.2 What are the recommendations for zinc supplementation in people with CF?

### Evidence Table

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ADA quality POSITIVE | Double-blind randomized placebo-controlled trial.  
n=24 boys | Primary Intervention(s):  
- 30-mg zinc tablets or similar looking placebo tablets daily | Results:  
- No significant difference in the median (IQR) no. of days of antibiotics (over 12 months) (p=0.79):  
  - Treatment group = 42 (14-97) d  
  - Placebo group = 38 (15-70) d  
- No significant differences in the percent-of-predicted FEV1, or change in FEV1 values at 12 months (P = 0.44).  
- Similar pseudomonas isolation rates between the 2 groups.  
- Similar adverse events reported between the 2 groups  
- 15 adverse events or hospitalisations in 13 children all related to PE. | Author Limitations:  
- Underpowered study (sample size too small)  
- The dose of zinc administered may not have been sufficient to have an impact on the outcomes | Appraiser Limitations:  
- A high proportion of children are zinc deficient at baseline and quite a high level of deficiency persists over the 12 months, even despite the intervention of 30mg  
- Not generalizable to the Australian/NZ context  
- All subjects poorly nourished with low BMI  
- No breakdown on percentage of the cohort who were PI vs. PS. |

| Abdualhamid I, Beck FW, Millard S, Chen X, Prasad A. | NHMRC Level II  
ADA quality Neutral | Double blinded randomised controlled trial.  
(pilot study)  
N = 26 (aged 7-18)  
N=13 tX and control groups | Primary Intervention(s):  
- Group A = daily dose of 30 mg of elemental Zn as Zn gluconate (15 mg/capsule).  
Note - all patients on Zn | Results:  
- Less oral antibiotics (days) in Zn group vs. placebo (P = 0.05)  
- Compared to placebo, effect of Zn was greater in pts who exhibited low plasma Zn at baseline (P = 0.025) than those | Author Limitations:  
- Small sample size  
- Large standard deviation for selected parameters | Appraiser Limitations: |
### Inclusion criteria:
- CF confirmation
- Mild to moderate lung disease

### Exclusion criteria:
- Presence of acute severe infection at the time of enrolment
- Renal disease
- Severe hepatic disease
- Gall bladder disease
- Sickle cell disease
- Use of oral immunosuppressive drugs (steroids, NSAIDS), diuretics and/or Zn supplements

Pts were randomly assigned to group A or B for 12 consecutive months.

### Primary Outcomes:
- Ht., wt., no. of hospitalisations, use of oral and IV antibiotics, pulmonary function test, plasma Zn

### Secondary Outcomes:
- Plasma Cu, inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, soluble IL-1 receptor antagonist and soluble TNF-α receptor 1)

### Note assessment of Zn status:
- Adequate Zn status - ≥90ug/dl
- Inadequate zinc status - <89ug/dl or 2SD below normal database of 110+-10ug/dl

Clinically accepted normal range 70-120ug/dl

### Results:
- All CF subjects PI, growth stunted and poor appetite and steatorrhea
- 1yr post Zn supplementation:
  - Serum Zn increased significantly from 63.5 (13.1) to 95.5 (32.0) g/dl (p= 0.003)
  - No. of infections decreased from 3 (1.25) to 2 (2.0) infections/year (p= 0.016)
  - FEV1 increased from 72.0 (38.4) to 76.5 (52)% (p= 0.02)
  - Improved albumin (p<0.01), energy intake (p= 0.02) and appetite (p=0.04).

### Conclusions:
- Inadequate zinc status at baseline followed by Zn supplementation resulted in sig fewer days oral antibiotics for people with CF
- No significant change in inflammatory cytokines between groups
- No change in plasma Zn levels, wt, ht, FEV1 in pts receiving Zn vs. placebo suggests that 30mg Zn/d is an insufficient dose. A dose of 45mg/d Zn was suggested by authors

### Author Limitations:
- The limitation of this retrospective study is the absence of a not treated control population with low serum Zn levels.
- The controls with normal Zn had less severe symptoms.
- Need long-lasting, double-blind, placebo-controlled study and look for the advantages of Zn supplementation in all or only in subgroups of CF patients.
<table>
<thead>
<tr>
<th>Case series with pre-test/post test</th>
<th>NHMRC Level IV</th>
<th>ADA quality NEGATIVE</th>
<th>Inclusion criteria:</th>
<th>N=30 Children (4-16yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion criteria:</td>
<td>Nil stated</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Intervention(s):**
- Elemental Zn 2mg/kg/day for 6 months

**Outcomes:**
- Serum Zn, BMI, FEV1 and number of hospitalisations before and after Zn administration
- Alkaline phosphatase and albumin levels
- Gender, age and hx. of Zn usage

**Results:**
- Height, weight and BMI all increased significantly (P=<0.001)
- BMI increases were only seen in those with BMI between 50th and 75th percentile
- BMI was not increased in those with abnormal pulmonary function
- Only those with normal pulmonary Fx saw an increase in BMI
- Patterns of PFTs were not changed
- Number of hospitalisations decreased significantly (p=0.023)

Note: 76.7% of participants were already taking Zn supplements regularly prior to the study.

**Appraiser Limitations:**
- No info re comorbidities such as CFLD and CFRD
- Statistical analysis unclear
- Unclear if Zn was measured fasting
- Dietary Zn intake was measure but not reported
- Method to assess supplementation adherence not reported

**Author Limitations:**
- Zn supplementation rate prior to the study is high (impacts on baseline Zn levels)
- Plasma Zn is an insensitive measure.
- Lack of control group pre and post study. This limits the validity of the anthropometric outcome measures.
- The Zn supplementation dose or treatment duration may have been inadequate

**Appraiser Limitations:**
- Lack of baseline characteristics reported i.e. gene mutations and CF co-morbidities
Conclusions:
- Supplementary Zn can increase BMI in CF mostly those with normal lung Fx. While Zn may decrease their number of hospitalisations, other factors also influence the hospitalization number.

Author Limitations:
- Not applicable to Aus and NZ context
  - Not specialist CF centre
  - Different socio-economic status
- More males than females in study
- Supplementation adherence rates not reported
- Dietary Zn intake not reported
- Small sample size
- No control group

References:


NHMRC Level IV
ADA quality POSITIVE

Retrospective cross sectional
N = 304 (18-66 years old)

Inclusion criteria:
- Adults (>17yrs) with CF who had their first plasma Zn assessed between 2009 and 2012
- CF confirmed by sweat test and/or genotype
- Good nutritional status and moderate lung disease.

Exclusion criteria:
- Chronic kidney disease undergoing dialysis
- Post lung transplant prior to Zn assessment

Intervention(s):
- Chart review of CF patients.
Data collected included the following:
- Demographics (age, gender), clinical characteristics (genotype, BMI, pancreatic insufficiency, pulmonary function), biochemical parameters (plasma Zn, albumin, total protein, glucose, HbA1c, fructosamine, CRP, retinol, transthyretin, 25-hydroxyvitamin D, alphatocopherol) and co-morbid conditions (diabetes, bone, kidney or liver disease, asthma and exacerbations).

Outcome(s):
- Plasma zinc status
Criteria for normal Zinc Status:
- Lab ref values 9.2-18.4umol/L

Protocol for Zn supplementation at

Results:
- Low plasma zinc concentration was found in 68/304 (22.4%)
- No subjects had plasma Zn above reference range
- Compared to subjects with normal Zn, those with low Zn had significantly lower FVC and FEV1.
- CF adults with low Zn:
  - 72% suffered from bone disease (vs 49% with normal zinc, p = 0.037)
  - 79% had impaired glycemic status (vs 58%, p = 0.016)
- Mean Zn intake (multivitamin + Zn supplement) = 14.5mg
- Correlation Zn with vitamin A and albumin.
- Negative trend between age and Zn

Author Conclusions:
- Nearly 25% of CF adults with good nutritional status and moderate lung disease had low plasma Zn concentration
- Low plasma Zn was associated with worse clinical outcomes (pulmonary function and a higher prevalence of
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>NHMRC Level</th>
<th>ADA Quality</th>
<th>Study Design</th>
<th>Study Centre</th>
<th>Impaired Bone and Glycemic Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akanli L, Lowenthal D,</td>
<td>Aetiology IV</td>
<td></td>
<td>Cross-sectional study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Intervention(s):**
- **Subjects:**
  - Seven-day home-based weighed food and supplement record
- **Controls:**
  - Food and supplement zinc intake data (obtained for healthy age-matched non-Hispanic white American children from the NHANES 1999-2000)

**Anthropometric measures also taken:**
- Growth status (height adjusted for genetic potential (AHAZ), Weight (WAZ), BMI Z scores (BMIZ)

**Outcomes:**
- Fasted plasma zinc.
- Serum alkaline phosphatase and albumin, coefficient of fat absorption (%COA, 72-hour fecal fat)

Note ref range (normal):
- 9.2-15.3umol/L (60-100ug/dL)

**Results:**
- Mean plasma zinc levels:
  - 65% had levels above the study reference range
  - No subjects had low zinc levels.
- Median (range) total daily zinc intake was 279% (83 - 988%) recommended dietary allowance (RDI).
- 2% CF children consumed < EAR for Zn vs. 19% of health controls (P=0.001)
- 64% CF children exceeded the Zn UL vs. 29% of controls (P = 0.003)
- The significantly higher total daily zinc intake of the children with CF was primarily caused by supplemental zinc intake.
- Growth status was suboptimal and forced expiratory volume at 1 second (FEV1) was 92 +/- 13% predicted in the CF cohort
- Plasma zinc was not correlated with growth, pulmonary or alkaline phosphatase status.

**Author Conclusions:**
- Zn intake and plasma zinc status were adequate based on current care in US centres included in study.
- The findings suggest that zinc was not a limiting micronutrient for preadolescent children with CF and PI and mild-to-moderate lung disease, and not likely contributing to their suboptimal growth status.

**Author Limitations:**
- Challenge of Zn as biomarker for Zn status and differing reference ranges
- Only pre-adolescent CF PI children included
- Further research is required to determine the relationship between zinc status and growth during other periods of rapid growth such as infancy and adolescence.

**Appraiser Limitations:**
- Intervening treatments and ancillary factors not reported
| **Gjonaj S, Dozor A.**  
*Plasma and Red Blood Cell Zinc in Cystic Fibrosis*  
Pediatr Pulmonol. 2003 Jan;35(1):2-7 | **ADa quality**  
*NEUTRAL* | **Inclusion criteria:**  
- Confirmed Dx of CF  
- Clinically stable for at least 2 weeks  
- PI  
- PERT adherence  
**Exclusion criteria:**  
- Known liver dysfunction  
- Renal failure  
- Malignancies  
- Collagen vascular disease  
- Taking medications known to effect Zn status (eg OCA's or corticosteroids)  
CF patients divided into 2 Groups based on nutrition status.  
- Group 1 normal status >90% ideal weight for height  
- Group 2 impending or nutritional failure  
Control group:  
- Healthy volunteers | **plasma and RBC Zn levels**  
**Secondary Intervention(s):**  
- Relationship of Zn levels to weight (%ideal wt) and FEV1 (%predicted value)  
- Weight, height, ideal weight for height, intake of Zn in vitamin  
**Primary Outcomes:**  
- Plasma and RBC Zn levels (non-fasting)  
**Secondary Outcomes:**  
- Albumin levels, Hb, mean corpuscular red cell volume (MCV)  
Zinc deficiency defined as:  
- 2SD below the normal means  
**compared to 4/40 (10%) with low plasma Zn concentrations (P<0.01)**  
- 13/38 (34%) in whom both values were obtained had low RBC Zn concentrations compared to 4/38 (11%) with low plasma Zn levels (P<0.022)  
- Neither low RBC nor plasma Zn levels correlated with nutritional status or lung function  
- No difference in either mean RBC Zn or mean plasma Zn concentrations compared with control means between 2 nutritional status groups  
**Conclusions:**  
- 1/3 CF group had low RBC Zn levels  
- Plasma Zn concentrations may not reflect overall Zn status.  
- Deficiency did not appear to be related to nutritional status or lung function.  
- The significance of low RBC Zn in CF remains unknown  
**Appraiser limitations:**  
- No information re supplement intake doses  
- No Ax of diet intake |
| **Van Biervliet S, Van Biervliet JP, Vande Velde S, Robberecht E.**  
*Serum Zinc Concentrations in Cystic Fibrosis Patients Aged Above 4 Years: A Cross-sectional*  
NHMRC Level IV  
**ADA quality**  
*NEUTRAL* | **Cross sectional study with historical control group**  
- n=101 CF  
- n= 174 Controls  
**Inclusion criteria:**  
- Treated during 12 months  
- Not currently on Zn supplementation | **Intervention(s):**  
- Fasting serum Zn measures  
The following also collected:  
- Serum vitamins (vit) A (retinol) and E (α-tocopherol), retinol-binding protein (RBP), albumin, ESR, total IgG, and cholesterol  
- Data on age, weight, height z-score, pancreatic and  
**Results:**  
- Median serum zinc = 82ug/dl, IQR 24  
- No difference in serum Zn concentration between CF patients and controls.  
- Zn levels below reference range:  
  - CF = 16.8%  
  - Healthy controls = 12.6%  
- In CF subjects:  
  - No difference in serum Zn concentration between PI and PS patients  
|  
| **Author Limitations:**  
- Small sample size  
**Appraiser Limitations:**  
- Study population not well described  
- Selection of subjects not well described.  
- No information re dietary Zn supplement intake  
- No record of steatorrhea |
<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Exclusion criteria:</th>
<th>Outcomes:</th>
</tr>
</thead>
</table>
| Biol Trace Elem Res. 2007 Oct;119(1):19-26. | • Nil described | • Fasting serum Zn levels  
• Correlation between serum Zn levels and other data collection measures | - All PS patients had Zn levels in reference range  
• Serum Zn was not associated with nutritional status  
  - No differences in growth or nutrition status those with low vs. high zinc levels.  
• Significant association between serum Zn and serum albumin ($p<0.0005$) and to vit A ($p<0.01$).  
• No associations between serum Zn and serum vit E, RBP, cholesterol, or CFTR.  
• A significant association serum Zn to forced vital capacity ($p<0.01$).  
• Serum Zn was not associated to inflammatory parameters or chronic Pseudomonas infection.  
Conclusions:  
• No difference between CF and controls regarding serum Zn status.  
• A subgroup of CF patients shows marginal serum Zn and could be at risk of its major metabolic consequences  
• Zn supplementation needs to be examined.  
• Association with pulmonary function decreased lung function of the low Zn group needs more investigation. |  
| Lack of detail regarding statistical measures used to determine reported associations |  

**Evidence Statement Matrix**

**Chapter 9 Q9.5.2 What are the recommendations for zinc supplementation in people with CF?**

**NHMRC Grade for recommendation: Grade D**

**Evidence statement:** There is inadequate evidence to assess the need for routine supplementation of zinc in people with CF. There is also inadequate evidence to establish recommendations for the supplement dose required to correct suspected zinc deficiency in CF.
<table>
<thead>
<tr>
<th>Evidence base</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>The evidence from each of the following studies indirectly addresses the PICO.</td>
<td></td>
</tr>
<tr>
<td>4 intervention studies</td>
<td></td>
</tr>
<tr>
<td>• 2 Level II studies</td>
<td></td>
</tr>
<tr>
<td>• n=40 CF children, positive quality</td>
<td></td>
</tr>
<tr>
<td>• n=26 CF children &amp; adolescents, neutral quality</td>
<td></td>
</tr>
<tr>
<td>• 2 Level IV studies</td>
<td></td>
</tr>
<tr>
<td>• n= 21 CF children, neutral quality</td>
<td></td>
</tr>
<tr>
<td>• n= 30 CF children, negative quality</td>
<td></td>
</tr>
<tr>
<td>4 level cross-sectional studies</td>
<td></td>
</tr>
<tr>
<td>• 4 Level IV studies</td>
<td></td>
</tr>
<tr>
<td>• n=62 children, positive quality</td>
<td></td>
</tr>
<tr>
<td>• n=101 children, neutral quality</td>
<td></td>
</tr>
<tr>
<td>• n= 53 children and adults, neutral quality</td>
<td></td>
</tr>
<tr>
<td>• n=304 adults, positive quality</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inconsistent relationships between deficient/suboptimal zinc status and clinical outcomes (nutritional, pulmonary, infection).</td>
<td></td>
</tr>
<tr>
<td>• Variable evidence of the effects of zinc supplementation on functional outcomes.</td>
<td></td>
</tr>
<tr>
<td>• Inconsistencies in evidence complicated by the variations in the cutoffs used to define zinc status; measures used to assess adequacy of diet intake; in the type, amount and frequency of zinc supplementation; in the outcomes measured; and variability in the baseline prevalence of zinc deficiency.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Indirect evidence only.</td>
<td></td>
</tr>
<tr>
<td>• Intervention studies with small sample sizes and likely underpowered.</td>
<td></td>
</tr>
<tr>
<td>• Variability in the baseline prevalence of zinc deficiency made it difficult to detect consistent changes due to zinc supplementation.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Studies mostly relevant to children.</td>
<td></td>
</tr>
<tr>
<td>• Only one study with data available for adults and no studies with available data for infants alone</td>
<td></td>
</tr>
<tr>
<td>• No Australian/NZ studies</td>
<td></td>
</tr>
<tr>
<td>• Two studies in predominantly malnourished populations and are poorly generalisable to Australian/NZ context.</td>
<td></td>
</tr>
<tr>
<td>• Mostly pancreatic insufficient patients, with mild-moderate lung function, without liver disease or diabetes and with variable nutrition status.</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Studies conducted mostly in the US and also in Belgium, Canada, India and Iran.</td>
<td></td>
</tr>
<tr>
<td>• Variations between countries in zinc bioavailability of dietary sources, the fortification of foods with zinc and the recommended dietary intakes.</td>
<td></td>
</tr>
<tr>
<td>• Differences in zinc supplements available and the type and amount of zinc included in CF and general multivitamin supplements.</td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL QUESTION

9.5.3 What is the safe upper limit for zinc supplementation for people with CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.
Chapter 10  Pancreatic Insufficiency and PERT

PICO

Q10.1.1 Does gastric emptying rate impact PERT efficacy in people with CF?
Q10.1.2 Does the timing of PERT administration in relation to a meal impact PERT efficacy in people with CF?
Q10.1.3 How should PERT be dosed for people with CF to support optimal fat absorption?
Q10.1.4 Is there evidence to support the use of acid suppression medication to improve PERT efficacy for individuals with CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:
- PERT
  - Cystic fibrosis, CF, pancreatic exocrine insufficiency or pancreatic enzyme replacement therapy

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
CLINICAL QUESTION
10.1.1 Does gastric emptying rate impact on the efficacy of PERT in CF?

Evidence table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
</table>
ADA: Neutral | Randomised double blinded placebo controlled cross-over trial  
N=10 children with CF  
N=12 healthy controls | Intervention:  
• Pancreatic lipase function was assessed with the C-MTG breath test.  
• Pts with CF had 2 C-MTG breath tests, double blinded on separate days, omitting their usual intake of PERT.  
• After a baseline breath sample 8 pancrease or placebo were taken with a test meal of 15g fat and 2 x 100mg of C-MTG capsules.  
• Breath samples were collected pre meal, and at 30 min intervals until 360 min after the meal.  
• Gastric emptying rates were assessed with the C-octanoic acid breath test. Following baseline breath samples, a test meal of 15g fat & 100uL C-octanoic acid was consumed. Usual quantity of PERT given. Breath samples were collected every 5-30min until 480min.  
Outcomes:  
• Relationship between pancreatic lipase activity and gastric emptying | Results:  
• No differences between the gastric emptying rates of pts with CF and healthy control subjects; however, the improvement in pancreatic lipase activity with PERT is reduced in pts with slow gastric emptying, which could explain the variations in improvement of fat digestion with enzyme supplementation.  
Conclusions:  
• If PERT is taken before each meal & snack there may be a mismatch between the gastric emptying of food & supplements.  
• In pts in whom PERT is unsuccessful it may be worth assessing gastric emptying first. If delayed GE diagnosed timing of PERT could be shifted to throughout or toward the end of the meal. | Author limitations:  
• C-MTG breath test can be expensive for those centres without a isotope ration mass spectrometer.  
Appraiser limitation:  
• Small sample size |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NHMRC level:</td>
<td>II</td>
</tr>
<tr>
<td>ADA: Positive</td>
<td></td>
</tr>
<tr>
<td>Randomised, double blind crossover trial.</td>
<td>n=18 CF children (5-17yrs)</td>
</tr>
</tbody>
</table>
| **Inclusion criteria:** | • Confirmed CF  
• PI  
• Stable dose of PERT with satisfactory symptom control within current recommendations (500-4000IU/g fat ≥ 6months)  
• Nil change re dose during study |
| **Exclusion criteria:** | • Severe pulmonary disease  
• Previous GI surgery or meconium ileus  
• Enteral nutrition  
• Medication affect GI motility |
| **Primary intervention:** | • $^{13}$C-mixed triglyceride ($^{13}$C-MTG) breath test to assess pancreatic lipase activity when Creon (1333IU/g fat) given 10min prior to test meal vs. 10min after test meal.  
• Breath samples taken before meal & at 30min intervals for 360min |
| **Secondary intervention:** | • $^{13}$C-octanoate breath test to assess gastric emptying  
• Breath samples taken before meal & at 15min intervals for 120mins then 30min intervals for 240mins  
• Light, low fat meal offered at 240min mark |
| **Primary outcome:** | • Timing of PERT on lipase activity |
| **Secondary outcome:** | • Effect of gastric emptying on lipase activity |
| **Results:** | **Primary** | • No significant difference in PCDR with PERT before (32.5±10%) or after meal (31.2±13.7%) at 360min (p=0.68).  
• When PERT was taken after a meal, PCDR was higher in normal vs. fast GE (p=0.04)  
**PCDR = percentage cumulative dose recovered** |
| **Secondary** | • 6/18 accelerated gastric emptying (37.3±5.4min)  
• 11/8 normal gastric emptying (55.7±15.2min)  
• 1/18 delayed gastric emptying (121.5min) |
| **Conclusions:** | • No significant difference in mean PCDR of $^{13}$C-MTG with PERT before or after meal in those with accelerated (p=0.06) or normal (0.31) gastric emptying  
• No correlation between gastric half emptying time and PCDR when PERT taken before (r= -0.29, p=0.24) vs. after (4=0.05, p=0.85) meal |
| Author limitations: | • Small sample size (unable to do sub-group analysis)  
• No concurrent control  
• Unable to assess intra-individual variability in results ($^{13}$C-MTG only taken once at each time point) |
| Appraiser limitations: | • Patients recruited as inpatient or outpatient  
- No mention of if study was done in inpatient or outpatient setting  
- Potential impact of being unwell if done in inpatient setting  
• Children only (no young children/infants or adults) |
**Evidence Statement Matrix**

**Chapter 10 Q10.1.1 Does gastric emptying rate impact PERT efficacy in people with CF?**

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** Limited evidence suggests that gastric emptying rate may have an impact on PERT efficacy in individuals with CF. Limited evidence suggests that those with fast gastric emptying may benefit from taking enzymes before a meal. This evidence refers to children only.

| Evidence base | B Good | Two randomised crossover studies with a small sample size  
|               |       | - One level II study – randomised cross-over trial (n=18 children; ADA positive)  
|               |       | - One level II study – double blind randomised placebo-controlled crossover study (n=10 children; ADA neutral) |

| Consistency   | B Good | Relatively good consistency between studies. 2 randomised control trials showed correlation between gastric emptying time and lipase activity  
|               |       | - One study found that when PERT was taken after a meal, lipase activity as measured by a breath test was higher in those with normal versus fast gastric emptying  
|               |       | - One study found a negative correlation between gastric emptying time and improvements in lipase activity as measured by a breath test |

| Clinical impact | B Good | Relevance of the evidence to the clinical question is satisfactory. Unlikely any risks to changing timing of enzymes based on gastric emptying rate |

| Generalisability | C Satisfactory | Studies included children only |

| Applicability    | B Good      | PERT is readily available in Australia and NZ although less preparations are available, when compared to the European and US market |
## Clinical Question

10.1.2 Does PERT timing impact PERT efficacy in CF?

### Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Haak N, Boase J, Davidson G, Butler R, Miller M, Kaambwa B, et al. Preliminary report of the C mixed triglyceride breath test to assess timing of pancreatic enzyme replacement therapy in children with cystic fibrosis. J Cyst Fibros. 2016</td>
<td>NHMRC level: II ADA: Positive</td>
<td>Randomised, double blind crossover trial. n=18 CF children (5-17yrs)</td>
<td>Aim to determine if PERT given after a meal, instead of before a meal, could result in improved lipase activity in CF children.</td>
<td>Results: <strong>Primary</strong>&lt;br&gt;• No significant difference in PCDR with PERT before (32.5±10%) or after meal (31.2±13.7%) at 360min (p=0.68).&lt;br&gt;• When PERT was taken after a meal, PCDR was higher in normal vs. fast GE (p=0.04)&lt;br&gt;<strong>PCDR = percentage cumulative dose recovered</strong>&lt;br&gt;<strong>Secondary</strong>&lt;br&gt;• 6/18 accelerated gastric emptying (37.3±5.4min)&lt;br&gt;• 11/8 normal gastric emptying (55.7±15.2min)&lt;br&gt;• 1/18 delayed gastric emptying (121.5min)&lt;br&gt;• No significant difference in mean PCDR of (^{13})C-MTG with PERT before or after meal in those with accelerated (p=0.06) or normal (0=0.31) gastric emptying&lt;br&gt;• No correlation between gastric half emptying time and PCDR when PERT taken before (r= -0.29, p=0.24) vs. after (4=0.05, p=0.85) meal</td>
<td>Author limitations:&lt;br&gt;• Small sample size (unable to do sub-group analysis)&lt;br&gt;• No concurrent control&lt;br&gt;• Unable to assess intra-individual variability in results ((^{13})C-MTG only taken once at each time point)&lt;br&gt;Appraiser limitations:&lt;br&gt;• Patients recruited as inpatient or outpatient&lt;br&gt;  - No mention of if study was done in inpatient or outpatient setting&lt;br&gt;  - Potential impact of being unwell if done in inpatient setting&lt;br&gt;• Children only (no young children/infants or adults)&lt;br&gt;Secondary intervention:&lt;br&gt;• (^{13})C-octanoate breath test to assess gastric emptying&lt;br&gt;• Breath samples taken before meal &amp; at 15min intervals for 120mins then 30min intervals for 240mins&lt;br&gt;• Light, low fat meal offered at 240min mark&lt;br&gt;Primary outcome:&lt;br&gt;• Timing of PERT on lipase activity&lt;br&gt;Secondary outcome:</td>
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<td></td>
<td></td>
<td>Inclusion criteria:</td>
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<tr>
<td></td>
<td></td>
<td>• Confirmed CF&lt;br&gt;• PI&lt;br&gt;• Stable dose of PERT with satisfactory symptom control within current recommendations (500-4000IU/g fat ≥6months)&lt;br&gt;• Nil changes re dose during study</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Exclusion criteria:</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• Severe pulmonary disease&lt;br&gt;• Previous GI surgery or meconium ileus&lt;br&gt;• Enteral nutrition&lt;br&gt;• Medication affect GI motility</td>
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</tbody>
</table>

** Comments:**
- No significant difference in PCDR with PERT before (32.5±10%) or after meal (31.2±13.7%) at 360min (p=0.68).
- When PERT was taken after a meal, PCDR was higher in normal vs. fast GE (p=0.04)
- 6/18 accelerated gastric emptying (37.3±5.4min)
- 11/8 normal gastric emptying (55.7±15.2min)
- 1/18 delayed gastric emptying (121.5min)
- No significant difference in mean PCDR of \(^{13}\)C-MTG with PERT before or after meal in those with accelerated (p=0.06) or normal (0=0.31) gastric emptying
- No correlation between gastric half emptying time and PCDR when PERT taken before (r= -0.29, p=0.24) vs. after (4=0.05, p=0.85) meal
**Evidence Statement Matrix**

<table>
<thead>
<tr>
<th>Chapter 10 Q10.1.2</th>
<th>Does the timing of PERT administration in relation to a meal impact PERT efficacy in people with CF?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHMRC Grade for recommendation:</strong></td>
<td><strong>Grade D</strong></td>
</tr>
<tr>
<td><strong>Evidence statement:</strong></td>
<td>Limited evidence suggests that PERT is equally effective in achieving normal lipase activity when taken before or after a meal in individuals with CF. Limited evidence suggests that changing PERT timing in relation to a meal on an individual basis may improve or normalise lipase activity in individuals with CF. This evidence refers to children only. Further research is required.</td>
</tr>
<tr>
<td>Evidence base</td>
<td>D Poor</td>
</tr>
<tr>
<td>Consistency</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>B Good</td>
</tr>
<tr>
<td>Generalisability</td>
<td>C Satisfactory</td>
</tr>
<tr>
<td>Applicability</td>
<td>B Good</td>
</tr>
</tbody>
</table>
**CLINICAL QUESTION**

10.1.3 How should PERT be dosed for people with CF to optimise fat absorption?

### Evidence table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Littlewood JM, Connett GJ, Sander-Struckmeier S, Henniges F. A 2-year post-authorization safety study of high-strength pancreatic enzyme replacement therapy (pancreatin 40,000) in cystic fibrosis. Expert Opinion on Drug Safety. 2011;10:197-203 | NHMRC Level IV ADA Quality: NEUTRAL | Observational, non-interventional study, single arm study N=64 CF patients with PI (mean age 20.7) | Intervention:  
  • Change to pancreatin 40,000 capsules from lower dose preparation  
Outcomes:  
  • Serious suspected adverse drug reactions including fibrosing colonopathy  
  • Maldigestion symptoms, body weight | Results:  
  • No serious suspected adverse drug reactions related to pancreatin 40000  
  • No cases of fibrosing colonopathy.  
  • Mean number of capsules taken per individual per day was notably reduced from 43.8 lower strength capsules to 24.6 of 40000IU capsules (as expected).  
  • 3 subjects discontinued Pancreatin 40000 due to ‘mild stomach ache/abdominal pain’ or ‘bowel did not settle.’  
  • Overall 36% patients had an increase in average daily lipase dose at last visit vs baseline & 55% had a decrease in average daily lipase dose.  
  • Percentage of patients with abdominal pain reduced- 24.2% at baseline to 10.7% at the end of the study.  
  • Percentage of patients with fatty stools reduced from 30.2% at baseline to 8.9% at the end of the study  
  • Mean body weight increased for patients <18 years of age, but remained stable in >18 years of age.  
  Conclusions:  
  • No safety concerns arose during this study in which most patients received doses of >10,000 lipase units per kg/day for 18 months | Author limitations:  
  • Due to observational study design with no control or comparison group it is not possible to determine what proportion of improvement in mal-digestion symptoms was due to pancreatin 40000 vs other factors.  
  • Symptom improvement may be due to improved compliance due to increased monitoring during the study period.  
  • Not possible to determine how much weight gain was due to growth in subjects <18 years of age, rather than the pancreatin 40000. Conversely a portion of patients had a reduction in body weight, and the reasons for this cannot be determined as this study did not collect info such as pulmonary fx.  
  • Limited sample size  
  Appraiser limitations:  
  • Non-serious drug reactions were not recorded or reported as part of this study.  
  • Outcome measures of malabsorption and weight are poorly described, subjective |
| Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K, Caras S. Efficacy and safety of Creon 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. Journal of Cystic Fibrosis. 2009;8:370-7 | NHMRC Level II | Double blind randomised placebo controlled two period crossover trial N=31 Males & females with CF | Primary objective of the study was to demonstrate superior efficacy of Creon over placebo in improving fat absorption as measured by the CFA. Intervention: • An individualised diet providing at least 100g/day was provided during days 1 to 5 of the crossover period. • Subjects were randomised 1:1 to one of two crossover treatment sequences: Creon then placebo or placebo then Creon. Creon 24000 capsules were administered to achieve a dose of 4000 IU lipase/ g fat. A "washout" period of 3 to 14 days separated the study periods when subjects had usual diet & enzymes. Blinding was maintained by provision of identical capsules and packaging for placebo and Creon. Outcome: • Efficacy and safety of Creon 24000 Results: • Mean CFA was significantly greater with Creon 88.6% than placebo 49.6% p<0.001. Conclusions: • The data in this study provide strong evidence for the effectiveness of Creon 24000 capsules at a dose of approx. 4000 lipase units/ fat in treatment of EPI in CF. | measures and prone to bias/ error etc • This study only looked at subjects who required ‘high doses’ of lipase (>40000IU/meal). | Author limitations: • The relatively high dose of 4000IU lipase/ g fat chosen together with dosing per gram of fat may not be easily compared with dosing practices commonly used in the clinical setting. • Lack of dose response data for PERT • CFA is not routinely determined in clinical practice • Short term duration of the study does not allow conclusions regarding long term tolerability or symptomatology Appraiser limitations: • Creon 24000 not a product available in Aust or NZ. • Placebo was not clearly defined, was difficult to tell if it was no enzyme or usual enzyme. • Funding & design of study is an obvious conflict of interest. |
| Konstan MW, Liou TG, Strausbaugh SD. Randomised, placebo controlled study with crossover design | NHMRC Level II | Randomised, placebo controlled study with crossover design | Intervention: • Dietitian developed, individualised high fat diet (2g | Results: • Patients treated with pancrealipase had significantly higher mean CFA% than | Author limitations: • Only limitation vaguely stated was short treatment period |

Inclusion criteria:
- PI confirmed by faecal Elastase
- Clinically stable at study entry
- Taking optimal doses of PERT product
- Adequate nutrition status per BMI cut-offs specified
- Able to swallow, able to eat high fat diet
- On birth control
- Ok to be on PPI or H2 therapy
- Informed consent.

Exclusion criteria:
- Known hypersensitivity to Ultrase MT or porcine proteins.
- Allergy to stool marker.
- Use of narcotics
- Regularly taking bowel stimulants
- Hx of bowel resection or portal HT.
- Acute pulmonary exacerbation, pancreatitis, GI conditions, uncontrolled DM, DIOS or any other conditions known to increase faecal fat loss.

Primary Outcomes:
- Stools collected- frequency and characteristics recorded by study personnel.
- 72hr faecal fat completed- The CFA%, CAN% calculated using fat and nitrogen content of stool & food.
- Adverse events (AE) assessed and recorded using MedDRA codification.

Secondary outcomes:
- Medical, physical, biochemical Ax- pre, during and post study.

Results:
- 76% of patients achieved a CFA% of >85% when treated with pancrealipase compared with 19% of placebo treated patients.
- Absorption of proteins measured by CAN% showed similar results. P=<0.00001 for the pancrealipase group.
- Patients treated with pancrealipase had reduced number of bowel movements per day compared with placebo- 1.7 vs 2.9 normal stool consistency movements respectively (statistical analysis not performed)
- 6 patients reported at least 1 treatment related AE on pancrealipase compared to 18 patients while on placebo. Most AEs were GI and consistent with CF. No clinically significant effects of treatment were noted physically, on labs or vital signs.

Conclusions:
- This pancrealipase (Ultrase MT with HP-55 coating, rather than Eudragit) is a safe and effective treatment for malabsorption associated with PEI.

Kashirskaya NY, Kapranov NI, Sander- NHMRC Level IV

Prospective open label multicentre study

Intervention:
- Creon micro administered at a dose of 5000 lipase units per

Results:
- Adverse events occurred in 40% of subjects- none were serious or led to

Author limitations:
- Difficulties measuring height
- Open –label study design
<table>
<thead>
<tr>
<th>Struckmeier S, Kovalev V.</th>
<th>ADA Quality: Neutral</th>
<th>N=40 children with CF</th>
<th></th>
<th>Conclusion:</th>
<th>Creon micro was well tolerated. Growth parameters increased over the 3 month treatment period owing to good intervention from CF Foundation guidelines.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety and efficacy of Creon Micro in children with exocrine pancreatic insufficiency due to cystic fibrosis. Journal of Cystic Fibrosis. 2015;14:275-81</td>
<td></td>
<td>Inclusion criteria:</td>
<td>1 month to &lt;4 years with EPI</td>
<td>Outcomes:</td>
<td>Safety- measured by AE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accessing eight centres in Russia between June and Dec 2012.</td>
<td></td>
<td></td>
<td>Efficacy Ax- height and body weight at baseline, month 1 and month 3 and compared with standard population using percentiles/z-scores. Stool frequency and consistency measures were also measures.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclusion criteria:</td>
<td>Intestinal/bowel resection/solid organ transplant impacting bowel</td>
<td></td>
<td>Acceptance of treatment and ease of use- using Likert scale for subjects and ease of use as per caregiver.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DIOS, GI malignancy, hx of fibrosing colonopathy</td>
<td></td>
<td>Results:</td>
<td>At 3 month mark, mean +/- SD increases from baseline z-scores were height for age 0.13 +/- 0.48, weight for age 0.2 +/- 0.39 and BMI for age 0.29 +/- 0.65.</td>
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<td></td>
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<td>120mL of formula or breastfeeding, or 1000 lipase units/Kg body weight/meal, according to the CF Foundation Guidelines.</td>
<td>Conclusions:</td>
<td>Treatment was rated easy by 95% of caregivers and acceptance by subjects was good/very good by 90%.</td>
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<tr>
<td></td>
<td></td>
<td>Creon micro given with liquid with pH &lt;5.5 or by adding it to acidic soft food.</td>
<td></td>
<td>Limitations (author noted)</td>
<td>Lack of placebo/control group</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Short study duration</td>
</tr>
<tr>
<td>Borowitz D, Goss CH, Stevens C, Hayes D, Newman L, O’Rourke A, et al.</td>
<td>NHMRC Level IV</td>
<td>Open label multicentre dose ranging study</td>
<td>N=23 subjects from 11 different centres (ages 13-45 years)</td>
<td>Results:</td>
<td>TCT increased the CFA of fat and nitrogen absorption in all groups except in the low dose group. At other dosing levels, the mean CFA and nitrogen absorption increases were 19.1% ± 24.9% and 17.8% ± 13.6% respectively whereas the mean stool weight decreased by 517 ± 362g.</td>
</tr>
<tr>
<td>Safety and preliminary clinical activity of a novel pancreatic enzyme preparation in pancreatic insufficient cystic fibrosis patients. Pancreas.</td>
<td>ADA Quality: Neutral</td>
<td>Intervention:</td>
<td>Subjects admitted to hospital discontinued usual PERT. Subjects received TCT containing lipase dose of 100, 500, 1000, 2500 or 5000 USP U/kg with each meal and snack for 3 days. 72hr 100g fat/ day diet, nil PERT, stool collected and measured. Within 14 days admitted to hospital routine. CFA was measured.</td>
<td>Conclusions:</td>
<td>TCT was well tolerated in this short term exposure study. The preliminary efficacy data demonstrate lipase and protease activity with little difference seen with lipase doses greater than 500USP U/kg per meal.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary outcomes:</td>
<td>To determine the acute safety and tolerability of 5 dose levels of TCT (TheraCLEC-Total), a cessation of treatment</td>
<td></td>
<td>Author limitations:</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Treatment CFA was lower than previous reports in the literature, authors cited precise methodology may have contributed to this.</td>
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<td></td>
<td>Subjects were instructed to take their complete dose of TCT enzymes within 5 minutes of the start of each meal – this may have resulted in less than optimal mixing of enzymes with food.</td>
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<td></td>
<td>Appraiser limitations:</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Small numbers, n = 23 not powered for formal statistical</td>
</tr>
<tr>
<td>Year</td>
<td>Study Design</td>
<td>Inclusion Criteria</td>
<td>Intervention</td>
<td>Limitations (author noted)</td>
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</table>
| 2006;32:258-63 | Open label multi centre single treatment arm study | - Children with CF and EPI
- 1 month - <7 years
- Accessing 9 centres across the US from April 2009 – June 2009 with weight >3.75Kg
- Already on a commercially available PERT with stable clinical condition | - Study drug given as 3000-, 6000-, and 12000- lipase unit capsules and the correct number of capsules to be consumed was calculated to provide 8000 lipase unit/Kg body weight/day without exceeding the max lipase dose of 10000 lipase units /Kg body weight/day. Patients on a higher dose before study, continued on higher dose (n?).
- According to CF consensus CF guidelines | - Patients received a mean +/- SD dose in lipase units/Kg bodyweight/day of 7542 +/- 1335 vs 6966 +/- 3392 on standard therapy.
- 50% patients has AEs but were mild but did not require cessation
- Clinical symptom assessment results were similar between treatments
- Slight preference for study drug over standard therapy with ease of accurate dosing- 33.3% caregivers thoughts study drug was easier, 5.6% thought study drug was harder |

| Borowitz D, Goss CH, Limauro S, Konstan MW, | Randomised, double blind, parallel dose-ranging study | | | | |

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Results</th>
<th>Author limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010;30:351-64</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Author limitations</th>
<th>Appraiser limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Small sample size</td>
<td>- Bias in choosing patients who would finish study etc.</td>
</tr>
<tr>
<td>- Lack of placebo/control group</td>
<td>- Lung function was not acknowledged – how severe a disease did this patients have/admissions and this may effect growth</td>
</tr>
<tr>
<td></td>
<td>- Short study duration</td>
</tr>
</tbody>
</table>

| Borowitz D, Goss CH, Limauro S, Konstan MW, | Randomised, double blind, parallel dose-ranging study | | | |

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Results</th>
<th>Appraiser limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010;30:351-64</td>
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</tbody>
</table>

<p>| Appraiser limitations | |
|-----------------------| |
| - Short duration - only for 28 days | |</p>
<table>
<thead>
<tr>
<th>Blake K, Casey S, et al.</th>
<th>ADA Quality: <em>Positive</em></th>
<th>N=117</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td></td>
<td></td>
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<tr>
<td>• CF &amp; PI</td>
<td></td>
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<tr>
<td>• Had baseline coefficient of fat (CFA) and coefficient of nitrogen absorption (CAN) determined in inpatient setting while not receiving PERT</td>
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<td></td>
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<tr>
<td><strong>Exclusion criteria:</strong></td>
<td></td>
<td></td>
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<tr>
<td>• Nil stated</td>
<td></td>
<td></td>
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<tr>
<td>PERT. They were then randomised to treatment with ALTU-135 continuing 5000 (low), 25,000 (mid) or 100,000 (highest) units of lipase per meal or snack for 28 days. After 14 days CFA and CNA were re-measured.</td>
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<tr>
<td><strong>Outcomes:</strong></td>
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<tr>
<td>• The primary outcomes were change from baseline in CFA and CAN treatments.</td>
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<tr>
<td>and 100000 units of lipase groups compared to 5000 group.</td>
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<tr>
<td>• Findings for coefficient of nitrogen absorption were similar.</td>
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<tr>
<td>• Subjects with baseline coefficient of fat absorption &lt;40% and &gt;40% in the 25000 and 100000 groups had a mean increase of 31 and 8 percentage points in coefficient in fat</td>
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<tr>
<td><strong>Conclusions:</strong></td>
<td></td>
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<tr>
<td>• ALTU-135 was efficacious during the 1 month period at the dose of 25000 units of lipase</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Van De Vijver E, Desager K, Mulberg AE, Staelens S, Verkade HJ, Bodewes FA, et al.</th>
<th>NHMRC Level III-3</th>
<th>ADA Quality: <em>Positive</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of infants and toddlers with cystic fibrosis-related pancreatic insufficiency and fat malabsorption with pancrelipase MT. Journal of Pediatric Gastroenterology and Nutrition. 2011;53:61-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td></td>
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<tr>
<td>• CF confirmed by genetic testing or abnormal sweat test combined with clinical signs.</td>
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<tr>
<td>• All subjects had a documented history of abnormal coefficient of faecal fat absorption (CFA) or lower than 15µg faecal elastase per gram, confirming a diagnosis of CF-related PI.</td>
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<tr>
<td><strong>Intervention:</strong></td>
<td></td>
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<tr>
<td>• Use of pancrease MT (pancrelipase microtablets, 2mm, enteric coated) orally</td>
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<tr>
<td>• Run in period (Day 1 – 5) where participants received 500U lipase/kg/meal at a maximum of 5 times per day</td>
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<tr>
<td>• Randomisation period (days 6 – 11) where participants were randomised to receive 500, 1000, 1500, 2000U lipase/kg/meal</td>
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<tr>
<td>• Study visits were conducted on day 1, day 6 and day 11.</td>
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<tr>
<td>• A carton was dispensed to the parent or guardian at visits 1 and 2 and contained 6 bottles of study medication. Each bottle contained 5 capsules. Each capsule contained the meal – specific dose required for each dose group and the appropriate number of</td>
<td></td>
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<tr>
<td><strong>Results:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
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</tr>
<tr>
<td>• Compliance, defined as use of the study medication, was 89 – 99%</td>
<td></td>
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<tr>
<td>• The changes in median weight from screening to the end of the study were 0.05kg (-1 to 0.2) in the 500U group, 0.0kg (-0.1 – 0.7) in the 1000U group, -0.05kg (-0.2 – 0.1) in the 1500U group and 0.15kg (-0.3 – 0.5) in the 2000U group.</td>
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<tr>
<td>• At the time of randomisation, the median CFA of fat was 93% (91-96) in the 500U group, 90% (85 – 95) in the 1000U group, 83% (67-93%) in the 1500U group and 92% (90 – 96) in the 2000U group.</td>
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<tr>
<td>• None of the 4 doses influenced the CFA relative to the baseline period.</td>
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<tr>
<td>• During the run in period the median cumulative % $^{13}$C was 11 (-8 – 59). After randomisation the median cumulative % $^{13}$C was 18 (14 – 23) in the 500U group, 14 (-1 – 17) in the 1000U group, 10 (10 –</td>
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</tbody>
</table>

| Author limitations: |
| • Large variation in results could be caused by a wide range of underlying residual endogenous lipase activity and perhaps insufficient breath sampling. |

| Appraiser limitations: |
| • Small sample size |
| • Inadequate recording of oral intake/ fat intake |

| Unclear how adherence was measured |
| Timing of PERT not defined |
Exclusion criteria:
- Nil stated
- Microtablets for the subjects weight in kilograms with a maximum of 10,000U lipase/kg/day.
- Parents were instructed to record in a diary the date, time and amounts of all foods and formula consumed and date and time of study medications.
- Patients had to maintain a defined diet containing 125 – 150% of the recommended daily allowance appropriate for patients with CF.

Primary outcome:
- Medication efficacy, assessed by 72 hour faecal fat exertion, expressed as a coefficient of faecal fat absorption (CFA) and $^{13}$C mixed triglyceride breath test.

Secondary outcome:
- Safety and palatability

27) in the 1500U group, and 3 (1 – 49) in the 2000U group.

Secondary outcome
- The mean palatability score was 2.8 during the run in period (range 0 -3) and 2.6 (range 0.3 – 2.8) during the randomisation period. Mean scores >2 were observed in the 500U, 1000U and 1500U group. The 2000U group scored 1.8.
- Gastrointestinal symptoms were reported in some patients – 3 adverse events were reported in 18 enrolled subjects (17%) during the run in period and 4 events during randomisation. During run in complaints were diarrhoea (1), vomiting (1), and rhinitis (1). In the 500U group complaints were abdominal pain (1), abnormal stools (1) and increased bowel movements (1). One patient randomised to 1000U group had constipation. In the 2000U group there was one event of vomiting and 1 of rhinitis.

Conclusions:
- Pancrease MT at a dose of 500IU lipase/kg/meal resulted in a CFA of approximately 89% in the population studied.
- Doses were well tolerated and palatability was rated fair to good.
- Increasing the dose higher than 500IU lipase/kg/meal does not increase the coefficient of fat absorption.
- In this study, there was a large variation in cumulative $\%$ $^{13}$C with the median cumulative $^{13}$C in the 500U and 1000U groups in the low – normal range and the median cumulative $^{13}$C in the 1500U group.
| Konstan MW, Stern RC, Trout JR, Sherman JM, Eigen H, Wagener JS, et al. | Ultrase MT12 and ultrase MT20 in the treatment of exocrine pancreatic insufficiency in cystic fibrosis: Safety and efficacy. Alimentary Pharmacology and Therapeutics. 2004;20:1365-71 | Randomized double blind placebo controlled crossover study | Intervention: The study compared two doses of one formulation of enteric-coated pancreatic enzymes: Ultrase MT12 (12 000 lipase units per capsule) and Ultrase MT20 (20 000 lipase units per capsule), to placebo in two separate safety and efficacy studies. The Pt took a high fat diet, the enzyme dose did not exceed 2500 IU of lipase per KG per meal. Primary outcome - was percent absorption of dietary fat, Secondary outcome - absorption of protein, Safety was assessed by laboratory values, vital signs and adverse events. | Results: A significant difference in both fat and protein absorption occurred with the enzyme therapy groups. The Ultrase MT12 and Ultrase MT20 groups experienced a mean fat and protein absorption 79.4% and 83.8%, and 87.3% and 88.6%, respectively, there was a significant difference in both fat (P = 0.0001) and protein (P = 0.0001) absorption between enzyme and placebo groups, with more fat and protein being absorbed in the enzyme group No adverse events related to study drug were reported. | Conclusion: The enzymes significantly increased fat and protein absorption. There were no major adverse events as a result of enzyme therapy. | NHMRC Level II | ADA Quality: Positive | Author limitations: Short time period. A longer period of reporting could potentially provide long term evidence of safety and efficacy. Appraiser limitations: Nil |

| Trapnell BC, Strausbaugh SD, Woo MS, Tong SY, Silber SA, | Randomised, placebo controlled PERT withdrawal study | Intervention: Usual PERT was discontinued, a high fat diet initiated (100g fat/day) and Pancrease | Results: Pancrease improved fat absorption as shown by significantly lower mean + SD change in CFA between open label and | Author limitations: The dose used in the study limits generalisation of the recommendations made with | NHMRC Level II | ADA Quality: |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Positive          | n=49                                                                                                                                |
| Inclusion criteria: | • Males & females aged 7 to 60 years with CF & PI                                                                                  |
| Exclusion criteria: | • Exacerbation of CF • DIOS • Clinically significant GI symptoms                                                                    |
| administered based on patients usual lipase requirements, to a maximum of 10000 IU lipase/kg/day. The average daily dose of lipase during open label & double blind phases (6274 & 6403 iu/kg/d). |
| Primary outcomes: | • 72hr stool collection under supervision in clinical research unit and day 3 & 6 of treatment.                                   |
|                    | - Weighed and analysed for fat & nitrogen using NMR spectroscopy. CFA & CAN calculated.                                            |
| Secondary outcomes: | • Drug taken, stool characteristics recorded in subject diary                                                                   |
|                    | • Adverse event information collected during each study visit.                                                                       |
| Results:           | double blind phases for Pancrease (-1.5 + 5.88%; p<0.001) compared to placebo (-34.1 + 23.03%).                                    |
| Conclusions:       | This study demonstrated Pancrease was effective in treating PI due to CF and was safe and well tolerated.                        |
| Appraiser limitations: | • PANCREAZE not a product available in Aus & NZ • Funding & design of study is an obvious conflict of interest.                |

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NHMRC Level II ADA Quality: Positive</td>
<td></td>
</tr>
<tr>
<td>Multicentre, randomised, double-blind, placebo-controlled, 2-period crossover, superiority study of the new formulation of pancrelipase delayed release 12,000-lipase unit capsules with placebo. Children with CF and PI aged 7-11 years</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>• On a PERT product at a</td>
</tr>
<tr>
<td>Intervention:</td>
<td>• Patients received pancrelipase 12,000-lipase unit capsules or identical placebo capsules. Target dose of 4000 lipase units/g dietary fat. Each patient received an individualised prospectively designed diet containing &gt;40% of calories from fat. No minimum daily dietary fat requirement was implemented.</td>
</tr>
<tr>
<td>Results:</td>
<td>• During pancrelipase treatment, the mean (SD) daily lipase dose was 4472 (743) units/g fat consumed (16,941 (3602) IU/kg body weight. Adherence was 100%. Mean (SE) CFA values for pancrelipase and placebo were 82.8% (2.7%) and 47.4% (2.7%) respectively, for a treatment difference of 35.4% (p&lt;0.001). The mean (SA) CAN values for pancrelipase and placebo were 80.3%</td>
</tr>
<tr>
<td>Author limitations:</td>
<td>• Limited age range investigated. Small sample size.</td>
</tr>
<tr>
<td>Appraiser limitations:</td>
<td>• 12,000IU preparation n/a in Australia.</td>
</tr>
</tbody>
</table>

regard other lesser doses used by other CF pts
to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clinical therapeutics. 2010;32:89-103

<table>
<thead>
<tr>
<th>Stable dose for &gt;3/12,</th>
<th>Patients remained on usual PERT day 0-14.</th>
<th>Stable body weight.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stable without acute respiratory disease for at least 1/12 pre-enrolment.</td>
<td>At visit 2 (day 1 of crossover), patients were randomised to 1 of 2 treatment sequences – pancrelipase followed by placebo or vice versa.</td>
<td>Stable body weight.</td>
</tr>
<tr>
<td>Stable body weight.</td>
<td>Each treatment was taken for 5 days.</td>
<td>Stable body weight.</td>
</tr>
</tbody>
</table>

Exclusion criteria:
- BMI<10%
- Ileus, malignancy of the digestive tract
- HIV, Coeliac disease, Chron’s disease
- Known allergy to pancrelipase, or exposure to an experimental drug within 30 days of the start of the study.

Primary outcomes:
- Primary – CFA – patients were administered 2 x 250mg doses blue food diet 72 hours apary marking beinning and end of each stool collection period. Stool colletions were performed during each crossover period.

Secondary outcomes
- CAN
- Clinical symptoms – Clinical Global Impression of disease symptoms.

Results:
- Mean (SD) fat intake for pancrelipase and placebo was 338.3g (59.8) and 346.6 (53.1)g respectively and mean nitrogen intake was 44.6 (20.2) and 45.3 (18.6)g.
- All stool characteristics were significantly improved and stool frequency was significantly reduced with pancrelipase compared with placebo. Symptoms of abdo pain, flatulence and stool consistency were less severe during receipt of pancrelipase compared with placebo. Symptoms remained stable on pancrelipase but worsened slightly on placebo.
- TAEs were reported in 5 patients during pancrelipase treatment and 9 patients during placebo. No TEAEs were considered related to pancrelipase treatment whereas 4 patients had TEAEs considered related to placebo (GI symptoms).

Conclusions:
- Pancrelipase delayed release capsules were associated with improvements in CFA, CAN, stool properties and EPI symptoms compared with placebo.
- Pancrelipase delayed release capsules appeared to be well tolerated.

<table>
<thead>
<tr>
<th>Wooldridge JL, Heubi JE, Amaro-</th>
<th>NHMRC Level II</th>
<th>Randomised double blind placebo controlled two</th>
<th>Intervention:</th>
<th>Results:</th>
<th>Author limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients in the randomised</td>
<td>EUR 1008 treatment compared to</td>
<td>Nil</td>
</tr>
</tbody>
</table>

**Wooldridge JL, Heubi JE, Amaro-**

<table>
<thead>
<tr>
<th>NHMRC Level II</th>
<th>Randomised double blind placebo controlled two</th>
<th>Intervention:</th>
<th>Results:</th>
<th>Author limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patients in the randomised</td>
<td>EUR 1008 treatment compared to</td>
<td>Nil</td>
</tr>
</tbody>
</table>
Inclusion criteria:  
- CF & PI  
- >7 years of age  
Exclusion criteria:  
- Nil stated  
trial could receive an of the four dosage formulations of EUR 1008 (5000, 10000, 15000 and 20000 units of lipase/capsule) with a starting dose of 1000 lipase /kg/meal and a targeted maximum dose of 2500 units of lipase/kg/meal and 4000 lipase / gram fat/day.  
- Patients in the supplemental study were given the 5000 IU lipase/capsule and were given 2000IU lipase/kg/meal. Maximum daily dose was limited to 10000 lipase units/kg.  
**Outcomes:**  
- Safety & efficacy of PERT placebo resulted in a significantly higher meal CFA 88.3% vs 62.8% p<0.001.  
**Conclusions:**  
- EUR 1008 led to clinically and statistically significant improvements in CFA in the randomised study, and control of malabsorption and clinical symptoms in both studies.  
**Appraiser limitations:**  
- EUR 1008 not a product available in Aust & NZ.  
- Funding & design of study is an obvious conflict of interest. |
| --- | --- | --- |
Inclusion criteria:  
- PI  
- CF >7 yrs age  
- Able to take PERT capsules  
Exclusion criteria:  
- Pregnant/breastfeeding  
- Unwilling to use birth control  
- Hx fibrosing colonopathy, organ transplant, significant bowel resection, acute/chronic diarrhoeal illness unrelated to PI  
**Intervention:**  
- Liprotamase 32,500 USP, 1 capsule mid meal x3 daily, 1 capsule with snacks twice daily.  
- The main meal dose was allowed to be increased from 1 – 2 capsules, based on strict criteria in study protocol, (steatorrhea, wt loss or lack of wt gain in paeds).  
**Primary Outcomes:**  
- Evaluation of long term safety and tolerability of Liprotamase treatment in subjects with CF related EPI  
**Results:**  
- Overall 211 (98.6%) of the 214 subjects experienced at least one treatment emergent adverse event (TEAE).  
- 36 (16.8%) of the subjects discontinued due to a TEAE.  
- There were another 33 withdrawals unrelated to study treatment.  
- 6 subjects (3%) had ALT values >5 times ULN, mostly transient.  
- Ht, wt & BMI z scores were relatively stable over the remaining treatment period.  
- FEV1 remained stable.  
**Conclusions:**  
- Treatment with a mean 5.5 capsules daily of Liprotamase with meals &  
**Author limitations:**  
- Possible selection bias as investigators may have invited participants with GI symptoms.  
**Appraiser limitations:**  
- Didn’t measure fat absorption in this study, only indirectly.  
- Possible Bias due to drug company involved in study design analysis and interpretation of data.  
- Almost 20% of participants withdrawing due to a TEAE is possibly an indication that some people don’t tolerate this enzyme  
- Author mentioned vitamin... |
<table>
<thead>
<tr>
<th>Munck A,</th>
<th>NHMRC Level IV</th>
<th>Prospective randomised study</th>
<th>Intervention:</th>
<th>Results:</th>
<th>Author limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Deranged LFT – liver transaminases &gt;5 x upper limit of normal, bilirubin &gt; 1.5 x upper limit of normal</td>
<td>• Nutritional status through serial measures of height, weight, BMI z scores at each time point, referenced to year 2000 CDC growth charts, as well as lung function FEV1, snacks for 12 months was safe &amp; well tolerated in CF subjects with EPI, Liver enzymes were not elevated beyond expected. Subjects maintained or gained weight &amp; BMI z scores. Pulmonary function was maintained.</td>
<td>• 5 Patients experienced 15 TEAEs judged possibly (n = 13) or probably (n = 2) related to medication.</td>
<td>• Median body wt increased 7.8 kg to 11 kg.</td>
<td>• 5 Patients experienced 15 TEAEs judged possibly (n = 13) or probably (n = 2) related to medication.</td>
<td>• Pts with wt to length ratios &gt;10th %ile were excluded</td>
</tr>
<tr>
<td>• Inability to discontinue enteral feeds</td>
<td>• Safety - frequency, duration, and severity on treatment emergent adverse events (TEAE).</td>
<td>• Median body lgth was 68.5 cm increased to 81 cm.</td>
<td>• Secondary outcomes:</td>
<td>• Median lgth for age %ile increased from 36.5th %ile to 42nd %.</td>
<td>• Small sample size</td>
</tr>
<tr>
<td>• Known hypersensitivity to food additives</td>
<td>• Growth parameters - weight, length, weight for age %ile, length for age %ile, weight for length %ile, &amp; Z scores</td>
<td>• Median lgth for age %ile increased from the 41.5th to the 55.5th %ile.</td>
<td>• Growth Z scores were variable.</td>
<td>• Although positive overall the improvement was not linear over time.</td>
<td>• Nil</td>
</tr>
<tr>
<td>• Pancreatic sufficiency</td>
<td>Exclusion criteria:</td>
<td>• Median wt for length %ile increased from the 41.5th to the 55.5th %ile.</td>
<td>• Mean wt for lgth z scores positive at all treatment visits.</td>
<td>Conclusions:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Weight to length ratio &lt;10th %ile</td>
<td>• Median wt for length %ile increased from the 41.5th to the 55.5th %ile.</td>
<td>• Median wt for lgth z scores positive at 6 and 12 months.</td>
<td>• Infants with CF safely tolerated long term Zenpep for up to 12/12.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Clinically unwell - Concomitant illness, acute URTI, or LRTI.</td>
<td>• Although positive overall the improvement was not linear over time.</td>
<td>• Although positive overall the improvement was not linear over time.</td>
<td>• Also wt for age %ile more than doubled</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary Outcomes:**

- Nutritional status through serial measures of height, weight, BMI z scores at each time point, referenced to year 2000 CDC growth charts, as well as lung function FEV1, snacks for 12 months was safe & well tolerated in CF subjects with EPI, Liver enzymes were not elevated beyond expected. Subjects maintained or gained weight & BMI z scores. Pulmonary function was maintained.

**Results:**

- Median body wt increased 7.8 kg to 11 kg.
- Median body lgth was 68.5 cm increased to 81 cm.
- Median lgth for age %ile increased from 36.5th %ile to 42nd %.
- Median wt for length %ile increased from the 41.5th to the 55.5th %ile.
- Growth Z scores were variable.
- Mean wt for lgth z scores positive at all treatment visits.
- Median wt for lgth z scores positive at 6 and 12 months.
- Although positive overall the improvement was not linear over time.

**Conclusions:**

- Infants with CF safely tolerated long term Zenpep for up to 12/12.
- Also wt for age %ile more than doubled

**Author limitations:**

- Pts with wt to length ratios >10th %ile were excluded
- Small sample size

**Appraiser limitations:**

- Nil

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**NHMRC Level IV**

**ADA Quality: Neutral**

**Prospective cohort study**

N=15 (3 withdrew)

Multi-site (6) study of patients who had completed previous study and continued treatment with ZENPEP. 12 month open label follow up.

**Inclusion criteria:**

- Between ages of 1 and 12 months diagnosed with CF
- Needing PERT
- Mmonoclonal fecal elastase >200 ug/g stool
- Weight to length ratio >10th %ile, and clinically stable

**Exclusion criteria:**

- Weight to length ratio <10th %ile
- Clinically unwell
  - Concomitant illness, acute URTI, or LRTI.

**Intervention:**

- Ongoing clinical care
  - ZENPEP 3000 lipase (PERT)

**Primary outcomes:**

- Safety - frequency, duration, and severity on treatment emergent adverse events (TEAE).

**Secondary outcomes:**

- Growth parameters
  - weight, length, weight for age %ile, length for age %ile, weight for length %ile, & Z scores

**Results:**

- Median body wt increased 7.8 kg to 11 kg.
- Median body lgth was 68.5 cm increased to 81 cm.
- Median lgth for age %ile increased from 36.5th %ile to 42nd %ile.
- Median wt for length %ile increased from the 41.5th to the 55.5th %ile.
- Growth Z scores were variable.
- Mean wt for lgth z scores positive at all treatment visits.
- Median wt for lgth z scores positive at 6 and 12 months.
- Although positive overall the improvement was not linear over time.

**Conclusions:**

- Infants with CF safely tolerated long term Zenpep for up to 12/12.
- Also wt for age %ile more than doubled

**Author limitations:**

- Pts with wt to length ratios >10th %ile were excluded
- Small sample size
Pancreatic enzyme replacement therapy for young cystic fibrosis patients. Journal of Cystic Fibrosis. 2009;8:14-8

**II**

ADA Quality: **Positive**

of crossover design

- **N= 39**

**Inclusion criteria:**
- CF
- PEI

**Exclusion criteria:**
- Meconium ileus
- Intestinal resection
- Severe concomitant diseases of other organs
- Allergy to pancreatin
- Suspected noncompliance of subject/family

**Comparison of Creon 10,000 preparation (10000IU lipase per capsule) to Creon for Children preparation (5000IU lipase per scoop of granules)**

**Primary Outcome:**
- Parent’s treatment preference

**Secondary outcomes:**
- Coefficient of fat absorption
- Clinical symptoms and safety parameters

- 51% of parents preferred CfC, 23% preferred C10 and 26% had no preference.
- Mean CFA was similar for both 77.8% vs 78.7%
- Safety and tolerability were good for both treatments
- GIT symptoms - no clinically relevant differences.
- Mean daily energy intake was 1100 kcal/day for a mean body weight of 10.1 kg.
- Fat intake was about 40 g/day with comparable mean daily lipase intakes during the CfC and C10 phases (3969 vs. 4310 U/kg/day).
- The mean faecal fat excretion was higher than desired (9.2 and 8.3 g per day during CfC and C10, respectively).

**Conclusions:**
- Those parents who had a preference preferred CfC over C10, but both enzyme preparations improved malabsorption to a similar degree
- Applied dosages could have been too low in some children reflected in suboptimal CFA.
- Parents may under report symptoms
- No attempt was made to optimise creon dose before the randomisation

**Appraiser limitations:**
- Parent preference is a very subjective primary outcome measure and the questionnaire used provided varying quality of responses.
- Low clinical impact/relevance of patient preference for one preparation over the other given there were no significant differences found in actual safety, tolerability, GIT symptoms and CFA between preparations. Hence this study is just about ease of handling CfC.

---

**Konstan MW, Accurso FJ, Nasr SZ, Ahrens RC, Graff GR.**
Efficacy and safety of a unique enteric-coated bicarbonate-buffered pancreatic enzyme replacement therapy in

**NHMRC Level II**

ADA Quality: **Positive**

Randomised, double blind, placebo controlled cross over

- **N=21**
- CF children (>7years) and adults with confirmed PI

**Multicentre – 5 centres across USA**

**Inclusion criteria:**
- Children aged 7-18 yrs and adults with confirmed CF
- PEI per faecal elastase

**Intervention:**
- Active study drug and identical placebo capsules. Treatment period (6-8days)-crossover/re-stabilisation (7-10 days)-placebo (6-8 days) OR vice versa.
- Subjects individually stabilised to an EC- bicarb buffered PERT dose at home.
- Individualised high fat diet (2g fat/kg/day) taken for entire comparison phase.

**Results:**
- Statistically significant improvement in fat & nitrogen absorption for active treatment vs placebo.
- Mean CFA was 82.5% with Enteric coated bicarbonate buffered PERT, compared with 46.3% with the placebo. P=<0.001
- Overall stool frequency decreased by 40% and stool weight decreased by 50% p=<0.001.
- No safety concerns were identified.
- The most common adverse event was GI complaints and these were more

**Author limitations:**
- Bicarb buffered PERT product compared to placebo not a non-buffered PERT product

**Appraiser limitations:**
- Compliance/outcome data
- Intake at home, drug taken stool frequency and characteristics ‘recorded in subject diary’ by subject at home – potentially very subjective
<table>
<thead>
<tr>
<th>Brady MS, Garson JL, Krug SK, Kaul A, Rickard KA, Caffrey HH, et al.</th>
<th>NHMRC Level II</th>
<th>Prospective randomised controlled trial with crossover design</th>
<th>Intervention:</th>
<th>Primary Outcome:</th>
<th>Results:</th>
<th>Conclusions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>An enteric-coated high-buffered pancrelipase reduces steatorrhea in patients with cystic fibrosis: a prospective, randomized study. J Am Diet Assoc. 2006;106:1181-6</td>
<td>ADA Quality: Neutral</td>
<td>N=18 CF patients with PI Aged 12.2-27.6 years</td>
<td>A unique EC high-buffered pancrelipase formulation vs usual brand of EC non-buffered PERT.</td>
<td>Feecal fat excretion per and 72hrs of stool collection, which were counted weighed and</td>
<td>Mean fat excretion decreased significantly in each subject during periods where EC high buffered pancrelipase compared with periods of EC non buffered enzymes.</td>
<td>EC high buffered pancrelipase decreased fat excretion, symbolising increased fat absorption, when</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusion criteria:</td>
<td>7 days in each treatment group- 3 days at home washout followed by 4 days at GCRC of:</td>
<td></td>
<td>Fat absorption 81.8% vs 75.1% respectively p=0.01</td>
<td>Author limitations:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CF &amp; PEI diagnosis</td>
<td>Controlled enzyme doses (at 50% of the subjects usual lipase dose &amp; given immediately before meals and snacks)</td>
<td></td>
<td>72% of patients (13/18 subjects) excreted less fat with EC high buffered PERT. Of these, 56% (10 subjects) decreased fat excretion by more than 5% (range 6-17%).</td>
<td>One patient did not adhere and their data was excluded.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consumption of large EC PERT &gt;1000IU lipase/kg/meal</td>
<td>Controlled food intake, weighted and recorded with even distribution of fat.</td>
<td></td>
<td>NB: &gt;5% considered clinically significant (arbitrarily chosen cutoff).</td>
<td>Relatively small sample size</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fat excretion &gt;15% of dietary fat intake when consuming 50% of usual enzyme dose</td>
<td></td>
<td></td>
<td>However, 5 subjects (28%) did not respond to the EC high buffered PERT.</td>
<td>Some variability in fat intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Adequate BMI</td>
<td></td>
<td></td>
<td></td>
<td>Open label study design= potential to bias subjective data.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mild lung disease</td>
<td></td>
<td></td>
<td></td>
<td>Duodenal PH was not determined, thus explanation of the effect of bicarb in the gut is hypothetical and can’t explain mechanism of action. Eg: why 5 subjects did not have a response at all.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No Abx</td>
<td></td>
<td></td>
<td></td>
<td>Short term study period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No major organ disease that affects digestion or absorption.</td>
<td></td>
<td></td>
<td></td>
<td>Appraiser limitations:</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Mishandling of lab specimens requiring a 3rd study period for some subjects, which was completed as an outpatient,</td>
</tr>
<tr>
<td><strong>Author</strong></td>
<td><strong>NHMRC Level</strong></td>
<td><strong>Inclusion criteria</strong></td>
<td><strong>Exclusion criteria</strong></td>
<td><strong>Intervention</strong></td>
<td><strong>Outcomes</strong></td>
<td><strong>Results</strong></td>
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</tr>
<tr>
<td>Baker SS, Borowitz D, Duffy L, Fitzpatrick L, Gyamfi J, Baker RD.</td>
<td>IV</td>
<td>&gt;4wks of age, CF diagnosis from accredited centres, Willingness to fill out questionnaire and collect small random stool specimen without stopping or changing PERT.</td>
<td>Acute diarrhea, Surgically created enterostomy, Short bowel</td>
<td>nil</td>
<td>Primary- pancreatic sufficiency- faecal elastase. Enzyme dosing, growth, abdominal pain, gassiness, constipation, number of stools.</td>
<td>&lt;2yrs of age- 25% of PS patients had a weight and height &lt;5th percentile compared with 8.8% of PI children. From age 3-20 there was no difference in the distribution of BMI percentiles between PS and PI. &gt;20years of age- 41% of PS patients were of healthy BMI compared with 74% of the PI. There was no relationship between PERT dosing and BMI. There was no significant difference between patients with PS and PI in number of daily stools and dose of PERT had no effect on number of stools. Gassiness and constipation were present significantly more in PI than PS patients. However higher PERD does did not decrease these symptoms.</td>
</tr>
<tr>
<td>Haupt M, Wang D, Kim S, Schechter MS, McColley SA.</td>
<td>III-2</td>
<td></td>
<td></td>
<td>nil</td>
<td>PERT dose</td>
<td>42561 patient visits from 14482 patients from 179 programs. Highest quartile programs had a mean enzyme dose of 1755 lipase</td>
</tr>
</tbody>
</table>

**Data Analysis:**
- Analysed using a Gravimetric method. Looked at faecal fat as a % of fat intake and g/kg/day
- Secondary Outcome:
  - Coefficient of fat absorption % of intake
  - Nitrogen excretion

**Subject Selection:**
- 20 subjects was required for 90% power and only 18 analysable data sets were received.
- Subjects usual enzyme brand varied between 6 different brands/capsule sizes

**Inclusion criteria:**
- >4wks of age
- CF diagnosis from accredited centres
- Willingness to fill out questionnaire and collect small random stool specimen without stopping or changing PERT.

**Exclusion criteria:**
- Acute diarrhoea
- Surgically created enterostomy
- Short bowel

**Intervention:** nil

**Outcomes:**
- Primary- pancreatic sufficiency- faecal elastase. Enzyme dosing, growth, abdominal pain, gassiness, constipation, number of stools.

**Results:**
- <2yrs of age- 25% of PS patients had a weight and height <5th percentile compared with 8.8% of PI children. From age 3-20 there was no difference in the distribution of BMI percentiles between PS and PI. >20years of age- 41% of PS patients were of healthy BMI compared with 74% of the PI. There was no relationship between PERT dosing and BMI. There was no significant difference between patients with PS and PI in number of daily stools and dose of PERT had no effect on number of stools. Gassiness and constipation were present significantly more in PI than PS patients. However higher PERD does did not decrease these symptoms.

**Conclusions:**
- PERT does not correlate with growth or gastrointestinal symptoms.
pancreatic enzyme replacement therapy dosing on nutritional outcomes in children with cystic fibrosis. Pediatric Pulmonology, 2011;46:395

| Exclusion criteria | 2-20 years of age  
| | Taking PERT  
| | CF Registry from January 1, 2005 – December 31, 2008  
| | Programs with <10 unique patients on enzyme supplementation were excluded from centre level analyses  
| | The highest reported enzyme dose on any encounter during the year.  
| | Individual enzyme dose was compared for all patients at programs within the top and bottom BMI percentile quartiles.  
| | Patient and centre level characteristics and median centre enzyme dose was also compared between top and bottom BMI-percentile performance quartiles.  
| | Demographic and clinical factors that may be confounders associated with nutritional outcomes including age at diagnosis, sex, race, FEV1% predicted.  
| | Units/kg/meal (95% CI: 1722, 1788) compared with 1628 lipase units/kg/meal (95% CI: 1595, 1660) for lowest quartile (P < .001).  
| | 52% of patients in top quartile programs had enzyme doses greater than 2000 lipase units/kg/meal.  
| | The median (25th, 75th percentile) enzyme dose from the last visit of all patients was 1755 (1329, 2150) lipase units/kg/meal, and the average BMI percentile of all patients was the 45.2 percentile (SD 27.0%).  
| | Although the top quartile programs' median enzyme dose was significantly higher than that of the bottom quartile, the median enzyme dose was lower than the maximum dose recommended by the CF foundation, ranging from 1787-1836 lipase units/kg/meal, less than the maximum recommended dose of 2500 lipase units/kg/meal.  
| | Note these values are less than the enzyme doses reported in the most recent CF Registry, reflecting the general trend of increased enzyme dose over time.  

Conclusions:  
- CF centres that prescribe higher average pancreatic enzyme dosing have better nutritional outcomes, as measured by average BMI percentile.  
- Even though the magnitude of difference in PERT dose may not appear large, only ~150 lipase units/kg/meal, reducing minor malabsorption at each meal could enhance weight gain over time.

variables  
- Several statistically significant differences exist between the patient characteristics of lowest and highest quartile programs.  
- Patients at top quartile programs were younger, despite not showing a statistically significant difference in age at diagnosis.  
- Top quartile and bottom quartile patients also demonstrated statistically significant differences in height and weight for age percentile.  
- Selection bias, information bias, and confounding.  
- CF Registry is not designed to capture all adverse events of enzyme replacement therapy.  

Appraiser limitations:  
- Nil.
### Evidence Statement Matrix

**Chapter 10 Q10.1.3 How should PERT be dosed for people with CF to support optimal fat absorption?**

**NHMRC Grade for recommendation:** Grade D

**Evidence statement:** There is insufficient evidence to suggest specific doses of PERT to support optimal fat absorption in individuals with CF. Doses within current guidelines of <4000 IU lipase/g of fat and <2500 IU lipase/kg/meal have been shown to be safe and efficacious. There is insufficient evidence to suggest a maximum dose of PERT. Studies show, however, that doses <10,000 IU lipase/kg/day are safe as assessed by adverse events. In a small number of studies, this maximum dose has been exceeded in the short term with no reports of adverse events including fibrosing colonopathy. There is insufficient evidence to suggest whether dosing per gram of fat or per kg of body weight per meal is more efficacious. Both methods have been shown to be efficacious. There is insufficient evidence to suggest how PERT is best dosed to optimise efficacy in enteral feeding.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>B Good</th>
</tr>
</thead>
</table>
| 19 studies | - One level IV observational, non-interventional, single arm study (n=64; ADA neutral)  
- One level IV prospective cohort study (n=12; ADA neutral)  
- Four level IV prospective open label multicentre studies (n=214, n=40, n=23, n=18; ADA neutral)  
- Five level II double blind randomised placebo controlled two period crossover studies (n=31, n=16, n=21, n=34, n=47; ADA positive)  
- One level II quality placebo controlled PERT withdrawal study (n=49; ADA positive)  
- One level II quality randomised placebo controlled crossover study (n=31; ADA neutral)  
- One level II prospective randomised crossover study (n=18; ADA neutral)  
- One level II prospective randomised crossover study (n=39; ADA positive)  
- One level III-3 phase 2 randomised, investigator-blinded, parallel group pilot study (n=16; ADA positive)  
- One level II randomised, double blind, parallel dose ranging study (n=117; ADA positive)  
- One level III-2 retrospective observational study (n=14482; ADA positive)  
- One level IV retrospective cross sectional study (n=1215; ADA neutral) |

<table>
<thead>
<tr>
<th>Consistency</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall poor consistency between studies due to differences in study design with enzyme preparations use, doses provided, treatment duration and the age of patients. Despite this, a wide range of doses was consistently shown to be safe.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevance of the evidence to the clinical questions is satisfactory. Longer term studies are required to fully address clinical impact of PERT dosing in CF</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>C Satisfactory</th>
</tr>
</thead>
</table>
| Studies included adults and children, adults only or children only.  
Common exclusion criteria included patients with pancreatic sufficiency, intestinal resection, diabetes, treatment with acid suppression medication, medical history of DIOS |

<table>
<thead>
<tr>
<th>Applicability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERT is readily available in Australia and NZ although less preparations are available, when compared to the European and US market</td>
<td></td>
</tr>
</tbody>
</table>
**CLINICAL QUESTION**

10.1.4 Does acid suppression medications improve PERT efficacy for people with CF?

**Evidence table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proesmans M, De Boeck K. Omeprazole, a proton pump inhibitor, improves residual steatorrhea in cystic fibrosis patients treated with high dose pancreatic enzymes. European Journal of Pediatrics. 2003;162:760-3</td>
<td>NHMRC Level II ADA Quality: Positive</td>
<td>Randomised cross-over design N=15 (CF subjects; median age 8.7 years) Inclusion criteria: • Patients with persistent symptomatic steatorrhea despite a daily dose of at least 10,000U lipase/kg per day were candidates for the study Persistent steatorrhea was defined as &gt;7g faecal fat/day (when fat intake is at least 100g/day) or fat absorption &lt;93% Exclusion criteria: • Severe lung disease with FEV1 &lt;30% • Pulmonary exacerbation in the previous month or liver cirrhosis with portal hypertension • Median daily lipase intake 13,500U/kg per day</td>
<td>Intervention: • Patients started at random with ‘no omeprazole’ or ‘omeprazole’ for a 1 month period and then crossed over to the other group • Patients &lt; 20kg were treated with 10mg daily, patients &gt;20kg received 20mg • At the end of each month, a 3 day stool collection and a 3 day weighed food record were obtained allowing calculations of caloric intake, daily intake of fat, protein and carbohydrate Outcomes: • Daily stool fat loss • Fat absorption</td>
<td>Results: • Daily intake of calories, fat, carbohydrate and protein was not significantly different between the two treatment periods • Median daily faecal fat loss decreased significantly (p&gt;0.01) during omeprazole treatment, 13g (11.5 – 16.5g/day) to 5.5g (4.9 – 8.1g/day) respectively. • The same improvement was noted when fat reabsorption was calculated, 87% (81 – 89%) versus 94% (90 – 96%) with omeprazole. • In all but one patient fat absorption improved - For this patient treated with 16,000U lipase/kg, fat loss was 10.7g/day (reabsorption 86.3%) without versus 14.3g/day (87.9%) with omeprazole – there was no obvious explanation for his lack of improvement</td>
<td>Author limitations: • Small sample size • Should have included all 24 patients and potentially analysed separately to give a ‘real life’ example of improvements when patients may not be compliant with enzyme supplementation Appraiser limitations: • No blinding</td>
</tr>
<tr>
<td>Francisco MP, Wagner MH</td>
<td>NHMRC Level II</td>
<td>Double blind randomised placebo-controlled crossover</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Sherman JM, Theriaque D, Bowser E, Novak DA.

Ranitidine and omeprazole as adjuvant therapy to pancrease lipase to improve fat absorption in patients with cystic fibrosis. *Journal of Pediatric Gastroenterology and Nutrition.* 2002;35:79-83

**ADA Quality:** Neutral

**Inclusion criteria:**
- CF & PI

**Exclusion criteria:**
- Pregnancy
- Cholestasis

**Measure of baseline PERT**

**Adjuvant therapy was commenced 3 days prior to admission.**

- Paeds <40kg had ranitidine 5mg/kg or 10mg/kg daily divided into equal doses 30mins prior to BF & D.
- Paeds >40kg & adults received 150mg or 300mg bd 30 mins before BF.

Each group was tested whilst having placebo.

The order of Rx was randomised.

Adults were also tested whilst receiving omeprazole 20mg/d 30 mins before BF.

Fat absorption was calculated & diet controlled.

**Outcomes:**
- Effect of gastric acid suppressant therapy with either ranitidine or omeprazole on CF pts receiving ph sensitive enteric coated microtablet.

**Results:**
- The linear model for all subjects showed no overall adjuvant drug effect on fat absorption p=0.32.
- In adults only drug treatments showed no difference in fat absorption p=0.15
- Paired t test subgroup analysis of adults showed a 4.97% p= 0.003 in mean fat absorption all other t tests showed no significance comparing low dose ranitidine to placebo.
- There was marked inter-subject & intrasubject variability in fat absorption.
- No overall sig improvement in fat absorption could be demonstrated

**Conclusions:**
- No overall sig improvement in fat absorption could be demonstrated

### Ng SM, Franchini AI.

Drug therapies for reducing gastric acidity in people with cystic fibrosis. *Cochrane Database Syst* 

**NHMRC Level I**

**ADA Quality:** Positive

**Systematic Review**

**N= 17 trials (273 participants)**

**Inclusion criteria:**
- All randomised and quasi randomised trials involving agents that reduce gastric acidity

**Intervention:**
- Agents that reduce gastric acidity- PPI or H2 Receptor antagonists.
- Other drug therapies such as prostaglandin E2 analogues & sodium bicarbonate.
- Compared to placebo mostly

**Results:**
- Primary outcomes:
  - Drug therapies that reduce gastric acidity improve gastrointestinal symptoms such as abdominal pain
  - Seven trials reported significant improvement in measures of fat malabsorption
  - Two trials report no significant

**Author limitations:**
- 14 trials were of a crossover design and did not have the appropriate info to conduct comprehensive meta- analysis.
- The number of trials assessing each of the different agents was small.
- The included trials were
<table>
<thead>
<tr>
<th>Exclusion criteria:</th>
<th>Primary outcome:</th>
<th>Secondary outcomes:</th>
<th>Conclusions:</th>
<th>Limitations (author noted)</th>
<th>Appraiser limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not RCT, examining agents which are not used to reduce gastric acidity eg prokinetic agents vs PPI, outcomes irrelevant to the study question.</td>
<td>Measures of nutritional status as assessed by weight, height and indices of growth.</td>
<td>Insufficient evidence to indicate whether there is an improvement in nutritional status, lung function, quality of life or survival.</td>
<td>Trials have shown limited evidence that agents that reduce gastric acidity are associated with improvements in gastrointestinal symptoms and fat absorption.</td>
<td>Insufficient evidence to indicate weather there is an improvement in nutritional status, lung function, quality of life or survival.</td>
<td>7 trials limited to children and 3 in adults only.</td>
</tr>
<tr>
<td>All doses and routes of administration were considered.</td>
<td>Symptoms related to increased gastric acidity such as epigastric pain or heartburn</td>
<td>Overall not able to draw firm conclusions from the evidence available.</td>
<td>Trials have shown limited evidence that agents that reduce gastric acidity are associated with improvements in gastrointestinal symptoms and fat absorption.</td>
<td>Due to lack of trials it was not possible to investigate heterogeneity between trials using chi2 test and I2 statistic.</td>
<td>Large variation between the trials in terms of design, duration, treatment and outcome measures.</td>
</tr>
<tr>
<td>All doses and routes of administration were considered.</td>
<td>Complications of increased gastric acidity such as gastric or duodenal ulcers.</td>
<td>Measures of lung function</td>
<td></td>
<td>Several studies did not adequately blind or discuss blinding risk of bias from incomplete data was unclear in 4 trials.</td>
<td></td>
</tr>
</tbody>
</table>
**Chapter 10 Q10.1.4 Is there evidence to support the use of acid suppression medication to improve PERT efficacy for individuals with CF?**

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** There is inconsistent and limited evidence to support the use of acid suppression medication to improve PERT efficacy for people with CF. There is some evidence to suggest that omeprazole may decrease faecal fat loss; however this evidence is only in children.

| Evidence base   | B Good | Two crossover studies with small sample sizes.  
|                |        |  
|                |        | • One level II randomised cross-over study (n=15 children; ADA positive) 
|                |        | One level II double blind randomised placebo-controlled crossover study (n=12 children and 10 adults; ADA neutral)  
| Consistency    | D Poor | One study found no effect of acid suppression on fat absorption.  
|                |        | One study found faecal fat loss significantly decreased with omeprazole treatment  
| Clinical impact| C Satisfactory | Relevance of the evidence to the clinical question is satisfactory  
|                |        | Studies had a small sample size  
|                |        | Safety of acid suppression medication was not assessed  
| Generalisability | C Satisfactory | Only 1 of 2 studies included adults  
| Applicability  | A Excellent | Acid suppression medication and PERT are readily available on the Australian and New Zealand market  

CLINICAL QUESTION

10.1.5 What are the risks of phthalates exposure via PERT for people with CF in Australia and New Zealand

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.
Chapter 11 Gastrointestinal Complications

11.1 Gastro-oesophageal Reflux

**PICO**

11.1.1 What are the nutrition considerations for the management of gastro-oesophageal reflux in CF?

**Search strategy:** See T2.4 Systematic Search Strategy

**Search terms:**

- Gastro-oesophageal reflux
  - Cystic fibrosis, CF, gastro-esophageal reflux disease or reflux or impendence pH monitoring or impendance pH monitoring or protein pump inhibitors or gastric emptying or acid-reflux

**Inclusion & exclusion criteria:**

**Inclusion criteria:**
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

**Exclusion criteria:**
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
**CLINICAL QUESTION**

11.1.1 What are the nutrition considerations for the management of gastro-oesophageal reflux in CF?

### Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results &amp; Conclusions</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Sheikh, S. I., Ryan-Wenger, N. A & McCoy, K. S. | NHMRC level IV ADA quality NEUTRAL | Retrospective chart review (pre and post procedure) 48 Children and adults with CF with uncontrolled GERD who underwent Nissen fundoplication 1990-2010 at Nationwide Children’s Hospital, Columbus OH | Intervention: Nissen fundoplication  
Outcomes:  
• Safety and efficacy (1-2 years data before and after procedure reviewed); Nutritional status | Results:  
• Mean weight increase in the 2 years after surgery was 2.26kg (p=0.011); also noted that in the total cohort that weight increased significantly before surgery  
• Better nutritional outcomes were noted among patients with milder lung disease (FEV1 >60%) compared to those with severe lung disease | Authors limitations:  
• Observational study design – no comparison group  
• Lack of 24 hr pH studies during 2 year follow-up period to objectively evaluate resolution of GERD after intervention  
Appraiser’s limitations:  
• Most of the participants re-commenced anti-reflux medications within 3 months of surgery |
| Boesch, R. P & Acton, J. D. | NHMRC level IV ADA quality NEUTRAL | Retrospective chart review 25 children with CF Underwent laparoscopic Nissen | Intervention: Laparoscopic Nissen fundoplication  
Outcomes:  
• Complications of fundoplication, nutritional status and pulmonary function | Results:  
• No statistically significant change in BMI, BMI percentile, or the slope of FEV1 one year post fundoplication  
Conclusion:  
• No significant improvement in | Authors limitations:  
• Retrospective study design  
• Small sample size  
Appraiser’s limitations:  
• Most subjects had a gastrostomy placed at time of fundoplication; |
<table>
<thead>
<tr>
<th>Study Title</th>
<th>NHMRC level</th>
<th>ADA quality</th>
<th>Study Design</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
<th>Authors Limitations</th>
<th>Appraiser’s Limitations</th>
<th>Conflicts of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabati, A. A., Kempainen, R.R., Milla, C.E., Ireland, M., Schwarzenberg, S.J., Dunitz, J. M. &amp; Khan, K. M.</td>
<td>IV</td>
<td>POSITIVE</td>
<td>Cross sectional study (using self-report surveys)</td>
<td>&gt;18 years and ability to read English</td>
<td>Hospitalised pts and those with known oesophageal pathology</td>
<td>N/A</td>
<td>Frequency and predictors of GORD and lung function</td>
<td>Females and patients reporting weight loss had more symptoms (mean GSAS symptom score 4.9 vs 4.0, p=0.025 and 5.3 vs 4.2, p=0.04) and more severe symptoms (mean GSAS distress score 5.6 vs 3.8, p =0.005 and 6.8 vs 4.0, p=0.01) compared to males and those that did not report weight loss.</td>
<td>Sample Size, Cross-sectional study design, Many subjects on acid suppression already, Possibility of selection bias</td>
<td>Possibility of recall bias from using self-report tools</td>
<td></td>
</tr>
<tr>
<td>DiMango, E, walker P, Keating C, Berdella M, Robinson N, Langfelder-Schwind E, Levy D, Liu X.</td>
<td>II</td>
<td>POSITIVE</td>
<td>RCT (Feasibility study only)</td>
<td>17 CF Adults (From two adult CF programs in New York City)</td>
<td>9 omeprazole arm, 8 placebo</td>
<td>Esomeprazole 40mg twice daily for 36 weeks</td>
<td>Pulmonary exacerbation rates (defined as: initiation of treatment with IV or oral antibiotics for &gt;7 days based on respiratory symptoms at discretion of treating doctor) Other health related outcomes</td>
<td>No significant changes in BMI in both groups</td>
<td>Small sample size, Underpowered study</td>
<td>Limited information given about blinding used in study</td>
<td>Emily DiMango serves on the advisory board of Gilead</td>
</tr>
</tbody>
</table>
versus placebo on pulmonary exacerbations in cystic fibrosis. BMC Pulmonary Medicine. 2014; 14 (1).

Inclusion criteria: >18 years and 2-4 respiratory exacerbations per yr requiring oral and/or IV antibiotics for each of the 2 years prior to study entry.

Exclusion: treated with PPIs, receiving enteral feeds, had smoked cigarettes within the previous 6 months, had previous anti-reflux surgery or clinical indicators for acid-suppressor treatments, being treated with medications that are known to interact with PPIs

Evidence Statement Matrix

Chapter 11 Q 11.1.1 What are the nutrition considerations for the management of Gastro-oesophageal Reflux (GOR) in Cystic Fibrosis?

NHMRC Grade for recommendation: Grade D

Evidence statement There is insufficient evidence available regarding nutrition considerations for the management of GOR, specific to CF. Further research into the impact of dietary factors on GOR in CF is warranted.

<table>
<thead>
<tr>
<th>Evidence Base</th>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 small studies looked at GOR in CF treated with Nissen fundoplication</td>
<td></td>
</tr>
<tr>
<td>o Level IV Ø quality study, n = 48 in children and adults with uncontrolled GOR</td>
<td></td>
</tr>
<tr>
<td>o Level IV Ø quality study, n = 25 in children</td>
<td></td>
</tr>
</tbody>
</table>

Pharmaceuticals
- Patricia Walker serves as a consultant to Giead Pharmaceuticals
<table>
<thead>
<tr>
<th>Consistency</th>
<th>D Poor</th>
<th>The fundoplication study results showed limited consistency- one study showed no significant change in BMI/weight 1 year post fundoplication, and the other showed a significant improvement in weight 2 years post-surgery. The acid suppression treatment studies showed no significant changes in BMI.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical impact</td>
<td>D Poor</td>
<td>Relevance of the evidence to the clinical question is restricted.</td>
</tr>
<tr>
<td>Generalisability</td>
<td>D Poor</td>
<td>Both fundoplication studies include children from 1 year of age but only one study also included adults. Only the adult CF population (no paediatrics) were studied in regards to acid suppressions and GOR. Both</td>
</tr>
<tr>
<td>Applicability</td>
<td>B Good</td>
<td>The studies were conducted in countries with an established health-care system.</td>
</tr>
</tbody>
</table>
11.2 **Distal intestinal obstruction syndrome**

**PICO**

11.2.1 What are the nutrition considerations for the prevention and management of DIOS in CF?

11.2.2 What are the nutrition considerations for the prevention and management of constipation in CF?

**Search strategy:** See [T2.4 Systematic Search Strategy](#)

**Search terms:**

- **DIOS**
  - Cystic fibrosis, CF, distal intestinal obstruction syndrome or meconium ileus or equivalent or constipation or intestinal obstruction

**Inclusion & exclusion criteria:**

**Inclusion criteria:**

- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

**Exclusion criteria:**

- Studies that didn't specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
**CLINICAL QUESTION**

11.2.1 What should be considered from a nutrition perspective for the prevention and management of DIOS in CF?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results</th>
<th>Comments</th>
<th>Author limitations</th>
<th>Appraiser limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Declercq D, Van Bieverlvt S, Robberecht E. Nutrition and pancreatic enzyme intake in patients with cystic fibrosis with distal intestinal obstruction syndrome. Nutr Clin Pract. 2015 Feb;30(1):134-7. doi: 10.1177/088453333614551883.</td>
<td>NHMRC Level III-2 ADA quality NEUTRAL</td>
<td>Case Control Inclusion criteria: • CF diagnosed by sweat test and genetics. Exclusion: • None described but the study implies patients who had a prior DIOS episode were excluded</td>
<td>Intervention(s): • Nil (n/a) Outcomes: • 3 day nutrition diary analysed for calories, protein, fat, fibre &amp; liquid. • Pancreatic enzyme intake (IU lipase and IU lipase per g dietary fat) Secondary Outcomes: nil</td>
<td>Results: • No significant difference between DIOS patients and controls for macronutrient intake • DIOS patients: - Significantly higher intake of fat at the time of their DIOS episode than 1 year earlier (p=.015) - Significantly higher intake of lipase at the time of DIOS than one year prior (P=.025) Note significance disappeared when PERT was expressed per g of fat eaten. • Control group: - Similar evolution in fat and lipase intake over the year.</td>
<td></td>
<td>2 different methods for diet data collection- retrospective after DIOS &amp; prospective 3 day diary for the year before the DIOS &amp; control patients. Possible that the increased PERT and fat intake at the time of the DIOS episode could just be a reflection of the different dietary data collection method’s. Small sample size.</td>
<td>No description of inclusion/exclusion criteria or demographics, disease severity and nutrition status of population. No discussion of withdrawal.</td>
</tr>
<tr>
<td>Munck A, Alberti C, Colombo C, Kashirskaya N, Ellemunter H, Fotoulaki M, Houwen R, Robberecht E,</td>
<td>NHMRC Level II ADA quality POSITIVE</td>
<td>Prospective observational longitudinal (cohort) study Inclusion criteria: N=102 (112 episodes of DIOS)</td>
<td>Intervention: N/A Primary outcome: • Incidence DIOS • Associated factors (DIOS risk factors) • DIOS treatment modalities in children and adults</td>
<td>Results: • DIOS Incidence: - Children (7.67 episodes per 1000 patient-years) - Adults (7.8 episodes per 1000 patient years) • Complete DIOS - Medical treatment failed in 11%</td>
<td></td>
<td>Cohort with classical CF may not resemble patients recruited from registries that could include milder phenotypes (generalisability) Definitions of CF comorbidities differed Lack of a 3-day nutrition and</td>
<td></td>
</tr>
</tbody>
</table>
• CF diagnosis  
• Confirmed episode of DIOS  
Exclusion:  
• Nil stated | - Longer hospitalization (4 [3; 7] days vs. 3 [1; 4], p = 0.002)  
• Associated CF co-morbidities for DIOS:  
  - Meconium ileus (40% vs. 18%, p = 0.0001)  
  - PI (92% vs. 84%, p = 0.03)  
  - CFLD (22% vs. 12%, p = 0.004)  
  - CFRD (49% vs. 25%, p = 0.0003)  
  - Pseudomonas aeruginosa (68% vs. 52%, p = 0.01)  
• Female gender was associated with recurrent DIOS (75% vs. 52%, p = 0.04)  
• Comparison of environmental factors showed no difference between incomplete DIOS and complete DIOS, but a higher rate of constipation in incomplete DIOS (49% vs 31%, p=0.05)  
Conclusions:  
• DIOS is complex in nature | Author limitations:  
• Nil  
Appraiser limitations:  
• No exclusion criteria  
• Nutrition support not described |
| --- | --- | --- | --- |
ADA quality NEUTRAL  
Cross-sectional N=40 [median age 13.5yrs (0-23yrs)]  
Inclusion criteria:  
• CF patients  
• Available diet history  
Exclusion criteria:  
• Nil stated | Intervention:  
• N/A (aetiology investigation)  
Primary outcome:  
• Fibre intake correlation with GI complaints (including DIOS)  
Secondary outcome:  
• PERT dose & fat intake correlation with GI complaints (including DIOS) | Results:  
• Fibre intake was adequate when compared with current recommendations.  
• No relation between fibre intake and GI complaints or DIOS.  
• > fibre intake in patients with DIOS (possibly as a therapeutic response to their gastrointestinal complaints).  
• Fat intake & lipase intake (IU/kg) were not different among patient groups  
Conclusions:  
• Overall adequate fibre intake is  
• No relation between low fibre intake and gastrointestinal problems  
• No relationship between GI symptoms & fat intake or lipase dosage | Author limitations:  
• Nil  
Appraiser limitations:  
• Opportunistic sample  
• No clear detail about inclusion and exclusion criteria  
• Limitations of using the diet history method (interview)  
• Dietitian interviewer not blinded  
• Small patient numbers when allocated to different groups (may have impacted getting statistical significant results) |
**Chapter 11 Q 11.2.1 - What are the nutrition considerations for the prevention and management of Distal Intestinal Obstruction Syndrome (DIOS) in CF?**

**NHMRC Grade for recommendation Grade C**

**Evidence statement:** There is some evidence to suggest that in Cystic Fibrosis, inadequate PERT, including poor adherence and under-dosing, is unlikely to play a role in DIOS. The impact of dietary intake, particularly inadequate fibre and fluid intake on DIOS is unclear. Overall there is inadequate evidence to determine the overall role of nutrition in the prevention and management of DIOS and care should be taken when considering the impact of diet on DIOS as the evidence base is small, limited to the European environment and limitations exist surrounding the dietary intake methodology employed. The impact of sodium intake on DIOS has not been accounted for.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence base</td>
<td>2 relatively small studies with a moderate risk of bias; 1 large multi-centre prospective longitudinal study with a low risk of bias</td>
</tr>
<tr>
<td></td>
<td>• One level II observational prospective longitudinal (cohort) study (n=102 CF children and adults; ADA positive)</td>
</tr>
<tr>
<td></td>
<td>• One level III-2 case control study (n=12 CF children and adults, n=36 control; ADA neutral)</td>
</tr>
<tr>
<td></td>
<td>• One level IV cross sectional study (n=40 CF children and adults; ADA negative)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>• The level II study found that insufficient PERT intake was not a pre-disposing factor for DIOS. Low fibre and fluid intake were frequently observed.</td>
</tr>
<tr>
<td></td>
<td>• The level III-2 study found no indication that nutritional factors (calories, fat, fibre &amp; fluid) or PERT played a role in the occurrence of DIOS</td>
</tr>
<tr>
<td></td>
<td>• The level IV study found no relationship between fibre intake and DIOS.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical impact</td>
<td>Relevance of the evidence to the clinical question is satisfactory however it is difficult to rule out the role of nutrition in DIOS prevention due to the limited number of studies and study limitations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalisability</td>
<td>Given the heterogeneous nature of CF and the fact that overall the studies address this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicability</td>
<td>Australian climate is different to the European climate studied in the body of evidence. Therefore it is difficult to apply the impact of fluid intake and hydration on DIOS prevention. The impact of sodium intake on DIOS was not studied.</td>
</tr>
<tr>
<td></td>
<td>• Adequacy of fibre intake was compared to the US fibre recommendations which differ from those used in Australia.</td>
</tr>
<tr>
<td></td>
<td>• Additional PERT preparations are available in Europe that aren’t available in Australia.</td>
</tr>
</tbody>
</table>
**CLINICAL QUESTION**

11.2.2 What should be considered from a nutrition perspective for the prevention and management of constipation in CF?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
</table>
- Chart audit  
- 3 day diet records  
  - Obtained 0-6 months before patients presented for the first time with constipation and were compared to with the last available dietary data obtained in the patients without constipation or DIOS | Results:  
- Constipation prevalence = 47%  
- Patients with constipation and CF vs. controls:  
  - Lower total fat absorption (0.86±0.09 vs. 0.90±0.07, p=0.012)  
  - History of MI (13% vs 5%, p=0.038)  
- Independent risk factors associated with constipation:  
  - Low total fat absorption (p=0.010; OR 0.002, 95%CI 0.000–0.24)  
  - MI at birth (p=0.024; OR 4.69, 95%CI 1.22–18.0)  
- Fibre and fluid intake were not significantly associated with constipation prevalence | Author limitations:  
- Nil  
Appraiser limitations:  
- Retrospective study planned like a prospective study |

Inclusion criteria:  
- Constipation as defined by the ASPGHAN CF Working Group Exclusion criteria:  
- History DIOS (complete or incomplete)  

**Primary outcome:**  
- Clinical characteristics (inc prevalence) and risk factors constipation
**Evidence Statement Matrix**

<table>
<thead>
<tr>
<th>Chapter 11 Q 11.2.2 What are the nutrition considerations for the prevention and management of constipation in CF?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHMRC Grade for recommendation</strong></td>
</tr>
<tr>
<td><strong>Evidence statement:</strong></td>
</tr>
<tr>
<td>Evidence base</td>
</tr>
<tr>
<td>Consistency</td>
</tr>
<tr>
<td>Clinical impact</td>
</tr>
<tr>
<td>Generalisability</td>
</tr>
</tbody>
</table>
| Applicability | D Poor | • Australian climate is different to that in the Netherlands. Therefore it is difficult to apply the impact of fluid intake and hydration on the prevalence of constipation in CF. The impact of sodium intake and constipation in CF was not studied.  
• Adequacy of fibre intake was compared to the local fibre recommendations that differ from those used in Australia.  
• Fat absorption was measured via an annual 3 day faecal fat test which is not routinely completed in Australia.  
• Only paediatric patients included in the study. |
11.3 Colon cancer screening

PICO

11.3.1 What are the nutrition considerations for colon cancer screening in CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:

Colon cancer screening
- Cystic fibrosis, CF, colon cancer, screening

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers

CLINICAL QUESTION

11.3.1 What are the nutrition considerations for colon cancer screening in CF?

Evidence Table

There were no studies available within the search strategy and criteria that addressed this PICO.
11.4 CF Related Liver Disease

PICO

11.4.1 Should vitamin K supplementation be recommended for all people with CF related liver disease?
11.4.2 What are the requirements for effective supplementation in episodes of vitamin A deficiency in people with CF related liver disease?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:
- Vitamin K
  - Cystic fibrosis, CF, nutrition diet, vitamin K, prothrombin, blood coagulation, cystic fibrosis related liver disease, deficiency, subclinical deficiency, supplementation

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers

CLINICAL QUESTION

11.4.1 Do all people with CF related liver disease require vitamin K supplementation?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.

CLINICAL QUESTION

11.4.1 How should vitamin A be supplemented for the CF population with vitamin A deficiency and CF related liver disease?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.
Chapter 12 CF related diabetes

This chapter is a narrative of CFRD aetiology, diagnosis, assessment and treatment and includes a general review and discussion of the available literature. No clinical questions and PICOs were identified for this chapter.
Chapter 13 Bone Health

PICOs

13.1.1 How and when should bone health and disease be assessed for people with CF?
13.1.2 Is there an ideal serum 25-hydroxyvitamin D level to aim for with people with CF?
13.1.3 What are the calcium requirements in CF to reduce the risk of low bone mineral density?
13.1.4 Should supplemental vitamin D be given to people with pancreatic sufficient cystic fibrosis as part of routine care?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:

Bone Health
- Cystic fibrosis, CF, nutrition, diet, bone mineral density, DEXA, BMD

Vitamin D
- Cystic fibrosis, CF, nutrition, diet, deficiency, subclinical deficiency, supplementation, vitamin D, vitamin D2, vitamin D3, cholecalciferol, hydroxycholecalciferol, calcifediol, ergocalciferol, calcidiol, vitamin D/blood/25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, 1-α-hydroxyvitamin D, 1-alpha-hydroxyvitamin D, calcitriol, alfacalcidol, paricalcitol, toxicity

Calcium
- Cystic fibrosis, CF, nutrition, diet, bone/s, calcium

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
CLINICAL QUESTION
13.1.1 How and when should bone mineral density be assessed for people with CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.

CLINICAL QUESTION
13.1.2 Is there an ideal serum 25-hydroxyvitamin D level to aim for with people with CF?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.

CLINICAL QUESTION
13.2.3 What are the calcium requirements to reduce the risk of low bone mineral density for people with CF?

Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
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<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haworth CS1, Jones AM, Adams JE, Selby PL, Webb AK.</td>
<td>NHMRC Level II ADA quality NEUTRAL</td>
<td>Double Blind Randomized Controlled Trial N=31</td>
<td>Intervention: • 1g Ca + 800IU D3 supplement daily for 12 months vs. placebo (all pts continued daily vitamin D 900IU) Primary Outcome: • Change in BMD Secondary Outcomes: • Change in biochemical markers (25-OHD, parathyroid hormone, corrected calcium, osteocalcin, bone specific alkaline)</td>
<td>Results: • After 12 months, treatment group (n=15) showed a reduced rate of bone loss compared to the control group (n=15) in the following: - Lumbar spine (mean difference 1.9% [CI -0.9 to 4.6%]) - Total hip (mean difference 0.7% [CI 2.2% to 3.5%]) - Distal forearm mean difference 1.7% (CI -2.2% to 5.5%). Note no statistically significant difference in any of the above findings</td>
<td>Author Limitations: • Small sample size • Study population characteristic statistically different at beginning of study • Risk of BIAS • Not representative of general population with small numbers, adults only Appraiser Limitations: • Adherence to recommend supplement regimes was approximately 3.1 days a week</td>
</tr>
</tbody>
</table>
supplementation on bone mineral density and bone metabolism in adult patients with cystic fibrosis.


<table>
<thead>
<tr>
<th>Evidence Statement Matrix</th>
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</thead>
</table>

**Chapter 13 Q13.2 What is the recommended dietary intake of calcium required to reduce the risk of low bone mineral density in people with CF?**

**NHMRC Grade for recommendation** Ungraded

**Evidence statement:** There is insufficient evidence available to provide specific calcium supplementation doses for people with CF. As a result, the calcium intake required to reduce the risk of low bone density in people with CF is unknown and in the absence of CF specific data, calcium intake and supplementation should align with dietary reference intakes.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>D Poor</th>
<th>One level II study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Randomised double blind placebo controlled trial investigating the effect of calcium and vitamin D supplementation on bone mineral density and bone metabolism in adult patients with cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• N=31 CF adults; neutral quality</td>
</tr>
</tbody>
</table>

**Consistency** N/A

**Clinical impact** D Poor

Although calcium and vitamin D supplementation was found to reduce the rate of bone turnover and bone loss in adult CF patients, the results didn’t reach statistical significance.

• Unable to assess overall clinical impact with one small study that includes adults with CF only.

**Generalisability** C Satisfactory

Adult patients only

**Applicability** A Excellent

Applicable to the Australian and New Zealand CF context.
### CLINICAL QUESTION

**13.1.4** Does calcium supplementation above the RDI improve bone mineral density (BMD) in people with CF?

### Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
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<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hillman LS1, Cassidy JT, Popescu MF, Hewett JE, Kyger J, Robertson JD. Percent true calcium absorption, mineral metabolism, and bone mineralization in children with cystic fibrosis: Effect of supplementation with vitamin D and calcium. Pediatr Pulmonol. 2008 Aug;43(8):772-80. doi: 10.1002/ppul.20863.</td>
<td>NHMRC Level II ADA quality NEUTRAL</td>
<td>Double-blinded randomized trial of 4 treatments within a single subject group N= 15</td>
<td>Intervention: Supplementation with one of the following:  • Vitamin D (1600IU D3)  • Calcium (500mg calcium carbonate BD)  • Vitamin D &amp; calcium (1600IU D3 + 1000mg calcium carbonate)  • Placebo Participants had 6/12 of each treatment with a 3/12 washout between each (note all patients also on multi-vitamin with addition 400IU vitamin D)</td>
<td>Results Primary outcome  • Significant improvement in DXA results for all groups but no significant difference between placebo and supplement groups Secondary outcomes  • No significant difference (p&gt;0.05) in % true calcium absorption between any of the groups (including placebo)  • No significant difference (p&gt;0.05) between any treatment &amp; placebo on any measure tested: serum 25-OHD, serum calcium, bone markers and urine calcium:creatinine</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Inclusion criteria:  • CF patients aged 3-15years</td>
<td></td>
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<td></td>
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<td>Exclusion criteria:  • Patients on oral or IV glucocorticoids  • Patients not in Tanner Stage I, II or III puberty</td>
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</tbody>
</table>

### Evidence Statement Matrix

**Primary outcomes**

- DXA at baseline and at beginning of each treatment period and at 36mo

**Secondary outcomes**

- Serum Ca, PO4, Mg, PTH, 25-OHD, 1,25(OH)2D, OC, BAP, TRAP, UrCa:Cr

**Conclusion**

Despite the results of this study not showing significance with the level of vitamin D and calcium supplementation prescribed, it is recommended to continue to aim for normal serum vitamin D levels (30-60ng/ml) and normal calcium intake.

**Author Limitations:**

- Treatment period too short

**Appraiser Limitations:**

- Small sample size & using the subjects as their own control
- Large drop-out rate
- Mostly males (n=10)
- Supplement dose (small) and not compared with larger doses
- Dietary intake of calcium & vitamin D not specified
Chapter 13 Q13.3 Does supplementing calcium above the recommended RDI improve bone mineral density in people with CF?

NHMRC Grade for recommendation Ungraded

**Evidence statement:** There is insufficient evidence to suggest that supplementing calcium above the RDI will improve bone mineral density in people with CF. If the RDI for calcium intake is unable to be met by diet, then calcium supplementation should be commenced.

| Evidence base | D Poor | One level II study  
|               |       | • Double blinded randomised control trial  
|               |       | • N=15 CF children; neutral quality  
| Consistency   | N/A    | -  
| Clinical impact | D Poor | Relevance of the evidence to the clinical question is satisfactory however it is difficult to apply results to clinical practice due to the study limitations and small sample size studied (n=15)  
| Generalisability | C Satisfactory | Study group specific to CF however only paediatric patients were studied and the sample size was small (n=15) and mostly males (n=10/15).  
| Applicability  | A Excellent | Applicable to the Australian and NZ CF context.  

Chapter 14 Special considerations for life stage and genotypes

14.1 Pregnancy

PICO

14.1.1 What are the nutrition considerations for the management of pregnancy in CF?
14.1.2 What recommendations around vitamin A supplementation and monitoring should be provided to females with CF who are pregnant or planning a pregnancy?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:

- **Pregnancy**
  - Cystic fibrosis, CF, CFTR, CFTR modulators, CFTR potentiators, CFTR correctors, CFTR combination therapy, ivacaftor, gene therapy

- **Vitamin A**
  - Cystic fibrosis, vitamin A, retinol, retinal, pregnancy, pregnant, gestation

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers

CLINICAL QUESTION

14.1.1 What are the nutrition considerations for the management of pregnancy in CF?

Evidence Table

There were no studies available within the search strategy and criteria that addressed this PICO.
CLINICAL QUESTION

14.1.2 What recommendations around vitamin A supplementation and monitoring should be provided to females with CF who are pregnant or planning a pregnancy?

Evidence Table
There were no studies available within the search strategy and criteria that addressed this PICO.
14.2 Genetic modulator therapies

**PICOs**

14.2.1 What are the implications of Ivacaftor on nutritional status in children >2 years and adults with cystic fibrosis who have at least one G551D or other gating mutation allele?

14.2.2 Are there any other nutritional considerations (energy, salt intake) that practitioners should take into consideration for people on Ivacaftor therapy?

14.2.3 What is role of gastrointestinal and/or other nutritional outcome measures in individuals with CF receiving Ivacaftor therapy?

**Search strategy:** See T2.4 Systematic Search Strategy

**Search terms:**

- Genetic modulator therapies
  - Cystic fibrosis, CF, CFTR, CFTR modulators, CFTR potentiators, CFTR correctors, CFTR combination therapy, ivacaftor, gene therapy

**Inclusion & exclusion criteria:**

**Inclusion criteria:**
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

**Exclusion criteria:**
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
**CLINICAL QUESTIONS**

14.2.1 What are the implications of Ivacaftor on nutritional status in children >2 years and adults with cystic fibrosis who have at least one G551D or other gating mutation allele?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and Quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results, Conclusions &amp; Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STRIVE:</strong> Ramsey et al. 2011. A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D mutation, N Engl J Med; 18, 1663-72</td>
<td>NHMRC level II ADA quality Positive</td>
<td>Phase III Randomised Control Trial n=161 (Ivacaftor 83; placebo 22) Adolescents and adults &gt;12 years with CF</td>
<td>Intervention: • Ivacaftor for 48 weeks Inclusion criteria ≥12 years ≥1 Gly551Asp allele FEV1 40-90%</td>
<td>Results: • Sweat chloride levels -47.9 (P&lt;0.001) • Weight +2.7 kg (P&lt;0.001) • BMI 0.9kg/m2 (p&lt;0.0001) Conclusion and limitations: Significant impact on sweat chloride levels and anthropometry measures. Weight gain and BMI addressed. Salt requirements may be reduced – no measure. Correlation between sodium, chloride and sweat chlorid not addressed. PERT not addressed. Body composition not addressed.</td>
</tr>
<tr>
<td><strong>ENVISION:</strong> Davies et al. 2013. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis and a G551D mutation, Am J Crit Care Med; 187 (11), 1219-25</td>
<td>NHMRC level II ADA quality Positive</td>
<td>Phase III Randomised Control Trial n=52 (Ivacaftor 26; placebo 22) Children 6-11 years with CF</td>
<td>Intervention: • Ivacaftor for 48 weeks Inclusion criteria 6-11 years ≥1 Gly551Asp allele FEV1 40-105% Weight ≥15kg</td>
<td>Results: • Sweat chloride levels -54.3 (P&lt;0.001) • Weight +2.8 kg (P&lt;0.001) BMI 1.1kg/m2 (p=0.0003) BMI-for-age z score: 0.45 (P&lt;0.001) Conclusion and limitations: Significant impact on sweat chloride levels and anthropometry measures. Potential nutritional implications – no but could infer from it. Mentions pH etc might change byt CFTR function in gut therefore pH implications</td>
</tr>
<tr>
<td><strong>Barry et al. 2014.</strong> Effects of ivacaftor in patients with cystic fibrosis who carry the G551D mutation and have severe lung</td>
<td>NHMRC level IV ADA quality Neutral</td>
<td>Case-control study n=56 (Ivacaftor 21; placebo 35) Post approval setting; severe</td>
<td>Intervention • Ivacaftor for 9 months Inclusion criteria ≥18 years</td>
<td>Results: • Weight +1.8kg (P=0.0058; median) • BMI +1.1 km2 (P=0.010; median)</td>
</tr>
<tr>
<td>Study</td>
<td>Title</td>
<td>Design</td>
<td>Patients</td>
<td>Intervention</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>KONNECTION: De Boeck et al. 2014</td>
<td>Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation, <em>J Cyst Fibr</em>, <a href="http://dx.doi.org/10.1016/j.jcf.2014.09.005">http://dx.doi.org/10.1016/j.jcf.2014.09.005</a></td>
<td>Phase III Randomised Control Trial</td>
<td>n=39</td>
<td>Ivacaftor therapy for 24 weeks total</td>
</tr>
<tr>
<td>PERSIST: McKone et al. 2014</td>
<td>Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study, <em>Lancet</em> (14), 70218-8</td>
<td>Phase II Randomised Control Trial extension study</td>
<td>n=192</td>
<td>Ivacaftor for 6 months</td>
</tr>
<tr>
<td>GOAL: Rowe et al. 2014</td>
<td>Clinical Mechanism of the Cystic Fibrosis Transmembrane Conductance Regulator Potentiator Ivacaftor in G551D-mediated Cystic Fibrosis, <em>Am J Crit Care Med</em>; 190 (2), 175-84</td>
<td>Longitudinal cohort study</td>
<td>n=10 (10 enrolled in pH substudy; 17 enrolled in sweat secretion substudy)</td>
<td>Ivacaftor 96 weeks (144 weeks on ivacaftor in total)</td>
</tr>
<tr>
<td>Study</td>
<td>NHMRC Level</td>
<td>ADA Quality</td>
<td>Design</td>
<td>Sample Size</td>
</tr>
<tr>
<td>------------------------------------------</td>
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</tr>
<tr>
<td>Sawicki et al. 2015.</td>
<td>IV</td>
<td>Neutral</td>
<td>Case control study</td>
<td>N=1074</td>
</tr>
<tr>
<td>Taylor-Cousar et al. 2016.</td>
<td>IV</td>
<td>Neutral</td>
<td>Cross sectional study</td>
<td>N=44</td>
</tr>
</tbody>
</table>
### Evidence statement matrix

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>Evidence statement</th>
<th>Evidence base details</th>
</tr>
</thead>
</table>
| **Chapter 14 Q14.2.1 What are the nutritional implications of Ivacaftor on nutritional status in adults and children >2 years with CF who have at least one G551D or other gating mutation allele?** | There is substantial high quality evidence that Ivacaftor improves nutritional outcomes, specifically weight and BMI, for adults and children >2 years with CF who have the G551D and other gating mutations. These findings appear to also be applicable to those with severe lung disease (i.e. awaiting transplantation or FEV1<40% predicted as evidenced by two level IV studies). | 5 Level II studies  
- All positive quality  
3 level IV studies  
- All neutral quality  
- Includes a mixture of Phase II and III randomised control trials plus studies completed in post approval (real life) clinical settings |

| Consistency   | Excellent | Findings consistently demonstrate a significant improvement in weight and BMI post commencement of Ivacaftor in both children and adults. Whereas adult subjects with mild to moderate lung disease appear to have an acute weight gain (within a month) and then a plateau, paediatric subjects and those with severe lung disease show continuous weight gain over time – these differences appear repeatable and can be explained. |

| Clinical impact | Excellent | The improvements in weight and BMI seen are in-line with current recommendations for ideal nutritional status for people with CF. |

| Generalisability | Excellent | Majority of studies completed in those with G551D but there is no reason to believe from current observational evidence that those with other gating mutations would behave differently.  
Almost all included studies were multi-centre and included Australian participants, it is therefore sensible to apply the above evidence to the Australian/NZ CF population who have at least one G551D or other gating mutation allele. |

| Applicability   | Good     | Ivacaftor is currently available in Australia for children and adults > 6 years with G551D and other gating mutations via the pharmaceutical benefits scheme. Whilst this medication is approved for use in New Zealand, access can be difficult as the high cost of this medication is not subsidised. |
**CLINICAL QUESTION**

14.2.2 Are there any other nutritional considerations (energy, salt intake) that practitioners should take into consideration for people on Ivacaftor therapy?

## Evidence Table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
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<td>NHMRC level II ADA quality Positive</td>
<td>Phase III Randomised Control Trial n=161 (Ivacaftor 83; placebo 22) Adolescents and adults &gt;12 years with CF</td>
<td>Intervention: • Ivacaftor for 48 weeks Inclusion criteria ≥12 years ≥1 Gly551Asp allele FEV1 40-90%</td>
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<td>NHMRC level II ADA quality Positive</td>
<td>Phase III Randomised Control Trial n=52 (Ivacaftor 26; placebo 22) Children 6-11 years with CF</td>
<td>Intervention: • Ivacaftor for 48 weeks Inclusion criteria 6-11 years ≥1 Gly551Asp allele FEV1 40-105% Weight ≥15kg</td>
<td>Results: • Sweat chloride levels -54.3 (P&lt;0.001) • Weight +2.8 kg (P&lt;0.001) BMI 1.1kg/m2 (p=0.0003) BMI-for-age z score: 0.45 (P&lt;0.001) Conclusion and limitations: Significant impact on sweat chloride levels and anthropometry measures. Potential nutritional implications – no but could infer from it. Mentions pH etc might change byt CFTR function in gut therefore pH implications</td>
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<td>NHMRC level IV ADA quality Neutral</td>
<td>Case-control study n=56 (Ivacaftor 21; placebo 35) Post approval setting; severe lung disease</td>
<td>Intervention • Ivacaftor for 9 months Inclusion criteria ≥18 years ≥1 Gly551Asp allele And/or actively listed for lung</td>
<td>Results: • Weight +1.8kg (P=0.0058; median) • BMI +1.1 kgm2 (P=0.010; median)</td>
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<td>Study</td>
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<tr>
<td>Flume et al 2012.</td>
<td>Ivacaftor therapy for 16 weeks (96 week extension)</td>
<td>≥12 years, Phe508del homozygous</td>
<td>Treatment effect</td>
<td>Sweat chloride levels -2.9 (p=0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weight no significant differences</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>BMI no significant differences</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adolescents &gt;12 years and adults with CF</td>
<td></td>
<td>Ivacaftor does not appear affective in this genotype – No nutritional implications to consider.</td>
</tr>
<tr>
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<tr>
<td>KONNECTION: De Boeck et al. 2014.</td>
<td>Ivacaftor therapy for 24 weeks total</td>
<td>≥6 years ≥1 non-Gly551Asp gating mutation allele FEV1&gt;40%</td>
<td>Treatment effect after 8 weeks</td>
<td>Sweat chloride levels 49.2 (P&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children &gt;6 years, adolescents and adults with CF</td>
<td></td>
<td>Paeds wt increase continued, adults plateaued</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BMI-for-age z-score 0.28 (P&lt;0.001)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Significant impact on sweat chloride levels and anthropometry measures.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wide range of ages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Difficult to interpret weight gains</td>
</tr>
<tr>
<td>PERSIST: McKone et al. 2014.</td>
<td>Ivacaftor for 6 months</td>
<td>See inclusion criteria for STRIVE and ENVISION studies</td>
<td>Treatment outcomes</td>
<td>Weight +4.1kg adolescents/adults</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weight +14.8kg children</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study, <em>Lancet</em> (14), 70218-8</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV ADA quality Positive</td>
<td></td>
<td></td>
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<tr>
<td>n=10 (10 enrolled in pH substudy; 17 enrolled in sweat secretion substudy) Post approval setting</td>
<td></td>
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</tr>
<tr>
<td>Ivacaftor 96 weeks (144 weeks on ivacaftor in total) Outcomes: Treated pts vs controls – sweat chloride levels and sweat secretion, BMI, GI factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sweat chloride levels -53.8 (P&lt;0.001) • No detectible difference in sweat secretion with ivacaftor • BMI +0.8kg/m², (p&lt;0.001) • Improve gastrointestinal pH(p=0.001) – ?secondary to increased intestinal bicarbonate secretion</td>
<td></td>
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<tr>
<td>Conclusion and limitations: Improved gastrointestinal pH likely related to increased intestinal bicarbonate secretion</td>
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</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>NHMRC Level IV ADA quality Neutral</td>
</tr>
<tr>
<td>Case control study N=1074 (Ivacaftor 189, controls 886)</td>
</tr>
<tr>
<td>Intevention Ivacaftor for up to 3 years Inclusion criteria See inclusion criteria for STRIVE and ENVISION studies Outcomes: Treatment effect vs F508 matched data from registry</td>
</tr>
<tr>
<td>Results: BMI-for-age z-scores: Year 1 -0.23 (P=0.002) Year 2 -0.26 (p&lt;0.001) Year 3 – 0.30 (p&lt;0.001) Acute improvement in BMI maintained. no significant difference in slope between two groups.</td>
</tr>
<tr>
<td>Conclusion and limitations Significant impact on anthropometry measures. Suggets weight/BMI plateau – acute improvements in BMI maintained but no difference between slopes of treatment group and data registry control group.</td>
</tr>
</tbody>
</table>

<table>
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</thead>
<tbody>
<tr>
<td>NHMRC Level IV ADA quality Neutral</td>
</tr>
<tr>
<td>Cross sectional study - Open label extension N=44 Severe lung disease</td>
</tr>
<tr>
<td>Intervention Ivacaftor for 24 weeks Inclusion criteria ≥6 years ≥1 Gly551Asp allele FEV1 ≤40% or actively listed for transplant Outcomes: Treatment effect – including weight</td>
</tr>
<tr>
<td>Results: Weight gain +3.3kg (not powered for statistical analysis) Weight gain observed within 2 weeks, continued to increase to week 24 – continuous improvement without plateau</td>
</tr>
<tr>
<td>Conclusion and limitations: Significant nutrition effects in pts with severe lung disease– weight gain improvement continues without the plateau effect seen in studies with milder lung disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bellin et al 2013. Insulin secretion improves in cystic fibrosis following avacaftor correction of CFTR: a small pilot study; <em>Pediatr</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>NHMRC Level IV ADA quality negative</td>
</tr>
<tr>
<td>Longitudinal cohort (pilot) N=5 Insulin effects</td>
</tr>
<tr>
<td>Intervention Ivacaftor therapy for 4 weeks Inclusion criteria ≥6 years ≥1 Gly551Asp allele Outcomes: Insulin secretion,</td>
</tr>
<tr>
<td>Results: Insulin response to oral glucose improved 66-178% in all subjects with long standing diabetes OGTt glucose levels were not lower in the two individuals</td>
</tr>
</tbody>
</table>
Evidence statement matrix

**Chapter 14** Q14.2.2 Are there any other nutritional considerations (energy, salt intake) that practitioners should take into consideration for people on Ivacaftor therapy?

**Evidence statement** Studies consistently report weight gain, improvements in BMI and reduction in sweat chloride levels. Causes of weight gain associated with Ivacaftor therapy are likely to be multifactorial and have not yet been investigated in detail. Emerging data from one phase III RCT trail in children >6 years suggests that fat intake and absorption may be improved. Whilst there is substantial high quality evidence that Ivacaftor therapy significantly improves sweat chloride levels for individuals with the G551D allele and other gating mutations, the relationship between sodium intake and sweat chloride levels is currently unknown and requires further study.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>Evidence statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>D Poor</td>
<td>A total of 8 studies that indirectly answer this PICO. 5 Level II studies • All positive quality 4 Level IV studies • 3 neutral quality, 1 negative quality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency</th>
<th>Clinical impact</th>
<th>Generalisability</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>B Good</td>
<td>C Satisfactory</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Conclusion and limitations:** Ivacaftor therapy may impact insulin secretion levels. More research needed

- Non randomized, non blinded, very small numbers, wide variety of ages

**Clinical question**

14.2.3 What is role of gastrointestinal and/or other nutritional outcome measures in individuals with CF receiving Ivacaftor therapy?

**Evidence Table**

There were no studies available within the search strategy and criteria that addressed this PICO.
Chapter 15 Complementary nutrition therapies

15.1 Probiotics

**PICOs**

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

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

**Search strategy:** See T2.4 Systematic Search Strategy

**Search terms:**

- Probiotics
  - Cystic fibrosis, CF, nutrition, diet, lactobacillus, probiotics, lactobacilli, microbiota

**Inclusion & exclusion criteria:**

**Inclusion criteria:**
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

**Exclusion criteria:**
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
### CLINICAL QUESTIONS

**15.1.1** What is the benefit of probiotic genus *Lactobacillus* supplementation for people with CF?

**15.1.2** Should probiotics be recommended routinely for people with CF?

### Evidence Table

Note the same studies, as outlined below, were used to answer PICO 15.1.1 and 15.1.2

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
</table>
PART 2: RCT Test the hypothesis that LGG administration restores intestinal microflora and decreases inflammation in CF children. 
Primary Intervention (RCT):  
• 6 x 10^9 CFU of LGG once daily for 1/12. 
Primary Outcome (RCT):  
• CLP and microflora (using FISH) pre and post LGG administration. 
Secondary Outcomes:  
1) Intestinal inflammation (calprotectin (CLP) and rectal nitric oxide (rNO)).  
2) Faecal bacterial (using faecal DNA analysis). | **Results:**  
**Primary Outcome (RCT):**  
• Significant reduction in *E. rectale*, *F. prausnitzii* and *Bacteroides* species strains in CF children vs. healthy controls (p<0.001).  
• Significant reduction in *Bacteroides* and *E. rectale* in CF children treated with antis vs. CF children not treated with antis (p<0.01).  
• After LGG administration, CF children had a significant increase in *Bacteroides* vs. placebo (p=0.03).  
• Not significant for *E rectale* and *F. prausnitzii*  
• CLP also significantly decreased after LGG administration compared to control (p<0.05).  
**Secondary Outcomes:**  
1) 19/22 CF children had CLP done; mean CLP was significantly higher than in healthy subjects (p<0.01). 12/19 CF children (63%) had CLP > 100ug/g. 12/22 CF children had rNO measured; mean rNO was significantly higher than in healthy subjects (p<0.01). | **Appraiser & author limitations:**  
• Small sample size – less than required in power calculation  
• Paediatric patients only  
• Limited information on demographics (i.e. pancreatic status not specified).  
• Majority children had severe/most common genotypes (i.e. Delta F508 either homo- or hetero-)  
• Bias with patient selection  
• Adherence not reported  
• Duration of probiotic administration unlikely to be long enough (i.e. 1/12) |
3) Relationship b/w intestinal microflora and intestinal inflammation.

faecal microbial communities with mean bands in healthy controls 26.73 compared with 16 in CF (p<0.001). Significant reduction in *E rectale* and *Bacteroides* species strains in CF children compared to healthy children.

3) Only significant for higher bands and CLP (i.e. faecal CLP >200ug/g showed significantly lower number of bands in upper part of the gel, or in other words, significantly lower *Bacteroides*).

Conclusions:
- Reduced faecal bacterial bands in CF children vs. healthy children – indicates reduced bacterial diversity (i.e. dysbiosis). Above further reduced when antis given in these same children.
- LGG administration restored the composition of intestinal microbiota making it more similar to healthy controls.

---

**Aim to determine if probiotic administration reduces the incidence and/or severity of pulmonary exacerbations in CF children.**

**Intervention:**
- Group A: LGG (6x10⁹ CFU/d) dissolved in ORS (period 1) for 6 months followed by just ORS for 6 months (period 2)
- Group B: ORS for 6 months (period 1) followed by LGG (6x10⁹ CFU/d) dissolved in ORS for 6 months (period 2 )

*NNote there was a 4 week washout period b/w the LGG and ORS administration periods.*

**Results:**

**Primary outcomes:**
1) Incidence/duration of pulmonary exacerbations:
   - Significantly higher incidence of PE in patients on ORS vs. LGG (71 vs. 45) pooled data
   - Mean duration of PE wasn’t significantly reduced in children receiving LGG or ORS as judged by the duration of antibiotic therapy.

2) Incidence of hospital admissions:
   - Significant reduction in number of hospital admissions on LGG (16 vs. 32)
   - No difference in mean LOS

**Appraiser & author limitations:**
- Not representative of the general CF population:
  - All PI
  - Children only
  - No data for <5 years in children or adults
- Single blinded – only the patients were blinded
- Increase in body weight may be a direct result of decreased pulmonary exacerbations (given close correlation)
- Power calculation required 30 per group (i.e. did not meet power calculations)
- Authors report decrease IgA in
Primary outcomes:
1. Incidence and duration of pulmonary exacerbations (PE).
2. Incidence and duration of hospital admissions required
3. FEV1
4. Body weight and BMI.

3) FEV1 (Complete data available for 29/38 pts only / 76% or only 67% if out of original 43 enrolled)
- ORS – no significant change in FEV1
- LGG – statistically significant FEV1 increase from baseline (p<0.008) for pooled data (53.8% vs 57.4%)

4) Body weight/BMI
- Significantly greater weight gain after LGG than ORS (pooled)
- Weight gain significant in period 1 for parallel and group A for longitudinal analysis
- BMI no significant results

Main conclusions:
- Probiotics may delay respiratory impairment
- A relationship exists between intestinal and pulmonary inflammation in CF
- Long term administration of LGG to CF children with PsA significantly decreases the incidence of PE and increases body weight in association with a decrease of IgG concentrations.

Discussion but report no change in results section.
- Side effects discussed but no information how this was measured.
- Outcome measures evaluated within two weeks after end of intervention / placebo - effects of probiotics still active?
- Less than 70% participants of original 43 enrolled had FEV1 outcome measures

Bruzese E, Raia V, Gaudiello G, Polito G, Buccigrossi V, Formicola V, Guarino A. Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration. Aliment Pharmacol Ther. 2004; 20: 813-
<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF:</td>
</tr>
<tr>
<td>• Mild-mod lung disease</td>
</tr>
<tr>
<td>• PI</td>
</tr>
<tr>
<td>• Colonised PsA</td>
</tr>
<tr>
<td>• PERT 1000IU lipase/g fat</td>
</tr>
<tr>
<td>• Preventative IV anitbiotics every 3 months</td>
</tr>
<tr>
<td>Children with IBD:</td>
</tr>
<tr>
<td>• Active disease</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
</tr>
<tr>
<td>• CF colonised cepacia</td>
</tr>
<tr>
<td>• Any child on drugs or clinical therapies which are known to impact intestinal inflammation</td>
</tr>
</tbody>
</table>

**Intervention:**

**Phase 1**
- 10 x CF children received a dose of 5x10^9 cfu daily of LGG for 4 weeks

**Phase 2**
- 5 x CF children received a dose of 5x10^9 cfu daily of LGG for 4 weeks

**Secondary outcome:**
- Mean faecal calprotectin concentration was significantly lower after probiotic therapy in CF children (140 ± 43 µg/g vs. 210 ± 42 µg/g) (p<0.01).
- Mean rectal NO production was significantly lower after probiotic therapy in CF children (4.3 ± 1.7 µM vs. 21.2 ± 12.6 µM) (p<0.01).

**Conclusions:**
- Intestinal inflammation is a major feature of CF and is reduced by LGG probiotic therapy.
- Intestinal microflora play a major role in pathogenesis of intestinal inflammation in children with CF.
- Further research required before widespread recommendation for probiotic use in CF.

---


Improvement of digestive health and reduction in proteobacterial populations in the gut microbiota of cystic fibrosis patients using a Lactobacillus reuteri probiotic preparation: A double blind RCT

**NHMRC Level II**

**ADA quality NEUTRAL**

**Inclusion criteria:**
- Fully informed CF patients ≥ 4 yrs
- Pancreatic sufficient and insufficient

**Exclusion criteria:**
- End stage CF
- Acute pulmonary exacerbation
- Immune-deficient

Aim to assess the effects of LR probiotic consumption on GI health, gut inflammation and metagenomic microbiota profiles

**Intervention:**
- Supplementation with 10^8 CFU Lactobacillus reuteri (LR) DSM 17938 x 1 tablet daily for 6 months

Randomised into either Group A (probiotic 1st / placebo 2nd) or Group B (placebo 1st / probiotic 2nd)

**Primary outcome:**
1. GI health (using GIQLI test)
2. General health (using SF-12 test)
3. GI status and inflammation

**Results:**

**Primary outcome:**
- GI health (GIQLI test)
  - Significant improvement (p=0.003) after probiotics
- Calprotectin
  - Significant improvement (p=0.003) after probiotics (33.8 vs. 20.3)
- No significant results for general health (SF-12), fat absorption coefficient or inflammatory markers.

**Secondary outcome:**
- Unbalance of CF microbiota compared to “what is expected of healthy individuals” including majority Proteobacteria (68.2%) compared to majority Firmicutes in healthy people (60%) and minority of Bacteroides (3.6%) compared to higher

**Appraiser & author limitations:**
- Small sample size.
- Patient compliance not measured.
- Only one strain of probiotics tested and dose did not differ for children and adults.
- Difference between PS and PI individuals not described.
- No representative of CF population (i.e. only 66% population were PI)
- Limited high level evidence available for what is defined as the “ideal” or healthy intestinal microbiota. The reference used here for defining “healthy” is from one paper only and no mention of
prospective study.  
Journal of Cystic Fibrosis. 2014(13); 716-722.

| prospective study.  
Journal of Cystic Fibrosis. 2014(13); 716-722. | condition | (using fat absorption coefficient; faecal calprotectin and inflammatory interleukins)  
Secondary outcome:  
Metagenomic microbiota profiles | levels in healthy people (25%).  
• Important changes noted after LGG administration including wider bacterial diversity (not significant).  
Conclusions:  
• Probiotic strain LR significantly reduces gut inflammatory marker faecal calprotectin and also significantly reduced self-reported intestinal comfort using the GIQLI test. | how this differs in children. |

| Di Nardo, G; Oliva, S; Menichella, A; Pistelli, R; Hollo De Biase, R; Patriarchi, F; Cucchiara, S and Stronati, L.  
Lactobacillus reuteri ATCC55730 in Cystic Fibrosis.  
JPGN. 2014; 58(1). | NHMRC Level II  
ADA quality NEUTRAL | RCT (prospective, double-blind, placebo controlled)  
CF children and adults  
61 patients (39 boys)  
6-29 years | Aim to evaluate the effect of  
Lactobacillus reuteri (LR) on the rate of PE and on URTI and gastrointestinal infections in CF patients.  
Intervention:  
• LR ATCC55730 x 10^{10} CFU  
(administered as 5 drops per day) x 6 months  
Primary outcome:  
1. Number of PE  
2. Number and duration of hospital admissions for PE  
3. Number of GI and URTI  
Secondary outcomes:  
1. Change in qualitative and quantitative bacteria present in the sputum  
2. FEV\textsubscript{1}  
3. Change in faecal calprotectin concentration  
4. IL-8 and TNF-a levels in plasma and induced sputum | Results:  
Primary outcome:  
• Risk of PE were significantly reduced in the LR group compared with the placebo group OR 0.06 (CI 0.0-0.49) (P<0.01)  
NNT=3  
• Number of URTI (only otitis) was significantly reduced in the LR group compared with the placebo group (P<0.05)  
• The 2 groups did not differ statistically in the mean number/duration of hospitalisations for PE and GI infections.  
Secondary outcome:  
No significant differences. |

Conclusions:  
LR reduces PE and URTI in patients with CF with mild-to-moderate lung disease.  
LR administration may have a beneficial effect on the disease course of CF. | Appraiser Limitations:  
• Only mild CF disease – not a representative sample of the population.  
• Method of recruitment not stated  
• Conduct of intervention unclear  
• Number of PI pts not stated  
• No measure of compliance with intervention.  
• Characteristics of dropouts not described.  
• Other therapies that may impact outcomes not described  
• Sample size did not meet that required as per power calculation.  
• Statistical methods used lacked detail on normality of data. |

<table>
<thead>
<tr>
<th>NHMRC Level</th>
<th>RCT (double blind)</th>
<th>Aim to assess the effect of probiotics on the status of intestinal inflammation in a group of children with CF by measuring faecal calprotectin (FC) levels.</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>n=47</td>
<td>CF children &gt; 4 years</td>
</tr>
<tr>
<td>ADA quality</td>
<td>NEGATIVE</td>
<td>Children were randomly assigned into two groups: (1) Probiotic (n=24) mean age of 8.56±4.19 years or (2) Placebo (n=23) mean age of 8.65±3.29 years.</td>
</tr>
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</table>

**Inclusion criteria:**
- CF > 4 yrs
- PI

**Exclusion criteria:**
- No non-steroidal anti-inflammatory drug (NSAID) last 2/52
- Not on antibiotic therapy at the time of the study.

**Intervention:**
- The probiotic group received one probiotic sachet daily for 4/52 and the placebo group received maltodextrin.
- Probiotic powder used was 1g Protexin Restor sachet, which contains FOS and a mixture of \(1 \times 10^9\) CFU/sachet bacteria (*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium infantis* (child-specific), *Lactobacillus bulgaricus*).

**Outcome:**
- Changes in FC levels before and after probiotic administration.
- A stool specimen was collected from the patients at the beginning of the study and after four weeks on the intervention.

**Results:**
**Pre-intervention:**
- Mean FC concentrations in the probiotic + placebo groups at baseline were 101.38 μg/g and 70.22 μg/g, respectively; there were no sig. differences between the two groups (p=0.1).
- 31 (of 47) enrolled patients at baseline (65.9%) had abnormal FC levels (>50 ug/g). Although 13 patients (41.9%) belonged to the placebo and 18 patients (58.1%) belonged to the probiotic group in random allocation, this difference was not sig. significant (p=0.230).

**Post-intervention:**
- Mean FC concentration after probiotics was 56.2 μg/g; significantly lower than 182.1 μg/g in the placebo group (p=0.031).
- Post intervention, 29 patients had FC concentrations < 50μg/g; 8 patients (27.6%) were placebo and 21 patients (72.4%) were probiotics. There was a sig. lower number of cases with a high FC level in the patients who used probiotics (p<0.001).

**Conclusions:**
- Approx. 2/3 of CF patients had intestinal inflammation based on FC levels. Probiotic administration was shown to decrease FC concentrations and subsequently intestinal inflammation in patients.
- Probiotic administration sig. changed the FC concentrations compared to the placebo group - microflora modifications can improve intestinal inflammation.

**Appraiser Limitations:**
- Small numbers
- Limited info about groups studied (e.g. severity of disease, gender, history of exacerbations)
- No patient outcomes noted (e.g. freq of exacerbations or gastro/steatorrhea symptoms)
- FC only measure of inflammation used – inflammatory markers not measured
- Mean difference in FC at baseline between groups was >30. Whilst p value NS this may be clinically significant difference.
- No info about method of randomisation
- No reasons accounted for drop outs
- No other potential confounding interventions mentioned (e.g. other medications)
- Limited info about statistical tests including normality of data. No confidence intervals provided. No power calculations to assess adequacy of sample size.
<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Study Design</th>
<th>Inclusion</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
<th>Conclusion</th>
<th>Appraiser Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jafari SA, Mehdizadeh-Hakkak A, Kianifar HR, Hebrani P, Ahanchian H, Abbasnejad E.</td>
<td>Effects of Probiotics on Quality of Life in Children with Cystic Fibrosis. A Randomized Controlled Trial. Iran J Pediatr. 2013 Dec;23(6):669-74.</td>
<td>RCT (prospective)</td>
<td>N=37 CF children N=20 cases and n=17 controls</td>
<td>Commercially available probiotic supplement 2 x capsules daily for 1 month (10^9 CFU of mixed probiotic strains).</td>
<td>Paediatric quality of life (using PedsQL 4.0 SF 15) Episodes of pulmonary exacerbation</td>
<td>QOL: Parental reports: significance after 3 months but not after 6 months (p=0.01 and p=0.17 respectively). Child reports: no significance after 3 or 6 months. Pulmonary Exacerbations: During and 3 months post-intervention, significant difference developed in number of pulmonary exacerbation between patients of the two groups (ANOVA P=0.0002 and P=0.0001 respectively). During intervention – no patients had pulmonary exacerbations. Post-intervention – significant difference b/w oral antibiotic treated pulmonary exacerbations pre vs post intervention (p=0.01).</td>
<td>Probiotics might be useful nutritional supplements in improving quality of life and reducing number of PEs in patients with CF however effects in this study on QOL seem to be temporary.</td>
<td>Small numbers Children only All PI (not representative of CF population) Longer treatment and follow up period may be required to reliably judge relationship between probiotic treatment and number of admissions in CF. Patients in this study were too young to evaluate PFTs Method of randomisation not described</td>
</tr>
</tbody>
</table>
| Weiss B1, Bujanover Y, Yahav Y, Vilozni D, Fireman E, Efrati O. | Probiotic supplementation affects pulmonary exacerbations in patients with cystic fibrosis. Pediatric | Case series | CF children and adults n=10 | 2 x commercially available probiotic tablets daily for 6/12. Each tablet: 6 x 10^9 CFU/day | Rate of PE, PFTs, bacterial colonisation, inflammatory markers. | No PE were noted during the intervention period by any patients. PE rate was significantly reduced in comparison to previous 2 years and 6 months post-intervention (P= 0.002). No significant results for FEV1. | No significant results. | Small numbers Other inflammatory cytokines may be needed to evaluate the effect of probiotics on lung inflammation. Mixed probiotic supplementation makes it difficult to discern if the result is due to a particular strain or
<table>
<thead>
<tr>
<th>Pulmonology 2010; 45</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(PE) at least 1/ year for 2 yrs prior to study, requiring IV antis for at least 14 days</strong></td>
</tr>
<tr>
<td><strong>Ability to produce sputum</strong></td>
</tr>
<tr>
<td><strong>Signed informed consent</strong></td>
</tr>
<tr>
<td><strong>No other chronic diseases except for CF-related disease</strong></td>
</tr>
</tbody>
</table>

**Exclusion criteria:**
- Nil described

**bacteria:** lactobacillus acidophilus, lactobacillus bulgaricus, bifidobacterium bifidum, streptococcus thermophiles (taken at least 2hrs apart from antibiotics).

**Primary outcome:**
- Number of episodes of PE in the treatment period compared to PE rates during 2 x 6/12 periods prior to the study.
- FEV1 measured prior to and at the end of probiotic treatment (best result of 3)

**Secondary outcome:**
- Change in qualitative and quantitative sputum bacteria
- IL-8 level in the sputum as marker of inflammation

**Author’s conclusions:**
- Probiotics reduce PE rate in patients with CF. Probiotics may have a preventative action against PE in CF patients.

<table>
<thead>
<tr>
<th>Evidence Statement Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chapter 15 Q15.1.1 Does dietary supplementation with probiotic genus Lactobacillus improve nutritional, gastrointestinal and/or respiratory status in individuals with CF?</strong></td>
</tr>
</tbody>
</table>

**NHMRC Grade for recommendation:** Grade C

**Evidence statement:** There is some evidence to suggest that dietary supplementation with a *Lactobacillus* genus probiotic may improve gastrointestinal and respiratory health outcomes for individuals with CF. The evidence from low quality and underpowered studies suggests that supplementation of a *Lactobacillus* genus probiotic may decrease intestinal inflammation and reduce the incidence and/or risk of pulmonary exacerbations in children and adults with CF. There is no evidence showing improvements in nutritional outcomes including BMI. There is no evidence for probiotic supplementation in infants with CF. Care should be taken at this time when applying this evidence to clinical practice.

**Evidence base**
- Six Level II RCTs (n=37, ADA neutral; n=47, ADA negative; n=61, ADA neutral; n=30, ADA neutral; n=38, ADA neutral; n=22, ADA neutral)
- One Level III-2 two phase case controlled study (n=30, ADA neutral)

**Evidence base**
- Poor
<table>
<thead>
<tr>
<th>Consistency</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>• One Level IV case series (n=10, ADA neutral)</td>
<td></td>
</tr>
<tr>
<td>• Intestinal inflammation – findings consistently demonstrate significant reduction in faecal calprotectin post probiotics.</td>
<td></td>
</tr>
<tr>
<td>• Pulmonary exacerbations – findings consistently demonstrate significant reduction in the incidence and/or risk of pulmonary exacerbations post probiotics.</td>
<td></td>
</tr>
<tr>
<td>• FEV(_1) – overall findings show no effect with regards to improvement of FEV(_1)</td>
<td></td>
</tr>
<tr>
<td>• Nutritional – findings consistently show no significant changes to BMI with probiotics</td>
<td></td>
</tr>
<tr>
<td>• The studies were not consistent in the <em>Lactobacillus</em> species or strain used or the duration of supplementation making it difficult to compare outcomes and evidence of efficacy.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical impact</th>
<th>C Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Relevance of the evidence to the clinical question is satisfactory.</td>
<td></td>
</tr>
<tr>
<td>• Size of the effect difficult to determine due to underpowered studies.</td>
<td></td>
</tr>
<tr>
<td>• Likelihood of adverse events with <em>Lactobacillus</em> genera probiotic supplementation is low.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Given the heterogeneous nature of CF and the fact that overall the studies address this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population in children and adults. There is no evidence for probiotic use in infants.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lactobacillus</em> probiotic genera are available on the Australian and New Zealand market however they are expensive and not available on PBS. Compliance may be an issue in the CF population.</td>
<td></td>
</tr>
</tbody>
</table>

**Q15.1.2 Is there evidence to recommend the routine or targeted use of probiotic supplements for improving health outcomes in individuals with CF?**

**NHMRC Grade for recommendation Grade C**

**Evidence statement:** There is some evidence to suggest that dietary supplementation with probiotics may improve health outcomes such as reducing intestinal inflammation and number of pulmonary exacerbations. This is evidence is underpowered and low quality. Studies are variable in the population studied, the health outcomes measured and the probiotic strain and duration of supplementation making it difficult to compare outcomes and evidence of efficacy. Care should be taken when applying this evidence in clinical practice.

**Evidence base**

<table>
<thead>
<tr>
<th>D Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Six Level II RCTs (n=37, ADA neutral; n=47, ADA negative; n=61, ADA neutral; n=30, ADA neutral; n=38, ADA neutral; n=22, ADA neutral)</td>
</tr>
<tr>
<td>• One Level III-2 two phase case controlled study (n=30, ADA neutral)</td>
</tr>
<tr>
<td><strong>Consistency</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>• One Level IV case series (n=10, ADA neutral)</td>
</tr>
<tr>
<td>• Intestinal inflammation – findings consistently demonstrate significant reduction in faecal calprotectin post probiotics.</td>
</tr>
<tr>
<td>• Pulmonary exacerbations – findings consistently demonstrate significant reduction in the incidence and/or risk of pulmonary exacerbations post probiotics.</td>
</tr>
<tr>
<td>• FEV$_1$ – overall findings show no effect with regards to improvement of FEV$_1$.</td>
</tr>
<tr>
<td>• Inflammatory markers – findings consistently demonstrate no improvement of inflammatory markers as measured by IL-8 and TNF-α post probiotics.</td>
</tr>
<tr>
<td>• The studies were not consistent in the probiotic species or strain used or the duration of supplementation making it difficult to compare outcomes and evidence of efficacy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Clinical impact</strong></th>
<th><strong>Satisfactory</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Relevance of the evidence to the clinical question is satisfactory.</td>
<td></td>
</tr>
<tr>
<td>• Size of the effect difficult to determine due to underpowered studies.</td>
<td></td>
</tr>
<tr>
<td>• Likelihood of adverse events with probiotic supplementation is low.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Generalisability</strong></th>
<th><strong>Good</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Given the heterogeneous nature of CF and the fact that overall the studies address this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population in children and adults. There is no evidence for probiotics in infants.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Applicability</strong></th>
<th><strong>Good</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Probiotics species and strains used in CF research, are available on the Australian and New Zealand market however they are expensive and not available on PBS. Compliance may be an issue in the CF population.</td>
<td></td>
</tr>
</tbody>
</table>
15.2 Glutathione

**PICOs**

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

**Search strategy:** See T2.4 Systematic Search Strategy

**Search terms:**

- Glutathione
  - Cystic fibrosis, CF, nutrition, diet, respiratory, glutathione, antioxidant, N-acetylcysteine, NAC

**Inclusion & exclusion criteria:**

**Inclusion criteria:**
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

**Exclusion criteria:**
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers
CLINICAL QUESTION
15.2.1 Does glutathione or N-acetylcysteine supplementation improve nutrition and/or respiratory outcomes in CF?

Evidence table

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visca A, Bishop CT, Hilton S, Hudson VM. Oral reduced L-glutathione improves growth in pediatric cystic fibrosis patients. J Pediatr Gastroenterol Nutr. 2015 Jun;60(6):802-10. doi: 10.1097/MPG.0000000000000738.</td>
<td>NHMRC Level II ADA quality NEUTRAL</td>
<td>RCT (dbl blind, placebo-controlled) N=44 Paediatric CF subjects</td>
<td>Aim to determine whether oral GSH could improve growth in paediatric CF patients and to determine whether oral GSH could improve other systemic clinical markers. Primary outcomes: • Weight • Height • BMI • Faecal calprotectin (CLP) Secondary outcomes: • White blood cell count (WBC) • Alanine transaminase (ALT) • Vitamin E • CRP • Self-reported GI symptoms</td>
<td>Results: • Baseline all characteristics were statistically similar with the exception of faecal CLP levels. Placebo group had significantly lowered CLP levels (p=0.008). CLP was a primary outcome however... • Nil adverse events Primary outcome: Weight, height, BMI (z scores and percentiles) and CLP levels all significantly higher in the GSH group compared to placebo after 6 months (p&lt;0.0001). • Weight percentile increased from 24th to 43rd • Height percentile increased from 36th to 43rd percentile • BMI percentile increased from 25th to 48th percentile • CLP levels decreased from 113 to 61 (placebo remained unchanged) Secondary outcome: • WBC – significant decrease in WBC levels at 6 months (p=0.0001) • CRP – significant decrease in CRP levels at 6 months (p=0.0001) • ALT levels sig decreased at 6 months (p=0.0001) • Vit E levels sig increased at 6 months (p=0.0001) • Self-reported GI symptoms sig improved in 8 out of 11 categories (exception being</td>
<td>Appraiser &amp; author limitations: • 44 patients (author’s stating small numbers) • Trial concluded at 6 months when improvements were still being seen. • No independent testing to confirm PI • Majority of patients were less than “ideal” in terms nutritional status with weights &lt; 50th % • GSH group had significantly higher CLP levels at baseline compared to the placebo group and then at the end of the 6 months the groups were comparable meaning that oral GSH may be mostly beneficial to those patients who have higher CLP levels or higher GI inflammation.</td>
</tr>
<tr>
<td>Long-term treatment with oral N-acetylcysteine: Affects lung function but not sputum inflammation in cystic fibrosis subjects. A phase II randomized trial.</td>
<td>ADA quality POSITIVE</td>
<td>Multi-centre: 11 accredited CF centres across the US</td>
<td>Primary outcomes:</td>
<td>Baseline characteristics were statistically similar between treatment and placebo groups.</td>
<td>FEV1 was not the primary outcome</td>
</tr>
<tr>
<td></td>
<td>N = 62</td>
<td>30 intervention</td>
<td>HNE activity in sputum did not differ from baseline to 24 weeks between NAC and placebo groups (p=0.14).</td>
<td>Primary outcome:</td>
<td>No follow up to see if FEV1 changes were sustained off treatment.</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria:</td>
<td>32 placebo</td>
<td>HNE activity in sputum from 0-168 days (HNE activity is a biomarker for neutrophil inflammation).</td>
<td>Secondary outcomes:</td>
<td></td>
</tr>
<tr>
<td>• Diagnosed CF</td>
<td></td>
<td></td>
<td>• Changes in spirometry indices (FEV1, FVC, FEF25-75%)</td>
<td>• FEV1: maintained baseline levels in treatment group compared to a decrease in the placebo group (significant p=0.02).</td>
<td></td>
</tr>
<tr>
<td>• Clinically stable</td>
<td></td>
<td></td>
<td>• Change in incidence and number of sinus and PE</td>
<td>• No differences detected in indices of inflammation, or GSH status.</td>
<td></td>
</tr>
<tr>
<td>• Mild moderate lung disease FEV1 40-85%</td>
<td></td>
<td></td>
<td>• Time to first sinus or PE</td>
<td>• Incidence of PE: less in the NAC group compared to placebo however this difference was not significant.</td>
<td></td>
</tr>
<tr>
<td>• Ability to tolerate sputum induction by 3% hypertonic saline</td>
<td></td>
<td></td>
<td>• Time to first new or increased use of antibiotics</td>
<td>• No other outcomes were significant b/w groups.</td>
<td></td>
</tr>
<tr>
<td>• Followed restrictions on consumption of antibiotics, antioxidants, anti-inflammatory medications</td>
<td></td>
<td></td>
<td>• Change in neutrophil count in sputum</td>
<td>Conclusions:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Change in IL-8 levels in sputum and blood</td>
<td>• Clinically relevant outcome in the secondary outcome: long-term treatment</td>
<td></td>
</tr>
</tbody>
</table>
### Placebo-controlled trial

Conrad et al. (2015) seminal paper.


- Nil stated
- Change in weight
- Change in QOL indices
- Frequency and severity of treatment-induced adverse events
- Changes in clinical laboratory parameters and vital signs
- Incidence of abnormal clinical laboratory measures
- Vital signs
- Physical exam results

**Intervention:** 24wks Oral NAC

- 1 x NAC tablet dissolved in liquid 3 times per day (900mg x 3 daily).

With oral NAC prevents lung function deterioration in CF, as the NAC cohort maintained baseline FEV1 and FEF25-75% throughout the 24-week period, but fell in the placebo control at the expected rate over the 6-month study period, even though the study was not powered for the parameter.

### Randomized, placebo-controlled study

- **DAULTEBAEV N, FISCHER P, AULBACH B, GROSS J, KUSCHE W, THYROFF-FRIESINGER U, WAGNER TO, BARGON J.**

A phase II study on safety and efficacy of high-dose N-acetylcysteine in patients with cystic fibrosis.


- **NHMRC Level II**
- **ADA quality NEUTRAL**

Randomized, placebo-controlled study (RCT), double-blind.

N = 21 randomized (adults 21-35 years)

**Inclusion criteria:**
- > 16 years of age
- Diagnosis of CF by repeated sweat tests
- Homo- or heterozygous for delta F508
- Stable disease within the last 4 weeks before enrolment and FEV1>40%.

**Exclusion criteria:**
- Exacerbation of CF within last 4 weeks
- Steroids or IV antibiotics

Aim to assess the safety of low-dose and high-dose N-acetylcysteine (NAC) as well as its effects on clinical parameters, concentrations of extracellular glutathione in sputum and blood, and inflammatory markers in induced sputum in patients with CF.

**Primary outcomes:**
- Adverse events: safety and efficacy (FEV1, extracellular glutathione in sputum and blood plasma & inflammatory markers.

**Secondary outcomes:**
- PFTs
- Antioxidant markers (extracellular glutathione in induced sputum and blood)

**Results:**
- Baseline groups were not significantly different in demographics (only p-value recorded was for FEV1).
- **Primary outcome:** Safety
  - No significant differences in adverse events between groups (both groups had mild-moderate adverse events which were mainly CF exacerbations).
  - Three adverse events were rated as “serious” – two were determined to be ‘non-related’ to the study drug and one was determined to be ‘possibly’ related to the study drug, that being a gastrointestinal bleed in the 700mg NAC group.
- **Secondary outcome:** PFTs
  - No difference in FEV1 at baseline between groups. FEV1 did not change significantly from baseline to

**Appraiser limitations:**
- Small sample size.
- Not a good representative population as all adults and mostly males (16 males; 5 females).
- No statistical power calculation completed.
- Duration potentially not long enough to see effect
- Biases and limitations not well described, particularly given all the non-significant results.
- Randomisation process not described.
- Data on quality of life was collected but not published or described – bias.
- Haemoptysis
- Known hypersensitivity to NAC or inactive ingredients of the study medication
- History of severe drug-related allergy
- Clinically-significant liver impairment

Intervention: (12 wks oral NAC)
- Low-dose = 700mg daily of NAC
- High-dose = 2800mg daily of NAC
- 21-day wash-out period followed by 24-day placebo run-in period, then treatment over 81 days.

Results:
- Primary outcomes:
  - Treatment significantly increased whole blood GHS levels in CF blood neutrophils (P=0.003).
  - Decreased sputum elastase activity (P=0.006)

Conclusions:
- High-dose NAC is a safe and well-tolerated medication in CF.
- Duration potentially too short to achieve changes in FEV1
- High-dose NAC tended to increase concentrations of extracellular glutathione in the sputum however did not reach significance
- Potential capacity to increase extracellular glutathione in CF airways.

Tirouvanziam R, Conrad CK, Bottiglieri T, Herzenberg LA, Moss RB, Herzenberg LA.

N= 18 (plus 9 healthy controls)

Comparative study with concurrent controls: non-randomised experimental trial.

NHMRC Level III-2
ADA quality NEGATIVE

Aim to determine if treatment with NAC can improve the redox imbalance in circulating neutrophils and if NAC can inhibit recruitment of neutrophils to CF airways.

Appraiser limitations:
- No changes to lung function as short-term study only.
- Study did not outline demographic/characteristic data of participants- thus unsure if groups comparable

Inclusion criteria:
- CF
- Stable disease
- Age >10
- Weight >25kg
- FEV1 >40%
- Ability to perform lung Fx and produce sputum
- Not pregnant.

Exclusion criteria:
- <10 years
- Weight <5th percentile or malnourished
- FEV1 <40%
- CF liver Dx
- Pulmonary exacerbation
- Consumption of antioxidants
- Use of acetaminophen
- Participation in other trials
- Not pregnant.

Intervention: Oral NAC
- Glutathione prodrug N-acetylcysteine (NAC), given orally in high doses (0.6-1.0g, x3 daily for 4/52).

Duration: 1/12

Primary outcomes:
- Decreased neutrophil burden in CF airways (P=0.003) and decreased number of airway neutrophils actively releasing elastase rich granuals (P=0.005)
- After excluding subjects without baseline airway inflammation, positive treatment effects were more pronounced.
- GHS pro-drug is safe to use in high doses in CF.
- No change in FEV1

Secondary outcomes findings:
- Not discussed or included in article.

Conclusions:
- Although pulmonary function was not improved in this short term trial, it leaves hope that long term treatment may improve pulmonary status outcomes. Long term safety, therapeutic effects and mode of action of high dose NAC treatment remain to be tested.
### Evidence Statement Matrix

**Chapter 15 Q15.3 Does antioxidant supplementation with oral glutathione or its precursor N-acetylcysteine improve nutritional and/or respiratory status in CF?**

**NHMRC Grade for recommendation Grade C**

**Evidence statement:** There is some evidence to suggest that dietary supplementation with oral glutathione may improve nutritional outcomes, specifically weight and BMI, for individuals with CF. This evidence is inconsistent in terms of dose and duration of supplementation studied. There is conflicting evidence to suggest that dietary supplementation with oral glutathione or N-acetylcysteine improves respiratory outcomes. There is insufficient evidence to recommend either glutathione or N-acetylcysteine as having superiority for improving nutritional and/or respiratory status in individuals with CF and there is insufficient evidence to recommend a specific formulation, dose or duration required to achieve desirable nutritional and respiratory outcomes.

**Evidence base**

<table>
<thead>
<tr>
<th>Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three Level II RCTs (n=70, ADA positive; n=47, ADA neutral; n=43, ADA neutral)</td>
</tr>
<tr>
<td>One Level III-2 non randomised comparative study (n=18, ADA negative)</td>
</tr>
<tr>
<td>One Level IV case series study (n=13, ADA negative)</td>
</tr>
</tbody>
</table>

**Consistency**

<table>
<thead>
<tr>
<th>Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ – findings inconsistent with regards to the effect on FEV₁.</td>
</tr>
<tr>
<td>Pulmonary exacerbations – studies inconsistent with regards to the effect on pulmonary exacerbations.</td>
</tr>
<tr>
<td>Nutritional status – findings consistently demonstrate a significant improvement in weight and BMI post oral glutathione.</td>
</tr>
<tr>
<td>Sputum neutrophils – findings inconsistent with regards to the effect on sputum neutrophils.</td>
</tr>
<tr>
<td>Inflammatory markers - findings consistently demonstrate no significant improvement in inflammatory markers.</td>
</tr>
<tr>
<td>Overall the evidence is inconsistent with regards to the study design, risk of bias, intervention studied and the dose and duration of intervention required to achieve the effect.</td>
</tr>
</tbody>
</table>

**Clinical impact**

<table>
<thead>
<tr>
<th>Satisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertain duration required to achieve the effect.</td>
</tr>
</tbody>
</table>
- Inability to determine the size of the effect due to underpowered studies.
- Unable to determine safety profile due to inconsistencies in the reporting of adverse events. Trend is towards a favourable safety profile.
- Relevance of the evidence to the clinical question is satisfactory.

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Given the heterogeneous nature of CF and the fact that overall the studies address this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population.</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>B Good</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glutathione and N-acetylcysteine supplements are available on the Australian and New Zealand market however compliance may be an issue in the CF population.</strong></td>
<td></td>
</tr>
</tbody>
</table>
15.3 Coconut Oil

PICTs

15.3.1 Is there evidence that dietary supplementation with coconut oil improves nutritional status in pancreatic insufficient people with CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:
- Coconut oil
  - Cystic fibrosis, CF, nutrition, diet, weight, coconut, coconut oil, MCT, medium chain triglycerides

Inclusion & exclusion criteria:

Inclusion criteria:
- Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
- Systematic reviews

Exclusion criteria:
- Studies that didn’t specifically address the PICO
- Case reports
- Guidelines and consensus documents
- Review papers

CLINICAL QUESTION

15.3.1 What is the benefit of coconut oil to people with CF?

Evidence Table

There were no studies available within the search strategy and criteria that addressed this PICO.
15.4 Herbal Supplements

PICOs

15.4.1 Is there evidence that dietary supplementation with specific herbal products or their components improves health outcomes in people with CF?

Search strategy: See T2.4 Systematic Search Strategy

Search terms:

Herbal supplements
  - Cystic fibrosis, CF, nutrition, diet, complementary therapies, herbal products, herbal medicines, garlic, curcumin, ginseng, turmeric, anti-bacterial, antioxidant, anti-inflammatory

Inclusion & exclusion criteria:

Inclusion criteria:
  - Studies specific to cystic fibrosis (must include subjects with cystic fibrosis)
  - Systematic reviews

Exclusion criteria:
  - Studies that didn't specifically address the PICO
  - Case reports
  - Guidelines and consensus documents
  - Review papers
**CLINICAL QUESTION**  
15.4.1 What is the benefit of herbal to people with CF?

**Evidence Table**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Level (NHMRC) and quality (ADA)</th>
<th>Study design and sample</th>
<th>Intervention and outcomes</th>
<th>Results</th>
<th>Comments</th>
<th>Appraiser limitations</th>
</tr>
</thead>
</table>
- Baseline characteristics similar at baseline.  
- FEV1: The percentage change in FEV1 between the treated and control groups was greater decline in the placebo group than the treated group however this did not reach significance; p=0.8  
- Weight: Not significant p=0.6(treatment group increased more weight than placebo but this was not significant).  
- Clinical score:  
  - Not significant p=0.16 however garlic group did have an improvement in symptoms compared to the placebo group.  
- IVAx (incidence and duration):  
  - 7 participants in the garlic group received intravenous antibiotics compared to 5 in the placebo group; however, days of antibiotic use was not reported.  
  Adverse events:  
- All events were “mild” (not requiring treatment):  
  - 5 participants in each group had abnormal liver function or triglyceride levels.  
  - 5 participants in the garlic group reported minor adverse effects |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
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- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |  
Exclusion criteria:  
- Abnormal clotting  
- Thrombocytopaenia  
- Raised LFTs  
- Pregnant or lactating |
(diarrhoea (two participants), halitosis (two participants), abdominal pain (one participant), dysuria (one participant), minor haemoptysis (one participant)).

- One participant from the placebo group reported a minor haemoptysis.

**Conclusion:**
- Garlic supplementation showed no significant improvement in the clinical parameters of lung function, weight and clinical symptoms.
- Demonstrated an encouraging but non-significant trend towards improvement in lung function, weight and symptom score with garlic supplementation.
- Adverse events were mild and were either predictable side effects of garlic or intrinsic features of CF.

---

**Evidence Statement Matrix**

**Chapter 15 Q15.5 Is there evidence that dietary supplementation with specific herbal products or their components improves health outcomes in individuals with CF?**

**NHMRC Grade for recommendation** Grade D

**Evidence statement:** There is no evidence that dietary supplementation with the specific herbal products garlic, curcumin or ginseng or their components improve health outcomes in individuals with CF. Garlic is the only herbal product that has been studied in humans with CF. The evidence relating to garlic supplementation for improving health outcomes in individuals with CF is minimal with only one trial demonstrating non-significant results for both respiratory and nutritional outcomes.

<table>
<thead>
<tr>
<th>Evidence base</th>
<th>D Poor</th>
<th>One Level II RCT (n=13, ADA neutral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>D Poor</td>
<td>Uncertain duration required to achieve the effect.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unable to determine the size of the effect.</td>
</tr>
<tr>
<td>Generalisability</td>
<td>C Satisfactory</td>
<td>• It may be clinically sensible to apply this evidence to the CF population however uncertainties remain.</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Applicability</td>
<td>B Good</td>
<td>• Herbal supplements are available on the Australian and New Zealand market however compliance may be an issue in the CF population.</td>
</tr>
</tbody>
</table>
Chapter 16 **Lung transplantation**

This chapter is a narrative of the CF nutrition lung transplantation considerations and includes a general review and discussion of the available literature. No clinical questions and PICOs were identified for this chapter.

Chapter 17 **Implementing, evaluating and maintaining the guidelines**
Chapter 18 **Appendices**
Appendix A  Expression of interest – Dietitian steering group

The ‘2006 Australian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis (CF)’ requires revision to remain contemporary. These guidelines outline the key nutrition issues that people with CF face; providing dietetic practitioners and other CF clinicians with clear, evidence based practice recommendations.

As with the previous edition, this update will be a collaborative approach between the Australian (Dietitians Association of Australia - DAA) and New Zealand (Dietitians New Zealand - DNZ) CF dietetic special interest groups. Where possible, a collaborative partnership with the Dietitians of Canada (DC) will also be formed. The Canadian dietitians are currently working on updating the international CF Practice-based Evidence in Nutrition pathway.

Role and function:

The role of this steering group will be to:

- Coordinate the revision of the ‘2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis’.
- Identify ways of finding motivated volunteers (within membership) to contribute towards content, ensuring that they are supported and acknowledged for their contribution.
- Ensure effective international collaboration.
- Develop a strategy to manage any actual or perceived conflicts of interest.
- Develop an inclusive strategy of obtaining ongoing stakeholder input from dietitians working in CF, other disciplines and consumers.
- Provide regular updates on progress to relevant professional associations (e.g. DAA, DNZ, and Cystic Fibrosis Australia).
- Submit revision for publication and/or endorsement and/or PEN approval.

Requirements:

**Essential:**
- Currently or recently working in the area of CF.
- Ability to commit to attend meetings, 1 hour each month.
- Time to read, and sometimes comment on material between meetings
- Depending on individuals involvement in writing sections of the guidelines actually time commitments could be highly variable and extensive.
- Ideas
- Enthusiasm

**Desirables:**
2 years CF experience, 5 years dietetic experience
Interest in evidence based practice & guideline development

Selection process:

Up to 15 steering group members will be selected (10 from Australia, 5 from New Zealand), ensuring that there is adequate representation from different geographical areas, as well as, from paediatric and adult CF services. All expressions of interest will be selected using a merit based system.

**Australia:** The Australian CF state conveners will meet on the12/7/2012 to review all expressions of interest and select Australian representatives. A quorum of more than 50% attendance of state conveners will be required to vote. (State CF conveners: Jodie Grunert – SA Paeds, Catherine Painter – SA adults, Angela Matson – QLD, Rachel Cavenagh - VIC, Nicole Micallef – TAS paeds, James Maclachlan - TAS adults, Christie Graham, NSW, Western Australia – Paul O’Neil).

**Please complete the attached expression of interest form and forward to Paul O’Neil by COB Thursday 5th July 2012 (Paul.Oneill@health.wa.gov.au)**

Successful applicants will be notified late July 2012.
Appendix B  Expression of interest – Interdisciplinary steering group

The ‘2006 Australian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis (CF)’ are due for review. This planned revision will provide a contemporary and comprehensive resource that addresses the many aspects of nutrition management of cystic fibrosis (CF), emphasising the dietitians role in the interdisciplinary CF team. The revision project sits primarily under the Thoracic Society of Australia and New Zealand (TSANZ) Clinical Care Resource Subcommittee (CCRS).

An existing steering group comprised of Australian Accredited Practicing Dietitians’ (APDs) and New Zealand Registered Dietitians (RDs), with clinical experience in assessing evidence and in the nutritional management of CF, will develop and write the guidelines. The dietetic steering group will report to the interdisciplinary steering group.

The interdisciplinary steering group will provide expert advice regarding the nutritional issues and interventions related to CF during the evidence based guideline development. The group will comprise of members with clinical leadership, and specific expertise. Members will not be a representative of a particular group or organisation but will be a member in their own right.

More specifically, the role and function of this steering group is to:

- Provide expert knowledge and guidance in their specialist areas. Including advising group if a TSANZ guideline or position paper in a particular area has already been developed or is currently in development.
- Provide input into the scope of the project and the clinical questions to be addressed
- Help develop practice recommendations
- Provide feedback on drafts of the guidelines and other publications
- Assist with developing a strategy to manage any actual or perceived conflicts of interest
- Submit revision for publication and/or endorsement

Required membership:

<table>
<thead>
<tr>
<th>Dietitians x2</th>
<th>Adult Respiratory Physicians x2</th>
<th>Paediatric Respiratory Physicians x2</th>
<th>Endocrinologist x2 (adult and paediatric)</th>
<th>Gastroenterologist x2 (adult and paediatric)</th>
<th>Pharmacist x1</th>
<th>Nurse Coordinator x1</th>
<th>Diabetes Educator x1</th>
<th>Social Worker/Psychologist x1</th>
<th>Physiotherapist x1</th>
<th>Librarian x2</th>
<th>Individual with CF</th>
</tr>
</thead>
</table>

Requirements:

Essential:

- Currently or recently working in the area of CF
- Ability to commit to attend meetings, 1-2 hours every 6 months
- Time to read, and sometimes comment on material between meetings
- Ideas
- Enthusiasm

Desirables:

- Interest in evidence based practice & guideline development

Selection process:

The TSANZ CCRS will vote on membership to this group.

Why consider joining this group?

Contribution to the interdisciplinary steering group may provide personal professional development by opportunities for career or clinical advancement with new skills and achievement, or increase individual knowledge to improve clinical practice and application, or to increase networking. Please note: The interdisciplinary steering group will not have rights of authorship (unless significant contributions are made to the content) and the group will be acknowledged in any publication.
Appendix C  CF Study Summary Template (completed example)
### Quality Criteria Checklists: Primary Research

#### RELEVANCE QUESTIONS

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/population group? (NA for some Epi studies)

2. Did the authors study an outcome (dependent variable) or topic that the patient would care about?

3. Is the focus of the intervention or procedure (dependent variable) or topic of study a common issue of concern to dentistry practice?

4. Is the intervention or procedure feasible? (NA for some epidemiological studies)

If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.

#### VALIDITY QUESTIONS

1. Was the research question clearly stated?
   - 1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?
   - 1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?
   - 1.3 Were the target population and setting specified?

2. Was the selection of study subjects/patients free from bias?
   - 2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognostic criteria), and with sufficient detail and without omitting criteria critical to the study?
   - 2.2 Were criteria applied equally to all study groups?
   - 2.3 Were health, demographics, and other characteristics of subjects described?
   - 2.4 Were the subjects/patients a representative sample of the relevant population?

3. Were study groups comparable?
   - 3.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)
   - 3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?
   - 3.3 Were concurrent controls used? (Concurrent preferred over historical controls)
   - 3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were presenting differences accounted for by using appropriate adjustments in statistical analysis?
   - 3.5 If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)
   - 3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?

4. Was method of handling withdrawals described?
   - 4.1 Were follow up methods described and the same for all groups?
   - 4.2 Was the number, characteristics of withdrawals (i.e., dropout, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 85%.)
   - 4.3 Were all enrolled subjects/patients (in the original sample) accounted for?
   - 4.4 Were reasons for withdrawals similar across groups?
   - 4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?

5. Was blinding used to prevent introduction of bias?
   - 5.1 In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?
   - 5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)
   - 5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk
**APPENDIX 5: QUALITY CRITERIA CHECKLISTS: PRIMARY RESEARCH**

<table>
<thead>
<tr>
<th>Factors</th>
<th>5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.5 In diagnostic study, were test results blinded to patient history and other test results?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervention factors described?</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>6.1 In RCT or other intervention trial, were protocols described for all regimens studied?</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6.2 In observational study, were interventions, study settings, and clinicians/providers described?</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?</td>
<td></td>
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<tr>
<td></td>
<td>6.4 Was the amount of exposure and, if relevant, subject/patient compliance measured?</td>
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<td></td>
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<tr>
<td></td>
<td>6.5 Were co-interventions (e.g., ancillary treatments, other therapies) described?</td>
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<tr>
<td></td>
<td>6.6 Were extra or unplanned treatments described?</td>
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<tr>
<td></td>
<td>6.7 Was the information for 6d, 6e, and 6f assessed the same way for all groups?</td>
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<tr>
<td></td>
<td>6.8 In diagnostic study, were details of test administration and replication sufficient?</td>
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<tr>
<td></td>
<td>7. Were outcomes clearly defined and the measurements valid and reliable?</td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>7.1 Were primary and secondary endpoints described and relevant to the question?</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>7.2 Were nutrition measures appropriate to question and outcomes of concern?</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>7.3 Was the period of follow-up long enough for important outcome(s) to occur?</td>
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<tr>
<td></td>
<td>7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?</td>
<td></td>
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<tr>
<td></td>
<td>7.5 Was the measurement of effect at an appropriate level of precision?</td>
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<tr>
<td></td>
<td>7.6 Were other factors accounted for (measured) that could affect outcomes?</td>
<td></td>
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<tr>
<td></td>
<td>7.7 Were the measurements conducted consistently across groups?</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>8. Was the statistical analysis appropriate for the study design and type of outcome indicators?</td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>8.1 Were statistical analyses adequately described the results reported appropriately?</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>8.2 Were correct statistical tests used and assumptions of test not violated?</td>
<td></td>
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<tr>
<td></td>
<td>8.3 Were statistics reported with levels of significance and/or confidence intervals?</td>
<td></td>
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<tr>
<td></td>
<td>8.4 Was &quot;intent to treat&quot; analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?</td>
<td></td>
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<tr>
<td></td>
<td>8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>8.6 Was clinical significance as well as statistical significance reported?</td>
<td></td>
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<tr>
<td></td>
<td>8.7 If negative findings, was a power calculation reported to address type 2 error?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>9. Are conclusions supported by results with biases and limitations taken into consideration?</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>9.1 Is there a discussion of findings?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.2 Are biases and study limitations identified and discussed?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10. Is bias due to study's funding or sponsorship unlikely?</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>10.1 Were sources of funding and investigator's affiliations described?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.2 Was there no apparent conflict of interest?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MINUS/NEGATIVE (-)**

If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.

**NEUTRAL (0)**

If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (0) symbol on the Evidence Quality Worksheet.

**PLUS/POSITIVE (+)**

If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.

---

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## Appendix E  ADA Quality Criteria Review Articles

### Quality Criteria Checklist: Review Articles

#### Relevance Questions

<table>
<thead>
<tr>
<th>Number</th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Will the answer if true, have a direct bearing on the health of patients?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>Is the outcome or topic something that patients/dentist/patient groups would care about?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>Is the problem addressed in the review one that is relevant to dental practice?</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>Will the information, if true, require a change in practice?</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

If the answers to all of the above relevance questions are “Yes,” the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.

#### Validity Questions

<table>
<thead>
<tr>
<th>Number</th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Was the question for the review clearly focused and appropriate?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Was the search strategy used to locate relevant studies comprehensive?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Were explicit criteria used to select studies to include in the review?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Was there an appraisal of the quality and validity of studies included in the review?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Were specific interventions/exposures described?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Was the outcome of interest clearly indicated?</td>
<td></td>
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<tr>
<td>7</td>
<td>Were processes for data abstraction, synthesis, and analysis described?</td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>Were the results clearly presented in narrative and/or quantitative terms?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>Are conclusions supported by results with biases and limitations taken into consideration?</td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>Were bias due to the review's funding or sponsorship unlikely?</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

#### Plus/Positive (+)

If most of the answers to the above validity questions are “Yes” (must include criteria 1, 2, 3, and 4), then the report should be designated with a plus (+) on the Evidence Quality Worksheet.

#### Neutral (0)

If the answer to any of the first four validity questions (1-4) is “No,” but other criteria indicate strengths, the report should be designated with a neutral (0) symbol on the Evidence Quality Worksheet.

#### Minus/Negative (-)

If most (six or more) of the answers to the above validity questions are “No,” the review should be designated with a minus (−) symbol on the Evidence Quality Worksheet.
Appendix F  Chapter structure + table keys

Please follow the order and structure below for topics. Font = Calibri 10 point. Reference sodium layout in main doc for further example.

Heading =  X.X (Section) Title

Heading =  Author (section leads)

(No heading) =  Background introduction
(Add text). Brief introductory paragraph of significance in CF. What is role. Why important.

Where found.

Heading =  DISEASE AETIOLOGY (relevant to CF)
(Add text) What is relationship to CF. What are the CF related causes? What influences X in CF
Conclude with info about prevalence

Heading =  (A) ASSESSMENT
Insert any assessment PICOs with numbering (ie PICO X.1.1)
Grade X: Add official recommendation.

Sub headings =  DIET (add text) Include points to consider re assessing
CLINICAL (add text) Signs and symptoms of X include..... specific anthropometrical considerations if relevant
BIOCHEMICAL AND LABORATORY DATA (add text) What biochemical, laboratory, data do we want people to pay special attention to?

Heading =  (D) NUTRITION DIAGNOSIS
(Add text) – Example PES statement - Nicole will add this if you are unsure

Heading =  (I) INTERVENTION
Insert any intervention PICOs with numbering -
Grade X: Add official recommendation.
(Add text) - provide succinct information supporting recommendation made above

Heading =  (M) MONITORING & EVALUATION
Insert monitoring and evaluation PICOs with numbering
Grade X: Add official recommendation.
(Add text) - provide succinct information supporting recommendation made above

Heading =  Translation into practice - Practice support information (highlighted section)
(Add text) Insert information that aids clinical practice and understanding

Heading =  REFERENCES
Embed references in Harvard format and include complete references at the end of document.

NOTES

- PICO questions
  (Refer to PICO question summary table in the exec summary of main doc to identify category (ie ax, dx, monitor / eval)
  All PICO’s are to be added to relevant section ie Assessment, intervention or monitoring & evaluation. Include PICO number.
• PICO grade X to follow
• PICO recommendation to follow directly after the question – and expanded with relevant explanatory/ supporting info (specific and succinct). Include tables etc of directly relevant information. Include references.
• Use exact headings and follow exact structure order as above. You focus on content headings & following structure— we will adjust fonts, layout, writing style etc if this aspect adds complexity for you.

BLUE TABLES - Summary of Evidence, Recommendations and Practice Points
These tables appear at the front of the document, following the executive summary
CHAPTER No. CHAPTER TITLE

<table>
<thead>
<tr>
<th>Question X. X **Add Section TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>QX.1 = PICO question number/s</td>
</tr>
<tr>
<td>Q X.2 (etc)</td>
</tr>
<tr>
<td>Add PICO question/s – repeat for the number of relevant PICO questions and number accordingly</td>
</tr>
<tr>
<td>As above. Continue for all PICO questions in consecutive order</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>R X.1 = recommendation for PICO number</td>
</tr>
<tr>
<td>GRADE X Add - indicate NHMRC level of evidence (ie GRADE A, B, C or D)</td>
</tr>
<tr>
<td>Add grade and recommendation relevant to PICO question / s. Repeat for the number of PICO questions OR Insufficient evidence to make a recommendation</td>
</tr>
<tr>
<td>As above. Continue for all PICO questions in consecutive order</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PRACTICE POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP X.1</td>
</tr>
<tr>
<td>Add consensus opinion related to evidence / or lack of evidence to guide practice for each PICO question.</td>
</tr>
<tr>
<td>Add practice points that were deemed relevant by the dietitian authorship group and the interdisciplinary expert committee, where there was insufficient high-quality data to guide clinical practice. In other words, the practice points are based on consensus expert opinion. Dietitians and other disciplines still require guidance to ensure good clinical practice. As with the practice recommendations, each practice point is numbered to be consistent with the chapter to which they pertain.</td>
</tr>
<tr>
<td>As above. Continue for all PICO questions in consecutive order</td>
</tr>
</tbody>
</table>

ORANGE TABLES - Evidence matrices these appear in Appendix C.

CHAPTER X. TITLE - X.X Topic Name

<table>
<thead>
<tr>
<th>QUESTION X.X.X **Add PICO question here</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence statement: Add evidence statement relevant to above PICO question</td>
</tr>
<tr>
<td>Evidence base</td>
</tr>
<tr>
<td>Excellent / good /</td>
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<td></td>
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<td>-----------</td>
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<tr>
<td><strong>Consistency</strong></td>
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<tr>
<td><strong>Clinical impact</strong></td>
</tr>
<tr>
<td><strong>Generalisability</strong></td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
</tr>
</tbody>
</table>