A COLLABORATION BY SPECIALIST DIETITIANS WITH EXPERIENCE IN NEUROENDOCRINE NEOPLASMS

A Dietitian Developed Practical Guidelines for the Dietary Management of Neuroendocrine Neoplasms

Literature review, best practice and consensus guidelines

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Summary

This guideline was developed by a group of dietitians specialising in NEN from around the world. It provides detailed information on nutritional issues often faced by patients with a NEN diagnosis, taking into consideration the impact of disease itself, treatments and past interventions as well as the large variation between different NEN diagnoses. This is the first nutrition NEN guideline. It has been developed to be used by qualified healthcare professionals, including dietitians to support patient care. The guideline can be read in full or in sections.

Contents

Abbreviations

AI - Adequate Intake

APTT – Activated Partial Thromboplastin Time

BAM – Bile Acid Malabsorption

BAPEN - British Association for Parenteral and Enteral Nutrition

BIA - Bioelectric Impedance Analysis

BMI - Body Mass Index

BNF - British National Formulary

CFA - Coefficient of fat absorption

CGM - continuous glucose monitoring

^{13}C-MTG - ^{13}C-Mixed Triglyceride

CRP - C-reactive protein

DEXA - Dual-Energy Absorptiometry

EFSA - European Food Safety Authority

FODMAP – Fermentable oligo-di-mono-saccharides- and polyols

GEP-NEN - Gastroenteropancreatic Neuroendocrine Neoplasm

GI – Glycaemic Index

HGS – Hand grip strength

HPB - hepato-pancreato-biliary

IBS – Irritable Bowel Syndrome

IU – International Unit

IV – Intravenous

MCV - mean cell volume

MMA - Methylmalonic acid

MDT – Multidisciplinary Team

MUST - Malnutrition Universal Screening Tool

NEN – Neuroendocrine Neoplasm

NAS – No Added Salt (low salt)

NICE – National Institute for Health and Care Excellence

NIS - Nutrition Impact Symptoms

NRS 2002 - Nutritional Risk Screening 2002

PAL - Physical Activity Level Factor

PEI – Pancreatic Exocrine Insufficiency

PERT – Pancreatic Enzyme Replacement Therapy

PG-SGA - The Patient Generated Subjective Global Assessment

PIVKA-II – Protein induced by vitamin K absence or antagonism-II

PN – Parenteral Nutrition

PPI – Proton Pump Inhibitor

PRRT - Peptide Receptor Radionuclide Therapy

PT – Prothrombin time

PTT - partial thromboplastin time

PTH - parathyroid hormone

PUFAs - Polyunsaturated fatty acids

QoL – Quality of Life

RDI - Reference Daily Intake

RE - retinol equivalent

REE - Resting Energy Expenditure

RI – Reference Intake

RNI - Reference Nutrient Intake

SGA - Subjective Global Assessment

SIBO – Small Intestinal Bacterial Overgrowth

SSA - Somatostatin Analogue

TEE - total energy expenditure

tHcy - Total plasma Homocysteine

TRPV - Transient receptor potential vanilloid-1

VAA – Vasoactive Amines

VLDL - Very low density lipoproteins

ZES - Zollinger Ellison syndrome

Introduction

Mette Bore, Tara Whyand and Yasmin Chotai de Lima

It is well established that malnutrition has negative clinical and financial consequences. The British Association for Parenteral and Enteral Nutrition (BAPEN) in September 2018 defined malnutrition as “a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measureable adverse effects on tissue/body form (body shape, size and composition) and function and clinical outcome” [1]. Within the body of research on neuroendocrine neoplasms (NENs), a study by Maasberg et al highlighted the impact of malnutrition on length of hospital stay and survival, even when adjusted for differentiation, grade, stage and treatment [2]. In addition to malnutrition of macronutrients, in the area of NENs there is growing recognition of the rates of micronutrient deficiencies, discussed further in this document. The causes and manifestations of malnutrition in NENs are

multifactorial and include suboptimal nutritional intake, alterations in energy/nutrient requirements and metabolism, and malabsorption [3]. The patient journey is often long, frequently involving different medical and surgical treatments. Treatment related side-effects add additional complications, requiring further modifications to micronutrient, and macronutrient intake, or therapies to aid with digestion. As noted with colorectal cancer, dietary therapy is complex, timely and unique to every individual patient [4]; this is very much the case with NENs.

There is a much larger body of evidence around clinical diagnostics and pharmacological management of NENs, but with less funding for nutrition research, there is limited data for the dietary management. There is a growing workforce of dietitians specialising in NENs as the need to identify and tackle malnutrition and support symptom management and quality of life (QoL) in this patient group is increasingly and more widely recognised.

Dietitians are the only health professionals qualified to assess, diagnose and treat diet and nutrition problems on an individual level. Dietitians have undertaken at least 3-5 years of university study and intensive training in clinical nutrition before qualification. Those specialising in NENs will have a number of years post-graduation specialist experience in gastroenterology, hepato-pancreato-biliary (HPB) surgery and/or oncology. Due to the complexities and variability in the disease, a specialist NEN dietitian is well placed to support patients. It should be noted that the United Kingdom spelling of dietitian has been used throughout the document but is synonyms with dietician, or as translated into other languages.

Currently, there are no international dietary guidelines specifically dedicated to NEN. Patients can require intensive long term management, often facing a number of complex issues, and as a result, expert international guidance for treating common nutritional problems is warranted. The aim of guideline development was to review the literature and produce guidance on the diet and nutrition management of the most common NENs, as well as set the agenda for future dietary research. Clinical

experience with consensus among the group was used where research is lacking. The document was created to support qualified dietitians seeing patients. It may be used to support other healthcare professionals but a recommendation of the group is that centres invest in a specialist NEN dietitian role.

The document is designed to either be read in full or in individual sections to support care of patients. The 'Micronutrients' overview section and 'Fat Soluble Vitamins' overview section should be read before referring to individual micronutrients.

Guideline Development

From July 2019 - June 2020, a team of 8 specialist NEN dietitians from around the globe joined to provide their expert opinions and create the first practical nutrition guidelines for international use. A literature search was carried out for journal articles and conference abstracts through PubMed, Google Scholar and ENETS Abstract Library for the terms: neuroendocrine tumors/tumours/neoplasms, carcinoid and: nutrition; nutritional deficiencies; diet; vitamins, trace elements, niacin, micronutrients, malnutrition screening, anthropometry, bile acid malabsorption, complementary therapy, and nutritional supplements. All relevant research was considered but the search was carried out in English and so was limited to papers in English. Relevant references from review papers were also used as well as ENETS Consensus Guidelines for specific tumour types to provide considerations on the impact of the disease and treatment on nutrition. A final review and edit of the guidelines was completed between April 2021 and April 2022 with the inclusion of any further recent literature and involving the addition of a specialist diabetes dietitian, pharmacist and NEN consultant.

Nutritional Status and Screening

Mette Borre and Tara Whyand

Background

Systematic nutrition screening on hospital admission followed by nutritional assessment and dietetic support has in a recent randomized control trial shown to

improve both clinical outcome and survival in medical and cancer patients [1]. The prevalence of malnutrition in cancer patients is estimated to be ~30% [2] to 70% among hospitalized patients depending on malignancy and tumour burden [2, 3, 4, 5]. Unintentional weight loss and loss of physical performance combined with systemic inflammation have a negative influence on outcome, including risk of infections, length of hospital stay, breaks and dose reduction of anti-cancer treatments and overall survival [6].

Malnutrition in cancer patients is a syndrome that involves early satiety, anorexia, unintentional weight loss, low body mass index (BMI), muscle wasting, lower performance status and loss of quality of life [3,4, 7]. Malnutrition is often caused by a combination of low food intake, systemic inflammation and anticancer-therapy [2,4, 8]. Sobotka et al highlights malnutrition involves altered body composition and body cell mass thereby diminishing physical and mental function and impairing clinical outcome from disease [9]. The recent Global consensus report defining malnutrition combines a phenotype criterion - reduced muscle mass, low BMI, weight-loss with an aetiology criterion - any chronic gastrointestinal condition that affects *absorption of nutrients* or reduced food intake or chronic disease burden or inflammation. Thus, malnutrition will be present if at least one phenotype criterion and one etiologic criterion are evident [10]. The European Society of Clinical Nutrition (ESPEN) recommend either BMI of <18.5 kg/m^2 or the combination of unintentional weight loss and at least one of either reduced BMI or a low fat free mass index (FFMI) to fulfil the definition. Reduced BMI depending on age is defined as <20 kg/m^2 and <22 kg/m^2 in subjects younger and older than 70 years respectively [11].

In NEN patients abdominal surgery, diarrhoea, bile acid malabsorption (BAM), malabsorption of fat-soluble vitamins and minerals, hormone release from tumour(s) and treatment with somatostatin analogues (SSAs) may affected nutritional status [12,13, 14]. Maasberg et al in their observational study evaluated the prevalence of malnutrition in 203 NEN patients using various methodological approaches including e.g. nutritional risk score and analysed the short- and long-term outcome of malnourished patients. Nutritional status was an important independent risk factor for poorer survival in the neuroendocrine setting. In addition, they reported that 21–25 % of the NEN patients were at risk of malnutrition, length of hospital stay was significantly

longer in malnourished NEN patients, and long-term overall survival was significantly reduced. In the subgroup of patients with high-grade (G3) neuroendocrine carcinomas the risk of malnutrition was shown to associate with poorer outcome [12]. One Italian observational study among patients with gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) showed an association between poorer nutritional status measured by Bioelectric Impedance Analysis (BIA), and tumour aggressiveness. The group also linked better nutritional status to stronger adherence to a Mediterranean diet [15] though diets may have been amended by subjects to be more energy dense to prevent worsening malnutrition.

Borre et al 2018 used the Nutritional Risk Score 2002 (NRS 2002) in their cross-sectional study including 186 patients. They observed that 38% of NEN outpatients were at nutritional risk even though low BMI (<20.5 kg/m2) was only evident in 12% of the patients. More than 40% of patients with a NEN reported weight loss. In the same study, more than 40% also reported change in performance status during their disease and 25% had low handgrip strength (HGS) [16].

Whyand et al 2019 observed that the vast majority of NEN patients had a normal BMI at their first visit to the clinic, though 39% of patients reported losing weight prior to diagnosis. Reduced muscle function measured by HGS was evident in more than half of patients with a new NEN diagnosis regardless of BMI [17].

In a recent study, Qureshi et al found that among 161 patients with GEP-NEN 14% of their patients had a Malnutrition Universal Screening Tool (MUST) score of >1 [13] (medium-high risk of malnutrition). They recommended the use of the MUST to assess malnutrition in all patients with GEP-NEN, and especially focusing on patients who were treated with long-acting SSAs. MUST-positive patients were two-fold more likely to be on treatment with long-acting SSAs [13], thus suggesting that SSA treatment may increase the risk of malnutrition in GEP-NEN patients. The possible etiopathogenic mechanisms include the suppression of pancreatic exocrine secretion by SSAs [18, 19] resulting in steatorrhoea [14, 20], the impairment of hepatic bile acid physiology [21, 22], malabsorption of nutrients e.g. fat-soluble vitamins [14, 23], vitamin B12, glucose, triglyceride, amino acid and calcium [24, 25, 26].

Early detection of malnutrition is important to identify patients at risk, to make preventive interventions and dietary treatment [3, 4, 5, 27]. A recent guideline from ESPEN emphasized the importance of nutritional screening and testing performance, given the negative impact of malnutrition on cancer treatment [28]. Research with NEN patients suggests the importance of measuring HGS in detecting signs of malnutrition and performance status [16, 17]. Studies on NEN have reported that patients experienced distress as a result of their symptoms, due to the impact on performance status and loss of appetite [29, 30]. Pevny et al found that among 25 patients undergoing systemic treatment, those that were malnourished at baseline as assessed by Subjective Global Assessment (SGA) had a significantly shorter 1 year survival. Those on everolimus showed lower anthropometry and BIA measures over time [31]. There is a risk however that a screening tool will miss patients at the early stages of malnutrition, especially in NEN where poor functional parameters have been noted even in the presence of a high BMI or absence of weight loss.

A two-step method to identify malnutrition is recommendable. First step consists of screening to identify nutritional risk and second step to assess the severity of malnutrition [1, 5, 32]. Screening for nutritional risk should be performed by trained healthcare professionals involved in patient care using a validated screening tool, and should include assessing for symptoms that can impact on nutritional status [5, 15, 31]. Where nutritional risk is identified, there should be a clear pathway for referring patients to a dietitian. The second step - assessment of malnutrition is a more detailed evaluation of metabolic, nutritional and functional variables and should be performed by a dietitian [5, 32].

Nutritional status is an important independent risk factor for poorer survival in the neuroendocrine setting and early detection of malnutrition is important to identify patients at risk and to guide intervention.

Nutrition Screening

Though there are many well accepted screening tools, there is no validated tool specifically for NEN. When screening, it is important that the method is efficient, quick and easy to perform, and has a good sensitivity and specificity [33, 4, 34]. Examples of screening tools to obtain a nutrition risk score include Nutritional Risk Screening 2002 (NRS 2002) and MUST [35]. NRS 2002 includes BMI, unintentional weight loss,

changes in food intake, a disease severity score and adjustment for age where the patient is ≥70 years old. MUST, which is one of the most commonly used screening methods in UK National Health Service and has been validated in cancer patients [35, 36], consists of a score for BMI, weight-loss and an acute disease score combined with dietary intake [35]. NST tool is the most widely used tool in Australia. Both the methods have sufficient efficacy and sensitivity [38], but compared to NRS 2002 the MUST score is easier and quicker to perform [32].

Recommendations:

- *All patients should be screened for malnutrition using a nutrition risk score tool, but it should not form the only pathway to a dietitian referral as patients may be missed. There are no validated tools for patients with a NEN diagnosis. The nutrition risk score can be performed by validated nutrition screening tools e.g. NRS 2002 or MUST.*
- *Nutrition Assessment should be carried out by an appropriately trained professional and should assess nutritional status as well as detection of symptoms signs of malabsorption that could affect nutritional status.*
- *Nutrition status should follow a two- part process of screening and nutrition assessment.*
- *To detect nutritional disturbances at an early stage, we recommend evaluation of nutritional intake, weight change and BMI at diagnosis which is repeated depending on the clinical situation.*
- *Development of a NEN specific nutrition screening tool is recommended.*

Albumin is Not a Reliable Nutritional Marker

Albumin is a visceral protein synthesized in the liver from amino acids coming from protein muscle catabolism or intestinal absorption. The liver has a daily capacity to synthesize up to 14 g of albumin and the synthetic rate represents the 5% of the total body albumin pool. More than 50% of albumin is located in the interstitial (extravascular) space while 40% is found in the vascular space [39]. Albumin is a carrier protein. It is the most abundant protein in serum and participates in maintaining oncotic pressure in the capillaries [39, 40, 41]. Normally, in a steady/stable situation the daily loss of albumin and its catabolism equals synthesis [38]. Albumin is characterized as an acute-phase protein, and is affected by systemic

inflammation, which leads to reduction in albumin synthesis and increase in degradation to a degree that correlates the injury [42]. Impaired liver function or diseases with systemic inflammation (e.g. sepsis, surgery and malignancy) result in low circulating levels of albumin. In contrast, anorexia nervosa with extreme weight loss, the level of albumin is often normal and unchanged [39, 43, 44].

Mechanism for hypoalbuminemia is also seen in different stages of albumin metabolism, e.g. in gastrointestinal losses, increased renal loss e.g. nephrotic syndrome or change in distribution e.g. fluid shift or edema [39, 40]. Hypoalbuminemia has shown to be a prognostic risk factor for mortality e.g. in elderly and in patients with hip fracture [45]. The half-life of albumin is about 20 days and a reduction in serum albumin in the acute setting occurs too rapidly to be caused by changes in synthesis and catabolism [39] and it is therefore a poor measure for adequate nutrient intake and an unreliable marker for malnutrition [39, 44].
Despite this, about half of different nutrition screening tools use laboratory test such as visceral proteins such as albumin [42]. NRS 2002 and MUST do not use laboratory tests [46]. Zhang et al. in a meta-analysis assessing different biomarkers including albumin and the roles in malnutrition using validated nutritional assessment tools. It was concluded that albumin is a marker of inflammation and not useful in detecting malnutrition [42, 47].

Recommendations:

- *Albumin is a marker of inflammation and on its own is not a marker of nutritional status.*
- *Albumin on its own is not suitable for assessing nutritional risk score or nutritional status in patients with NEN's.*

Nutrition assessment

Mette Borre

Individualised dietary intervention performed by a dietitian is beneficial for patients with cancer and affects nutritional intake, status, and quality of life [1, 2, 3]. A thorough nutritional assessment gives information about nutritional status and any disordered

eating [3] including for patients with a NEN diagnosis [4]. The Patient Generated Subjective Global Assessment (PG-SGA) developed for patients with cancer is a very sensitive tool and capable of detecting changes in nutritional status and identifies a range of nutrition impact symptoms [5].

The lack of consensus regarding how best to measure and define muscle mass is a challenge. Methods can be time consuming, require extensive training and may not be available in the clinical setting. Examples of methods to measure lean body tissue include dual-energy absorptiometry (DEXA), anthropometry with skinfold callipers and tape measure, and BIA [6].

In one study, during Nutrition assessment with the dietitian, 43% of patients with a NEN diagnosis reported weight loss and loss of performance status during their disease. On initial assessment 25% already had low handgrip strength [7]. In a study by Whyand et al 19 females and 24 males, aged 22-85 years were measured and questioned in the NEN clinic within three months of their diagnosis. Of the newly diagnosed patients 93% had a BMI ≥20kg/m^2. Weight loss leading up to diagnosis was reported in 17/43 (39%) patients and was predominantly among those with a small intestinal or appendiceal primary (53%) [8].

Food intake

Change or reduction in food intake should be recognized as well as the determination of factors that affect sufficient food intake [2, 9, 10, 11, 12, 13]. Quantification of energy and protein intake is important. The dietary energy and protein intake should be assessed for at least two days using methods such as food diaries, diet history, or food recalls, qualitatively and, if possible, quantitatively [2, 3, 14, 15]. Consider the impact of any diet restrictions/special diets on macronutrient and micronutrient intake.

Nutrition Impact Symptoms (NIS)

NIS is a major issue in NENs. Reduced food intake may result from a variety of causes. In finding the underlying causes for reduced food intake and weight loss, NIS can help the nutritional care of these patients [5, 10, 11]. A NIS questionnaire provides additional important clinical information before the nutritional intervention and identifies if any issues or symptoms are reversible or treatable. NIS could consist of

changes in appetite, smell and taste, nausea, vomiting, gastro intestinal dysmotility (diarrhoea, constipation), dry mouth and pain when eating, drug related side-effects, infections, acute and chronic pain, fatigue, presence of ascites, dysphagia and other eating and psychological related issues [10, 11]. Borre et al 2018 used a NIS questionnaire in their cross-sectional study including 186 patients with NEN. The most prevalent NIS among patients, rated as moderate to severe were: diarrhoea, stomach ache, dry mouth, nausea, varied appetite and altered appetite for over 3 months. Low HGS as well as impaired level of function and being at nutritional risk were associated with NIS [7]. In a study by Whyand et al. indigestion and food related abdominal pain was the most commonly reported symptoms among 37% (*n* 16 of the 43 patients included) and 52% (*n* 9) of the 17 patients with a small bowel or appendiceal NEN reported food related abdominal pain. Digestion problems were evenly spread across all diagnoses [8].

Anthropometry

The use of BMI has limitations and malnutrition within 'healthy' or 'overweight' categories can be overlooked despite significant weight loss [2]. According to ESPEN guidelines a reduced BMI is defined as <20 kg/m^2, borderline underweight is BMI 18.5-20.0kg/m^2 and malnutrition is defined with a BMI <18.5kg/m^2 [16]. Whyand et al. found that 93% of newly diagnosed patients had a BMI ≥20kg/m^2 [8]. This is similar to the study by Borre et al. where only 12% had a BMI <20kg/m^2 and the mean BMI was 25kg/m^2 [7]. In the study by Qureshi et al. the mean BMI was even higher (26.7kg/m^2) despite high rates of malnutrition being identified on screening [17]. Unintentional weight loss of ≥5% over ≤6 months is considered significant, regardless of BMI. It should be a priority to obtain repeated weight measures, and where possible other anthropometry over time, including in the outpatient setting. Body weight and height can be measured in light clothing without shoes and should be corrected for oedema and/or ascites.

Performance status, hand-grip-strength, dual-energy absorptiometry (DEXA) or bioelectrical impedance

All patients should be questioned about performance status (daily activity, physical ability and self-reported level of function e.g. confined to bed, not confined to bed or exercising) and noted if their level of function is unchanged or impaired after the NEN diagnosis. Performance status can be assessed using the performance scale

of the Eastern Cooperative Oncology Group (PS-ECOG) [18] or the Karnofsky Performance Scale 0-100% [19].

Other tools can be used to monitor daily activity or to quantitate physical performance (e.g. walking tests) or muscle function (e.g. dynamometers). HGS measured with a dynamometer can be used both as an independent nutritional assessment tool in cancer patients and as a marker of nutritional status [20, 21]. In the study of Whyand et al 21/43 (49%) of patients had a low HGS [8]. In the study by Borre et al, 25 % of the patients had a low HGS and being at nutritional risk was shown to be more common among patients with a low HGS [7]. HGS is an easy, quick and relatively cheap measurement.

Other accurate methods of measuring fat free mass include computerised tomography (CT), DEXA, air displacement plethysmography, and BIA [22]. These methods require trained staff to analyse results. In the case with CT and DEXA, scans carried out routinely can be utilized, reducing the burden on the patient. In addition, Biomarkers such as prealbumin can be prognostic indicators of disease outcome in malnourished patients, and be used alongside other assessment methods, though not commonly used in clinical practice [23].

Recommendation:

- *In patients with abnormal screening, we recommend objective and quantitative assessment of: weight, height, BMI, nutritional intake, NIS, muscle mass, muscle function, physical performance and degree of systemic inflammation.*

Requirements for Energy and Protein

Erin Lang, Tara Whyand and Yasmin Chotai de Lima

Establishing, or as a minimum estimating, energy and protein requirements for patients with a NEN diagnosis is important to guide optimal nutritional intake. The energy and protein requirements of these patients is relatively unknown and research is yet to explore the energy expenditure of patients with NEN before, during and after treatment, as well as the impact of grade and metastasis. Guidance can only be taken from general cancer guidelines, guidelines pertaining to specific treatments, and knowledge of the characteristics of NEN. Heterogenous in nature, NENs can present

at varying sites in the body and also vary in grade and aggressiveness [1, 2]. The 5-year survival rate for NEN ranges from 28-95% and NEN prognosis is generally higher in comparison to other cancer types such as adenocarcinoma [1, 2]. It is unlikely that a single recommendation for energy and protein intake is relevant for all NENs. Factors impacting the energy and protein requirements of patients may include the type of NEN and primary tumour location (e.g. lung, small intestine, colon, pancreas), grade, tumour burden, treatment received, presence of secretory syndromes (such as in carcinoid syndrome, glucagonomas and insulinomas), and metabolic syndromes such as cancer cachexia and ectopic Cushing syndrome.

Energy requirements

The gold standard for measuring resting energy expenditure (REE) is indirect calorimetry [3]. If available this method is the optimal way to determine the energy expenditure of an individual and establish recommended energy intake. In the absence of indirect calorimetry guidance on energy requirements for patients with NEN can be taken from more general cancer guidelines. The European Society for Clinical Nutrition and Metabolism (ESPEN) provide a recommendation of 25-30kcal/kg/day total energy expenditure (TEE) for patients with cancer [3, 4]. In the presence of advanced cancer or cancers of the pancreas or lung, REE is higher and therefore TEE is also estimated to be higher, due to a systemic inflammatory response [3]. Gastric and colon cancers are predicted to have lower REE and TEE, and requirements potentially closer to that of healthy individuals [3]. An instance where gastric cancers have elevated REE is after surgery. Preparation for and recovery from major gastrointestinal surgery should be taken into account when determining energy needs [3, 4]. After completing the largest literature review on requirements to date, the British Dietetic Association (BDA) Parenteral and Enteral Nutrition Group (PENG) have documented average REE for different conditions, including various cancers combined with conditions of weight loss/cachexia and weight stability depending on age and BMI. The TEE is then calculated after multiplication with a factor for physical activity level (PAL) ranging from 1.0 to 1.4 (or more if physically active) [5]. Increased liver size was found to correlate with increased REE in patients with colorectal cancer. It was also found that liver size increased as patients neared death [6]. Another study compared patients with advanced pancreatic cancer to healthy individuals. In the presence of cachexia, REE was significantly higher among patients compared to

healthy controls, however PAL and TEE were significantly lower [7]. The only NEN where literature on requirements was found by PENG is for phaeochromocytomas. The PENG guidelines document a REE for phaeochromocytoma as 23kcal/kg/day pre-adrenalectomy and 21kcal/kg/day 1 year after surgery [5]. In the original study, surgery resulted in normalisation of urine catecholamine and plasma metanephrine levels (as well as decreased prevalence of hypertension and diabetes mellitus). Indirect calorimetry was used to measure REE. REE was significantly lower 1 year after adrenalectomy compared to before surgery (where patients were deemed to be in a hypermetabolic state). Prior to surgery Harris-Benedict predictive equation underestimated energy requirements. Interestingly there was no correlation between concentration of circulating cytokines or inflammatory markers and REE [8].

Based on clinical experience, where patients are stable and have a low grade, non-functioning NEN, they often maintain their nutritional status following a healthy diet with no need for additional kilocalories or stress factor.

If cancer cachexia is suspected in cancer patients, estimated energy requirements should be adjusted based upon this. A best practice guideline from 2006 recommends the TEE for weight stabilisation in patients with cancer cachexia receiving supportive care and treatment is 120kJ/kg/day (28kcal/kg/day) [9]. In the USA a total of ≥35 kcal/kg are recommended, and if weight gain or repletion is required 40kcal/kg are promoted [10]. In general, a combination of systemic inflammation, resulting altered metabolism and reduced anabolic stimuli (such as physical activity) increases energy requirements in cancer [4]. PENG also highlight the importance of monitoring patients as any calculation is merely a guide [5]. This is particularly relevant to NENs, where the patient journey is often long and changeable.

Protein requirements

ESPEN guidelines for nutrition in cancer recommend an average total protein intake of >1g/kg/day and if possible up to 1.5g/kg/day, though 2g/kg/day maybe needed to obtain positive protein balance [3] (though additional conditions, especially renal

failure need to be considered when calculating requirements). Targeting 1.2 - 1.5g/kg/day may be helpful to restore and maintain lean body mass, and increased protein is required if severe lean body mass depletion is present [3, 4]. PENG guidelines suggest a similar protein recommendation for all cancer patients and survivors of >1g/kg/day (with 1.2g/kg/d minimum if undergoing radiotherapy), and up to 1.5g/kg/day for those with advanced disease or other risk factors such as weight loss and inflammatory response [5]. Surgical patients and those with diagnosed cancer cachexia also have a recommended protein intake of 1.4 - 1.5g/kg/day [9, 11]. In the USA it is recommended that 1.5-2.5g/kg/day is consumed [10]. There is no data on specific protein requirements for different NEN diagnoses. The rate of protein turnover or losses may be impacted by factors specific to NENs. Protein requirements may be vastly different depending on the site, grade, if a functioning NEN, and treatment(s) that the patient is going through but research is needed in the area.

In serotonin producing NEN's niacin deficiency is common and leads to the potential for pellagra to develop [12, 13]. These nutritional problems are common due to overproduction of serotonin from tryptophan [12, 13]. Pellagra is also caused by inadequate intake of tryptophan and/or niacin [14]. Although consuming proteins with larger ratios of tryptophan to other amino acids is recommended in some countries to combat this problem [15], there are no clinical studies to suggest additional tryptophan is absorbed. In humans, tryptophan has relatively low tissue storage [16] and so intake has to be regular. Tryptophan is also not the body's preferred pathway of niacin production as it requires 60mg tryptophan to make just 1mg of niacin [17]. Anecdotally in the clinical setting some patients suffering with carcinoid syndrome take L-tryptophan food supplements, however there are no clinical trials to prove tryptophan absorption or repletion in patients with carcinoid syndrome, and safety of using these supplements is not established [18]. Therefore the group do not recommend use of tryptophan supplements to prevent or correct niacin deficiency. The 'Niacin' section of this guideline provides further information and recommendations.

For patients following a vegetarian or vegan diet, it may be more difficult to meet protein requirements and so suitable high protein sources should be discussed and

encouraged. Quality of protein is impacted by digestibility, quantity of amino acids and essential amino acid composition. Plant based protein containing foods tend to have lower digestibility due to other compounds present in the food, though cooking and processing can improve digestibility. In addition, most animal protein sources are 'complete proteins, while not the case for many plant based foods. 'A 'complete protein' is a protein source where all 9 essential amino acids are contained within that food. Combining foods in a meal to provide a 'complete protein' is possible by including a plant based protein source and other grain, such as consuming legumes (rich in lysine but deficient in methionine) with corn (deficient in lysine but contains methionine), or beans with rice or wheat (such as beans on toast) [19]. Also to note, a food is often not eaten in isolation. Despite this, animal studies have shown that a subsequent meal containing amino acids limited in the previous meal can supplement the previous meal [19] suggesting less need to combine foods in one meal. Soy is a complete protein and so is a useful source of protein for those avoiding meat [20]. As with meat eaters, a variety of protein sources should be encouraged with focus on the protein portion at each meal (to support meeting requirements). For obvious reasons, a lacto-ovo vegetarian diet (including milk and eggs) is easier to follow, and more likely to enable adequate protein intakes than a diet that also avoids these foods. Therefore it might be necessary to have discussions with patients around possible compromises to any food restrictions on a case by case basis, assessing the reason for restrictions and dealing with any non-evidenced based diets. Ensuring that adequate amounts of energy from fat and carbohydrate are present at each meal will also support protein sparing (ensuring protein is available for tissue repair and building) [19]. As with meat eaters, to obtain protein synthesis, some evidence suggests protein should be included in each meal. In prevention of sarcopenia in older adults, Paddon-Jones et al. suggested ~25 - 30g of plant or animal based protein consumed at each meal (3 times a day) results in maximum protein synthesis, while consuming in excess of 30g of protein in one meal does not lead to further protein synthesis in addition to this [21]. For patients following a vegan diet, the UK Vegan Society has published a Vegan Eatwell Guide highlighting any other nutrients that need to be considered/supplemented (mainly omega 3 fatty acids, vitamin D, B12, iodine, and selenium) [22]. It is felt with the current evidence, that it is possible to meet protein requirements with a vegetarian or even vegan diet with good planning, support, and possibly use of oral nutritional supplements in patients with a NEN diagnosis, however

where patients are struggling with poor appetite, need to restrict fibre intake, or have additional complications discussed in this document, some restrictions may need to be lifted (such as addition of milk, eggs and/or fish). For those that are avoiding animal protein on assessment, the stress and emotional impact of introducing these foods should also be considered.

There is a large body of evidence that a plant based diet does boast environmental and health benefits for the general population [23], and further research on its' use among patients living with cancer is warranted. The American Institute of Cancer Research, and the World Cancer Research Fund support a plant based diet, with reduced intakes of meat for cancer prevention and living beyond cancer [24, 25]. There is no data on the role of diet or dietary compounds and NEN prevention or prevention of reoccurrence. It may be appropriate to consider cancer prevention recommendations where patients are living with a low grade NEN with a long prognosis or after curative treatment with no evidence of recurrence.

For all patients it should also be considered that protein breakdown requires gastric and pancreatic enzymes. The main site of absorption of peptides is at the terminal ileum [26]. Disease and inflammation can impact on amino acid utilisation, which has led to studies investigating the impact of individual amino acid supplementation on cachexia and outcomes with mixed results. Supplementation with individual amino acids or branch chain amino acids continues not to be recommended by ESPEN due to insufficient evidence [27]. The impact of NENs, gastrointestinal surgeries, microbiota and SSAs is an area for future research.

Recommendations:

- *Where available, indirect calorimetry should be used to determine REE and should be reassessed with any changes to the patient (such as surgical resection)*
- *In the absence of research examining the nutritional requirements in NEN (and where indirect calorimetry is not available), clinical consensus from published cancer guidelines should be used to estimate energy and protein requirements:*

- For phaeochromocytoma REE 23kcal/kg/day + PAL pre-adrenalectomy and 21kcal/kg/day + PAL 1 year after surgery
-

- *Due to the heterogeneity of NEN, clinician discretion must be used on an individual basis when estimating energy requirements and monitoring is essential.*
- *Tumour factors (NEN grade, primary tumor location, NEN functionality, and presence of metastases), treatments and individual factors (weight loss, malnutrition, lean body mass depletion, and nutrient malabsorption) should all be taken into account when estimating requirements.*
- *Functional tumours and carcinoid syndrome can elicit symptoms that impact on nutrient intake and absorption, in turn leading to complications of malabsorption, depletion of lean body mass and malnutrition; factors that may increase energy and protein requirements, though further research is needed.*
- *Where patients are avoiding animal protein, the reason for this should be assessed. Patients should be supported to meet their protein requirements, with the possible need for some restrictions to be lifted. This should be dealt with on a case by case basis.*
- *Research into NEN specific factors impacting on protein and energy requirements should be carried out.*

Micronutrients

Tara Whyand, Adele Hug, Yasmin Chotai de Lima

There is growing evidence that micronutrient deficiencies are highly prevalent in NENs. This is likely due to a combination of issues including malabsorption secondary to treatments and surgeries, complications caused by the NENs themselves, as well as potentially inadequate intake due to NIS. This section discusses vitamins and minerals that in a clinical setting deficiency is often seen and/or where there is existing literature on NENs and deficiencies, but is not an exhaustive list. It is important to consider deficiencies in other micronutrients not discussed in this chapter. Where patients are experiencing deficiencies, a referral to a dietitian should be made to ensure adequate dietary intake and to support advice on appropriate supplementation. Centres may have their own policies or guidelines

on supplementation, and where these exist local guidance should be used over the supplementation advice in this document.

Niacin

Vitamin B_3 or niacin refers to nicotinamide and nicotinic acid and is one of the 8 water-soluble B vitamins which keep the digestive system, skin and nervous system functioning normally [1]. The UK reference intake for 19-64 year olds is 16.5mg for men and 13.2mg/d for women [2] and the recommended dietary allowance for adults in the USA is 16mg for men and 14mg for females, with 17mg and 18mg needed for pregnancy and lactation respectively [3]. Best sources from food are meat, salmon, cod, milk, cheese, eggs and some fortified breakfast cereals [4]. A range of 23-70% of nicotinamide and nicotinic acid is absorbed from food [1].

Early symptoms of niacin deficiency are weight loss, decreased strength and appetite, ill-defined disturbances of the digestive tract, weakness, irritability and distractibility (prior to dermal lesions). Severe deficiency of niacin results in pellagra. The WHO describes pellagra as dermatitis, especially effecting areas exposed to the sun, which starts as an erythema with pruritus. The rash may progress to become chronic, hard, rough, and scaly with the formation of crusts due to haemorrhaging. A band of dermatitis often encircles the neck. Pellagra can affect the digestive tract and nervous system. Patients may have stomatitis, glossitis, gastroenteritis, and diarrhoea with profuse watery and sometimes bloody stools. Suffers may also experience depression, anxiety, tremor, dementia and reduced or absent tendon reflexes. In severe cases encephalopathy may occur, and if left untreated it is fatal [5].

There is no functional biochemical test to measure total body stores [3]. Assessment of whole blood 'niacin number', (a ratio derived from two biologically active forms of niacin NAD/NADP × 100) has been used to identify deficiency. 'Niacin number' suggests deficiency as it accounts for the fact that with reducing niacin status, NAD levels decline while NADP levels remain fairly constant [3]. A more accurate and reliable measurement uses urinary excretion products of niacin metabolism – N^1-methylnicotinamide (N^1-MN) or 2-pyridone [3, 5]. These measurements indicate low

levels before clinical signs of deficiency. All these biochemical tests do not diagnose pellagra, and clinical assessment is needed [3].

NEN's can produce various biogenic amines and polypeptide hormones of which serotonin is the most prominent [6]. Serotonin is derived from the essential amino acid tryptophan. In patients with carcinoid syndrome up to 99% of tryptophan is catabolised to form serotonin, which is the basis for the occurrence of niacin deficiency in this patient group [7]. Niacin deficiency in the NEN setting has been examined in an American study including 36 newly diagnosed patients with carcinoid syndrome, 32 newly diagnosed patients without carcinoid syndrome and 24 healthy controls. This study used calculation of 'niacin number' to diagnose deficiency where <130 suggested deficiency. It was found that 28% of patients with carcinoid syndrome experienced niacin deficiency and 12.5% of those with a serotonin producing NEN but no carcinoid syndrome also showed deficiency. One of the patients with carcinoid syndrome was clinically diagnosed with pellagra [8]. This is in contrast to 5 of 25 patients with carcinoid syndrome developing symptoms of pellagra, as visually assessed in a UK study [9]. In a Dutch study of 42 patients with carcinoid syndrome, 45% of patients had tryptophan deficiency and/or pellagra at diagnosis. Urine N1-Methylnicotinamide (N^1-MN) levels were measured prior and after starting niacin supplementation. Thirty three patients started nicotinamide supplementation in a mean dose of 144mg/day which led to high normal levels of N^1-MN in 86% of the deficient patients, although the range of doses was variable between 5 and 300mg/day [10]. It has been shown that giving niacin supplementation in carcinoid syndrome not only resolves several common symptoms of carcinoid syndrome and pellagra, such as skin lesions and diarrhoea, but also generally improves the health of patients [11, 12].

As previously discussed (in the 'Protein requirements' section), although protein needs are thought to be high, specifically choosing proteins with high tryptophan levels are unlikely to treat tryptophan or niacin deficiency. A total of 60mg tryptophan is required to make 1g niacin, and 100g of dietary protein/day is needed in the absence of niacin to ensure adequate niacin levels in normal circumstances (in absence of carcinoid

syndrome) [5, 13]. In the clinical setting patients have attempted to treat niacin deficiency by taking L-tryptophan supplements, but it is unknown if this tryptophan is absorbed, if it is converted to serotonin, or if these supplements are safe [14]. Nicotinamide supplements appear the most plausible and safest method to combat this nutritional problem.

The Carcinoid Cancer Foundation recommends niacin supplementation for patients experiencing weight loss, flushing, poor appetite, or elevated serotonin levels. They advise 25 - 50mg twice daily in the form of niacinamide/nicotinamide [15]. Practice in many units is to prevent niacin deficiency with early prophylactic supplementation. These doses are unlikely to treat deficiency promptly however. The WHO recommends treating pellagra with 300 mg of nicotinamide in divided doses, and treatment should continue for 3–4 weeks. Nicotinamide does not produce the side effects seen with administration of nicotinic acid (such as flushing). Acute inflammation of the tongue and mouth, and diarrhoea, subside in a few days, while dementia and dermatitis usually improve within the first week of treatment [5].

Recommendations:

- *Ideally patients with serotonin secreting NENs should be tested for niacin deficiency using urinary metabolites* (N^1-MN or 2-pyridone) where available.
- *All patients with a serotonin producing NEN diagnosis (in the absence of deficiency) should supplement with 25 – 50mg twice a day (total of 50 – 100mg daily) niacin (as nicotinamide). Further research is needed to assess if this dosing is sufficient.*
- *Treatment of niacin deficiency should follow WHO recommendations: 300mg per day nicotinamide in divided doses, for 3-4 weeks [5]. If other B vitamin deficiencies are suspected give as a multi-B supplement.*
- *Tryptophan supplements should not be recommended as they may be unsafe and it is unknown if they are utilized as intended.*
- *Following a high protein diet will not sufficiently prevent or treat niacin deficiency or pellagra caused by secretions of serotonin.*

Vitamin B12

Vitamin B12, also known as cobalamin is an essential coenzyme [1]. It is required with folic acid for the syntheses of DNA and red blood cells and is vitally important in maintaining the health of the myelin sheath insulating nerve cells [2]. The UK reference intake (RI) for 19-64 year olds is 1.5µg/d [3] and the daily value is 2.4µg/d for Americans 4 years of age or older [4]. Best sources from food are meat, salmon, cod, milk, cheese, eggs and some fortified breakfast cereals [5]. Approximately 40% of B12 is absorbed from food, and the majority of this occurs in the terminal ileum [1]. The absorption of vitamin B12 is based on intrinsic factor, a protein produced by the parietal cells of the cardiac and fundic mucosa of the stomach, which binds the vitamin to allow its absorption through the gastrointestinal tract, by way of a receptor on the intrinsic factor that is specific to cells at the terminal ileum. In cases of gastric or ileal resection or disease of the gastric mucosa or terminal ileum, vitamin B12 deficiency develops as a result of malabsorption [1]. Pernicious anaemia is a macrocytic anaemia due to deficiency of intrinsic factor or atrophy of the gastric mucosa reducing the number of parietal cells that are responsible for the production of intrinsic factor [6, 7]. Severe cases of pernicious anaemia, due to gastrectomy or ileal resection causes neuropathy [8].

The main biomarkers of cobalamin status include blood concentrations of cobalamin, transcobalamin (holoTC) and the metabolites methylmalonic acid (MMA) and total plasma Homocysteine (tHcy). Serum holotranscobalamin (holoTC) is the only form that cells can take up and therefore holoTC is more reflective of B12 status than total B12, cobalamin or holohaptocorrin but there is lack of consensus on cut off values [13]. Raised total serum Homocysteine (Hcy) can indicate deficiency as B12 is required for homocysteine recycling, though Hcy can also be raised in the presence of folate deficiency, B6 deficiency, hypothyroidism and renal failure [13].

Methylmalonic acid (MMA) is involved in a reaction that uses B12 as a cofactor and so high levels of plasma MMA may indicate B12 deficiency, though other conditions can cause raised MMA levels (including SIBO and kidney disease) [13]. Elevated mean cell volume (MCV) can indicate deficiency as a physiological correlate of B12 deficiency, however excess alcohol consumption, drug use and myelodysplastic syndrome can increase levels also [13].

The limitations of all biomarkers make a combination necessary to assess cobalamin status [1]. Levels should be assessed every 6 months as a minimum in those at risk of deficiency where prophylactic supplementation is not needed (as per supplementation column).The sensitivity and specificity of these biomarkers can be affected by factors unrelated to cobalamin status. The limitations of all biomarkers make a combination of biomarkers necessary to assess cobalamin status [1].

Type 1 and 2 gastric NENs (due to chronic hypergastrinaemia) are associated with chronic atrophic gastritis and Zollinger-Ellison syndrome respectively. The recent 'ENETS Consensus Guidelines Update for Gastroduodenal NENs' includes monitoring of vitamin B12 every 6-12 months as part of the type 1 gastric NEN conservative management algorithm. For type 3 gastric NENs, surgical resection (including partial or total gastrectomy), is the main treatment [9]. The study by Lind and colleagues, included 50 consecutive patients with small intestinal NEN's, divided in two cohorts of 25 patients, one including patients not on B12 supplements, the other one had patients treated with vitamin B12 supplementation for a minimum of 6 months). They found 32% of their patients not taking supplements had subnormal B12 levels. The reported prevalence of vitamin B12 deficiency was 41% in patients who all had undergone ileum resections of 70–100 cm, whilst in the second cohort nobody had subnormal values, thus highlighting the importance of vitamin B12 supplementation in patients with small bowel NEN and/or intestinal resections [10].

The underlying cause of deficiency should be treated if possible. The British National Formulary (BNF) advises prophylactic vitamin B_{12} be given after total gastrectomy or total ileal resection. It also states that the vitamin should be administered after partial gastrectomy if a vitamin B12 absorption test shows B12 malabsorption, where intramuscular is likely needed. Hydroxocobalamin has replaced cyanocobalamin as the advised form of vitamin B_{12} therapy as it is retained in the body for longer [11]. Prophylactic treatment of 1mg is advised as intramuscular injections every 2-3 months [12]. The BNF discusses treating deficiency in adults (in the presence of pernicious anaemia or other macrocytic anaemias without neurological involvement) with intramuscular injections of 1mg 3 times a week for 2 weeks, followed by 1mg every 2-3 months. In the presence of

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pernicious or other macrocytic anaemias with neurological involvement, the starting dose is 1mg once a day on alternate days until no further improvement, followed by 1mg every 2 months. This approach replenishes stores, followed by maintenance treatment, which is often life-long [11, 12].

Recommendations:

- *For patients with type 1 gastric NEN assess B12 level on diagnosis. If deficient then treat and retest 3 months later. Monitor vitamin B12 every 6-12 months going forward, or if B12 within normal range on diagnosis.*
- *Treat vitamin B12 deficiency appropriately depending on cause (i.e. if due to lack of intrinsic factor or resection of absorption site intramuscular injection is warranted).*
- *Patients with gastric or small intestinal NEN should have vitamin B12 levels assessed on diagnosis and 3 months after treating deficiency. Level should monitored every 6-12 months thereafter, or every 6-12 months if not deficient on diagnosis.*
- *After* partial gastrectomy*, or terminal ileal resection patients should have vitamin B12 levels monitored every 6-12 months.*
- *Prophylactic treatment is recommended for patients who have undergone total gastrectomy or total ileal resection.*

Copper

Copper is essential as an enzymatic cofactor in processes involving connective tissue formation, iron metabolism and haematopoiesis, and central nervous system function [1]. The UK RI for 19-64 year olds has remained unchanged since 1991 at 1.2mg/d [2] and the daily value recommended for Americans 4 years of age or older is 2mg per day [3]. Best sources from food are nuts, shellfish and organ meat. Approximately 50% of copper is absorbed from food, and the majority of this occurs in the upper intestine [4]. Clinical manifestations of copper deficiency are pancytopenia (including hypochromic anaemia unresponsive to iron supplementation), skeletal abnormalities, myocardial disease, depigmentation of hair (pre-mature greying), and neurologic abnormalities such as difficulty walking [5] aneurisms, and floppy skin due to problems with elastin and collagen synthesis [4]. In humans, between 80 and 95% of the copper in plasma is ceruloplasmin.

In copper deficiency, serum copper and ceruloplasmin levels are low but if the deficiency is not severe, these levels can be normal and thus do not reflect copper status in the body. Additionally, as ceruloplasmin is an acute phase reactant, ceruloplasmin and copper levels can be elevated in inflammatory states even in the setting of marginal copper deficiency [6]. In a recent study of 166 patients on parenteral nutrition, copper levels had no correlation with C-reactive protein (CRP) levels, unlike zinc, selenium, and albumin, which were negatively correlated with CRP [7]. This highlights the difficulty in interpreting serum copper levels in the setting of inflammation.

In a study of 66 NEN patients, of which 64 were diagnosed with a small intestine primary tumour, 4.7% (3 patients) were found to be deficient in copper.
Dietary adequacy for copper was not assessed [8].

The underlying cause of deficiency should be treated if possible. Since zinc can interfere with copper absorption, care must be taken to avoid copper preparations that also contain significant quantities of zinc, as may be the case with multivitamin tablets.

Hematologic symptoms may improve within one to three weeks with use of a parenteral multiple trace element product that contains 1 mg to 1.3 mg copper per day [9]. For severe deficiency, 2 mg to 4 mg parenteral copper per day can be administered separately in IV fluid [10]. The upper dose of 4 mg/day, combined with an average diet, is unlikely to exceed the provisional maximum tolerable daily intake of 0.5 mg/kg/day [11].

Recommendations:

- *Copper levels should be tested at diagnosis and at least yearly if the patient is likely to malabsorb.*

- *Caution should be taken interpreting results in the presence of inflammation.*
- *Use oral supplementation if the patient has a functioning upper digestive tract.*
- *Use parenteral/IV copper if the patient does not have a functioning upper gastrointestinal tract or they have a severe deficiency.*
- *Supplementation of micronutrients above the RI is not recommended without testing first, as blood levels should govern dosing levels and if and when to stop.*

Iron

Iron is the central molecule in haemoglobin, and so is essential for oxygen transport. Animal sources of iron can be found in the haem structure, whereas plant sources are found in the non-haem form only. Non-haem forms of iron are less bioavailable, with around 10% being absorbed by the body compared to 15-25% of haem iron [1]. As such, vegetarians may need to consume more iron-containing foods. There is evidence that vegetarians and vegans may compensate for lower iron intake by becoming more efficient at absorbing it [2]. Although more likely to have low-normal levels of iron than the general population, neither vegetarians nor vegans are at increased risk of iron deficiency anaemia [3].

It was thought bioavailability may be improved by consuming alongside vitamin C, which is a reducing agent, however this advice has recently been changed. Conversely, tannins in tea and coffee may inhibit absorption. However, in practice the overall composition of the diet has a greater impact on iron status than the presence of enhancing or inhibiting agents [4].

Cooking with cast iron cookware may improve iron status, however the level of mineral migration is dependent on chemical and physical composition of foods cooked, as well as frequency of use [5]. Rich food sources of iron include liver, meat (especially red), beans, dried fruit, whole-grains, leafy greens and fortified breakfast cereals and flour [4].

Iron status relies upon serum indicators, including serum ferritin, transferrin saturation and soluble transferrin receptor [6]. Concentration of serum ferritin is the most commonly used diagnostic indicator of iron deficiency, however, this level is raised in the presence of inflammation, even when iron becomes less available for transport. For an estimated 90% of cases, serum ferritin has been found to be successful in indicating a change in iron status in patients. However, for the individuals with the 10% highest and lowest iron levels, ferritin as an indicator of change in iron status is successful in only 60% of cases [7]. It is not stated whether there was a difference in success between the highest and lowest iron cases. For these cases, haemoglobin was found to be a more successful indicator. Serum ferritin has the benefit of having a low reliance on control groups for accuracy [7].

A common nutritional issue for patients with cancer, including NEN is iron deficiency anaemia [8]. Achlorhydria (low secretion of HCl in the stomach) is also associated with iron deficiency. Iron deficiency anaemia is confirmed when serum ferritin levels are below 15 ug/L in the absence of inflammation [7]. As patients with chronic inflammatory conditions may show raised ferritin levels, even when iron deficiency anaemia is present haemoglobin level should be tested. CRP protein test may confirm inflammatory status.

Elemental iron at doses of 100- 200mg per day should be given for iron deficiency anaemia, either as ferrous sulphate, ferrous fumarate or ferrous gluconate [9]. Menstruating women may need an additional 50-100mg of elemental iron daily to compensate for additional loss [7]. IV iron may be indicated where rapid replacement is required, oral iron supplementation is not tolerated, there is decreased intestinal absorption, where there are increased requirements, or functional deficiency [8]. Caution should be taken with IV iron as there has been serious hypersensitivity reactions reported, and should only be administered by appropriately trained staff [9].

Recommendations:

- *Iron levels should be monitored along with routine bloods by assessing ferritin, CRP and hemoglobin levels.*
- *Oral supplementation should be the first line treatment for mild or moderate deficiency, however in severe deficiency, poor tolerance of oral supplementation, functional deficiency, or cases of malabsorption, IV infusion maybe required. This should be done with involvement of the medical team to ensure that causes of iron deficiency have been considered.*
- *Where patients do not tolerate a tablet form of iron, anecdotally, some patients have found a liquid formulation better tolerated, though these are often lower dose than prescribed tablet or IV formulations.*
- *A dietitian should assess the diet for adequate dietary intake and advise on food sources where appropriate.*

Selenium

In the diet, selenium, exists as 4 forms; L-selenomethionine, L-selenocysteine, selenate and selenite [1]. A total of 25 selenoproteins with a variety of functions, including antioxidant effects, T-cell immunity, thyroid hormone metabolism, selenium homeostasis and transport, and skeletal and cardiac muscle metabolism, have been identified in humans [2]. For 19-64 year olds, the UK RI is 75µg/d for males and 60µg/d for females [3] and the daily value is 70µg per day for Americans 4 years of age or older [4].

Selenium sources include Brazil nuts, fish, meat and eggs. Selenium is well absorbed and 90% of it is absorbed in the duodenum and upper jejunum [5]. The most commonly used measures of selenium status are plasma and serum selenium concentrations [6]. Quantification of one or more selenoproteins (such as glutathione peroxidase and selenoprotein P) is also used as a functional measure of selenium status [7]. Plasma or serum selenium concentrations of 8 micrograms (mcg)/dL or higher in healthy people typically meet needs for selenoprotein synthesis [8].

Patients with pancreatic adenocarcinoma having a Whipple pancreaticoduodenectomy commonly become deficient in selenium [9]. Selenium deficiency affects the expression and function of selenoproteins and has been involved in the degeneration of organs and tissues leading to the manifestation of Keshan and Kashin-Beck diseases [1].

In one study, 16% of 66 patients predominantly with small intestinal NENs, but some with pancreatic NENs, were found to be deficient in selenium [10]. There may also be a negative influence of radiation exposure during peptide receptor radionuclide therapy (PRRT) on selenium levels. In one study, four weeks after PRRT, 18 of 21 patients showed a significant decrease in selenium levels [11]. The theory behind this suggests decreasing selenium levels lead to protective selenoproteins being compromised resulting in impaired protection against oxidative stress [12].

In 4 patients who had surgery to the upper gastrointestinal tract (2 had a pancreaticoduodenectomy, 1 patient underwent a total gastro-pancreatectomy, and 1 patient had an oesophageal resection and reconstruction with jejunal autotransplantation) all developed malabsorption syndrome within 2 yrs and had very low selenium levels. They were treated with 10–20 days of supplementation with daily intravenous administration of selenious acid 0.16 mg/d (100 µg/d of selenium). A maintenance regimen of oral sodium selenite 0.13 mg/d (60 µg/d of selenium) was given [13]. Though not NEN patients, this suggests impact of surgeries on selenium status.

Recommendations

- *Test selenium levels if a patient has no duodenum or no healthy /functioning duodenum and proximal jejunum left. Patients having Roux-en-Y gastric bypass, large duodenal resections and Whipple's operations usually require selenium supplementation.*

- *There is insufficient evidence to give selenium supplementation during PRRT without testing blood levels first.*
- *Supplementation of micronutrients above the RI is not recommended without testing first, as blood levels should govern dosing levels and if and when to stop.*

Zinc

Zinc (Zn) is an essential trace element. It has a catalytic role in each of the six classes of enzymes and helps with wound healing and processing of fat, carbohydrate and protein in food [1]. For 19-64 year olds, the RI is 9.5mg/d for males and 7mg/d for females [2]. Meat, legumes, eggs, fish, and grains and grain-based products are rich dietary zinc sources and once absorbed, albumin is the major transporter [1]. Zinc is primarily absorbed in the duodenum and proximal jejunum and absorption is mainly affected by phytates in wholegrains, legumes, nuts and seeds. Cells with a rapid rate of turnover, such as those of immune, gastrointestinal systems, and skin, are particularly vulnerable to zinc deficiency, accounting for the initial effects of dermatitis, diarrhoea, alopecia, and loss of appetite [3]. Not only can zinc deficiency cause diarrhoea, but chronic diarrhoea conditions can cause zinc deficiency, thereby worsening diarrhoea [4].

Surgical resection and bypass of the upper intestine, especially the duodenum may also cause zinc deficiency [5]. In a study of 66 patients with predominantly small intestinal NENs, 51.6% were deficient in zinc [6], possibly reflecting significant malabsorption of zinc in this patient group. It is unclear if these patients also had diarrhoea because of their zinc deficiency.

Treatment of proven deficiency can be undertaken by oral or intravenous routes. In adults of 31 kg and above, 45 mg (Zn^{2+} 100 micromole elemental zinc) is given 1–3 times a day. *Solvazinc*® tablets contain zinc sulfate monohydrate 125 mg (45 mg zinc). Alternatively, 6.5 mg of elemental zinc can be given by daily intravenous injection [7].

Recommendations

- *Consider zinc deficiency as a cause of diarrhoea and as a consequence of chronic malabsorption. Test zinc levels in anyone with chronic diarrhoea.*
- *Test zinc levels if a patient has no duodenum or no healthy/functioning duodenum and proximal jejunum left. Patients having Roux- en-Y gastric bypass, large duodenal resections and Whipple's operations usually require zinc supplementation.*
- *Supplementation of micronutrients above the RI is not recommended without testing first as blood levels should govern dosing levels and if and when to stop.*
- *Consider supplementing zinc with copper to prevent copper deficiency.*

Fat-soluble vitamins

Adele Hug, Tara Whyand and Yasmin Chotai de Lima

For fat-soluble vitamins (A, D, E and K) to be absorbed, via diet or supplementation, they must be incorporated into micelles which contain cholesterol, fatty acids and phospholipids. This process requires both bile from the liver and pancreatic enzymes so if either of these functions are impaired, deficiency of these vitamins may occur as a result of fat malabsorption [1].

Studies of healthy humans' intestinal perfusion have shown that SSAs interfere with the absorption of nutrients. Commencing on SSA therapy significantly decreases duodenal absorption of carbohydrates and triglycerides [2] therefore also potentially causing vitamin deficiencies in this patient group. One study found that 62% of the 57 patients assessed from a Gastrointestinal NET clinic had small intestinal bacterial overgrowth (SIBO) [3]. Presence of poorly digested nutrients in the small bowel may provide some explanation for the higher rates of SIBO, whereby macronutrients can act as a food source for bacteria when not digested and absorbed further up the gastrointestinal tract.

Early studies in small numbers of patients who have had resection of varying lengths of intestine showed that resection of more than 100 cm of the terminal ileum leads to insufficient intra-intestinal bile salt concentrations, which might in turn lead to steatorrhoea and fat-soluble vitamin malabsorption [4, 5]. Unfortunately existing guidelines provide unclear advice on the management of ileal resections. The guidelines of both the British Society of Gastroenterology [6] and American Gastroenterology Association [7] state that fat-soluble vitamins may need to be supplemented if <200 cm of small bowel remains after resection, but neither suggests a specific screening regimen.

Bile Acid Malabsorption (BAM) is discussed in more detail in a later section, but this and its treatment can impact on fat-soluble vitamin levels. Treatment with bile acid sequestrants can interfere with absorption of vitamins A, D, K and folic acid [8, 9] and supplementation may be required when treatment is prolonged [9].

The latest ESPEN guidelines on chronic intestinal failure strongly recommend that baseline serum vitamin concentrations are measured according to laboratory availability at the onset of home parenteral nutrition, then at least once a year. The guidelines discuss fat-soluble vitamins in detail with regard to home parenteral nutrition [10].

Fat-soluble vitamin deficiencies cause a wide variety of health problems, ranging from night blindness and osteoporosis, to bleeding and dry skin [11]. In a global survey of patients on SSA treatment, 51% of patients reported at least 1 type of fat-soluble vitamin deficiency [12]. A study by Ewang-Emukowhate et al. of 66 patients on SSAs for NEN found that 47% of patients were deficient in one or more fat soluble vitamins, with 32% (*n*=17) having multiple deficiencies. It is important to note that SSA treatment duration did not affect vitamin levels [13] and therefore deficiencies can develop quickly after treatment commences, perhaps more so in patients with lower baseline levels. The study also identified 53% (*n*=35) of patients reported taking multivitamins, vitamin D or a combination of both. Average duration of SSA use was 6.3 years and 94% of patients had been on SSA for over a year [13].

The group consensus is that levels of fat soluble vitamins should be assessed 3 months after any of the treatments discussed below that increase risk of developing deficiency (including 3 months after starting SSA). If deficient, supplementation should be started immediately and levels rechecked after 3 months. Levels should be monitored every 6-12 months thereafter, or as standard where patients were not deficient on initial assessment. Where patients are deficient, a referral to a dietitian should be made to ensure adequacy of diet intake and advise on Pancreatic Enzyme Replacement Therapy (PERT) as appropriate. Centres may have their own policies or guidelines on supplementation, and where these exist local guidance should be used over the supplementation advice in this document.

Vitamin A

Vitamin A is a fat-soluble vitamin obtained from the diet either as preformed vitamin A (mainly retinol and retinyl esters) in foods of animal origin or as pro-vitamin A carotenoids (β-carotene α-carotene, β-cryptoxanthin) in plant-derived foods [1]. The biological value of substances with vitamin A activity is expressed as retinol equivalent (RE). Vitamin A is involved in vision as retinal, which plays a central role in the mechanisms of photo- transduction. Vitamin A is also involved in the systemic maintenance of the growth and integrity of cells in body tissues through the action of retinoic acid, which acts as regulator of genomic expression [1, 2]. The UK reference nutrient intake (RNI) for 19-64 year olds is 700µg/day (2333IU) for men and 600µg/day (2000IU) for women [3] and the reference daily intake (RDI) in the United States for 4 years or older is 900µg (3000IU) [4, 5].

Foods rich in retinol include organ meat (especially liver), meat, butter, retinol-enriched margarine, dairy products and eggs, while foods rich in β-carotene include vegetables and fruits such as sweet potatoes, carrots, pumpkins, dark green leafy vegetables, sweet red peppers, mangoes and melons [2]. Preformed vitamin A is efficiently absorbed (70–90%). The absorption of β-carotene appears to be highly variable (5–65%), depending on food- and diet-related factors (including presence of fat), genetic characteristics and the health status of the subject. The intestine is the primary tissue where dietary provitamin A carotenoids are converted to retinol [2].

The most specific clinical consequence of vitamin A deficiency is xerophthalmia, which encompasses a clinical spectrum of ocular manifestations [2]. Deficiency occurs if plasma vitamin A (retinol from all trans retinol + cis retinol) is <0.8µmol/L [6]. Serum retinol <0.7µmol/L suggests severe depletion of stores (and 0.35µmol/L suggests severe deficiency). As serum retinol is homeostatically controlled it does not always correlate with intake or signs of deficiency [7] and labs will often use a higher reference range. When taking blood for vitamin A analysis, blood samples are promptly stored in a cold dark place [8].

Vitamin A toxicity may increase risk of bone fractures especially in those with an increased risk of osteoporosis. High intakes can be teratogenic to foetuses in pregnant women [10], and can also be damaging to the liver [11].

In regards to deficiency in NEN, a Dutch study of 54 of patients with a NEN and on SSA's found 6% (*n*=3) were deficient in vitamin A. Resection of a longer portion of small bowel showed an association with lower plasma vitamin A levels ($p = 0.004$), but interestingly not the plasma levels of other fat-soluble vitamins [9]. A UK-based study of 66 NEN patients on SSA's showed 8.6% were deficient in vitamin A [12].

In a NEN feasibility study by de Hosson et al. patients with a plasma vitamin A level <0.8µmol/L ($n = 3$), were given 25,000 IU retinol once daily for 14 days, followed by 5000 IU once daily until sufficient levels were reached, which was achieved by week 18 [6]. The World Health Organisation (WHO) recommendations for treating deficiency focus on children and women of reproductive age. For women of reproductive age with night blindness or Bitot's spots, it is advised they are given 5000-10 000 IU daily for at least 4 weeks. Malnourished deficient children are given a much higher dose for a shorter duration (200 000IU on day of diagnosis and the following day) [13]. It is not clear if these doses correlate with advice/practice in developed countries where malnutrition may not be to the same degree as with children in underdeveloped countries, or where deficiency is due to malabsorption. Further research is also needed to investigate how promptly levels correct if absorption is

improved (such as use of pancreatic enzymes to support pancreatic exocrine insufficiency) in addition to supplementation.

Recommendations:

- *Consensus from the group that doses from the study by de Hosson et al. [6] (25,000 IU once daily for 14 days, followed by 5000 IU once daily until sufficient) are recommended to treat deficiency in patients with NEN (including for women who are not pregnant)*
- *Further research is warranted around treating deficiency in patients with a NEN diagnosis.*
- *The cause of deficiency should be dealt with where possible.*

Vitamin D

Vitamin D is a fat soluble vitamin. There are 2 forms of vitamin D - vitamin D_2 (ergocalciferol) and vitamin D_3 (colecalciferol) [1]. The main source of vitamin D_3 is via endogenous synthesis in the skin following exposure to UV-B radiation [2]. The molecule is modified by enzymes in the liver and kidneys via hydroxylation to produce calcitriol (the most active form of vitamin D); therefore liver or kidney disease may impact on vitamin D status. In the intestine, calcitriol binds to vitamin D receptors to facilitate calcium and phosphorus absorption. In the kidney, it stimulates the parathyroid hormone (PTH) dependent tubular reabsorption of calcium [3]. In the bone, PTH and 1,25-dihydroxyvitamin D interact to activate the osteoclasts responsible for bone reabsorption. In addition, 1,25-dihydroxyvitamin D suppresses PTH gene expression, inhibits proliferation of parathyroid cells, and is involved in cell differentiation and anti-proliferative actions in various cell types [2].

The RNI in the UK and daily value for Americans for ≥4 years is: 10µg/day (400IU/day) [4, 5]. Oily fish such as salmon, sardines, pilchards, trout, herring, kippers and eel contain reasonable amounts of vitamin D, but the highest content is in cod liver oil [6]. The vitamin D2 content in mushrooms can be significantly increased by exposure to sunlight, even for a short period of time [7]. Vitamin D from dietary sources is absorbed throughout the small intestine. The European Food Safety Authority panel considers that the average vitamin D absorption from a usual diet is about 80% and limited data

are available on the effect of the food or supplement matrix on absorption of vitamin D (vitamin D_2 or vitamin D_3) [2].

Vitamin D deficiency leads to impaired mineralisation of bone due to an inefficient absorption of dietary calcium and phosphorus, and is associated with an increase in PTH serum concentration. Clinical symptoms of vitamin D deficiency manifest as rickets in children, and osteomalacia in adult, though insufficiency and deficiency have been more recently linked to other health issues, including depression, cardiovascular disease and immune response [8].

The National Institute of Clinical Excellence (NICE) categorise insufficiency as 25–50 nmol/L and deficiency is less than 25 nmol/L (9). Risk factors are broad and can include inflammatory bowel disease, bile acid sequestrants, hyperparathyroidism and chronic kidney disease.

Consuming too much vitamin D through supplementation can lead to hypocalcaemia, which can weaken bones and cause heart and kidney damage. Vitamin D from UVB rays cannot lead to vitamin D overdose as production is down regulated with increasing levels (10). Caution and close monitoring is recommended for patients on cardiac glycosides (where hypercalcaemia can enhance effects of these medications, risking toxicity) and patients on thiazide diuretics where urinary excretion of calcium maybe reduced [9].

A Dutch study of 54 of patients with a NEN or acromegaly and on SSA's found 28% (*n*=15) were deficient in vitamin D. Prevalence of vitamin D deficiency was similar in the acromegaly and serotonin producing NEN patient groups (11). In a UK study of 66 patients on SSA's, 19% were deficient in vitamin D (12). In a smaller group of 38 NEN patients in Wales, 76% (*n*=29) were deficient (13). A study of 186 patients with NEN's in Denmark showed that 34% (*n*=63) of patients took a vitamin D or vitamin D and calcium supplement combined (14).

In a recent study by Motylewska et al. including a total of 36 NEN patients and 16 control subjects, a mild vitamin D deficiency was observed in both groups. Of note, SSA therapy did not increase vitamin D deficiency. Moreover, the concentration of vitamin D in the studied group was not significantly influenced by primary tumour localisation, patient age, or season [15]. A recent retrospective-prospective study evaluated the prevalence of vitamin D deficiency in 138 patients with GEP-NENs in comparison to a control group and explored the possible role of vitamin D deficiency as a prognostic factor for NENs [16]. NEN patients had lower vitamin D levels compared to the controls. No significant correlation between vitamin D levels and the staging or grading of the disease was found. Furthermore, vitamin D supplementation exerted a positive effect on overall survival.

A recent study by Lind et al., including 50 patients with disseminated small bowel NENs, divided in two cohorts of 25 patients (one including naive patients, the other cohort of patients treated with vitamin D supplementation for a minimum of 6 months). The study found that low serum levels of vitamin D and low bone density (using DEXA scans) are common in this setting of patients. In the first cohort, 29% of the patients were severely and 17% moderately vitamin D deficient and 76% had low bone density. In the second cohort with vitamin and mineral supplementation, none had severe vitamin D deficiency, but 28% had moderate deficiency; 60% had low bone density. Based on these findings, the authors concluded that, despite normal BMI and preserved appetite, low serum levels of vitamin D and low bone density were common in these patients. Furthermore, they recommended vitamin D and calcium supplementation in small intestine NETs in order to counteract both severe deficiency of vitamin D and secondary hyperparathyroidism [3].

Robbins et al. in their recent study including 183 patients with GEP-NEN, observed a high percentage of vitamin D insufficiency (31.3%) and deficiency (35.5%) at baseline. Of note, previous abdominal surgery, but not treatment with somatostatin analogues predicted vitamin D levels. Furthermore, the authors found that simple advice to

increase vitamin D intake using over-the-counter preparations was associated with significant improvement of vitamin D deficiency/insufficiency. Low vitamin D levels persisted in 15% of GEP-NEN patients, despite over-the-counter supplementation, so additional measures of vitamin D replacement might be necessary in specific settings [1].

The mechanisms underlying the possible association between vitamin D deficiency and NEN's are still far from being clearly understood. Some possible explanations include social isolation and reduced sun exposure, gastrointestinal and pancreatic surgeries, decreased dietary intake, diarrhoea, medical therapy (including somatostatin analogues and corticosteroids) [1, 9, 15]. Magnesium also plays a role in vitamin D biosynthesis and activation as a cofactor. Vitamin D binding protein and the activities of 3 enzymes important to vitamin D status are magnesium dependant. Studies have also found that supplementing magnesium along with vitamin D lead to better replenished vitamin D levels compared to vitamin D alone [17].

In the UK, NICE recommend treating deficiency with fixed loading dose(s) of up to 300 000 IU in total with either weekly or daily doses, with some patients requiring IM, followed by a lifelong maintenance dose. NICE further recommend ensuring adequate intake of calcium [9]. As vitamin D deficiency is highly prevalent, not just among NENs, most health services have their own protocol for treating deficiency. In practice use of vitamin D spray has seen better results in treating deficiency than oral supplementation in some patient cases where malabsorption is present. A systematic review looking into buccal spray compared to other forms of supplement concluded that buccal spray is not superior. Many of the studies had limitations however [18].

Recommendations:

- *Use local guidelines to treat deficiency of vitamin D. In the UK, for example, NICE recommend treatment of deficiency with fixed loading dose(s) of vitamin D (up to a total of ~300 000 IU in total) as either weekly or daily split doses. In some*

circumstances IM injection of vitamin D maybe required. This should then be followed with a lifelong maintenance dose of 800 IU per day, though for certain groups, such as people with malabsorptive disorders, higher doses of 2000 IU to (occasionally) 4000 IU per day may be needed [9].

- *For those with insufficiency, maintenance dosing as above (800 IU to 4000 IU) should be advised [9].*
- *Most centers have their own guidelines which fall within these recommendations which should be used.*
- *Consider use of vitamin D spray in cases of malabsorption, though further evidence is needed to determine efficacy.*
- *NICE also recommends ensuring adequate dietary calcium intakes (700 mg per day for most people and 1000 mg per day for individuals with osteoporosis), while avoiding over intake of calcium from supplements [9].*
- *Ensure patients with low vitamin D status have normal magnesium levels and if not also replace magnesium along with vitamin D supplementation.*

Vitamin E

Though present in 8 chemical forms, this section will refer to alpha-tocopherol as this is the only form recognised to meet requirements [1]. A fat-soluble vitamin, alpha-tocopherol is considered crucial for human health. Alpha-tocopherol is an antioxidant involved in a complex defence system to protect polyunsaturated fatty acids (PUFAs) within cellular member phospholipids and plasma lipoproteins and prevent free-radical reactions [2].

From a usual diet, absorption of 75% is average and requires presence of fat. For adults, the European Food Safety Authority (EFSA) has set an adequate intake (AI) for alpha-tocopherol as 13mg/day for men and 11mg/day for women [3]. This is a change from the 1991 COMA recommendations of alpha-tocopherol equivalents (α-TEs). There is international variation to the recommendation of alpha-tocopherol/day due to its dependence on intake of PUFAs. The United States recommend 15mg/day for over 14 years of age using a conversion to calculate mg from α-TEs [4, 5].

Vegetable oils and vegetable oil spreads, egg yolk, nuts, seeds, whole grain cereals and some fatty fish are the main dietary sources of alpha-tocopherol. The absorption of alpha-tocopherol follows usual lipid pathways in the duodenum involving hydrolysation by pancreatic enzymes, emulsification and incorporation into micelles and uptake via non-specific transporters into the enterocytes for solubilisation before secretion into the lymph or portal vein. From here they are transported via chylomicrons in the lymphatic pathway to be secreted into systemic circulation to hepatocytes for incorporation into very low density lipoproteins (VLDL) and distributed to peripheral tissues. Storage is mostly in adipose tissue. Vitamin E excess may result in clotting disturbances but there is little evidence regarding toxicity and its effects [3].

Secondary alpha-tocopherol deficiency has been reported in severe malnutrition, fat malabsorption, cholestatic liver disease and cystic fibrosis with a plasma/serum concentration of between 2.5-12µmol/L [6-9]. Deficiency due to poor intake has not been reported.

The reference range in the Dutch NEN study classified vitamin E deficiency as < 19.2 µmol/L [10] although there is a lack of agreement on reference figure for deficiency, with huge variation between 5 - 19.2 µmol/L [11]. The study of 54 of patients with a NEN or acromegaly and on SSA's found 15% (*n*=8) were deficient in plasma vitamin E and 58% (*n*=31) were deficient in erythrocyte membrane vitamin E (a longer term measure of Vitamin E status). Prevalence of vitamin E deficiency was similar in the acromegaly and serotonin producing NEN patient groups in the Fiebrich study [12]. In a UK study of 66 patients on SSA's, 5% were deficient in serum vitamin E [13]. In a smaller group of 11 NEN patients in Wales, none were deficient in plasma vitamin E [14].

In the presence of raised serum lipid concentrations, vitamin E segregates from cellular membranes into circulating lipoproteins. Vitamin E deficiency can be missed if serum lipid levels are pathologically elevated, while conversely, where lipid concentrations are low, deficiency may be overestimated. Medications that effect serum lipid levels may also impact on results. There is lack of agreement on which

lipid levels should be tested to ensure vitamin E deficiency is accurately assessed, but cholesterol is a simple measure that has been found to lead to good results. It is therefore recommended that serum cholesterol levels are assessed when measuring vitamin E [15]. Some units may use a vitamin E:cholesterol or vitamin E:total lipid ratio.

The Dutch study used 100mg alpha-tocopherol acetate once daily as a replacement and recommend that it should be supplied until sufficient values are reached [10].

Recommendations:

- *Check vitamin E or alpha-tocopherol status alongside cholesterol levels in patients who are showing signs of fat malabsorption.*
- *As per the Dutch study by de Hosson, 100mg alpha-tocopherol acetate once daily should be administered orally until sufficient levels are reached in those who are deficient [10].*
- *More research is needed on treating and prevention of deficiency in this patient group.*

Vitamin K

Vitamin K is a family of fat-soluble compounds comprised of phylloquinone (vitamin K1) and menaquinones (vitamin K2). Vitamin K is a co-factor for the Gla-proteins that are involved in physiological processes such as blood coagulation and bone mineralisation [1].

The adequate intake (AI) is set at 1µg/kg/body weight for all ages and both male and females, however this AI is related to phylloquinone only due to limited human physiological evidence for menaquinones [1]. The daily value for Americans over 4 years is 80µg/day [2].

Phylloquinone is found in dark green leafy vegetables and brassicas such as cabbage, broccoli and cauliflower. Menaquinones are found in animal products such as meat, cheese and eggs, and the only vegetarian source is the fermented soya product Natto [1, 3]. All food source compounds of vitamin K are absorbed via complex processes in the intestine in the presence of dietary fat and transported into the blood via lipoproteins. It is important to consider the need to include dietary fat in the meal if only plant-based sources are consumed. It has been estimated that 5-7% of plant based dietary phylloquinone is absorbed. This rises to 13% up to 80% for supplementation. However EFSA have not advised an absorption percentage for Vitamin K due to lack of evidence [1]. Menaquinones are also produced by anaerobic colonic bacteria however the degree of absorption remains uncertain. Research suggests substantial quantities of long chain menaquinones in the colon and it is thought this contributes to meeting requirements [4]. The liver, and to a smaller extent, bones and other tissues store Vitamin K, but it has a fast turnover within the body [1].

The only biomarker that is associated with adverse clinical symptoms with Vitamin K deficiency is prothrombin time (PT), though not a sensitive marker of intake or status. A specialist panel concluded that there is currently no measurable marker to demonstrate Vitamin K status by itself. Protein induced by vitamin K absence or antagonism-II (PIVKA-II) antigen concentration has been noted to increase significantly in presence of deficiency compared to baseline, and levels may support assessing status [2]. Deficiency is demonstrated in adults by bleeding, with an increased PT or (activate) partial thromboplastin time (PTT or APTT) due to low activity of blood coagulation factors. [1]. There is no evidence of toxicity in adults.

A Dutch study of 54 of patients with a NEN or acromegaly and on SSA's found 63% (*n*=34) were deficient in vitamin K1 [5]. Prevalence of vitamin K1 deficiencies was similar in the acromegaly and serotonin producing NET patient groups. In a UK study of 66 patients on SSA's, 47% were deficient in vitamin K1 [6].

Menadione (vitamin K3) and menadiol sodium phosphate (vitamin K4) are water-soluble synthetic forms of vitamin K [1]. Caution is needed on using menadiol as a vitamin K replacement in those with vitamin E deficiency due to the risk of haemolysis [7]. Where absorption is an issue liquid sublingual or intravenous administration of phytomenadione is likely to result in better replacement of deficiency than oral tablets or capsules. Some intravenous preparations can be administered orally off licence, with guidance on dosing and administration route based on International Normalised Ratio (INR) [8].

Recommendation:

- *Check vitamin K along with other fat soluble vitamins in situations where fat malbsorption may be present (including SIBO) and replace as appropriate with oral preparation, or IV in cases of severe malabsorption.*
- *Avoid using menadiol in the presence of vitamin E deficiency.*

Probiotics

Tara Whyand

Intestinal microbiota composition is an area of interest in gastroenterology, as it has been reported to be involved in a large number of intestinal and extra-intestinal diseases [1], although it has not gained much attention in NEN care.

A study including 66 patients with NENs, 50 patients with Crohn's Disease (CD) and 30 patients with chronic idiopathic diarrhoea reported similar abnormalities in the composition of gut microbiota in patients with small intestinal NEN's and CD [2]. *Faecalibacterium prausnitzii (F. prausnitzii)*, is normally one of the most abundant bacterial species found in the gut [3]. In patients with NEN's, there was a significant depletion of *F. prausnitzii* though this was reversible with systemic chemotherapy and interferon alpha-2b treatment in patients with small intestinal NEN. SSAs had no influence on *F. prausnitzii* concentrations [2].

In the past few years, researchers have reported a tentative connection between response levels to immunotherapy and the microbiome [4]. A working knowledge of the microbiome for a NEN patient is vital as we move forward in the age of

individualized nutrition, and an understanding of the microbiome's influence on immune responses and NEN is key. It is also important to understand factors influencing the gut microbiome and strategies to manipulate the microbiome with diet or probiotics to augment therapeutic responses.

Probiotic bacteria are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host [5]. Taking probiotics is a popular choice for patients with a NEN [6, 7], although care and consideration of risk versus benefit is required if a patient is at risk of neutropenia, for example during chemotherapy or PPRT [8].

Recommendation:

- *There are no clinical trials of probiotics in NEN's and no specific strains or formulations can be recommended. Discussion of probiotic use should form part of discussion prior to some treatments, particularly if there is risk of neutropenia.*
- *Fecal microbiota analysis and probiotic interventions are an interesting area for future research, especially in immunotherapy.*

Dietary management of carcinoid syndrome

Tara Whyand

Patients with carcinoid syndrome may present with nutritional issues due to diarrhoea, maldigestion and flushing which can impact both on appetite and utilisation of nutrients [1, 2]. Carcinoid flushing is described as a dry flush, with a sensation of heat and reddening often on the face and chest, sometimes associated with purple spider-like veins on the nose or upper lip. Carcinoid syndrome is diagnosed by the presence of symptoms and elevated 5-hydroxyindoleacetic acid (5-HIAA). Levels of 5-HIAA are assessed either from a 24-hour urine test or, developed more recently, a blood test measuring fasting plasma levels. Foods high in serotoninergic agents and foods rich in 5-hydroxytryptophan need to be avoided for 24 - 48 hours before testing to avoid a false positive result (though do not need to be avoided at other times) [2].

Where complete surgical resection is not possible, SSAs are used as the first line treatment, with response generally seen after about 12 months. Short acting

octreotide is used for refractory carcinoid syndrome [2, 3]. Telotristat ethyl has been associated with significant improvement in diarrhoea and other symptoms of carcinoid syndrome over 1-3 months of therapy. Improvement in symptoms can also be seen with PRRT [2]. However, some patients do not experience sufficient relief with medical treatment or do not tolerate treatments.

In 2000 Monica Warner presented data from her 1999 nutrition survey, on the management of carcinoid syndrome. Of the 97 patients surveyed 35% of reported a reaction to food (either flushing, diarrhoea or both). When problem foods/meals were identified, large meals, alcohol, fatty foods and certain foods were identified as triggering a reaction. A trend was noted among many of the specific foods as those also being high in vasoactive amines (VAAs) [1].

VAAs are compounds that contain amino groups and act on blood vessels causing permeability or vasodilation, and include histamine and serotonin, among others [4]. The release of vasoactive substances is a marker of carcinoid syndrome. The most prominent of these substances is serotonin, which is then metabolized to 5-hydroxyindoleacetic acid (5-HIAA) [5]. However, the VAA histamine, and other substances may also be released. Figure 1 provides an overview of the potential involvement of VAAs (including from the diet) in carcinoid syndrome. Further information on serotonin metabolism and consequential niacin deficiency is contained in the ‘Niacin’ section. Both serotonin and histamine can be found in some foods and drinks. VAAs are produced by bacterial fermentation. Ageing food and drinks for long periods may also lead to elevated levels, as does the decay of food [6]. The VAA’s in food and drinks include beta-phenylethylamine, tyramine, tryptamine, putrescine, cadaverine, spermine and spermidine, and histamine [6]. Table 1 outlines the foods and drinks that are very high in vasoactive amines. Eating fresh foods wherever possible and quickly freezing leftovers can limit the process of bacterial fermentation and VAA production in severe cases of carcinoid syndrome [6, 7].

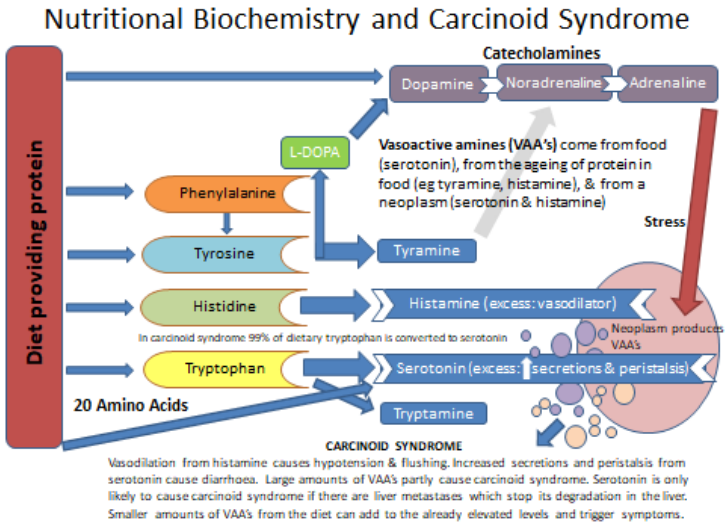


Figure 1 Nutritional Biochemistry and Carcinoid Syndrome [6-14]. Meat, poultry and fish	All cured meat especially pork products e.g. ham, salami, pepperoni, game, bacon, sausages, fresh pork, fresh or canned (salted) tuna, canned sardines, anchovies, mackerel, salmon, herring, processed fish products (fish pastes, smoked, dried or pickled fish), fish sauce
Dairy	Blue cheese, parmesan, brie, camembert, emmental, old gouda, mature cheddar and other hard cheeses
Fruit	Oranges, bananas, tangerines, pineapple, grapes, strawberries, tomatoes.
Vegetables, beans and nuts	Pickled cabbage, aubergine, spinach, broad beans, peanuts, almonds, Brazil nuts, cashews, chestnuts, hazelnuts, macadamia nuts, pecans, pistachios, and walnuts.
Soya	Fermented soy products including miso and tempeh
Drinks	Green tea, champagne, wine (especially fermented in oak barrels), coffee, cocoa, chocolate, beer, fresh fruit juices (from fruit list) and smoothies eg strawberry and banana.

Table 1. Foods and beverages most likely to contain high levels of VAA's [6, 16-21]

Monica Warner found a number of patients reacting to foods had a reaction to high amine containing foods. Alcohol can commonly cause facial flushing in the absence of a NEN, although it was found to cause 38% of patients to flush and 34% to have diarrhoea [1]. It is not clear if these symptoms were carcinoid syndrome as alcohol type was not described. Wine contains some histamine but in a placebo-controlled study, Kanny et al. found no correlation between wine histamine content and wine intolerance, and concluded that other VAA's or sulphites may be more relevant in intolerance to wine [22].

Fatty foods were also found to trigger diarrhoea by Warner [1], however this may have been due to other causes, which are now better understood, and the description of diarrhoea was not assessed to distinguish from steatorrhoea. A high fat diet or large meal can cause steatorrhoea, due to Bile Acid Malabsorption (BAM), pancreatic exocrine insufficiency or Small Intestinal Bacterial Overgrowth (SIBO). Fat can also worsen symptoms among sufferers of Irritable Bowel Syndrome (IBS), as it affects small intestinal motility [23] and may make meal related abdominal pain worse [24].

High fibre items such as fruit and vegetables can also stimulate the bowel, but are unlikely to cause such an interaction which stimulates actual carcinoid syndrome. Certain fruits and vegetables were included in the foods triggering symptoms in Werner's survey [1]. Other possible explanations include the high fibre content which stimulates the bowel, as well as amounts of fermentable oligo-di-mono-saccharides-and polyols (FODMAPs). FODMAPs are carbohydrates which largely ferment in the bacteria-rich large bowel (though not all fruit and vegetables identified in the survey are high in FODMAPs) [25]. In patients with SIBO, the bacteria ferment these carbohydrates further up in the small bowel producing hydrogen which gets absorbed and is exhaled in the breath [26]. Patients who are positive for a marked rise in hydrogen after taking the FODMAP lactulose (using the hydrogen breath test), often have symptoms of gas and diarrhoea, which can be confused with other causes of diarrhoea. Like in other gastrointestinal diseases and surgery of the gastrointestinal

tract, SIBO is common place within the NEN patient group [27] and it should be excluded especially if excessive wind occurs alongside diarrhoea.

Spicy foods were also linked to carcinoid syndrome [1], although again a possible link has not been established. Assuming these patients have gut hypersensitivity, the evidence for spices causing gastrointestinal symptoms is variable in hypersensitive patients with IBS [23]. Capsaicin is the active component in hot peppers and, in spicy food, this compound is responsible for accelerating gastrointestinal transit via the transient receptor potential vanilloid-1 (TRPV) causing abdominal pain and burning sensations in healthy individuals [28]. Increased TRPV receptors have been found in individuals with visceral hypersensitivity [28-31]. In addition, pain and stress are non-dietary potential triggers of carcinoid flushing. It is also possible that other components of spicy meals such as onions and garlic triggered symptoms because they contain high levels of FODMAPs [24].

Eads et al published an algorithm to support identifying if diarrhoea is secretory or non-secretory based on the osmolar gap from a spot stool collection. It further recommends tests and treatments depending on the cause (or suspected) cause(s) of diarrhoea [32]. The causes of diarrhoea are often multifactorial and it may take a systematic approach to target each cause individually until improvement or resolution is seen. Using a stool chart and asking for a description of stools can be helpful in targeting the most likely causes first, as well as diagnostic tests (where available), taking into account the clinical picture.

Recommendation:

- *When a patient has a functioning serotonin producing tumour it is important to consider carcinoid trigger foods/drinks using a food and symptom diary, noting diarrhoea and flushing within an hour or two of eating/drinking. Only the offending foods and drinks should be excluded from the diet.*

- *A detailed assessment of symptoms should be carried out considering all causes of diarrhoea, including carcinoid triggers, Pancreatic Exocrine Insufficiency (PEI), BAM, SIBO, IBS, pellagra, and infection, among other causes that are not necessarily specific to NENs.*
- *Where a patient develops symptoms of carcinoid syndrome (which were not present before), a return of symptoms, or an increase in carcinoid syndrome symptoms, the medical team should be made aware as this may indicate disease progression or a need to review medical treatment.*
- *Ensure all patients with a carcinoid syndrome are on 25 – 50mg niacin in the form of nicotinamide twice a day (total of 50 – 100mg daily).*
- *Assess for any signs/symptoms of niacin deficiency (see niacin section).*

Carcinoid Heart Disease

Adele Hug

Carcinoid heart disease is a major cause of morbidity and mortality among patients who have carcinoid syndrome. Severe dysfunction of the tricuspid & pulmonary valves due to fibrosis caused by excessive circulating vasoactive substances (mainly serotonin) can lead to oedema, ascites, pulsatile hepatomegaly and right-sided heart failure. Other clinical features include dyspnoea, and fatigue. Diagnosis and assessment of severity of carcinoid heart disease involves echocardiography and biomarkers, mainly N-terminal pro-B-type natriuretic peptide (NT-proBNP), chromogranin A and 5-HIAA [1]. Although there are no specific nutritional intervention studies in patients with NEN's, fluid & salt restriction may be used to improve symptoms of oedema or ascites in patients with right heart failure related to carcinoid heart disease [2]. Consensus from the group is that a no added salt (NAS) diet may be helpful in the presence of fluid retention; however there should be discussion with the medical team before recommending any fluid restrictions, and if on a fluid restriction there should be close monitoring. From clinical experience, patients are often malnourished when presenting with carcinoid heart disease, and require extensive nutrition support advice to prevent any further weight loss.

Recommendations:

- *Patients presenting with carcinoid heart disease should be screened for malnutrition with a low threshold for referring to a dietitian.*
- *Nutritional status should be assessed and malnutrition should be treated with nutrition support advice, with the potential use of alternative nutrition support if the patient is failing to meet nutritional requirements orally (and taking into account prognosis and QoL).*
- *A NAS diet can be advised in the presence of oedema or ascites. Further studies are required to assess the impact of a NAS diet.*
- *If a fluid restriction is trialed, this should be done with involvement of the medical team and with close monitoring.*

Functioning NENs and Non-Functioning Pancreatic NENs

Yasmin Chotai de Lima and Tak Wai Ho

Pancreatic neuroendocrine neoplasms (pNENs) and NENs arising in the small intestine may be functional (associated with a functional syndrome) or non-functional. Functional NENs produce specific syndromes while non-functional pNENs frequently secrete a range of peptides but do not usually produce specific symptoms [1]. Development of symptoms of a syndrome (where previously there were none) is also possible and may indicate disease progression, and so should be highlighted to the medical team.

There has been an increased prevalence of NENs arising in the pancreas partly due to better recognition and diagnostics [2]. There is a lack of scientific evidence around diet and pNENs. Therefore, evidence around other diagnoses with similar characteristics is often turned to in the clinical setting and was also used to support parts of this section. This section will discuss functional NENs that result in syndromes involving pancreatic peptides in relation to nutrition, and non-functional NENs arising in the pancreas. Carcinoid syndrome will not be discussed here; see sections 'Dietary Management of Carcinoid Syndrome' and 'Carcinoid Heart Disease'.

Functional NEN syndromes:

Insulinomas

Insulinomas involve secretion of insulin resulting in hypoglycaemia. Some patients may experience postprandial hypoglycaemia. Location of the tumour in >99% of cases

is the pancreas (1/3 in the head, 1/3 in the body and 1/3 in the tail) and <10% are malignant. The main symptoms are secondary to hypoglycaemia (headaches, confusion, visual disturbances, dizziness, lethargy, abnormal behaviour and/or amnesia) or catecholamine excess secondary to hypoglycaemia (hunger, nausea, palpitations, tremor, sweating, weakness, feelings of warmth, and/or anxiety). If left untreated hypoglycaemia may result in seizure or coma [1, 3].

Patients may be 'hypoglycaemia unaware'. There may also be a delayed release of counter hormones in response to low blood glucose levels compared to those without an insulinoma [4]. Patients should therefore be encouraged to monitor blood glucose levels regularly and take dietary steps to prevent hypoglycaemia.

There is no consensus or evidence on how frequently blood glucose levels should be monitored. Some recommend the use of commercially available continuous glucose monitoring systems (CGM) [5]. For patients CGM is likely to be preferred over finger-stick glucose monitoring as it is more practical, however unfortunately accessing CGM may be an issue. Collaboration with the Diabetes Department, who are familiar with CGM, can support any funding requests, give advice on accessing CGM and making the right choice. Where patients can access CGM, devices that offer predictive alerts highlighting an upcoming hypo should be used. In practice, monitoring capillary blood glucose concentration is encouraged on waking, pre and/or post meals, prior to and after exercise (during exercise if prolonged), if experiencing any symptoms of hypoglycaemia, before bed, and in some cases (especially if 'hypoglycaemia unaware', not on treatment, or if starting a new treatment) at least once during the night [6]. If patients are stable on medication and recognise early signs of hypoglycaemia, they may be able to reduce the frequency of monitoring, however the impact of insulinomas on blood glucose levels are less predictive than in diabetes, making it more difficult to manage [5]. Monitoring frequency should be guided by the multidisciplinary team (MDT).

To prevent hypoglycaemic episodes, the 2016 ENETS Consensus Guidelines Update as part of the minimal consensus statement recommends small frequent meals

alongside medical treatment [3]. The main treatment is Diazoxide. SSAs and everolimus may also be effective, however in some cases SSAs may increase hypoglycaemia due to inhibition of hyperglycaemic hormones and so patients should monitor blood glucose levels on commencement of somatostatin analogues [3]. Though not mentioned in the ENETS Consensus Guidelines Update, glucocorticoids may be used to stabilise blood glucose levels [7]. Side effects of glucocorticoids include osteoporosis and muscle wasting, among others [8] and advise on bone health and supporting muscle maintenance should be given where patients are requiring long-term or high dose steroids.

Insulin secretion can be constant regardless if a patient is in a fasted state or not. Increased insulin secretion following a glucose load has also been observed in some patients, similar to 'reactive hypoglycaemia' [9, 10]. Evidence for both treating reactive hypoglycaemia and for maintaining blood glucose levels in the context of diabetes suggest following a low glycaemic index (GI) diet [11]. This advice has proven beneficial in the clinical setting for patients with an insulinoma diagnosis to maintain blood glucose levels. Based on clinical experience, it is recommended that patients follow a low GI diet by incorporating whole grain carbohydrates, fibre, protein and fats within meals and snacks. They should eat regularly, eating around 6 times a day, including a bedtime snack based around low GI carbohydrates, and possibly waking to have a snack in the night/early hours [6]. Though there are no clinical trials with insulinomas, there has been some use of cornstarch in clinical practice and published case reports [12]. Uncooked corn-starch (also known as corn flour and food grade maize starch) is commonly used in glycogen storage disease. Hydrolysis by pancreatic amylase allows slow release of glucose, maintaining normoglycaemia for a mean of 4.25 hours in glycogen storage disease – type 1 [13]. Uncooked cornstarch should be trialled where patients are unable to prevent hypos with the above advice, while monitoring its effectiveness. It can be useful at bedtime with or without a bedtime snack and/or at increments throughout the day. To advise on timings the dietitian should consider severity and frequency of hypos and physical activity. A starting dose of 1g carbohydrate from corn starch/kg body weight every 4-6 hours has shown a reduction in frequency of hypos in clinical practice. This should be increased or decreased dependent on glucose levels and this may differ depending on time of day,

oral intake and physical activity. Ideal body weight should be considered for patients with a high BMI. In practice, mixing the uncooked corn-starch with milk for additional low GI carbohydrates has been found also lead to better effect, with the quantity of milk dependent on the desired consistency.

One publication makes reference to nocturnal nasogastric tube feeding [14] though it is not used routinely in the clinical setting and there is no evidence on preferred choice of feeds or impact of tube feeding on outcomes. Tube feeding should be considered on a case by case basis. It would be logical to take into consideration any issues around malabsorption, the trend of the patient's weight (and the need to avoid exacerbating weight gains due to effects of disease), nutritional requirements and the need for continuous carbohydrate administration when decision making, and in choosing a feed, timing and rate. The practicalities of tube feeding in the community should also be considered, including administration of the feed and support. A risk assessment and contingency plan should be in place in case of tube blockage or displacement. Patients should be monitored closely, including anthropometric measurements. The publication also highlights that some patients require continuous IV dextrose to maintain blood glucose levels [14].

All patients should be given hypoglycaemia treatment advice. As there are no clinical trials on effective hypoglycaemia treatment for insulinomas, treatment advice given to patients with diabetes has been found to be effective in clinical practice. One case report saw a recovery of symptoms with 10g of glucose [9] but blood glucose levels were not monitored and so it is unclear if this was enough carbohydrate to normalise blood glucose levels as well as symptoms. Therefore, the Joint British Diabetes Societies for Inpatient Care (2018) [15] or equivalent guidelines should be followed where blood glucose level drops < 4.0 mmol/L:

1. Treat with 15 - 20g of fast acting carbohydrate. Orange juice may be used but other juices should be avoided due to the high proportion of carbohydrate coming from fructose.

Depending on the country some drinks used historically no longer contain adequate concentrations of glucose due to sugar tax (such as in the UK).

2. Patients should recheck blood glucose levels 10 - 15 minutes later. If still < 4.0 mmol/L retreat as per step 1 (only for a maximum of 3 treatments in total). Note - if blood glucose remains < 4.0 mmol/L after 3 cycles or 30 - 45 minutes patients should seek medical attention.
3. Once >4 mmol/L follow up with a low-medium GI snack containing carbohydrate, or patients can have their meal if due and if the meal contains carbohydrate.

Many patients present with increased body weight due to the anabolic effects of insulin as well as hyperphagia. Diazoxide can also cause weight gain, as well as oedema, hirsutism and renal impairment [1]. Based on clinical practice, dietary advice can minimise or prevent further weight gains by encouraging regular meals and snacks that contain adequate amounts of low GI carbohydrates, and reducing reliance on high GI carbohydrates. This encourages proactive avoidance of hypos rather than constantly treating reactively. Patients may struggle with the impact of weight gains and so understanding what is important to the patient and providing support is an important part of patient care. A dietitian is well placed to manage this. If patients are continuing to gain unwanted weight, they can also reduce their energy intake from fat, in lines with healthy eating guidelines. Some patients may have been given nutrition support advice in the past if they experienced weight loss initially, so it is important to take a clear diet history, including assessing for use of any oral nutritional supplements that the patient may still be taking.

Surgical removal of the insulinoma will completely reverse the syndrome though this may take time in patients with a large insulinoma where insulin effects may continue for a period [17].

Recommendations:

- *All patients with an insulinoma should have a consultation with a dietitian.*

- *Provide advice on treating hypoglycemia to all patients with an insulinoma.*
- *Encourage regular low GI meals and snacks based around starchy carbohydrate, including a bed time snack, and possibly a snack during the night/early hours.*
- *Uncooked cornstarch at bedtime with or without a bedtime snack and/or at increments throughout the day should be advised where patients continue to have hypos despite current management. Consider severity and frequency of hypos and physical activity when advising on dosing and timing. Dosing of 1g carbohydrate/kg of body weight (or ideal body weight where BMI ≥25kg/m^2) every 6 hours is used in one unit with good outcomes.*
- *IV dextrose, or tube feeding are additional treatments that may reduce hypoglycemia episodes if regular low GI meals and snacks and medical treatment are unsuccessful. These should be implemented on a case by case basis taking into account the full clinical picture, risks, with input from a dietitian and working with the MDT.*
- *Any change in symptoms should be highlighted to the medical team.*
- *Any patients that have been placed on long term steroids should receive bone health advice.*

Gastrinomas

Gastrinomas result in secretion of gastrin and cause a clinical syndrome known as Zollinger Ellison syndrome (ZES). Tumours may be in the duodenum (70% of cases), pancreas (25%) or 5% are in other sites (stomach, liver, bile duct, ovary, heart and lung); 40-70% are malignant. Pancreatic gastrinomas may occur in any part of the pancreas [1, 3]. ZES results in severe peptic disease, gastroesophageal reflux disease and oesophageal symptoms due to gastric acid hyper-secretion. Patients may also experience weight loss, diarrhoea, abdominal pain and heartburn [1, 3, 18]. Gastric acid hyper-secretion also results in inactivation of pancreatic enzymes [19, 20]. In the clinical setting where steatorrhoea remains despite medical treatments, pancreatic enzyme replacement therapy (PERT) has been helpful in minimising steatorrhoea. As non-enteric coated microsphere preparations are more likely to be degraded by acid [20], enteric coated microsphere preparations are more likely to be effective for patients with a gastinoma.

Oesophageal symptoms may involve bleeding, perforation and stricture. Patients may complain of dysphagia [21]. Any of these symptoms should be highlighted to the managing team as maybe life threatening. Though there are no published studies supporting diet advice, in clinical practice nutrition should be optimised and symptoms overcome via use of a texture modified diet, nutrition support advice, use of oral nutritional supplements, and potentially artificial nutrition support.

The main treatment to control gastric acid hypersecretion is proton pump inhibitor medication (PPIs). PPIs will usually be used long term and are often still needed for years post curative surgery, where acid secretion may remain high. Long term use of PPIs increases risk of deficiencies in B12, Mg and iron, and possibly risk of fractures [3, 22, 23]. Gastric acid is required to cleave vitamin B12 from its bound protein to allow association with intrinsic factor. Several studies have seen reduced vitamin B12 levels with long term PPI use. B12 levels should therefore be monitored and supplemented if needed. Baseline levels should be assessed, and additional consideration should be given to patients at risk of B12 deficiency (e.g. those who have had surgery involving the stomach or terminal ileum, and patients avoiding animal protein) [3, 22, 23].

Hypomagnesaemia has been observed in patients treated with PPIs for at least 3 months. Magnesium levels should be measured at baseline and monitored while patients are on treatment [3, 22, 23].

Iron absorption may be impacted by use of PPIs, particularly non-haem iron. Gastric acid helps dissociate iron salts from non-haem iron containing foods. Studies have found variable results regarding iron absorption and deficiency [22]. Patients should be made aware of what signs to look out for and levels should be assessed if patients are showing any symptoms of deficiency. This should be treated as per local guidelines.

There have been conflicting studies on whether PPIs increase risk of fractures. Patients should be encouraged to consume adequate amounts of calcium and vitamin D (which may involve supplementation of vitamin throughout the year). Patients that are at risk of osteoporosis should be monitored as per local guidelines [3, 17, 22, 23].

Regular use of PPIs can increase risk of small intestinal bacterial overgrowth (SIBO) due to increased pH of the small bowel, where a low pH normally protects against bacterial migration and overgrowth [24, 25]. Patients experiencing unresolved diarrhoea, bloating, abdominal pain, nocturnal defecation, steatorrhoea, nausea, flatulence, or vomiting, should be investigated for SIBO. There is a lack of consensus on the best diagnostic method and treatment of SIBO; therefore local protocol should be used at present.

Recommendations:

- *Look out for any signs of dysphagia and highlight any oesophageal symptoms to the medical team.*
- *Where patients have steatorrhoea despite medical treatment, start patients on PERT, ideally an enteric formulation (see section titled Pancreatic Exocrine Insufficiency).*
- *Monitor for deficiencies in B12, magnesium, iron and fat soluble vitamins and treat as needed (see micronutrient sections earlier in this document).*
- *Encourage adequate consumption of calcium and vitamin D (and support supplementation where appropriate).*
- *Look out for symptoms of SIBO in patients who have been on long term PPIs.*

VIPoma

VIPomas involve secretion of vasoactive intestinal peptide. The main site is the pancreas (90% in adults) with 10% occurring in other sites (neural, adrenal, periganglionic). VIPomas are malignant in 40-70% of cases. Symptoms include severe diarrhoea, hypokalaemia and dehydration. Medical treatment with somatostatin analogues (first line treatment) or interferon α are effective at reducing symptoms in most cases [1, 3]. There are no studies on diet and VIPomas. The best

method for replacing of electrolytes and hydration should be discussed with the MDT for each patient, taking into account symptoms and nutritional status of the patient. In clinical practice oral rehydration salts can be useful where a patient is not able to maintain electrolyte levels and has persistent diarrhoea. In such cases the patient should be closely monitored, including blood urea and electrolytes. In clinical practice some patients have required parenteral nutrition either for full nutrition, or solely for fluids and electrolytes where losses resulted in malnutrition that could not be managed via oral or enteral nutrition, or patients had electrolyte disturbances requiring regular admissions.

Recommendations:

- *Monitor nutritional status of patients with a VIPoma closely; prompt and regular dietetic input should be provided where patients are failing nutritionally.*
- *Consider rehydration salts to maintain fluid balance and electrolyte levels. If patients are not able to maintain nutrition, hydration and/or electrolyte levels orally, consider parenteral rout.*
- *Ensure other causes of diarrhea (such as PEI when on SSAs) are also treated.*

Glucagonoma

This is a NEN arising in the pancreas. It is characterised by over secretion of glucagon. Glucagonomas are malignant in 50-80% of cases. Symptoms include a rash (necrolytic migratory erythema), hyperglycaemia, glucose intolerance, diarrhoea, angular stomatitis, painful glossitis, and weight loss [1, 3, 18]. Some clinical cases have reported the rash responds to zinc and a high protein diet [26] though there is a lack of studies to support this. Zinc levels should be assessed on diagnosis and any deficiency treated and monitored. Patients are often cachectic. In order to provide nutrition support while reducing risk of hyperglycaemia it is reasonable to advise a high energy diet, focusing on protein and fat to increase energy intake, minimising high glycaemic index carbohydrates. Patient's HbA1c should be monitored as they may benefit from a moderate to low carbohydrate diet if raised.

The ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre- and Perioperative Therapy advise patients to commence somatostatin analogue treatment and nutritional supplementation prior to surgery to promote healing [17].

Recommendations:

- *Where medical treatment is not adequately controlling symptoms, dietetic input should be provided.*
- *Assess and monitor zinc levels (see 'Zinc' section).*
- *Monitor HbA1c every 3-6 months.*
- *Provide nutrition support advice with focus on energy from protein and fat.*
- *Consider a moderate to low carbohydrate diet where HbA1c is raised.*

Somatostatinoma

The biologically active peptide secreted with somatostatinomas is somatostatin. Location may be the pancreas (55%) or the duodenum/jejunum (44%). Somatostatinomas originating in the duodenum are not always associated with somatostainoma syndrome. Greater than 70% are malignant. Symptoms include diabetes, cholelithiasis, weight loss, steatorrhoea and diarrhoea [1, 3, 18]. Based on the knowledge that somatostatin inhibits pancreatic enzyme secretion [27], PERT should be used where there are symptoms of PEI including unexplained weight loss (see section on PEI). Where patients have lost weight, they should also be given nutrition support advice and monitored for diabetes.

Recommendations:

- *Monitor for signs of PEI and commence PERT where appropriate.*
- *Monitor nutritional status and need for nutrition support advice.*
- *Monitor glycaemic control and provide diabetes management advice; refer to a diabetes team where needed.*

P-NEN causing carcinoid syndrome

Serotonin and possibly tachykinins are secreted in these very rare pNENs. They originate in the pancreas and causes carcinoid syndrome, as the name suggests. These make up only <1% of all carcinoid tumours [1, 3]. See section titled 'Dietary Management of Carcinoid Syndrome.

Non Functioning pNENs and General issues affecting functioning and non-functioning pNENs

Where patients are asymptomatic and well-nourished it is reasonable to encourage healthy eating advice [6]. However, there is increased awareness of malnutrition occurring among patients with a NEN diagnosis [18]. Where patients are unable to meet their nutritional requirements due to effects of the tumour or treatment on oral intake, artificial nutrition support may be needed. Enteral nutrition is preferred over parenteral nutrition (PN) but where not feasible or able to provide sufficient nutrition then PN can be instigated. The same ethical considerations should be made as for benign diseases and other cancers, including benefits, risks and prognosis, especially in advanced malignancies [28].

Diseases that lead to loss of functioning pancreatic parenchyma, obstruction of the main pancreatic duct, decreased stimulation or inactivation of pancreatic enzymes are known to cause PEI [19]. Qureshi et al. found higher rates of malnutrition in subjects with gastro-entero-pancreatic NENs on somatostatin analogue therapies and those with lower faecal elastase concentrations [29]. In these situations PERT should be commenced (see section titled 'Pancreatic Exocrine Insufficiency'). There is a high chance (80%) of PEI in pancreatic cancer affecting the head of the pancreas but it is not known if this is the same for NENs located in the head of the pancreas, where disease is often less aggressive as in adenocarcinomas. If there is a loss of pancreatic parenchyma, obstruction of the main pancreatic duct, decreased stimulation or inactivation of pancreatic enzymes, PERT should be commenced. This includes duodenal resections where cholecystokinin secretion is inhibited, impacting on stimulation of the pancreas [19]. If there are symptoms of PEI but no obvious mechanism, then further investigations should be carried out including testing for PEI (see 'Pancreatic Exocrine Insufficiency' section), SIBO, and bile acid malabsorption (see 'Bile Acid Malabsorption' section) and treated accordingly.

Patients who undergo a surgical resection of part or the whole pancreas should receive a dietetic assessment and advice post-surgery as a minimum (but ideally also pre-surgery, such as part of prehab). As per ESPEN guidelines: Clinical Nutrition in Surgery, placement of a nasojejunal tube or needle catheter jejunostomy in patients undergoing major pancreatic surgery should be considered, especially if the patient is malnourished. 'Enhanced Recovery After Surgery' (ERAS) program should be

followed after pancreatic resections [30]. Surgical removal of the head of the pancreas is highly likely to result in PEI, and total pancreatic resection will result in PEI, and so patients should be educated on PERT promptly post-surgery (if not done pre-surgery) [19]. If the whole pancreas is removed, then patients should also receive specialist dietetic advice on diet and insulin dosing from an adequately trained dietitian working in diabetes, and be referred to a specialist diabetes service.

Recommendations:

- *Patients should be followed up closely and supported with symptom control, nutrition support and treatment/prevention of vitamin and mineral deficiencies.*
- *Routine use of PERT is not encouraged (as it is with head of pancreas adenocarcinomas) but should be used where PEI is likely and in the presences of symptoms of PEI (including unplanned weight loss or fat soluble vitamin deficiencies).*
- *Patients should be supported nutritionally at diagnosis and throughout their journey as there are likely to be changes in nutritional needs.*

Pancreatic Exocrine Insufficiency (PEI) and Pancreatic enzyme replacement therapy (PERT)

Caley Schnaid

Background and Assessment Methods

Pancreatic exocrine insufficiency (PEI) is not uncommon in patients with Neuroendocrine Neoplasms (NENs) and may be caused by a number of factors. PEI is a consequence of pancreatic surgery (partial or total pancreatectomy) causing reduced or total loss of pancreatic function, or gastrointestinal surgery (including oesophagectomy, gastrectomy and duodenal resection/bypass) causing asynchrony between motor and secretory functions, impaired enteropancreatic feedback, and inadequate mixing of pancreatic secretions with food. SSAs, used to control NEN disease progression and to reduce syndromes [1], may also interfere with the synthesis of pancreatic enzymes by inhibiting plasma amino acid uptake by pancreatic acinar cells [2]. In a survey by Whyand et al [3], 84% of NET patients on somatostatin analogues that took part reported that they had steatorrhoea to varying degrees.

The gastrointestinal symptoms of PEI include steatorrhoea (pale, oily, floating stools), bloating, distension, flatulence, abdominal cramps, indigestion, diarrhoea, faecal urgency and reflux [4]. The severity of symptoms is dependent on the degree of PEI, with steatorrhoea only evident when duodenal lipase falls below 5-10% of normal post-prandial levels [5]. Absence of steatorrhoea is therefore not a useful indicator to rule out PEI as it only occurs when pancreatic function is severely reduced. Other symptoms of PEI, which may also be classified as consequences of fat malabsorption, are weight loss, fat-soluble vitamin (A, D, E and K) and mineral (selenium, zinc, magnesium, calcium, phosphate, potassium) deficiencies, osteopenia and osteoporosis [4].

A faecal fat test, for the quantification of the coefficient of fat absorption (CFA), is the gold standard for the diagnosis of fat maldigestion. However, this is limited by patient compliance of fat consumption and stool collection, in addition to the handling of stool samples in the lab [6]. Chaudhry et al [7] found that there was a lack of association between faecal elastase and steatorrhoea in patients with NENs. Many patients experience steatorrhoea while on treatment with SSAs but exhibit a normal faecal elastase. PEI in this patient group is not fully understood, for example faecal elastase results may differ depending on the timing of treatment, and therefore faecal elastase test may not be suitable for use in this cohort of patients. A ^{13}C-Mixed Triglyceride (^{13}C-MTG) breath test has been developed as an alternative test to diagnose PEI in the clinical setting. Neither of these tests are widely available in clinical practice and as a result many clinicians will trial pancreatic enzyme replacement therapy (PERT) without a formal diagnosis of PEI and simply monitor the clinical response [4]. It is necessary to take a detailed history of symptoms, stool type, colour, frequency and any dietary triggers to assess whether a patient may be experiencing PEI [3].

Fat maldigestion is the most common consequence of PEI, resulting in steatorrhoea, weight loss and malnutrition from fat malabsorption [5, 8]. Some less obvious consequences of fat maldigestion are deficiencies of fat-soluble vitamins (A, D, E and

K), lipoproteins and micronutrients (selenium, zinc, magnesium, calcium, phosphate, potassium) [4,5, 8]. Vitamin A deficiency can cause night blindness. Low Vitamin D levels can lead to osteopenia, osteoporosis and elevated parathyroid hormone [4]. See section on fat soluble vitamins for further detail.

Dietary management

Routine nutritional assessment is essential to ensure the early detection of malnutrition. This includes monitoring weight and anthropometric parameters, vitamins A, D, E, K, B12, iron and calcium levels [5]. Supplementation should be prescribed to replace deficiencies (see separate sections on individual micronutrients).

Fat restriction is no longer considered in the management of PEI. Restriction of fat intake results in insufficient intake of fat-soluble vitamins, which are already being malabsorbed in patients with PEI. In addition, the maintenance of lipase activity during intestinal transit requires the presence of dietary triglycerides [6].

Dominguez-Munoz [8] suggests small, frequent meals and the avoidance of difficult-to-digest food. Medium-chain triglycerides are directly absorbed by the intestinal mucosa and therefore may be valuable to provide extra energy for patients who are losing weight or not responding to PERT.

Pancreatic Enzyme Replacement Therapy

Enzyme formulations are measured in terms of units for each individual enzyme activity. In 1995 the Food and Drug Administration (FDA) ruled that PEI “drug products” could no longer be over the counter in America. In Europe and America the enzyme activity and dosage is regulated. There are a range of over the counter vegetarian/plant based enzymes now available however dosing is significantly lower, especially for lipase and there are less stringent monitoring of bioavailability, and products are often not enteric coated [9]. In countries where PERT needs to be purchased by the patient (with over the counter products often being cheaper than

prescribed drugs), and where patients wish to avoid porcine sources, further research and development of alternative products is warranted. Interruptions in porcine based PERT supply chain may also be overcome by alternative, non-porcine products, further highlighting the need for development in this area.

Patient education is important when starting PERT. Patients need to understand why they require PERT, and to ensure that dose and timing of the enzymes is optimal.

Table 2 demonstrates a methodical approach to supplementing pancreatic enzymes, amending advice if there are insufficient improvements in symptoms of PEI. Dose is increased as required based on symptoms of maldigestion and malabsorption. Other considerations are: (i) the addition of a proton pump inhibitor or H2 antagonist, as gastric acid suppression prevents acid denaturing the enzymes and (ii) the addition of an anti-diarrhoeal to increase transit time [4].

Table 2: A Stepwise Approach to Managing Pancreatic Enzyme Replacement Therapy [4]

Step 1	Commence pancreatic enzyme replacement therapy by a dietitian with experience in PERT at a dose of: o 44,000 – 75,000 units lipase with meals, o 22,000 – 50,000 units lipase with snacks, milk based drinks and nutritional supplements/sip feeds. o Patients should distribute capsules throughout their meals, and swallow with a cold drink. o Check glucose levels within 2 weeks of commencing enzymes
Step 2	Trial an alternative enzyme product.
Step 3	Add a proton pump inhibitor or H2 antagonist
Step 4	Double the dose of enzymes with meals, snacks and supplements 88 000 - 150,000 units lipase with meals

	44 000 - 100,000 units lipase with snacks, milk based and nutritional supplements / sip feeds
Step 5	Increase dose further 132 000 - 200,000 units lipase with meals 88 000 - 125,000 units lipase with snacks, milk based and nutritional supplements / sip feeds Consider adding anti-diarrhoeal medication to reduce transit speed
Step 6	Investigate to exclude other conditions such as: infectious diarrhoea; bile acid malabsorption; small intestinal bacterial overgrowth; coeliac disease; lactase deficiency; disease reoccurrence; delayed gastric emptying
Step 7	Ensure nutritional intake is optimised, using supplements, sip feeds and if necessary, peptide, medium chain triglyceride based enteral nutrition, and if necessary, an elemental formula
Step 8	If malabsorption cannot be controlled and nutritional status is poor, parenteral nutrition should be considered

Recommendations:

- *Consider PEI as a possible cause of diarrhea in patients on SSAs.*
- *Ensure regular monitoring for those patients at risk of PEI (including anthropometric measures and fat soluble vitamin levels – see separate sections).*
- *Do not restrict fat intake, rather prescribe pancreatic enzyme replacement therapy to aid digestion of fat, protein and carbohydrates from food and beverages.*
- *Refer to dietitian experienced in managing PEI.*
- *Ensure correct dose and timing of PERT.*
- *If symptoms persist, consider adding other drug therapy to optimise PERT.*

Bile Acid Malabsorption (BAM)

Bea Sijtema and Tara Whyand

Bile acid Malabsorption (BAM) is also known as bile acid diarrhoea (BAD). In this section for consistency the term BAM will be used. Bile acids are produced in the liver, stored in the gall bladder and secreted in the duodenum. The production and secretion is stimulated when eating fatty foods. Bile acids play an important role in the emulsification of lipids, aiding their digestion and absorption in the small bowel. Approximately 95% of bile acids are reabsorbed over a relatively short section of the terminal ileum [1]. This results in a functional circulation of bile acids, transporting them back to the liver. An interruption of this circulation is thought to be the predominant cause of BAM [2]. BAM is a result of large amounts of unconjugated bile acids entering the colon, stimulating water secretion, increasing intestinal motility and shortening colonic transit time.

Surgery of the small bowel, disease of the terminal ileum, cholecystectomy, bacterial overgrowth and pancreatic insufficiency, can cause BAM [1]. GEP-NEN patients may well be familiar with one or more of these possible causes.

BAM is described as a cause for diarrhoea in GEP-NEN patients [3]. A study of 57 patients with GEP-NENs showed 80% of patients had BAM, diagnosed using a SeHCAT scan, as the gold standard for diagnosing BAM [4].

Symptoms can be severe and can include urgency of defecation, abdominal bloating/cramps, flatulence, abdominal pain, steatorrhoea and nocturnal defecation, and frequently have a negative impact on quality of life [5]. A study by Watson et al demonstrated that dietary intervention can be effective in managing BAM [5]. Dietary intervention was also shown to be an effective method for managing BAM symptoms experienced by patients previously treated for cancer [6]. In this study a total of 114 patients diagnosed with SeHCAT scans were evaluated. Of the subjects, 44% were taking colesevelam, before dietary advice. A significant improvement in abdominal pain and nocturnal defecation was shown after dietary intervention, advising a low fat diet where 20% of energy is from fat. Although this study was not specific for GEP-NEN patients, a personalised low-fat diet as a complimentary intervention should be

considered, as it may lead to improvement of symptoms and quality of life. Further studies are warranted to determine the degree of fat restriction that is effective and the long-term sustainability of this intervention by patients.

Though the SeHCAT scan is widely available, BAM remains underdiagnosed [6]. Symptoms for that reason are not always treated optimally, and treatments are often considered ineffective or poorly tolerated [7]. Medical treatment consists of bile sequestering agents. These agents may interfere with the absorption of fat-soluble vitamins (A, D, E and K) and folate. During long-term use, periodic monitoring of fat soluble vitamin levels is recommended [1], and supplementation may be required when treatment is prolonged [BNF accessed 2019].

Recommendations:

- *Be aware of the possibility that BAM can cause diarrhea in patients with a GEP-NEN diagnosis.*
- *Monitor fat soluble vitamin and folate levels during long-term use of bile sequesting agents.*
- *Although there is no evidence specific for GEP-NENs, consider a personalised low-fat diet to manage severe symptoms of bile acid malabsorption including where bile acid sequesting agents do not provide adequate improvement in symptoms, or where these medications are not tolerated.*
- *Supplement diet with medium chain triglyceride sources/based oral nutritional supplements where patients are unable to meet their energy requirements.*

Dietary Management of Bowel Obstructions

Yasmin Chotai de Lima

Mesenteric fibrosis remains a major cause of morbidity and mortality for patients with NEN of the small intestine and may occur in up to 50% of cases [1]. Desmoplastic reaction, which can occur in the small or large bowel is thought to occur from a complex combination of vasoactive amines, the tumour microenvironment and growth factors [2, 3].

Mesenteric fibrosis can cause a number of nutritional issues including bowel ischemia, bowel obstruction and ascites due to encasement of mesenteric vessels or kinking of the small intestine and compromise of mesenteric vasculature [4, 5]. Therefore patients are at very high risk of developing malnutrition.

A recent literature review of management of malignant bowel obstruction found management remains fairly unchanged, including the use of parenteral nutrition [6]. The ESPEN practical guideline: Clinical Nutrition in Cancer advise the use of enteral or parenteral nutrition (PN) to feed a patient where it is deemed appropriate to feed the patient and the oral rout is not feasible. The guidelines encourage weighing up the risks and benefits, and highlight that the risks of PN often outweigh the benefits where patients have a prognosis of less than 2 months [7]. Where there is complete bowel obstruction or significant ischemia of the bowel, PN should be initiated where appropriate, taking into account prognosis, and patient wishes. Where there maybe treatment/surgical options then there should be little delay in starting PN to ensure nutrition is not compromised while reviewing treatment options.

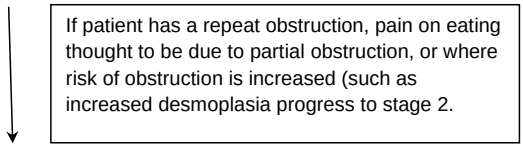
There is a lack of evidence around diet and preventing bowel obstructions in NEN. From what is known about digestion of food, a step wise approach has been found to be helpful in a clinical setting, see Figure 2. Where patients require artificial nutrition support (either enteral tube feeding or PN), there should be a multidisciplinary approach to decision making. If the patient trajectory is that they will likely progress quickly to requiring PN, then consider starting PN without a trial of enteral nutrition. From clinical experience, the patient journey is often long and changeable and patients may need to progress down the steps discussed in Figure 2. A retrospective review of patients who had a venting PEG inserted for decompression in the presence of malignant gastrointestinal obstructions, observed a reduction in nausea and vomiting, with minimal complications associated with tube placement [8]. Decompression of the stomach maybe required to prevent obstructive symptoms for some patients. Where a gastric tube is placed on drainage or for aspiration, patients should be fed past the stomach.

PERT should be continued where there remains an indication for PERT, and the patient is eating and drinking or receiving enteral tube feeding. Consensus from the

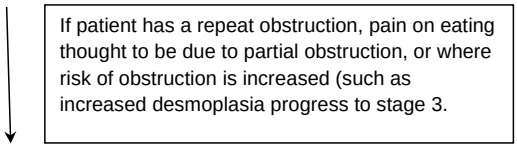
group and based on clinical experience, stopping PERT can worsen gastrointestinal symptoms and exacerbate malnutrition.

Figure 2: Stepwise approach to altering nutrition in to avoid bowel obstructions

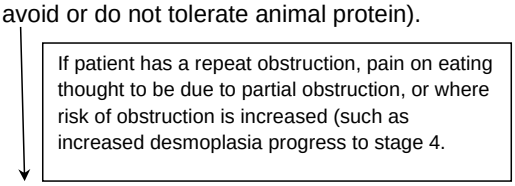
1. Advise a diet low in insoluble fibre, while also avoiding tough or fatty meat. Foods should also be soft, and chewed well before swallowing. Encourage spreads, sauces, gravies, etc. to soften foods. Well-cooked oats or other sources of soluble fiber cooked till soft or blended can be eaten if tolerated.



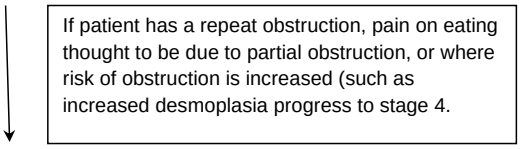
2. Advise a low fiber, moist, soft diet. The pressure from a fork should be able to cut or breakup the food. Encourage spreads, sauces, gravies, etc. to soften foods.



3. Advise a pureed diet where food can only be eaten with a spoon (as falls through the prongs of a fork). Foods should be completely liquidised. Patients should be encouraged to use high energy, high protein sauces, fortify foods, and are likely to require oral nutritional supplements in order to meet their nutritional requirements. From clinical experience, some patients may tolerate small amounts of completely blended beans or pulses, such as hummus or thin, pureed dhal (and these maybe an important source of protein to patients who chose to avoid or do not tolerate animal protein).



4. Discuss with the multidisciplinary team, considering recent scans, treatment options and prognosis, whether enteral tube feeding or PN should be trialed. If the site of obstruction can be bypassed (such as feeding via a nasojejunal tube) then enteral nutrition is the preferred option. Where a patient is likely to progress quickly onto PN, consider starting PN sooner rather than later. Consider placing patient nil by mouth.



5. If patient is currently fed via enteral tube feeding into the stomach, change to PN or jejunal feeding (if this bypasses the site of obstruction). Consider a venting PEG (as long as there is no ascites present and is physiologically possible) or wide-bore nasogastric tube for decompression.

From literature around liver cirrhosis, ascites can cause early satiety [9]. Patients who have ascites should be encouraged with regular meals and snack and high energy, high protein advice. They may require oral nutritional supplements.

Recommendations:

- *Patients who are at risk of bowel obstructions should be referred to a dietitian.*
- *Systematically alter diet or feeding rout depending on symptoms. Provide detailed advice on foods to include and avoid, taking into considerations the patient's current diet habits, likes and dislikes.*
- *Consider prognosis, patient wishes, impact on QoL and symptoms when decision making around artificial nutrition support.*
- *Do not discontinue PERT (as long as still indicated) despite bowel obstructions.*
- *Nutritional status should be monitored closely throughout the patient journey.*

Surgery

Patients should receive dietetic input as part of their work up to surgery to provide nutrition support advice (for both micro and macronutrients) and PERT advise (if appropriate) to optimise nutrition, and therefore surgical outcomes.

Pre-hab and ERAS

References

Introduction

1. BAPEN. What is malnutrition? 2018. https://www.bapen.org.uk/malnutrition-undernutrition/introduction-to-malnutrition (accessed 27 2021).
2. Maasberg S**,** Knappe-Drzikova B, Vonderbeck D, Jann H, Weylandt KH, Grieser C, Pascher A, Schefold JC, Pavel M, Wiedenmann B, Sturm A, Pape UF. Malnutrition Predicts Clinical Outcome in Patients with Neuroendocrine Neoplasia. Neuroendocrinology 2017; 104: 11-25.
3. Whyand T, Pupkevich M, Chotai de Lima Y. The Essential Role of Functional Nutrition Assessment in NET Clinics. ENETs 2019 Poster abstract (D60)
4. Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy. Am J Clin Nutr 2012;96: 1346e53.

Nutritional Status and Screening

1. Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, Kutz A, Tribolet P, Bregenzer T, Braun N, Hoess C, Pavlicek V, Schmid S, Bilz S, Sigrist S, Brändle M, Benz C, Henzen C, Mattmann S, Thomann R, Brand C, Rutishauser J, Aujesky D, Rodondi N, Donzé J, Stanga Z, Mueller B. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. Lancet 2019 8; 393(10188):2312-2321. doi: 10.1016/S0140-6736(18)32776-4. Epub 2019 Apr 25.
2. Bozzetti **F**, Mariani L, Lo Vullo S; The SCRINIO Working Group, Amerio ML, Biffi R, Caccialanza R, Capuano G, Correja I, Cozzaglio L, Di Leo A, Di Cosmo L, Finocchiaro C, Gavazzi C, Giannoni A, Magnanini P, Mantovani G, Pellegrini M, Rovera G M, Rovera L, Sandri G, Tinivella M, Vigevani E: The nutritional risk in oncology: a study of 1,453 cancer outpatients. Support Care Cancer 2012; 20: 1919–28.
3. Fearon K**,** Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE: Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011; 12 (5): 489–495.
4. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, Strasser F, Thoresen L, Jagoe RT, Chasen M, Lundholm K, Bosaeus I, Fearon KH, Baracos

VE. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol. 2015 1;33(1):90-9.

5. Isenring E**,** Cross G, Kellett E, Koczwara B, Daniels L. Nutritional status and information needs of medical oncology patients receiving treatment at an Australian public hospital. Nutrition and Cancer.2010 62 (1): 62:220–28.

6. Pan H, Cai S, Ji J, Jiang Z, Liang H, Lin F, Liu L. The impact of nutritional status, nutritional risk, and nutritional treatment on clinical outcome of 2248 hospitalized cancer patients: a multi-center, prospective cohort study in Chinese teaching hospitals. Nutrition and Cancer 2013; 65 (1): 62-70.

7. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Cancer: disease and nutrition are key determinants of patients quality of life Support Care Cancer 2004; 12: 246–52.

8. Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? Eur J Cancer 1998; 34 (4): 503-9.

9. Sobotka L, Editor. Basics in clinical nutrition. 4th ed. Galen; 2012.

10. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, Baptista G, Barazzoni R, Blaauw R, Coats AJS, Crivelli AN, Evans DC, Gramlich L, Fuchs-Tarlovsky V, Keller H, Llido L, Malone A, Mogensen KM, Morley JE, Muscaritoli M, Nyulasi I, Pirlich M, Pisprasert V, de van der Schueren MAE, Siltharm S, Singer P, Tappenden K, Velasco N, Waitzberg D, Yamwong P, Yu J, Van Gossum A, Compher C; GLIM Core Leadership Committee, GLIM Working Group. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. J Cachexia Sarcopenia Muscle. 2019; 10(1): 207-217. doi: 10.1002/jcsm.12383.

11. Cederholm T**,** Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, Muscaritoli M, Nyulasi I, Ockenga J, Schneider SM, de van der Schueren MA, Singer P. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr. 2015; 34(3): 335-40. doi: 10.1016/j.clnu.2015.03.001. Epub 2015 Mar 9.

12. Maasberg S**,** Knappe-Drzikova B, Vonderbeck D, Jann H, Weylandt KH, Grieser C, Pascher A, Schefold JC, Pavel M, Wiedenmann B, Sturm A, Pape UF. Malnutrition Predicts Clinical Outcome in Patients with Neuroendocrine Neoplasia. Neuroendocrinology 2017; 104: 11-25.

13. Qureshi S, Burch N, Druce M, Hattersley JG, Khan S, Gopalakrishnan K, Darby C, Wong JLH, Davies L, Fletcher S, Shatwell W, Sothi S, Randeva HS, Dimitriadis G K, Weickert MO. Screening for malnutrition in patients with gastro-entero-pancreatic neuroendocrine tumours: a cross-sectional study. BMJ Open 2016; 6:e010765. doi: 10.1136/bmjopen-2015.

14. Ewang-Emukowhate M et al. Assessment of fat-soluble vitamins and trace elements in neuroendocrine tumour (NET) patients on somatostatin analogues. *Endocrine Abstracts* (2018) **60** P24 | DOI: 10.1530/endoabs.60.P24.

15. Barrea L, Altieri B, Muscogiuri G, Laudisio D, Annunziata G, Colao A, et al. Impact of Nutritional Status on Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET) Aggressiveness. Nutrients. 2018 Dec 1;10(12):1854. doi: 10.3390/nu10121854.

16. Borre M, Dam GA, Knudsen AW, Gronbaek H: Nutritional status and nutritional risk in patients with neuroendocrine tumors. Scand J Gastroenterol 2018;53:1-9.

17. Whyand T, Pupkevich M, Chotai de Lima Y. The Essential Role of Functional Nutrition Assessment in NET Clinics. *Endocrine Abstracts* (2018) D60 https://www.karger.com/Article/Pdf/498995.

18. Boden G, Sivitz MC, Owen OE, Essa-Koumar N, Landor JH. Somatostatin suppresses secretin and pancreatic exocrine secretion. Science 1975;190:163–5. 10.1126/science.1166308 [PubMed] [CrossRef] [Google Scholar]

19. Hopman WP, van Liessum PA, Pieters GF, Smals AG, Tangerman A, Jansen JB, Rosenbusch G, Lamers CB, Kloppenborg PW. Pancreatic exocrine and gallbladder function during long-term treatment with octreotide (SMS 201-995). Digestion 1990;45(Suppl 1):72–6. 10.1159/000200266 [PubMed] [CrossRef] [Google Scholar]

20. Ho PJ, Boyajy LD, Greenstein E, Barkan AL. Effect of chronic octreotide treatment on intestinal absorption in patients with acromegaly. Dig Dis Sci 1993; 38:309–15. 10.1007/BF01307549 [PubMed] [CrossRef] [Google Scholar].

21. Magnusson I, Einarsson K, Angelin B, Nyberg B, Bergström K, Thulin L. Effects of somatostatin on hepatic bile formation. Gastroenterology 1989;96:206–12. [PubMed] [Google Scholar]

22. Hussaini SH**,** Pereira SP, Veysey MJ et al. Roles of gall bladder emptying and intestinal transit in the pathogenesis of octreotide induced gall bladder

stones. Gut 1996; 38:775–83. 10.1136/gut.38.5.775 [PMC free article] [PubMed] [CrossRef] [Google Scholar.

23. Fiebrich HB, Van Den Berg G, Kema IP et al. Deficiencies in fat-soluble vitamins in long-term users of somatostatin analogue. Aliment Pharmacol Ther 2010;32:1398–404. 10.1111/j.1365-2036.2010.04479.x [PubMed] [CrossRef] [Google Scholar].

24. Evensen D, Hanssen KF, Berstad A. The effect on intestinal calcium absorption of somatostatin in man. Scand J Gastroenterol 1978; 13:449–51. 10.3109/00365527809181920 [PubMed] [CrossRef] [Google Scholar]

25. Krejs GJ, Browne R, Raskin P. Effect of intravenous somatostatin on jejunal absorption of glucose, amino acids, water, and electrolytes. Gastroenterology 1980; 78:26–31. [PubMed] [Google Scholar]

26. Lamrani A, Vidon N, Sogni P et al. Effects of lanreotide, a somatostatin analogue, on postprandial gastric functions and biliopancreatic secretions in humans. Br J Clin Pharmacol 1997;43:65–70. 10.1111/j.1365-2125.1997.tb00034.x [PubMed] [CrossRef] [Google Scholar]

27. McMillan DC. The systemic inflammation-based Glasgow prognostic score: a decade of experience in patients with cancer. Cancer Treat Rev 2013; 39: 534e40.

28. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Fearon K, Hütterer E, Isenring E, Kaasa S, Krznaric Z, Laird B, Larsson M, Laviano A, Mühlebach S, Muscaritoli M, Oldervoll L, Ravasco P, Solheim T, Strasser F, de van der Schueren M, Preiser JC. Espen guidelines on nutrition in cancer patients. Clinical Nutrition 2017; 36: 1-38.

29. Fröjd C, Larsson G, Lampic C, von Essen L. Health related quality of life and psychosocial function among patients with carcinoid tumours. A longitudinal,prospective, and comparative study. Health Qual Life Outcomes 2007;5:18. doi:10.1186/1477-7525-5-18

30. Larsson G, Haglund K, Von Essen L. Distress, quality of life and strategies to “keep a good mood” in patients with carcinoid tumours: patient and staff perceptions. Eur J Cancer Care (Engl) 2003;12:46–57. doi:10.1046/j.1365- 2354.2003.00322.x.

31. Pevny S, Maasberg S, Karber M, Knappe-Drizikova B, Weylandt K H, Pavel M, Wiedenmann B, Jann H, Pape U F. Systemic anti-cancer therapies in neuroendocrine tumor patients impair nutritional status. *Endocrine Abstracts* (2018)

https://www.enets.org/systemic-anti-cancer-therapies-in-neuroendocrine-tumor-patients-impair-nutritional-status.html.

32. Reber E, Strahm R, Bally L, Schuetz P, Stanga Z. Efficacy and Efficiency of Nutritional Support Teams. J Clin Med. 2019 Aug 22; 8(9). pii: E1281. doi: 10.3390/jcm8091281. Review. PMID: 31443543.

33. Stratton RJ, Hackston A, Longmore D, Dixon R, Price S, Stroud M, King C, Elia M. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. Br J Nutr. 2004; 92(5):799-808.

34. Isenring E**,** Elia M. Which screening method is appropriate for older cancer patients at risk for malnutrition? nutrition 2015; 31:594e7.

35. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M: ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003;22:415-421.

36. Boleo-Tomé C, Monteiro-Grillo I, Camilo M, Ravsco P. Validation of the Malnutrition Universal Screening Tool (MUST) in cancer. Br J Nutr 2012; 108:343–8. 10.1017/S000711451100571X [PubMed] [CrossRef] [Google Scholar] 2014. http://www.ncbi.nlm.nih.gov/pubmed/25905385 [Google Scholar].

37. BAPEN. Introducing “MUST”. 2015. http://www.bapen.org.uk/screening-for-malnutrition/must/introducing-must (accessed 03 Dec 2015).

38. Reber E, Gomes F, Vasiloglou MF, Schuetz P, Stanga Z. Nutritional Risk Screening and Assessment. J Clin Med. 2019 Jul 20; 8(7). pii: E1065. doi: 10.3390/jcm8071065.

39. Franch-Aras G. The meaning of hypoalbuminemia in clinical practice. Clinical Nutrition 2001; 20 (3): 265-69.

40. Ballmer PE. Causes and mechanism of hypoalbuminemia. Clinical Nutrition 2001; 20 (3):271-73.

41. Doweiko JP, Nompleggi DJ. The role of albumin in human physiology and pathophysiology, part III: Albumin and disease states. JPEN J Parenteral Enteral Nutr 1991;15:476–83. [PubMed] [Google Scholar].

42. Keller U. Nutritional Laboratory Markers in Malnutrition. Journal of Clinical Medicine 2019; 8, 775; doi:10.3390/jcm8060775.

43. Lee JL, Oh ES, Lee RW, Finucane TE. Serum albumin and Prealbumin in Calorically Restricted Nondiseased Individuals: A Systematic Review. Am J Med 2015; 128: 1203.

44. Kim S, McClave S, Martindale R, Miller KR, Hurt R. Hypoalbuminemia and Clinical Outcomes: What is the Mechanism behind the Relationship? Am Surg. 2017; 83(11):1220-27.
45. Cabrerizo S, Cuadras D, Gomez-Busto F, Artaza-Artabe I, Marín-Ciancas F, Malafarina V. Serum albumin and health in older people; Review and meta-analysis. Mauritas 2015; 81: 17-27.
46. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M: ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003;22:415-421.
47. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of Blood Biomarkers Associated with Risk of Malnutrition in Older Adults: A Systematic Review and Meta-Analysis. Nutrients 2017; 9, 829

Nutritional Assessment

1. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Dietary Counseling Improves Patient Outcomes: A Prospective, Randomized, Controlled Trial in Colorectal Cancer Patients Undergoing Radiotherapy. Journal of Clinical Oncology 2005; 23: 1431-38.
2. Isenring E, Cross G, Kellett E, Koczwara B, Daniels L. Nutritional status and information needs of medical oncology patients receiving treatment at an Australian public hospital. Nutrition and Cancer.2010 62 (1): 62:220–28.
3. Reber E, Gomes F, Vasiloglou MF, Schuetz P, Stanga Z. Nutritional Risk Screening and Assessment. J Clin Med. 2019 Jul 20;8(7). pii: E1065. doi: 10.3390/jcm8071065.
4. Laing E, Kiss N, Krishnasamy M, Michael M. Nutritional complications and the management of patients with gastroenteropancreatic neuroendocrine tumours. Neuroendocrinology. 2019 25. doi: 10.1159/000503634. [Epub ahead of print] Review. PMID: 31550712
5. Bauer, J Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr 2002; 56: 779-85.
6. Cederholm T**,** Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, Baptista G, Barazzoni R, Blaauw R, Coats AJS, Crivelli AN, Evans DC, Gramlich L, Fuchs-Tarlovsky V, Keller H, Llido L, Malone A, Mogensen KM, Morley JE, Muscaritoli M, Nyulasi I, Pirlich M, Pisprasert V, de van der Schueren MAE,

Siltharm S, Singer P, Tappenden K, Velasco N, Waitzberg D, Yamwong P, Yu J, Van Gossum A, Compher C; GLIM Core Leadership Committee, GLIM Working Group. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. J Cachexia Sarcopenia Muscle. 2019; 10(1): 207-217. doi: 10.1002/jcsm.12383.

7. Borre M, Dam GA, Knudsen AW, Gronbaek H: Nutritional status and nutritional risk in patients with neuroendocrine tumors. Scand J Gastroenterol 2018;53:1-9.

8. Whyand T, Pupkevich M, Chotai de Lima Y. The Essential Role of Functional Nutrition Assessment in NET Clinics. *Endocrine Abstracts* (2018) D60 https://www.karger.com/Article/Pdf/498995.

9. Caccialanza R, Pedrazzoli P, Cereda E, Gavazzi C, Pinto C, Paccagnella A, Beretta GD, Nardi M, Laviano A, Zagonel V. Nutritional Support in Cancer Patients: A Position Paper from the Italian Society of Medical Oncology (AIOM)and the Italian Society of Artificial Nutrition and Metabolism (SINPE). Journal of Cancer 2016, 7(2): 131-135.

10. Kubrak C, Olson K, Baracos VE. The head and neck symptom checklist©: an instrument to evaluate nutrition impact symptoms effect on energy intake and weight loss. Support Care Cancer 2013; 21 (11): 3127-36.

11. Omlin A, Blum D, Wierecky J, Haile S R, Ottery FD, Strasser F. Nutrition impact symptoms in advanced cancer: frequency and specific interventions, a case-control study. J Cachexia Sarcopenia Muscle 2013; 4: 55-61

12. Pan H, Cai S, Ji J, Jiang Z, Liang H, Lin F, Liu X. The impact of nutritional status, nutritional risk, and nutritional treatment on clinical outcome of 2248 hospitalized cancer patients: a multi-center, prospective cohort study in Chinese teaching hospitals. Nutrition and Cancer 2013; 65 (1): 62-70.

13. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Fearon K, Hütterer E, Isenring E, Kaasa S, Krznaric Z, Laird B, Larsson M, Laviano A, Mühlebach S, Muscaritoli M, Oldervoll L, Ravasco P, Solheim T, Strasser F, de van der Schueren M, Preiser JC. Espen guidelines on nutrition in cancer patients. Clinical Nutrition 2017; 36: 1-38.

14. Ribaudo JM, Cella D, Hahn EA, Lloyd SR, Tchekmedyian NS, Von Roenn J, Leslie WT. Re-validation and shortening of the functional assessment of anorexia/ cachexia therapy (FAACT) questionnaire. Qual Life Res 2000;9:1137e46.

15. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC. The european organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365e76.

16. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, Muscaritoli M, Nyulasi I, Ockenga J, Schneider SM, de van der Schueren MA, Singer P. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr. 2015; 34(3): 335-40. doi: 10.1016/j.clnu.2015.03.001. Epub 2015 Mar 9.

17. Qureshi S, Burch N, Druce M, Hattersley JG, Khan S, Gopalakrishnan K, Darby C, Wong JLH, Davies L, Fletcher S, Shatwell W, Sothi S, Randeva HS, Dimitriadis G K, Weickert MO. Screening for malnutrition in patients with gastro-entero-pancreatic neuroendocrine tumours: a cross-sectional study. BMJ Open 2016; 6:e010765. doi: 10.1136/bmjopen-2015.

18. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern cooperative oncology group. Am J Clin Oncol 1982;5:649e55.

19. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 1980;45:2220e4.

20. Norman K, Stobäus N , Smoliner C , Zocher D , Scheufele R, Valentini L, Lochs H, Pirlich M Determinants of hand grip strength, knee extension strength and functional status in cancer patients. Clinical Nutrition 2010; 29: 586-91.

21. Norman K, Stobäus N, Gonzalez C, Schulzke JD, Pirlich M. Hand grip strength: Outcome predictor and marker of nutritional status. Clinical Nutrition 2011; 30: 135-42.

22. Borga M, West J, Bell JD, Harvey NC, Romu T, Heymsfield SB, Leinhard OD. Advanced body composition assessment:from body mass index to body composition profiling. Journal of Investigative Medicine 2018; 66(5):1-9.

23. Keller U. Nutritional Laboratory Markers in Malnutrition. Journal of Clinical Medicine 2019; 8, 775; doi:10.3390/jcm8060775.

Requirements for Energy and Protein

1. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012;61:6–32. doi:10.1136/gutjnl-2011-300831.

2. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol 2017;3:1335–42. doi:10.1001/jamaoncol.2017.0589.

3. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;11-48. Doi:10.1016/j.clnu.2016.07.015.

4. Arends J, Baracos V, Bertz H, Bozzeti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr 2017;36:1187-1196. doi: 10.1016/j.clnu.2017.06.017.

5. PENG Parenteral and Enteral Nutrition Specialist Group. Estimating nutritional requirements in adults. In 'A Pocket Guide To Clinical Nutrition', 5th Edition, BDA 2018.

6. Lieffers J R, Mourtzakis M, Hall K D, McCargar L J, Prado C M M, Baracos V E. A viserally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr 2009; 89: 1173-9. doi: 10.3945/ajcn.2008.27273.

7. Moses A W G, Slater C, Preston T, Barber M D, Fearon K C H. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer 2004; 90: 996-1002. doi: 10.1038/sj.bjc.6601620.

8. Petrak O, Haluzikova D, Kavalkova P, Strauch B, Rosa J, Holaj R, Brabcova Vrankova A, Michalsky D, Haluzik M, Zelinka T, Widimsky J. Changes in energy metabolism in phaeochromocytoma. Journal of Clinical Endocrinology & Metabolism 2013; 98: 1651-58. https://doi.org/10.1210/jc.2012-3625.

9. Bauer J, Ash S, Davidson W, Hill J, Brown T, Isenring E, et al. Evidence Based Practice Guidelines for the Nutritional Management of Cancer Cachexia. Nutrition and Dietetics 2006; 63 (Suppl. 2): S5-S32. doi:10.1111/j.1747-0080.2006.00099.x

10. Forchielli ML, Miller SJ. Nutritional goals and requirements. In Merritt R (ed). A.S.P.E.N Nutrition Support Manual. 2nd ed. Silver Spring, MD: ASPEN Publishing; 2005;5 0-51.

11. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. ESPEN Guidelines on Parenteral Nutrition: surgery. Clin Nut 2009;28(4):378-86. Doi: 10.1016/j.clnu.2009.04.002.

12. Shah GM, Shah RG, Veillette H, Kirkland JB, Pasieka JL, Warner RR. Biochemical assessment of niacin deficiency among carcinoid cancer patients. Am J Gastroenterol. 2005 Oct;100(10):2307-14.

13. Bouma G, van Faassen M, Kats-Ugurlu G, de Vries EG, Kema IP, Walenkamp AM. Niacin (Vitamin B3) Supplementation in Patients with Serotonin-Producing Neuroendocrine Tumor. Neuroendocrinology. 2016;103(5):489-94. doi: 10.1159/000440621. Epub 2015 Sep 4

14. World Health Organisation (WHO). Pellagra and its prevention and control in major emergencies (2000) [Accessed June 12, 2020]. Available from: https://www.who.int/nutrition/publications/en/pellagra_prevention_control.pdf.

15. Altieri B, Barrea L, Modica R, et al. Nutrition and neuroendocrine tumors: An update of the literature. Rev Endocr Metab Disord. 2018;19(2):159-167. doi:10.1007/s11154-018-9466-z.

16. Reilly JG, McTavish SF, Young AH. Rapid depletion of plasma tryptophan: a review of studies and experimental methodology. J Psychopharmacol. 1997; 11(4):381-92.

17. Horwitt MK, Harper AE, Henderson LM. Niacin-tryptophan relationships for evaluating niacin equivalents. Am J Clin Nutr. 1981 Mar; 34(3):423-7.

18. Fernstrom JD. A Perspective on the Safety of Supplemental Tryptophan Based on Its Metabolic Fates, *The Journal of Nutrition.* 2016;146, (12): 2601S–2608S, https://doi.org/10.3945/jn.115.228643.

19. Chaney S G. 2006 Principals of nutrition I: macronutrients, chapter 27 in Textbook of Biochemistry with Clinical Crrelations 6th ed. [Thomas M. Devlin editor] 1075-1076.

20. Hoffman J R, Falvo M J. Protein – which is best? Journal of Sports Science & Medicine 2004; 3:118-30. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3905294/.

21. Paddon-Jones D, Rasmussen B B. Dietary protein recommendations and the prevention of sarcopenia. Curr Opin Clin Nutr Metab Care 2009; 12: 86-90. doi: 10.1097/MCO.0b013e32831cef8b.

22. Vegan Eatwell Guide. The Vegan Society 2020[accessed 29 April 2021]. Available from:

https://www.vegansociety.com/sites/default/files/uploads/downloads/The%20Vegan%20Eatwell%20Guide_1.pdf

23. British Dietetic Association [accessed 29 April 2021]. Available from: https://www.bda.uk.com/resource/british-dietetic-association-confirms-well-planned-vegan-diets-can-support-healthy-living-in-people-of-all-ages.html.

24. American Institute for Cancer Research (AICR). 10 Cancer Prevention Recommendations [accessed June 12, 2020]. Available from: https://www.aicr.org/cancer-prevention/

25. World Cancer Research Fund Cancer prevention recommendations – Plant foods and cancer prevention 2021 [accessed 29 April, 2021]. Available from: https://www.wcrf-uk.org/uk/preventing-cancer/cancer-prevention-recommendations/enjoy-more-grains-veg-fruit-and-beans.

26. Tortora G J and Derrickson B. 2006 The digestive system, chapter 24 in Principals of Anatomy and Physiology11th Ed. [Bonnie Roesch editor] 895 – 987.

27. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guidelines: Clinical Nutrition in cancer. Clin Nutr 2021;2898-291348. Doi: 10.1016/j.clnu.2021.02.005.

Micronutrients

Niacin

1. EFSA. Dietary reference values for Nutrients Summary report. [Accessed June 13, 2020] Available from: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2017.e15121

2. Committee on Medical Aspects of Food Policy (1991) Dietary Reference Values for Food Energy and Nutrients for the United Kingdom.

3. U.S. Department of Health & Human Services (2021) Niacin fact sheet for health professionals. [Accessed May 23, 2021] Available from: https://ods.od.nih.gov/factsheets/Niacin-HealthProfessional/.

4. NHS. Vitamins and Minerals. [Accessed June 13, 2020] Available from: https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-b/

5. World Health Organisation (WHO). Pellagra and its prevention and control in major emergencies (2000) [Accessed June 12, 2020]. Available from: https://www.who.int/nutrition/publications/en/pellagra_prevention_control.pdf.

6. Kema IP, de Vries EG, Slooff MJ, Biesma B, Muskiet FA: Serotonin, catecholamines, histamine, and their metabolites in urine, platelets, and tumor tissue of patients with carcinoid tumors. Clin Chem 1994;40:86-95.

7. Fleischmajer R, Hyman AB. Clinical significance of derangements of tryptophan metabolism: A review of pellagra, carcinoid and H disease. Arch Dermatol 1961;84:563– 73.

8. Shah GM, Shah RG, Veillette H, Kirkland JB, Pasieka JL, Warner RR. Biochemical assessment of niacin deficiency among carcinoid cancer patients. *Am J Gastroenterol.* 2005;100(10):2307-2314. doi:10.1111/j.1572-0241.2005.00268.x

9. Bell, HK, Poston, GJ, Vora, J, et al. Cutaneous manifestations of the malignant carcinoid syndrome. Br J Dermatol 2005;152: 71–75.5

10. Bouma G, van Faassen M, Kats-Ugurlu G, de Vries EG, Kema IP, Walenkamp AM. Niacin (Vitamin B3) Supplementation in Patients with Serotonin-Producing Neuroendocrine Tumor. *Neuroendocrinology*. 2016;103(5):489-494. doi:10.1159/000440621

11. Swain CP, Tavill AS, Neale G. Studies of tryptophan and albumin metabolism in a patient with carcinoid syndrome, pellagra, and hypoproteinemia. Gastroenterology 1976;71:484–9.

12. Warner, RR. Carcinoid case presentation and discussion: The American perspective. Endocr Relat Cancer 2003;10: 489–496.

13. Horwitt MK, Harper AE, Henderson LM. Niacin-tryptophan relationships for evaluating niacin equivalents. Am J Clin Nutr. 1981 Mar; 34(3):423-7.

14. Fernstrom JD. A Perspective on the Safety of Supplemental Tryptophan Based on Its Metabolic Fates, The Journal of Nutrition. 2016;146, (12): 2601S–2608S, https://doi.org/10.3945/jn.115.228643.

15. Warner ME. Nutritional Concerns For The Carcinoid Patient: Developing Nutrition Guidelines For Persons With Carcinoid Disease. Carcinoid Cancer Found 2008. [accessed January 19, 2017]. Available from: http://www.carcinoid.org/for-patients/general-information/nutrition/nutritional-concerns-for-the-carcinoid-patient-developingnutrition-guidelines-for-persons-with-carcinoid-disease/.

Vitamin B12

1. EFSA. Dietary reference values for Nutrients Summary report. [Accessed June 13, 2020] Available from: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2017.e15121
2. Simonson W. Vitamin B12 deficiency - detection and treatment considerations. Geriatr Nurs. 2018 Jul - Aug;39(4):477-478. doi: 10.1016/j.gerinurse.2018.06.013. Epub 2018 Jul 11.
3. Committee on Medical Aspects of Food Policy (1991) Dietary Reference Values for Food Energy and Nutrients for the United Kingdom.
4. U.S Food and Drug Administration (FDA). Daily Values. [Accessed June 13, 2020]. Available from: https://www.accessdata.fda.gov/scripts/interactivenutritionfactslabel/assets/InteractiveNFL_Vitamins&MineralsChart_March2020.pdf
5. NHS. Vitamins and Minerals. [Accessed June 13, 2020] Available from: https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-b/
6. Annibale B, Lahner E, Fave GD. Diagnosis and management of pernicious anemia. Curr Gastroenterol Rep. 2011 Dec;13(6):518-24. doi: 10.1007/s11894-011-0225-5
7. Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. BMJ. 2014 Sep 4;349:g5226. doi: 10.1136/bmj.g5226.
8. World Health Organisaion. Conclusions of a WHO technical consultation on folate and vitamin B12 defiencies. Food and Nutrition Bulletin. 2008; 29(2 supplement) https://www.who.int/nutrition/publications/micronutrients/FNBvol29N2supjun08.pdf
9. Delle Fave G, O'Toole D, Sundin A, Taal B. Ferolla P, Ramage JK, Ferone D, Ito T, Weber W, Zheng-Pei Z, De Herder WW, Pascher A, Ruszniewski P. ENETS consensus guidelines update for gastroduodenal neuroendocrine neoplasms. Neuroendocrineology. 2016 Jan; 103: 119-24. doi: 10.1159/000443168.
10. Lind A, Wängberg B, Ellegård L. Vitamin D and vitamin B12 deficiencies are common in patients with midgut carcinoid (SI-NET). Eur J Clin Nutr. 2016 Sep;70(9):990-4. doi: 10.1038/ejcn.2016.40.
11. British National Formulary. Megaloblastic anaemia. Overview. [Accessed June 13, 2020] Available from: https://bnf.nice.org.uk/treatment-summary/anaemia-megaloblastic.html

12. British National Formulary. Hydroxocobalamin. Indications and Dose. [Accessed June 13 2020]. Available from: https://bnf.nice.org.uk/drug/hydroxocobalamin.html

13. National Institute for Health and Care Excellence. Active B12 assay for diagnosing vitamin B12 deficiency. [Accessed January 5 2020]. Available from https://www.nice.org.uk/advice/mib40/chapter/Introduction.

Copper

1. Ross AC, Caballero BH, Cousins RJ, Tucker KL, Ziegler TR. Modern Nutrition in Health and Disease: Eleventh Edition. Philadephia, USA: Lippincott Williams & Wilkins; 2014.

2. Committee on Medical Aspects of Food Policy. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. London: HSMO; 1991.

3. Administration USFaD. Vitamins and Minerals Chart. 2020.

4. Euorpean Food Safety Authority. Dietary reference values for nutrients. Summary Report. EFSA Supporting Publication. 2017;2017:e15121.

5. Danks DM. Copper deficiency in humans. Annu Rev Nutr. 1988;8:235-57.

6. Shike M. Copper in parenteral nutrition. Gastroenterology. 2009;137(5 Suppl):S13-7.

7. Salota R, Omar S, Sherwood RA, Raja K, Vincent RP. Clinical relevance of trace element measurement in patients on initiation of parenteral nutrition. Ann Clin Biochem. 2016;53(6):680-5.

8. Ewang-Emukowhate M, TChotai De Lima, Y, C T, D M, Hayes A, Grossman A, Nair D, et al. Assessment of fat-soluble vitamins and trace elements in neuroendocrine tumour (NET) patients on somatostatin analogues. Endocrine Abstracts. 2018;60:24.

9. Fessler TA. Trace elements in parenteral nutrition: a practical guide for dosage and monitoring for adult patients. Nutr Clin Pract. 2013;28(6):722-9.

10. Livingstone C. Review of Copper Provision in the Parenteral Nutrition of Adults. Nutr Clin Pract. 2017;32(2):153-65.

11. WHO. Copper. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) [Accessed February 3 2020] Available from: http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=2824

Iron

1. Demeyer, D., De Smet, S. and Ulens, M., 2014. The near equivalence of haem and non-haem iron bioavailability and the need for reconsidering dietary iron recommendations. *European journal of clinical nutrition*, *68*(6), pp.750-751.

2. Hunt, J.R. and Roughead, Z.K., 1999. Nonheme-iron absorption, fecal ferritin excretion, and blood indexes of iron status in women consuming controlled lactoovovegetarian diets for 8 wk. *The American journal of clinical nutrition*, *69*(5), pp.944-952.

3. Saunders, A.V., Craig, W.J., Baines, S.K. and Posen, J.S., 2013. Iron and vegetarian diets. *The Medical Journal of Australia*, *199*(4), pp.S11-S16.

4. Scientific Advisory Committee on Nutrition (SACN), 2010. Iron and Health. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/339309/SACN_Iron_and_Health_Report.pdf.

5. Quintaes, K.D., Amaya-Farfan, J., Tomazini, F.M., Morgano, M.A., de Almeyda Hajisa, N.M. and Neto, J.T., 2007. Mineral migration and influence of meal preparation in iron cookware on the iron nutritional status of vegetarian students. *Ecology of food and nutrition*, *46*(2), pp.125-141.

6. Pfeiffer, C.M. and Looker, A.C., 2017. Laboratory methodologies for indicators of iron status: strengths, limitations, and analytical challenges. *The American journal of clinical nutrition*, *106*(suppl_6), pp.1606S-1614S.

7. World Health Organisation, 2007. Assessing the iron status of populations, second ed. https://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/9789241596107.pdf.

8. Cancer Research UK (CRUK). Types and grades of stomach NETs https://www.cancerresearchuk.org/about-cancer/neuroendocrine-tumours-nets/stomach-nets/types-grades.

9. British National Formulary 2021. Anaemia, iron deficiency. [Accessed 10th June 2021. https://bnf.nice.org.uk/treatment-summary/anaemia-iron-deficiency.html.

10. Cançado, RD and Munoz., 2011. Intravenous iron therapy: how far have we come?. *Rev Bras Hematol Hemoter*, 33(6), pp. 461-69.

11. British National Formulary. 2021. Iron Sucrose, available at https://bnf.nice.org.uk/drug/iron-sucrose.html [Accessed 9th September 2021].

Selenium

1. Authority) EEFS. Dietary reference values for nutrients. Summary Report. EFSA Supporting Publication. 2017;2017:e15121.

2. Rayman MP. Selenium and human health. Lancet. 2012;379(9822):1256-68.

3. Committee on Medical Aspects of Food Policy. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. London: HSMO; 1991.

4. Administration USFaD. Vitamins and Minerals Chart. 2020.

5. Doley J. Minerals and Older Adults. In: Watson R, R., Preedy VR, editors. Bioactive Food as Dietary Interventions for the Aging Population2013. p. 335 - 56.

6. Timofte D, Livadariu R, Bintintan V, Diaconu C, Ionescu L, Sandberg AA, et al. Metabolic disorders in patients operated for pancreatic cancer. Rev Med Chir Soc Med Nat Iasi. 2014;118(2):392-8.

7. Sunde RA. Selenium. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. Modern Nutrition in Health and Disease. 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012:225-37.

8. Terry EN, Diamond AM. Selenium. In: Erdman JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition. 10th ed. Washington, DC: Wiley-Blackwell; 2012:568-87.

9. Sunde RA. Selenium. In: Coates PM, Betz JM, Blackman MR, et al., eds. Encyclopedia of Dietary Supplements. 2nd ed. London and New York: Informa Healthcare; 2010:711-8.

10. Ewang-Emukowhate M, TChotai De Lima, Y, C T, D M, Hayes A, Grossman A, Nair D, et al. Assessment of fat-soluble vitamins and trace elements in neuroendocrine tumour (NET) patients on somatostatin analogues. Endocrine Abstracts. 2018;60:24.

11. Moncayo R, Traeger A. Decreased selenium levels after peptide receptor radionuclide therapy (PRRT) in patients with neuroendocrine tumours: implications for the antioxidant status. Eur J Nucl Med Mol Imaging. 2011;38(8):1580-1.

12. Michiels C, Raes M, Toussaint O, Remacle J. Importance of Se-glutathione peroxidase, catalase, and Cu/Zn-SOD for cell survival against oxidative stress. Free Radic Biol Med. 1994;17(3):235-48.

13. Yagi M, Tani T, Hashimoto T, Shimizu K, Nagakawa T, Miwa K, et al. Four cases of selenium deficiency in postoperative long-term enteral nutrition. Nutrition. 1996;12(1):40-3.

Zinc

1. EFSA NDA Panel (EFSA Panel on Dietetic Products NaA. Scientific Opinion on Dietary Reference Values for zinc. ESFA Journal. 2014;12(3844).

2. Committee on Medical Aspects of Food Policy. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. London: HSMO; 1991.

3. Aggett PJ. (1989) Severe zinc deficiency in Zinc in Human Biology [Mills CF editor].

4. Hambidge KM. Zinc and diarrhea. Acta Paediatr Suppl. 1992; 381: 82-86.

5. Sallé A, Demarsy D, Poirier AL, Leliévre B, Topart P, Guilloteau G, Bécouarn G and Rohmer V. Zinc deficiency: a frequent and underestimated complication after bariatric surgery. Obesity Surgery. 2010: 20; 1660-1670.

6. Ewang-Emukowhate M, TChotai De Lima, Y, C T, D M, Hayes A, Grossman A, Nair D, et al. Assessment of fat-soluble vitamins and trace elements in neuroendocrine tumour (NET) patients on somatostatin analogues. Endocrine Abstracts. 2018;60:24.

7. British National Formulary. 2021. Zinc deficiency. https://bnf.nice.org.uk/treatment-summary/zinc-deficiency.html. [Accessed 10th September 2020].

Fat Soluble Vitamins

1. Johnson EJ, Mohn ES. Fat-soluble vitamins. World Rev Nutr Diet. 2015;111:38-44.

2. Lamrani A, Vidon N, Sogni P, Nepveux P, Catus F, Blumberg J, et al. Effects of lanreotide, a somatostatin analogue, on postprandial gastric functions and biliopancreatic secretions in humans. Br J Clin Pharmacol. 1997;43(1):65-70.

3. Donnelly L, Tailor S, Reid K, Williams M, Lewis J, Jones B, Rees A, Khan M. A Prospective Service Evaluation of Systematic Gastroenterological Assessment and Management on Patients with Neuroendocrine Tumours in South East Wales. 2017.

4. Booth CC, Alldis D, Read AE. Studies on the site of fat absorption: 2 Fat balances after resection of varying amounts of the small intestine in man. Gut. 1961;2(2):168-74.

5. Aldini R, Roda A, Festi D, Sama C, Mazzella G, Bazzoli F, et al. Bile acid malabsorption and bile acid diarrhea in intestinal resection. Dig Dis Sci. 1982;27(6):495-502.

6. Nightingale J, Woodward JM, Gastroenterology SBaNCotBSo. Guidelines for management of patients with a short bowel. Gut. 2006;55 Suppl 4:iv1-12.

7. Association AG. American Gastroenterological Association medical position statement: short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124(4):1105-10.

8. Reboul E, Borel P. Proteins involved in uptake, intracellular transport and basolateral secretion of fat-soluble vitamins and carotenoids by mammalian enterocytes. Prog Lipid Res. 2011;50(4):388-402.

9. Excellence NNIfHaC. BNF: Bile Acid Sequestrants 2020 [Available from: https://bnf.nice.org.uk/drug-class/bile-acid-sequestrants.html.

10. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35(2):247-307.

11. Authority) EEFS. Dietary reference values for nutrients. Summary Report. EFSA Supporting Publication. 2017;2017:e15121.

12. Whyand T, Bouvier C, Davies P. Prevalence of self-reported side effects in neuroendocrine tumour patients prescribed somatostatin analogues. British Journal of Nursing. 2018;27(13):738-44.

13. Ewang-Emukowhate M, TChotai De Lima, Y, C T, D M, Hayes A, Grossman A, Nair D, et al. Assessment of fat-soluble vitamins and trace elements in neuroendocrine tumour (NET) patients on somatostatin analogues. Endocrine Abstracts. 2018;60:24.

Vitamin A

1. EFSA NDA Panel (EFSA Panel on Dietetic Products NaA. Scientific opinion on Dietary Reference Values for vitamin A. EFSA Journal 2015;13(4028).

2. Authority) EEFS. Dietary reference values for nutrients. Summary Report. EFSA Supporting Publication. 2017;2017:e15121.

3. Policy CoMAoF. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. London: HSMO; 1991.

4. Administration USFaD. Converting Units of Measure for Folate, Niacin, and Vitamins A, D, and E on the Nutrition and Supplement Facts Labels: Guidance for Industry. . 2019.

5. Administration USFaD. Vitamins and Minerals Chart. 2020.

6. de Hosson LD, Stelwagen J, Bouma G, Sijtema B, Huitema S, van Faassen HJR, et al. Towards optimal personalized diet and vitamin supplementation in NET patients. Endocr Relat Cancer. 2018;25(3):L23-L6.

7. Public Health England. Vitamin A deficiency: migrant health guide 2014 [accessed 29 April 2021]. Available from: https://www.gov.uk/guidance/vitamin-a-deficiency-migrant-health-guide

8. Greaves RF, Woollard GA, Hoad KE, Walmsley TA, Johnson LA, Briscoe S, et al. Laboratory medicine best practice guideline: vitamins a, e and the carotenoids in blood. Clin Biochem Rev. 2014;35(2):81-113.

9. Fiebrich HB, Van Den Berg G, Kema IP, Links TP, Kleibeuker JH, Van Beek AP, et al. Deficiencies in fat-soluble vitamins in long-term users of somatostatin analogue. Aliment Pharmacol Ther. 2010;32(11-12):1398-404.

10. (SACN) SACoN. Review of Dietary Advice on Vitamin A. London: TSO; 2005.

11. National Institutes of Health. Vitamin A fact sheet for health professionals [accessed 30 April 2021]. Available from: https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/.

12. Ewang-Emukowhate M, TChotai De Lima, Y, C T, D M, Hayes A, Grossman A, Nair D, et al. Assessment of fat-soluble vitamins and trace elements in neuroendocrine tumour (NET) patients on somatostatin analogues. Endocrine Abstracts. 2018;60:24.

13. World Health Organisation (WHO). Indicators for assessing vitamin A defiiency and their application in monitoring and evaluating intervention programmes 1998. Available from https://apps.who.int/iris/bitstream/handle/10665/41947/9241545062.pdf?sequence=1&isAllowed=y.

Vitamin D References

1. Robbins HL, Symington M, Mosterman B, Goodby J, Davies L, Dimitriadis GK, et al. Supplementation of Vitamin D Deficiency in Patients with Neuroendocrine Tumors Using Over-the-Counter Vitamin D3 Preparations. Nutr Cancer. 2018;70(5):748-54.

2. Authority) EEFS. Dietary reference values for nutrients. Summary Report. EFSA Supporting Publication. 2017;2017:e15121.

3. Lind A, Wängberg B, Ellegård L. Vitamin D and vitamin B12 deficiencies are common in patients with midgut carcinoid (SI-NET). Eur J Clin Nutr. 2016;70(9):990-4.

4. (SACN) SACoN. Vitamin D and Health.: Crown Copyright; 2016.

5. Administration USFaD. Vitamins and Minerals Chart. 2020.

6. Dietitians BTAoU. Vitamin D 2019 [Available from: https://www.bda.uk.com/uploads/assets/01d7715f-c4f7-42e7-96f67018f035b0ea/Vitamin-d-food-fact-sheet.pdf.

7. Jasinghe V.J, Perera CO. Distribution of ergosterol in different tissues of mushrooms and its effect on the conversion of ergosterol to vitamin D2 by UV irradiation. Food Chemistry. 2005;92(3):541-6.

8. Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc. 2011;86(1):50-60.

9. Excellence. NIoHaC. Scenario: Management of vitamin D deficiency or insufficiency in adults 2018 [Available from: https://cks.nice.org.uk/topics/vitamin-d-deficiency-in-adults-treatment-prevention/management/management/.

10. (SACN). SACoN. Vitamin D and Health.: Crown Copyright; 2016.

11. Fiebrich HB, Van Den Berg G, Kema IP, Links TP, Kleibeuker JH, Van Beek AP, et al. Deficiencies in fat-soluble vitamins in long-term users of somatostatin analogue. Aliment Pharmacol Ther. 2010;32(11-12):1398-404.

12. Ewang-Emukowhate M, TChotai De Lima, Y, C T, D M, Hayes A, Grossman A, Nair D, et al. Assessment of fat-soluble vitamins and trace elements in

neuroendocrine tumour (NET) patients on somatostatin analogues. Endocrine Abstracts. 2018;60:24.

13. Lim S, Reynolds M, Chaudhry R, Blackhouse J, Rees A, Khan M. Nutritional assessment and vitamin deficiencies in patients with NETs. Endocrine Abstracts. 2018.

14. Borre M, Dam GA, Grønbaek H. Use of biologically based complementary medicines in patients with neuroendocrine tumors. Scand J Gastroenterol. 2019;54(8):998-1002.

15. Motylewska E, Gawronska J, Niedziela A, Melen-Mucha G, Lawnicka H, Komorowski J, et al. Somatostatin Analogs and Tumor Localization Do Not Influence Vitamin D Concentration in Patients with Neuroendocrine Tumors. Nutr Cancer. 2016;68(3):428-34.

16. Massironi S, Zilli A, Bernasconi S, Fanetti I, Cavalcoli F, Ciafardini C, et al. Impact of Vitamin D on the Clinical Outcome of Gastro-Entero-Pancreatic Neuroendocrine Neoplasms: Report on a Series from a Single Institute. Neuroendocrinology. 2017;105(4):403-11.

17. Rosanoff A, Dai Q, Shapses SA. Essential nutrient interactions: dose low or suboptimal magnesium staus interact with vitamin D and/or calcium status. Advances in Nutrition.

18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7146176/

Vitamin E References

1.National Institutes of Health, Vitamin E fact sheet for health professionals. https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/ [Accessed 21/07/2021]

2. Raederstorff D, Wyss A, Calder PC, Weber P, Eggersdorfer M. Vitamin E function and requirements in relation to PUFA. Br J Nutr. 2015;114(8):1113-22.

3. EFSA NDA Panel (EFSA Panel on Dietetic Products NaA. Scientific opinion on Dietary Reference Values for vitamin E as α -tocopherol. ESFA Journal. 2015;13(4149):72.

4. Administration USFaD. Vitamins and Minerals Chart. 2020.

5. Administration USFaD. Converting Units of Measure for Folate, Niacin, and Vitamins A, D, and E on the Nutrition and Supplement Facts Labels: Guidance for Industry. . 2019.

6. Farrell PM, Bieri JG, Fratantoni JF, Wood RE, di Sant'Agnese PA. The occurrence and effects of human vitamin E deficiency. A study in patients with cystic fibrosis. J Clin Invest. 1977;60(1):233-41.

7. Jeffrey GP, Muller DP, Burroughs AK, Matthews S, Kemp C, Epstein O, et al. Vitamin E deficiency and its clinical significance in adults with primary biliary cirrhosis and other forms of chronic liver disease. *Journal of Hepatology*. 1987;4(3):307-17.

8. Eggermont E. Recent advances in vitamin E metabolism and deficiency. Eur J Pediatr. 2006;165(7):429-34.

9. Kemnic TR, Coleman M. Vitamin E deficiency: StatPearls; 2019 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK519051/.

10. de Hosson LD, Stelwagen J, Bouma G, Sijtema B, Huitema S, van Faassen HJR, et al. Towards optimal personalized diet and vitamin supplementation in NET patients. Endocr Relat Cancer. 2018;25(3):L23-L6.

11. Greaves RF, Woollard GA, Hoad KE, Walmsley TA, Johnson LA, Briscoe S, et al. Laboratory medicine best practice guideline: vitamins a, e and the carotenoids in blood. Clin Biochem Rev. 2014;35(2):81-113.

12. Fiebrich HB, Van Den Berg G, Kema IP, Links TP, Kleibeuker JH, Van Beek AP, et al. Deficiencies in fat-soluble vitamins in long-term users of somatostatin analogue. Aliment Pharmacol Ther. 2010;32(11-12):1398-404.

13. Ewang-Emukowhate M, TChotai De Lima, Y, C T, D M, Hayes A, Grossman A, Nair D, et al. Assessment of fat-soluble vitamins and trace elements in

neuroendocrine tumour (NET) patients on somatostatin analogues. Endocrine Abstracts. 2018;60:24.

14. Lim S, Reynolds M, Chaudhry R, Blackhouse J, Rees A, Khan M. Nutritional assessment and vitamin deficiencies in patients with NETs. Endocrine Abstracts. 2017 52.

15. Ford L, Farr J, Morris P, Berg J. The value of measuring serum cholesterol-adjusted vitamin E in routine practice. Ann Clin Biochem 2006; 43: 130-34.

Vitamin K

1. Turck D, Bresson JL, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, et al. Dietary reference values for vitamin K. EFSA J. 2017;15(5):e04780.

2. Administration USFaD. Vitamins and Minerals Chart. 2020.

3. Kaneki M, Hodges SJ, Hedges SJ, Hosoi T, Fujiwara S, Lyons A, et al. Japanese fermented soybean food as the major determinant of the large geographic difference in circulating levels of vitamin K2: possible implications for hip-fracture risk. Nutrition. 2001;17(4):315-21.

4. Vitamin K fact sheet for health professionals 2021 [Available from: https://ods.od.nih.gov/factsheets/VitaminK-HealthProfessional/]

5. Fiebrich HB, Van Den Berg G, Kema IP, Links TP, Kleibeuker JH, Van Beek AP, et al. Deficiencies in fat-soluble vitamins in long-term users of somatostatin analogue. Aliment Pharmacol Ther. 2010;32(11-12):1398-404.

6. Ewang-Emukowhate M, TChotai De Lima, Y, C T, D M, Hayes A, Grossman A, Nair D, et al. Assessment of fat-soluble vitamins and trace elements in neuroendocrine tumour (NET) patients on somatostatin analogues. Endocrine Abstracts. 2018;60:24.

7. Excellence. NIoHaC. BNF: Menadiol sodium phosphate 2020 [Available from: https://bnf.nice.org.uk/drug/menadiol-sodium-phosphate.html.

8. National Institute for Health and Care Excellence: Phytomenadione 2021 [Available from: https://bnf.nice.org.uk/drug/phytomenadione.html].

Probiotics

1. Swidsinski A, Weber J, Loening-Baucke V, et al. Spatial organization and composition of the mucosal flora in patients with inflammatory bowel disease. J Clin Microbiol. 2005;43:3380–3389/ponziani doi: 10.1128/JCM.43.7.3380-3389.2005.

2. Dörffel Y, Swidsinski A, Loening-Baucke V, Wiedenmann B, Pavel M. Common biostructure of the colonic microbiota in neuroendocrine tumors and Crohn's disease and the effect of therapy. Inflamm Bowel Dis. 2012;18(9):1663-71. doi: 10.1002/ibd.21923.

3. Lopez-Siles, M, Duncan, S, Garcia-Gil, L, Martinez-Medina M. *Faecalibacterium prausnitzii*: from microbiology to diagnostics and prognostics. ISME J. 2017; 11**,** 841–852. https://doi.org/10.1038/ismej.2016.176.

4. Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA. The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. Cancer Cell. 2018;33(4):570-580. doi:10.1016/j.ccell.2018.03.015.

5. FAO/WHO: Guidelines for the evaluation of probiotics in food. Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food; Ontario, Canada: 1-11, 2002. [Accessed June 21st 2020]. Available from: http://www.fao.org/3/a-a0512e.pdf.

6. Borre M, Dam GA, Grønbaek H. Use of biologically based complementary medicines in patients with neuroendocrine tumors. Scand J Gastroenterol. 2019;54(8):998-1002. doi:10.1080/00365521.2019.1646799.

7. Whyand T, de Lima YC, Davies P. Complementary and alternative medicine use during chemotherapy for neuroendocrine tumours. Br J Nurs. 2019;28(6):387-393. doi:10.12968/bjon.2019.28.6.387.

8. Doron S, Snydman DR. Risk and safety of probiotics. Clin Infect Dis. 2015;60 Suppl 2(Suppl 2):S129-34. doi: 10.1093/cid/civ085.

Management of Carcinoid Syndrome

1. Warner M. Nutritional concerns for the carcinoid patient: developing nutrition guidelines for persons with carcinoid disease. Carcinoid Cancer Foundation 2000, updated 2008 [Accessed June 21, 2020]. Available at: https://www.carcinoid.org/for-

patients/general-information/nutrition/nutritional-concerns-for-the-carcinoid-patient-developing-nutrition-guidelines-for-persons-with-carcinoid-disease/.

2. Artale S, Barzeghi S, Grillo N, Maggi C, Lepori S, et al. Role of diet in the management of carcinoid syndrome: clinical recommendations for nutrition in patients with neuroendocrine tumors. Nutrition and Cancer. 2020. doi: 10.1080/01635581.2020.1838572.

3. de Herder WW, Feelders RA, Hofland J. Medical treatment of neuroendocrine neoplasms. Current Opinion in Endocrine and Metabolic Research. 2021; 18: 139-144.

4. Maintz L, Novak N. Histamine and histamine intolerance. Am J Clin Nutr. 2007;85:1185–11896. doi: 10.1093/ajcn/85.5.1185.

5. van der Lely AJ, de Herder WW. Carcinoid syndrome: Diagnosis and medical management. Arq Bras Endocrinol Metabol 2005;49:850–860. doi: 10.1590/s0004-27302005000500028.

6. Skypala IJ, Williams M, Reeves L, Meyer R, Venter C. Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence. Clin Transl Allergy. 2015;5:34. doi:10.1186/s13601-015-0078-3.

7. BDA Food Allergy Specialist Group. Sensitivity to histamine and other vasoactive amines. BDA. 2018.

8. Lips CJM, Lentjes EGWM, Ho¨ppener JWM. The spectrum of carcinoid tumours and carcinoid syndromes. Ann Clin Biochem 2003; 40: 612–627. doi:10.1258/000456303770367207.

9. de Herder WW. Biochemistry of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab. 2007;21(1):33-41. doi:10.1016/j.beem.2006.12.002.

10. Liu EH, Solorzano CC, Katznelson L, Vinik AI, Wong R, Randolph G. AACE/ACE disease state clinical review: diagnosis and management of midgut carcinoids. Endocr Pract. 2015;21(5):534–45. doi: 10.4158/EP14464.DSC.

11. Vinik AI, Gonin J, England BG, Jackson T, McLeod MK, Cho K. Plasma substance-P in neuroendocrine tumors and idiopathic flushing: the value of pentagastrin stimulation tests and the effects of somatostatin analog. J Clin Endocrinol Metab. 1990;70(6):1702–9. doi: 10.1210/jcem-70-6-1702.

12. Borman RA, Burleigh DE. Heterogeneity of 5-HT receptors mediating secretion in the human intestine. Ann N Y Acad Sci. 1997;812:224–5. doi: 10.1111/j.1749-6632.1997.tb48183.x.

13. Oberg K, Theodorsson-Norheim E, Norheim I. Motilin in plasma and tumor tissues from patients with the carcinoid syndrome. Possible involvement in the increased frequency of bowel movements. Scand J Gastroenterol. 1987;22((9)):1041–8. doi: 10.3109/00365528708991954.

14. Chaney SG. 2006 Principles of nutrition I: macronutrients, chapter 27 in Textbook of Biochemistry with Clinical Correlations 6th Ed. [Thomas M Devlin editor] 1071 – 1087.

15. Soga J, Yakuwa Y, Osaka M. Carcinoid syndrome: a statistical evaluation of 748 reported cases. J Exp Clin Cancer Res. 1999;18((2)):133–41.

16. Vlieg-Boerstra BJ, van der Heide S, Oude Elberink JN, Kluin-Nelemans JC, Dubois AE. Mastocytosis and adverse reactions to biogenic amines and histamine-releasing foods: what is the evidence? Neth J Med. 2005;63:244–9.

17. Visciano P, Schirone M, Tofalo R, Suzzi G. Biogenic amines in raw and processed seafood. Front Microbiol. 2012;3:188. doi: 10.3389/fmicb.2012.00188].

18. Linares DM, del Rio B, Ladero V, Martinez N, Fernandez M, Cruz Martin and Alverez MA. Factors influencing biogenic amines accumulation in dairy products. Front Microbiol. 2012;3:180.

19. Chung BY, Cho SI, Ahn IS, Lee HB, Kim HO, Park CW, Lee CH. Treatment of atopic dermatitis with a low histamine diet. Ann Dermatol. 2011;23(Supp 1):S91–S95. doi: 10.5021/ad.2011.23.S1.S9.

20. Shukla S, Kim J-K, Kim M. Occurrence of biogenic amines in soybean food products, soybean and health, Prof. Hany El-Shemy (Ed.), ISBN: 978-953-307-535-8, InTech; 2011. doi:10.5772/19021.

21. Halász A, Baráth A, Simon-Sarkadi L, Holzapfe W. Biogenic amines and their production by microorganisms in food. Trends Food Sci Technol. 1994;5(2):42–49. doi: 10.1016/0924-2244(94)90070-1.

22. Kanny G, Gerbaux V, Olszewski A, Frémont S, Empereur F, Nabet F, Cabanis JC, Moneret-Vautrin DA. No correlation between wine intolerance and histamine content of wine. J Allergy Clin Immunol. 2001 Feb; 107(2):375-8.

23. Hammer HF, Phillips SF, Camilleri M, Hanson RB. Rectal tone, distensibility, and perception: reproducibility and response to different distensions. Am J Physiol. 1998;274(3):G584-G590. doi:10.1152/ajpgi.1998.274.3.G584

24. McKenzie YA, Bowyer RK, Leach H, Gulia P, Horobin J, O'Sullivan NA, Pettitt C, Reeves LB, Seamark L, Williams M, Thompson J, Lomer MC; (IBS Dietetic Guideline Review Group on behalf of Gastroenterology Specialist Group of the British Dietetic Association). British Dietetic Association systematic review and evidence-based practice guidelines for the dietary management of irritable bowel syndrome in adults (2016 update). J Hum Nutr Diet. 2016 Oct;29(5):549-75. doi: 10.1111/jhn.12385.

25. Catassi G, Lionetti E, Gatti S, Catassi C. The Low FODMAP Diet: Many Question Marks for a Catchy Acronym. Nutrients. 2017;9(3). pii: E292. doi: 10.3390/nu9030292.

26. Ghoshal UC. How to interpret hydrogen breath tests. J Neurogastroenterol Motil. 2011;17(3):312-7. doi: 10.5056/jnm.2011.17.3.312.

27. Whyand T, Koffas A, Toumpanakis C, Mandair D, Caplin M. Assessment of small intestinal bacterial overgrowth (SIBO) in NET patients. 14th Annual ENETS conference (2017) [Accessed June 21, 2020]. Available from: https://www.enets.org/assessment-of-small-intestinal-bacterial-overgrowth-sibo-in-net-patients.html.

28. Holzer P. TRPV1: a new target for treatment of visceral pain in IBS?. *Gut*. 2008;57(7):882-884. doi:10.1136/gut.2008.149724.

29. Bhat YM, Bielefeldt K. Capsaicin receptor (TRPV1) and non-erosive reflux disease. Eur J Gastroenterol Hepatol. 2006;18(3):263-270. doi:10.1097/00042737-200603000-00006.

30. Akbar A, Yiangou Y, Facer P, Walters JR, Anand P, Ghosh S. Increased capsaicin receptor TRPV1-expressing sensory fibres in irritable bowel syndrome and their correlation with abdominal pain. Gut. 2008;57(7):923-929. doi:10.1136/gut.2007.138982.

31. Chan CL, Facer P, Davis JB, et al. Sensory fibres expressing capsaicin receptor TRPV1 in patients with rectal hypersensitivity and faecal urgency. Lancet. 2003;361(9355):385-391. doi:10.1016/s0140-6736(03)12392-6.

32. Eads J, Reidy-Lagunes D, Soars H, Chan J, Lowel A et al. Differential diagnosis of diarrhea in patients with neuroendocrine tumors. Journal of Neuroendocrine Tumours and Pancreatic Disease and Science. 2020; 49; 1123-1130. doi: 10.1097/MPA.0000000000001658.

Carcinoid Heart Disease

1. Davar J, Connolly HM, Caplin ME, Pavel M, Zacks J et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: an expert statement. J Am Coll Cardiol. 2017; 14;69(10):1288-1304. doi: 10.1016/j.jacc.2016.12.030. PMID: 28279296.

2. Hassan SA, Banchs J, Iliescu C, Dasari A, Lopez-Mattei J, Yusuf SW. Carcinoid heart disease. Heart. 2017; 103(19):1488-1495. doi: 10.1136/heartjnl-2017-311261. Epub 2017 Jun 8. PMID: 28596302.

Functioning NENs and Non-Functioning Pancreatic NENs

1. Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, et al. ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms: Functional Pancreatic Endocrine Tumor Syndromes. Neuroendocrinology. 2012 Feb;95(2):98-119.

2. Wiedenmann B, Pavel, M, Kos-Kudla B. Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2011 Aug;94:177-190.

3. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016 Jan;103:153-171.

4. Mitrakou A, Fanelli C, Veneman T, Perriello G, Calderone S, Platanisiotis D, et al. Reversibility of unawareness of hypoglycemia in patients with insulinomas. N Engl J Med. 1993 Sep;329:834-839.

5. Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Ito S, Ogawa O, et al. Diagnosis and management of insulinoma. World J Gastroenterol. 2013 Feb;19(6):829–837.

6. Whyand T, Davies P, Caplin M. Food and Neuroendocrine Tumours (NETs). R Free Hosp Neuroendocr Tumour Unit 2014. [accessed January 19, 2020]. Available from: http://s3-eu-west-1.amazonaws.com/files.royalfree.nhs.uk/Patient_resources/NETs/ Food_and_NETs.pdf

7. https://www.ncbi.nlm.nih.gov/books/NBK278981/

8. https://bnf.nice.org.uk/treatment-summary/corticosteroids-general-use.html

9. Iida K, Ohara T, Hino Y et al. Glucose-responsive insulinoma in a patient with postprandial hypoglycemia in the morning. Intern Med. 2010 Oct;49:2123–7.

10. Saddig C, Goretzki PE, Starke AA. Differentiation of insulin secretion patterns in insulinoma. World J Surg. 2008 Feb;32: 918-929.

11. Brun JF, Fedou C, Mercier J. Postprandial Reactive Hypoglycemia. Diabetes & Metabolism. 2000 Nov;26:337-351.

12. https://www.frontiersin.org/articles/10.3389/fendo.2020.00010/full

13. https://adc.bmj.com/content/archdischild/74/6/546.full.pdf

14. Nakano S, Sato T, Hosokawa M, Takagi C, Yoshida F, Ishii T, et al. A pediatric case of insulinoma and a novel MEN1 mutation: the efficacy of the combination

therapy of diazoxide and cornstarch. Clinical Pediatric Endocrinology. 2018 Jan;27(3):197-199.

15. de Herder WW, Schaik EV, Kwekkeboom D, Feelders RA. New theraputic options for metastatic malignant insulinomas. Clinical Endocrinology. 2011; [accessed January 19, 2020]. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2265.2011.04145.x

16. Joint British Diabetes Societies for Inpatient Care. The Hospital Management of Hypoglycaemia in Adults with Diabetes Mellitus 3rd edition 2018. [accessed September December 10, 2018] Available from: https://diabetes-resources-production.s3.eu-west-1.amazonaws.com/resources-s3/2018-05/JBDS_HypoGuidelineRevised2.pdf%2008.05.18.pdf.

17. Kaltsas G, Caplin M, Davies P, Ferone D, Garcia-Carbonero R, Grozinsky-Glasberg S, Hörsch D, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre- and Perioperative Therapy in Patients with Neuroendocrine Tumors. Neuroendocrinology. 2017 Mar;105:245-254.

18. Laing E, Kiss N, Michael M, Krishnasamy M. Nutritional complications and the management of patients with gastroenteropancretic Neuroendocrine Tumors. Neuroendocrinology. 2019. [accessed December 10 2019]. Available from: https://www.karger.com/Article/Pdf/503634.

19. Muñoz JE. Pancreatic exocrine insufficiency: Diagnosis and treatment. Journal of Gastroenterology and Hepatology. 2011 Feb;26 Suppl. 2:12–16.

20. Brennan GT, Saif MW. Pancreatic Enzyme Replacement Therapy: A Concise Review. JOP. 2019; 20(5): 121-125.

21. Bondeson A-G, Bondeson L, Thompson N W. Stricture and Perforation of the Esophagus: Overlooked Threats in the Zollinger- Ellison Syndrome. World J. Snrg. 1990 May;14:361-364.

22. Ito T, Jensen R T. Association of long-term proton pump inhibitor therapy with bone fractures and affects on absorption of calcium, vitamin B12, iron and magnesium. Clinical Gastroenterology and Hepatology. 2013 May;11(5): 483-490.

23. Electronic Medicines Compendium. Omeprazole 40 mg gastro-resistant tablets. 2017. [accessed December 12 2019]. Available from: https://www.medicines.org.uk/emc/product/664/smpc#CLINICAL_PRECAUTIONS

24. Lo W-K, Chan WW. Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. Clinical Gastroenterology and Hepatology. 2013 May;11(5):483-490.

25. Whyand T, Koffas A, Toumpanakis C, Caplin M. Assessment of small intestinal bacterial overgrowth in NET patients. 2017. ENETS Abstracts , Abstract #1698.

26. Bloom SR, Polak JM, Path FRC. Glucagonoma syndrome. The American Journal of Medicine. 1987 May;82(5)Supplement 2: 25-36.

27. Friess H, Bordinh K, Ebert M, Malfertheiner P, Kemmer T, Dennler H-J, Buchler M W. Inhibition of pancreatic secretion under long-term octreotide treatment in humans. Digestion. 1994;55(supplement 1):10-15.

28. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al.; ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guidelines on Nutrition in cancer patients. Clin Nutr. 2017 Feb; 36(1): 11-48.

29. Qureshi SA, Burch N, Druce M, Hattersley JG, Khan S, Gopalakrishnan K, et al. Screening for malnutrition in patients with gastroentero-pancreatic neuroendocrine tumours: a cross-sectional study. BMJ Open. 2016 May; 6(5):e010765.

30. Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al.; ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guideline: Clinical Nutrition in Surgery. Clin Nutr. 2017 Feb; 36(1): 623-650.

Pancreatic Exocrine Insufficiency (PEI) and Pancreatic enzyme replacement therapy (PERT)

1. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. J Clin Oncol. 2009; 27(28):4656-63.

2. Gullo L, Pezzilli R, Ancona D, Labate AM, Barbara L. Effect of octreotide, a long-acting somatostatin analogue, on plasma amino acid uptake by the pancreas. Pancreas. 1991; 6(6):668–72. https://doi.org/10.1097/00006676-199111000-00008.

3. Whyand T, Bouvier C, Davies P. Prevalence of self-reported side effects in neuroendocrine tumour patients prescribed somatostatin analogues. Br J Nurs. 2018 Jul 12;27(13):738-744. doi: 10.12968/bjon.2018.27.13.738.

4. Phillips ME. Pancreatic Resection: Nutritionals implications and long term follow up. Practical Gastroenterol. 2016; 150:18-26.

5. Working Party of the Australasian Pancreatic Club: Smith RC, Smith SF, Wilson J, Pearce C, Wray N, Vo R, et al. Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. Pancreatology. 2016; 16:164-180. https://doi.org/10.1016/j.pan.2015.12.006.

6. Domínguez-Muñoz JE. Pancreatic exocrine insufficiency: Diagnosis and treatment. J Gastroenterol Hepatol. 2011 Mar;26 Suppl 2:12-6. doi: 10.1111/j.1440-1746.2010.06600.x.

7. Chaudhry R, Newbould R, Williams M,Reid K, Donnelly L, Lewis J et al. Evaluation of faecal elastase 1 in symptomatic patients with neuroendocrine tumours. Endocrine Abstracts. 2016; 46:23. https://doi.org/10.1530/endoabs.46.P23.

8. Domínguez-Muñoz JE. Pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency: When is it indicated, what is the goal and how to do it? Adv Med Sci 2011;56(1):1-5. doi: 10.2478/v10039-011-0005-3.

9. Kuhn RJ, Eyting S, Henniges F, Potthoff A. In vitro comparison of physical parameters, enzyme activity, acid resistance, and pH dissolution characteristics of enteric-coated pancreatic enzyme preparations: implications for clinical variability and

pharmacy substitution. J Pediatr Pharmacol Ther 2007; 12(2):115-128. doi 10.5863/1551-6776-12.2.115.

Bile Acid Malabsorption (BAM)

1. Barkun A, Love J, Gould M, Pluta H, Steinhart AH. Bile acid malabsorption in chronic diarrhea: Pathophysiology and treatment. Can J Gastroenterol 2013;27(11):653-659. doi:10.1155/2013/485631.
2. Camilleri M. Bile Acid diarrhea: prevalence, pathogenesis, and therapy. Gut Liver. 2015;9(3):332-339. doi:10.5009/gnl14397.
3. Clement D, Tesselaar M, van Leerdam M, Srirajaskanthan R, Ramage J. Nutritional and vitamin status in patients with neuroendocrine neoplasms. World J Gastroenterol. 2019;25(10):1171-1184. doi:10.3748/wjg.v25.i10.1171.
4. Donnelly L, Tailor S, Reid K, Williams M, Lewis J, Jones B,et al. A Prospective Service Evaluation of Systematic Gastroenterological Assessment and Management on Patients with Neuroendocrine Tumours in South East Wales. ENETS abstract 14th Annual ENETS conference (2017). [accessed June 11, 2020]. Available from: https://www.enets.org/a-prospective-service-evaluation-of-systematic-gastroenterological-assessment-and-management-on-patients-with-neuroendocrine-tumours-in-south-east-wales.html. [Google Scholar].
5. Watson L, Lalji A, Bodla S, Muls A, Andreyev HJ, Shaw C. Management of bile acid malabsorption using low-fat dietary interventions: a useful strategy applicable to some patients with diarrhoea-predominant irritable bowel syndrome? Clin Med (Lond). 2015;15(6):536-540. doi:10.7861/clinmedicine.15-6-536.
6. Jackson A, Lalji A, Kabir M, Muls A, Gee C, Vyoral S, et al. The efficacy of a low-fat diet to manage the symptoms of bile acid malabsorption – outcomes in patients previously treated for cancer. Clin Med (Lond). 2017;17(5):412-418. doi:10.7861/clinmedicine.17-5-412.
7. Wedlake L, Thomas K, Lalji A, Anagnostopoulos C, Andreyev HJ, Effectiveness and Tolerability of Colesevelam Hydrochloride for Bile-Acid Malabsorption in Patients With Cancer: A Retrospective Chart Review and Patient Questionnaire. Clin Ther. 2009 Nov;31(11):2549-58. doi: 10.1016/j.clinthera.2009.11.027.

8. National Institute for Health Care Excellence. Colesevelam Hydrochloride. 2019. https://bnf.nice.org.uk/drug/colesevelam-hydrochloride.html [Accessed 21 October 2019].

Dietary Management of Bowel Obstructions

1. https://www.karger.com/Article/Abstract/486097
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7943728/ ,
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7443843/
4. https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.31079
5. Basher Hmoud, Singal AK, Kamath PS. Mesenteric venous thrombosis. Journal of Clinical and Experimental Hepatology. 2014: 4;257-263.
6. https://link.springer.com/article/10.1245/s10434-021-10922-1
7. https://www.espen.org/files/ESPEN-Guidelines/ESPEN-practical-guideline-clinical-nutrition-in-cancer.pdf
8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3326983/
9. https://journals.lww.com/jcge/fulltext/2002/01000/nutritional_problems_in_end_stage_liver_disease_.18.aspx