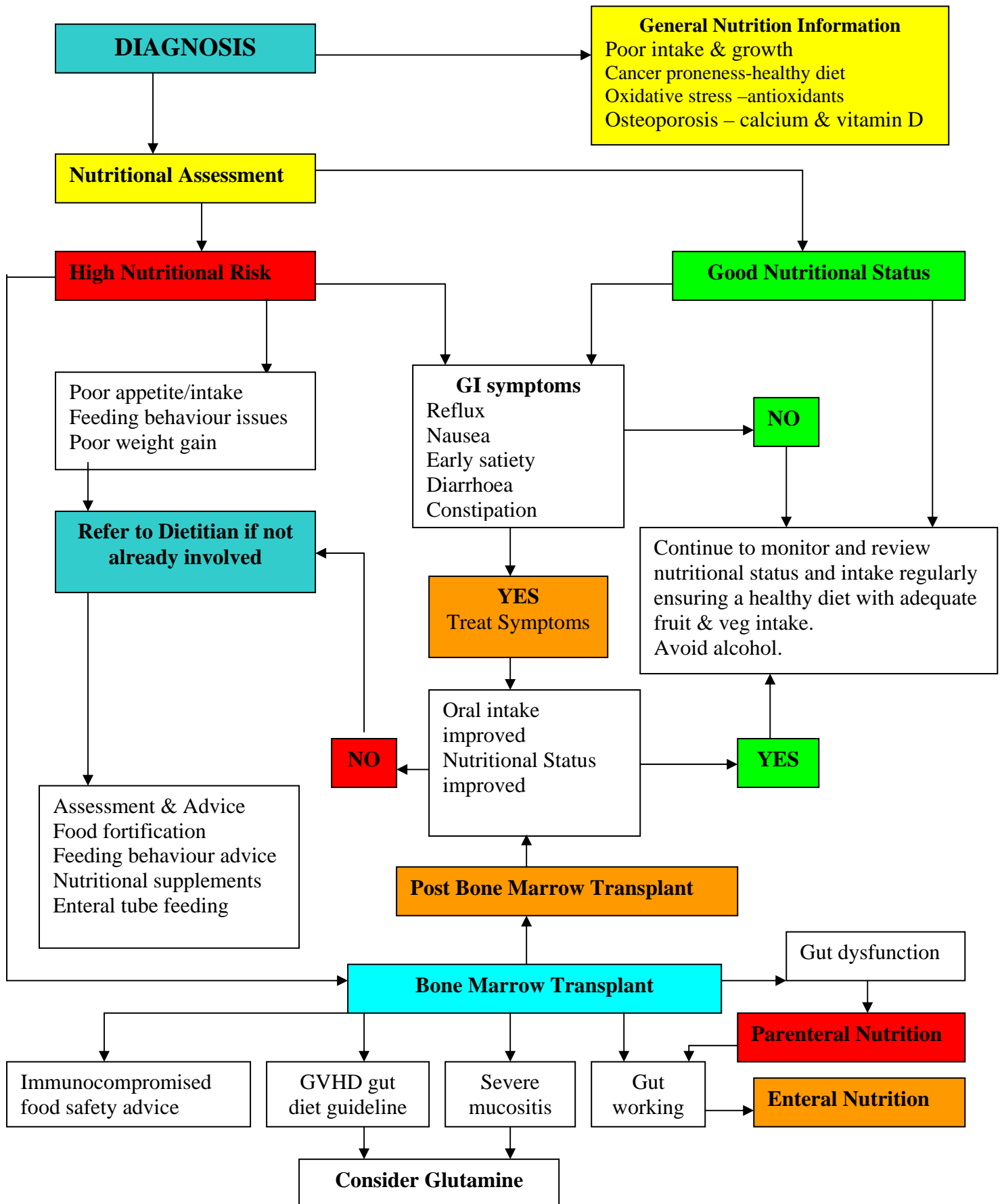


## Nutritional Management of Patients with Fanconi Anaemia



## Guidelines for the Nutritional Management of Patients with Fanconi Anaemia

The following guideline is aimed at health professions involved in the care of patients with fanconi anaemia (FA) based on the algorithm. Several fact sheets have been produced giving practical advice and information related to different aspects of nutrition and FA for patients, parents and carers which corresponds to the different stages highlighted in the algorithm.

The minimum requirement of nutritional care is to ensure all patients and families receive the general information leaflet and receive regular nutritional assessment and a general enquiry as to their intake and any nutritional concerns when they have a medical review. Poor appetite and dietary intake is common among FA patients and assessment of growth on appropriate centile charts in order to distinguish between the short stature commonly associated with FA and reduced weight for height, indicating malnutrition, should be a routine component of care.

As well as ensuring an adequate protein and calorie intake, in order to improve weight gain and growth, due to the oxidative stress and cancer proneness of FA a good fruit and vegetable intake is recommended aiming for at least 5 portions daily. Patients with FA who are able to consume an adequate diet should base their intake on The Balance of Good Health (The Foods Standards Agency).



The general information sheets for families gives practical ideas on how to increase fruit and vegetable intake. As patients with FA are also more prone to osteoporosis it discusses sources of calcium and vitamin D in the diet. Alcohol should be avoided as it has been shown to increase chromosomal breakage in FA and increase risk of oral cancers.

Patients with a poor oral intake and deemed to be a high nutritional risk (refer to nutritional assessment and intervention) will require a referral to a dietitian for advice on food fortification, dietary supplements and in some cases supplementary enteral tube feeding.

## **Oxidative stress and antioxidants**

The prominent role of the FA protein family involves DNA damage response and/or repair as well as being involved in Re-dox, cytokine regulation and apoptosis [1]. Oxidative stress is considered to be an important pathogenic factor in bone marrow failure in FA. Cellular responses inducing resistance to oxidative stress are important for cellular survival, organism life span and cancer prevention [2]. Significant evidence supports excessive apoptosis of haematopoietic stem/progenitor cells, induced by stresses, most significantly oxidative stress, as a critical factor in the pathogenesis of bone marrow failure and leukaemia progression in FA [2,3].

Subsequently labs have reported FA bone marrow (BM) cells are hypersensitive to a variety of extracellular biological apoptotic cues, including interferon- $\gamma$  (IFN- $\gamma$ ) and tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) [2,4,5,6]. In particular TNF- $\alpha$  is considered as an important pathological factor involved in the abnormal haemopoiesis by suggesting that excessive apoptosis in FA haematopoietic cells is induced by TNF- $\alpha$  overproduction and it has been reported that TNF- $\alpha$  is over expressed in BM of FA patients and increased in the serum of patients. Abnormalities of TNF- $\alpha$  production could be considered at the origin of progressive BM failure and the cellular and chromosomal hypersensitivity to DNA damage observed in FA patients.

Studies have revealed that TNF- $\alpha$  induced apoptosis in Fancc MEFs is Apoptosis Signal-Regulating Kinase -1 (Ask1) dependent and that Fancc cells exhibit an altered intracellular redox environment, predisposing to stimuli that activate Ask1 through reactive oxygen species (ROS) generation, such as oxidants and TNF- $\alpha$ . This leads to a cycle in which TNF- $\alpha$  induces hyperactivation of Ask1 and the downstream effector p38. Ask 1 is a unique mitogen-activated protein kinase (MAPK) [2,5].

TNF- $\alpha$  also activates the transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B). Inversely activation of both NF- $\kappa$ B and MAPKs plays an important role in the induction of many cytokines, including TNF- $\alpha$  itself. Both oxidative stress and impaired DNA repair contribute to the activation of the ataxia telangiectasia mutated (ATM) pathway recently reported in FA and it has been described that both ATM and ROS may induce NF- $\kappa$ B and MAPKs. Consequently it has been speculated that FA cells suffer permanent stress due to both intracellular ROS increase and accumulation of endogenous DNA damage that leads to MAPK and NF- $\kappa$ B signalling activation. MAPK activation in turn contributes, through the alteration of the matrix metalloproteinase - 7 (MMP-7) expression, to the overproduction of TNF- $\alpha$ . Since TNF- $\alpha$  is able to activate NF- $\kappa$ B and MAPKs, these factors form an autocrine loop that results in the escalation of their own levels and consequently, of the severity of the pathogenesis. In accord with this it has been shown that NF- $\kappa$ B and MAPK over activation is causative of BM failure, myelodysplastic syndromes and leukaemia. It has been reported that NF- $\kappa$ B and MAPK inhibition as beneficial in BM failure and leukaemia [6].

It has been suggested that clinical strategies based on the use of pharmacologic approaches such as antioxidants or Etanercept to block stress-response pathways and/or TNF- $\alpha$  activity should be considered [7,8,9].

### **The role of antioxidants**

Due to the relationship between oxidative stress and both cancer proneness and bone marrow failure the role of antioxidants might provide protection against both malignancies and the onset of aplastic anaemia in FA patients. As well as the role of antioxidants to suppress the excess apoptosis in response to TNF- $\alpha$ , which acts via increased production of ROS another scenario is oxidative stress causing telomere shortening and ensuing telomere dysfunction may form the basis for malignant transformation in FA cells. Telomere dysfunction did not evoke damage response in FA cells, in contrast to normal p53 upregulation in control cells [10].

### **Antioxidants used in studies**

There have been studies looking at antioxidants in FA cells or FA mice and these are referenced and the outcomes briefly summarised below.

Fancc<sup>-/-</sup> murine embryonic fibroblasts (MEFs), pretreated with antioxidants (selenomethionine or N-acetylcysteine) protected Fancc<sup>-/-</sup>MEFs from hydrogen peroxide induced apoptosis to wild type [WT] levels [3].

Mice transplanted with preleukaemic Fancc<sup>-/-</sup> BM cells accumulated high levels of ROS but administration of N-acetylcysteine [NAC] significantly reduced ROS and the time required to develop leukaemia was significantly reduced in mice treated with NAC.

One study suggested that vitamin C suppresses the priming effect of IFN- $\gamma$  in FAS and IFN- $\gamma$  treated FA cells[4]. However a later study found that Vitamin C did not prevent telomere shortening and warned about the dual activity of vitamin C as oxidant and antioxidant in different settings [10].

A study looking at the anti oxidant Tempol, a nitroxide antioxidant and a superoxide dismutase mimetic, found a reduction in oxidative DNA damage in tempol treated FA fibroblasts and mice suggests that its tumour delaying function may be attributed to its antioxidant activity [12]. Other studies suggest tempol acts as a chemopreventative agent in a mouse model of human cancer prone syndrome and that its chemoprotective effect is not due solely to the reduction of oxidative stress and damage but may also be related to redox-mediated signaling functions that include the p53 pathway [13,14].

### **The role of dietary antioxidants**

Currently there has been limited studies exploring the role of dietary antioxidants in FA and hence unless clinical studies are undertaken it is difficult to make specific recommendations, particularly for paediatric patients where information on doses, pharmacokinetics and effects is very limited, especially as the antioxidants in question are generally not recommended for <12 or 18 years of age. Some potent dietary antioxidants such as quercetin, rutin, alpha-lipoic acid and resveratrol have been shown to affect transcription factors such as NF- $\kappa$ B and subsequently inhibit TNF- $\alpha$  production [15,16,17,18,19,20,21,22] and hence in theory would be beneficial to FA patients.

Whilst it is clear based on the evidence on FA phenotype and on the evidence of nutrition in counteracting oxidative stress and malignant transformation [9] without clinical studies, which would be difficult due to small patient numbers for recruitment

and study design relying on the most appropriate choice of antioxidant already approved for safe human use with minimal or no adverse effects [23], it would be prudent to consider the following when discussing antioxidants with FA patients and their families.

Data on doses and pharmacokinetics, particularly in children is lacking. There is no available data regarding the safety of long-term use of high doses of antioxidants in general bearing in mind that FA is a life long condition. The interaction between high dose antioxidants and other medication the patient is on is not known.

Some antioxidants at certain doses or situations are potentially toxic or exert a pro-oxidant effect. Quercetin becomes oxidised while exerting its antioxidative capacities and potentially toxic oxidation products are formed [17,24] and it has been reported in vitro that long term treatment with quercetin resulted in pro-oxidative and pro-apoptotic effects [25].  $\alpha$ -lipoic acid demonstrates antioxidant activity, both in its oxidised and reduced forms, however the reduced form, dihydrolipoic acid, can also demonstrate a pro-oxidant effect [26,27,28]. The pro-oxidant effect of lipoic acid is achieved by the same mechanism as seen with vitamins C and E, whereby transition metals may be reduced, forming reactive radical species [26]. Animal studies looking at toxicity of  $\alpha$ -lipoic acid have shown it is generally safe but large doses are toxic [29]. For this reason a recent study in sickle cell patients limited the dose to 200mg/day, which would be the minimum amount necessary to produce an antioxidant effect [30]. The same dose was used in a study looking at redox balance in children with Down's syndrome [31].  $\alpha$  lipoic acid has caused allergic skin reactions and possible hypoglycaemia [26]. Despite substantial progress in the understanding of resveratrol currently there have been very few clinical studies and those currently undertaken have been phase I studies [19] hence more studies are required looking at effects and any potential toxicity from resveratrol in both normal and disease context. Rutin is a glycoside of quercetin in which the hydrogen of the R-4 hydroxyl group is replaced by a disaccharide. Two recent papers by the same author reported that previous studies conducted by them found that rutin inhibited the overproduction of free oxygen radicals by the FA blood and bone marrow leucocytes in in vitro experiments and significantly decreased the state of oxidative stress in FA children [21,22]. The study they refer to was published in 1992. They looked initially at the effect of rutin on leucocytes of healthy individuals and on the leucocytes of 9 FA patients and concluded that rutin was found to be an effective inhibitor of the luminol-dependent chemiluminescence produced by FA leucocytes [32]. However they only gave rutin (10mg/kg t.d.s) to 3 patients. Two patients had it for a year and 1 patient for up to 3 years. No side effects were observed and after 6 months of rutin it was found that chromosomal aberrations diminished from 15.5 to 7.7% in one patient but no change was observed in the other two patients. Haemoglobin levels after 6 months of rutin had increased in all 3 patients. They commented on the increase in height and weight in only one of the patients [33]. It is obviously difficult to draw any definite conclusions from the study as patient numbers were so small and there have been no further papers since.

Most evidence supporting supplementation with dietary antioxidants or single supplements is based on in vitro or animal studies and does not always translate into positive effects in clinical trial. This could be as a result of a number of factors such as stability of the antioxidant in biological systems, inter-individual variability for

bioavailability and metabolism [26]. The quality of commercially available supplements in terms of bioavailability stated levels have been shown to vary between manufacturers [26]. The effect of taking the antioxidant as a food may have added benefit due to the mixture or synergy between other antioxidants and compounds in the diet which may have an important effect on bioavailability [26,31]. A diet containing all contributing dietary antioxidants in a balanced combination should be recommended and hence in the patient information leaflet advice is given on how to include more fruit and vegetables in the diet. The role of dietary antioxidant supplements is also discussed, along with dietary sources of the previously discussed antioxidants with the aim of giving families an informed choice. It is however important they discuss further with their doctor or dietitian and also make them aware if they do decide to use any antioxidant supplements.

Patients and families may ask about general multivitamin supplementation. The following advice should be considered.

- FA patients who are eating well and include a good variety of foods in their diet should not need to take a vitamin supplement.
- FA patients currently on tube feeds or nutritionally complete sip feeds should not need an additional vitamin supplement as their requirements will be met by the tube feed or sip feed.
- FA patients not on any additional feeds or sip feeds and only eat a limited variety of foods may benefit from an additional multivitamin supplement. It is however preferable to try to get vitamins and minerals from food and hints on how to increase fruit vegetables intake are given in the patient information leaflet.
- Vitamins in excess can be toxic therefore a megadose of a single vitamin or combination of vitamins should be avoided. Some megadoses are also known to have a pro-oxidant effect e.g. vitamin C.
- A general age appropriate supplement which does not give above the daily recommended amount [RDA] would be suitable to use. Ideally long-term supplement use is not recommended.
- Patients with FA who are receiving blood transfusions will receive iron from this and therefore do not need an additional source hence a supplement which does not contain any iron or only a small amount. [no more than 15% RDA] should be advised.

Some FA patients may require supplementation of specific nutrients depending on plasma levels. e.g vitamin D.

## Nutritional Assessment

The following is the minimum guideline for assessing anthropometric data in FA patients

	Diagnosis	Any in patient admission	Out patient clinic review
<u>WEIGHT</u>	√	√	√
<u>HEIGHT</u>	√	√	√
<u>Plot on centile chart/BMI chart</u>	√	√	√
<u>BMI/% Wt:Ht</u>	√	√	√

- Weight and height should routinely be recorded in the medical notes.
- A copy of a centile chart should be placed in the medical notes and routinely updated.
- For patients referred to and reviewed by a dietitian weight, height, BMI or percentage weight:height should be recorded in the dietetic notes.

## Referral to dietitian

Patients currently not being seen by a dietitian, a referral should be made if they have any of the following criteria:

- Percentage weight : height <90%
- Weight two centiles below height centile
- A decrease in current percentiles for weight (or height) of two centile positions
- If using a BMI chart – a BMI centile <9<sup>th</sup> centile
- Patients over 18 years – a BMI ≤ 18
- Failure to gain weight over a 3-6 month period. (1 month period for infants).
- A reduction in their normal oral intake or appetite.
- Significant feeding behaviour issues

**NB** – Over nutrition and metabolic syndrome are now being seen in FA patients and is associated with impaired glucose tolerance/diabetes and abnormal lipid levels [46]. A dietetic referral should be made if they have any of the following criteria:

- Percentage weight:height > 110%
- Weight two centiles above height centile
- If using a BMI chart – a BMI centile ≥98<sup>th</sup> centile
- Patients over 18 years – a BMI >25
- Abnormal plasma lipid and/or glucose levels

On referral each FA patient should be assessed on an individual basis and the appropriate nutritional intervention recommended taking into account their age and clinical condition with subsequent regular dietetic review.

The general information for patients and families does include general advice on poor appetite and food fortification, feeding behaviour advice, nausea, diarrhoea and constipation.

A feed thickener ( e.g Thixo-D, Sutherland Health Ltd or Thick & Easy, Hormel Health Labs) should be considered in infants with gastro-oesophageal reflux.

## **Nutritional Assessment**

Measurement of plasma vitamins and minerals to a certain extent will depend on the patient's clinical condition and how often they are reviewed in clinic. For example post BMT patients will attend clinic regularly initially when routine bloods will be done.

Ideally the following should be monitored at least every 6 –12 months

Urea, creatinine

Sodium, potassium, calcium, magnesium, phosphate

Vitamin A, D, E and C

Vitamin B12

Folate

PTH

FBC

Ferritin

Glucose

Fasting lipid levels (overweight and obese patients)

Selenium

Zinc

Copper

## Osteoporosis

Patients with FA are at increased risk of developing osteoporosis. This is due to several factors which will vary between patients. Maximising peak bone mass during skeletal growth in infancy, childhood and adolescence is considered to be important for the primary prevention of osteoporosis however this is not always achievable in children with FA due to problems with growth. Other risk factors include:

- Gut abnormalities resulting in a reduced absorption of calcium.
- Poor dietary intake of calcium and vitamin D.
- Being underweight for height. (in adults a body mass index (BMI) <19).
- Reduced exposure to sun.
- Some patients with kidney problems may be unable to convert vitamin D to its active form. 1,25-dihydroxyvitamin D (calcitriol).
- In woman low levels of the female hormone oestrogen.
- In men low levels of the male hormone testosterone.
- Patients who have undergone a bone marrow transplant who required a prolonged period of time on corticosteroids for management of graft versus host disease.
- Patients who have undergone a bone marrow transplant who had a prolonged period of gut graft versus host disease resulting in problems with malabsorption.

Calcium is vital for bone health and vitamin D is needed to absorb the calcium from our diets and therefore it is important to ensure an adequate intake of both nutrients.

Patients considered more at risk, those who have a low plasma level of vitamin D or those who are unable to obtain an adequate intake of vitamin D and calcium from their diet should be prescribed a vitamin D and calcium supplement.

## **Bone Marrow Transplant**

FA patients who require haematopoietic stem cell transplants (HSCT) can be especially challenging nutritionally due to problems with mucositis, gut dysfunction and graft versus host disease (GVHD) involving the gut. Nowadays fludarabine reduced intensity conditioning regimens in donor transplants have significantly improved survival, reduced acute GVHD and lowered toxicity and are being successfully used in FA patients [7].

Nutritional support is an important aspect of supportive care for patients undergoing HSCT and is provided to minimise the nutritional morbidity of both the conditioning regimens, leading to mucositis of the gastrointestinal tract and complications resulting from the procedure such as GVHD and veno-occlusive disease (VOD) of the liver[34,35,36,37,38].

### **Prior to HSCT**

In order to maximise nutritional status prior to transplant patients should be assessed by a dietitian. Patients deemed to be of a poor nutritional status should commence dietary supplements or enteral tube feeding prior to transplant.

### **Food Safety Advice**

Patients should receive information on food safety advice due to being immunosuppressed post HSCT. Restrictions are generally followed until immunosuppression is stopped or depending on local policy.

### **Enteral Nutrition**

FA patients undergoing HSCT will require additional nutritional support and it is highly preferably to use the enteral route. Enteral nutrition has numerous practical and physiological advantages over parenteral nutrition including a lower risk of infection and other catheter related complications. Enteral feeding will preserve intestinal function and integrity and therefore prevent the risk of bacterial translocation. It has a trophic effect on the gut and continuation of feeding, even if a minimal amount, during the period of maximum gut toxicity may accelerate healing [39].

If a standard polymeric feed is not tolerated or the patient already has signs of gastrointestinal toxicity then an amino acid based formula or a peptide based feed should be considered [37].

### **Parenteral nutrition**

Parenteral nutrition should be commenced if gut dysfunction is anticipated for >5 days e.g.

- Severe mucositis and enteritis
- Neutropenic enterocolitis
- Ileus
- Severe GVHD of the gastrointestinal tract

## **Glutamine**

It is well documented that glutamine is a major fuel and important nitrogen source for enterocytes and plays a key role in maintaining mucosal cell integrity and gut barrier function [van Acker *et al.*, 1999]. Studies looking at the role of oral and parenteral glutamine in adult HSCT patients have shown a reduction in mucositis, improved nitrogen balance, a lower incidence of clinical infections, lower rates of microbial colonisation and reduced length of hospital stay [40,41,42]. There are very few published studies looking at either enteral or parenteral glutamine in paediatric HSCT patients. However in a randomised double blind study of 120 children undergoing HSCT who were given a total oral dose of 4g/m<sup>2</sup> or placebo daily until day 28 post transplant or discharge it was demonstrated that although no significant difference in mean mucositis score was observed a significant reduction in the total number of days of intravenous analgesia and parenteral nutrition was demonstrated in the glutamine group perhaps reflecting the role of glutamine in improving lower gut mucositis. [43].

An oral dose of up to 0.65g/Kg has been shown to be safe and acceptable to use in paediatric patients [44].

Currently there are no studies looking at the role of parenteral glutamine in paediatric HSCT patients partly due to stability problems adding glutamine to small volumes of parenteral nutrition in paediatric patients. Although now available as a dipeptide of glutamine and alanine (Dipeptiven, Fresenius Kabi) its safety and efficacy in children has not yet been determined but is used in some centres.

Due to the chromosomal instability of FA and subsequently potentially increased toxicity problems from the conditioning regimen it may be prudent to consider the use of glutamine in FA patients undergoing HSCT.

## **Dietary management of gastrointestinal GVHD**

The nutritional management of both acute and chronic GVHD can be challenging however the introduction of a 5 phased dietary guideline allows structure in the reintroduction of foods in a slow stepped manner. The decision to advance the diet is dependent upon the patient's gastrointestinal symptoms together with the need to ensure an adequate nutritional intake [45].

A brief outline is given below and more information is given in reference 45.

Phase 1 – Gut rest (Grade IV GVHD)

Phase 2 – Introduction of a clear liquid diet and amino acid based enteral feed (Grade III GVHD).

Phase 3 – Introduction of a very basic low fat, low fibre, low acid, low irritant, lactose free diet (Grade III-II GVHD).

Phase 4 – Continuation of a low fat, low fibre, low acid, low irritant, low lactose diet (Grade II GVHD).

Phase 5 – Lactose free diet (Grade II-I GVHD)

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