

Chapter 4

Gastrointestinal, Hepatic, and Nutritional Problems in FA

Sarah Jane Schwarzenberg, MD and Nada Yagizi, MD

Introduction

Patients with Fanconi anemia experience many gastrointestinal, hepatic, and nutritional consequences of the disease and its treatment. This chapter will cover anatomic gastrointestinal abnormalities, gastrointestinal symptoms common in FA, nutritional growth failure in FA and supplemental nutritional support, and hepatic complications of FA therapy. A brief review of complications of hematopoietic stem cell transplant (HSCT) that are more common in FA will be included.

Polypharmacy

As with any complex disease process, the involvement of multiple subspecialists introduces the risk that medications prescribed by one physician will interact adversely with those prescribed by another. It is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

Radiation Exposure

Because FA patients have increased sensitivity to radiation, physicians involved in managing the patient should be in close contact with the pediatric radiologist. The radiologist may help reduce exposure to diagnostic radiation in several ways. The radiologist may

determine that non-radiation imaging techniques (ultrasound or MRI) may be substituted for CT scanning. CT scans, when necessary, can be limited to the area considered most important. In addition, pediatric and adult CT protocols differ in the amount of radiation used in each scan. *Care should be taken to use pediatric-specific CT scanners managed by qualified pediatric radiologists, as they can minimize radiation exposure when radiographs are essential.* In some cases, digital radiographs may require less radiation than cut films and are thus preferred.

Gastrointestinal Tract Anatomic Abnormalities

Approximately 7% of patients with FA have gastrointestinal tract anatomic abnormalities.¹ The most common anomalies are esophageal atresia (EA) with or without tracheoesophageal fistula (TEF), duodenal atresia, and anal atresia or ectopic anus. Most anomalies are diagnosed and treated in early infancy, often long before the diagnosis of FA. Although the gastrointestinal tract abnormalities may be isolated, they may also be associated with other congenital anomalies, including the VACTERL spectrum of disorders (**V**ertebral defects, **A**nal **A**tresia, **C**ardiac abnormalities, **T**racheo**E**sophageal abnormalities, **R**enal defects, **L**imb lesions). Patients with FA may experience complications of these anatomic abnormalities and their surgical treatment throughout their lives. The majority of patients with these anomalies do not have FA. However, because of the importance of knowing the diagnosis of FA early to prevent complications, the expert group developing these recommendations suggests that all children exhibiting the VACTERL spectrum of disorders be tested for FA (see Chapter 2). As the long-term

complications of these anomalies are similar in FA and non-FA patients, the following discussion derives from the general literature regarding these anomalies.

Esophageal atresia and tracheoesophageal fistula

Long-term complications of esophageal atresia and tracheoesophageal fistula are related to the severity of the primary lesion and the quality of the repair. A longer gap between the proximal and distal segments makes the repair more difficult and increases the risk of late strictures. The most common long-term complications of EA/TEF are gastroesophageal reflux (GER), abnormal esophageal motility and tracheomalacia.² Diagnosis and management of GER is essential to reduce pain, bleeding, and the development of strictures; anti-reflux surgery is often necessary. Respiratory symptoms, including cough, pneumonia, and wheezing may suggest the need for bronchoscopy. Recurrent TEF should be considered when pneumonia or pain develops after a period of relatively good health.

If the esophageal segments are very short or if significant complications occur, colon interposition to replace the esophagus may be required. This procedure is associated with many complications, including anastomotic leaks and swallowing problems, particularly pain with solids and frequent reflux and vomiting. There may also be a long-term risk of colonic cancer in the interposed segment.

Duodenal atresia

Duodenal atresia is less frequent than EA and can be a severe anomaly. Complications occur in 12-15% of patients and include abdominal pain, chronic alkaline reflux, and blind loop syndrome. There is frequently poor duodenal motility above the anastomosis with recurrent obstruction-like episodes.³ When evaluating

an FA child with poor weight gain, a history of correction of duodenal atresia or stenosis in infancy can suggest evaluation of intestinal motility or small bowel overgrowth.

Anal atresia

After anal atresia repair, 30% of patients have fecal incontinence, 50% have occasional soiling, and an undetermined number have constipation with or without encopresis.^{4,5} Management of these complications requires the intervention of a team, including a knowledgeable pediatric gastroenterologist and a pediatric surgeon with experience in anal repair. While bowel control may be achieved with medical management in most cases, some patients benefit from antegrade continence enema (ACE) procedures.

Gastrointestinal Symptoms

Many patients with FA complain of gastrointestinal symptoms, including poor oral intake, nausea, abdominal pain, and/or diarrhea. These symptoms are the source of significant discomfort and may contribute to poor weight gain in FA patients. Patients and their families must be questioned during routine clinic visits regarding gastrointestinal symptoms, as it is common for patients to fail to spontaneously disclose these concerns.

In FA, causes of poor oral intake may include complications of anatomic gastrointestinal abnormalities (strictures or complications of repair), chronic inflammation and/or infection, medication side effects, and neurologic/behavioral problems.

Nausea can result from infections, particularly urinary tract infections or sinusitis. Infection or some medications may cause delayed gastric emptying. This is

usually a transient problem, resolving with resolution of the infection or stopping the medication. Psychological stress, anxiety, and depression can also present with nausea. Abdominal pain may result from partial obstruction caused by complications of anatomic abnormalities, abnormal gastrointestinal motility, small bowel overgrowth or gallbladder disease. Possible causes of diarrhea include opportunistic infection of the gastrointestinal tract, small bowel overgrowth, medications, and short bowel with malabsorption. Constipation with encopresis is common, and families may mistake encopresis for diarrhea.

In all cases, the initial evaluation of gastrointestinal symptoms in FA begins with a good history and physical exam. Most problems can be diagnosed at this level, without resorting to further study. If the patient has non-specific poor oral intake, with or without nausea and abdominal pain, evaluation for evidence of occult infection may be useful. Laboratory studies, including urine culture and measurement of serum C-reactive protein or erythrocyte sedimentation rate, may point to infection or systemic inflammation. Patients with diarrhea should have stool examination for ova and parasites, giardia antigen, cryptosporidium, and other opportunistic agents. While small bowel cultures are diagnostic in suspected small bowel overgrowth, duodenal intubation is relatively contraindicated in a patient with both increased radiation sensitivity and increased risk for bleeding. Hydrogen breath test or an empiric trial of metronidazole is a better choice.

As a general rule, radiographic studies should be avoided when possible, given the increased sensitivity of FA patients to radiation. Radiographic imaging of the gastrointestinal tract should be reserved for children

with compelling clinical evidence of bowel obstruction, whenever possible. Gastroesophageal reflux, gastritis, and other peptic disease can be diagnosed either clinically or by endoscopic biopsy, without the need for imaging.

Peptic disorders should be treated with proton pump inhibitors (omeprazole 1 to 2 mg/kg/day or lansoprazole 0.5 mg/kg/day) rather than H₂-antagonists, because of the risk of marrow suppression from the latter. For small children who cannot take pills or capsules, some pharmacies compound suspensions. These suspensions are not homogeneous or stable and should be avoided. The most reliable proton pump inhibitor therapy is given by prescribing suspensions made dose-by-dose, using either proprietary suspension packets or effervescent tablets. Alternatively, a proton pump inhibitor capsule can be opened, and the estimated amount of beads necessary for the dose placed on a small spoonful of applesauce and given immediately. Beads should not be chewed or crushed.

Gastric emptying delay can be suspected clinically, when patients complain of nausea, early satiety and vomiting of food eaten several hours earlier. Some patients may have no symptoms at all. The most common study used is the nuclear medicine gastric emptying study, which involves radiation. Omitting a gastric emptying study and initiating a trial of medical therapy is acceptable to avoid radiation exposure. Some centers make ultrasound diagnosis of delayed gastric emptying available. A trial of erythromycin (5 mg/kg/dose, three times per day) or metoclopramide (< 6 yrs old: 0.1 mg/kg/dose; > 6 yrs old: 2.5-5 mg four times per day) or domperidone in Canada and Europe (0.3 mg/kg/dose four times per day) may be given. Prior to

prescribing, the physician must determine if the patient is on any medication that may interact adversely with the gastric emptying medication. An important interaction for erythromycin is the azole group (fluconazole, itraconazole or ketoconazole).

In cases of severe, intractable nausea without a detectable cause, a trial of ondansetron may be warranted if there is no improvement with metoclopramide or domperidone.

Supplemental Nutrition

Many patients and families complain of poor growth in children with FA. Each clinical visit must include an assessment of growth. Weight and height, measured appropriately for age, are plotted on appropriate growth curves and either weight-for-height (for children <3 years) or body mass index (BMI) for age (for children >3 years) determined. Poor linear growth may be caused by the genetic defect of FA, or the multiple endocrine abnormalities documented in these patients,⁶ or growth suppression by inflammation associated with infection. Children with these conditions will have a normal weight-for-height or BMI for age. Evaluation by a pediatric endocrinologist would be appropriate for this group of children.

Malnutrition, whether the result of poor oral intake, high energy utilization or excessive stool losses, results in a growth curve demonstrating low weight-for-height or low BMI for age. Attention must also be paid to children losing weight or slowing their growth rate. In one series, 22% of FA patients were underweight, indicative of malnutrition.⁶ Assessment of muscle mass, skin and mucus membrane integrity, and degree of energy and activity can be done at the time of routine physical

exam. This allows a global assessment of nutritional status at each visit.

When poor weight gain or weight loss is documented, both poor oral intake and/or diarrhea with malabsorption must be considered. Analysis of a prospective three-day dietary record may indicate deficits in protein and calorie intake. Dietary counseling, with or without evaluation by a feeding specialist, may be enough to improve oral intake in some patients. Patients with FA may also have deficiencies or increased need for specific vitamins and minerals, including folate and zinc. Even children with adequate weight-for-height may benefit from a vitamin-mineral supplement given daily.

Children who are persistently less than 85% expected weight for height (for children < 3 years of age) or have a BMI percentile for age persistently < 3d percentile, or who have failed to gain weight over a 3-6 month period may require supplemental feeds to achieve normal nutritional status. Supplemental feeds are formula feeds delivered directly into the stomach or small intestine, bypassing appetite and food interest. In situations where they are necessary, they are used to allow the child to achieve normal growth to meet his/her genetic potential, have energy to meet the demands of daily living, and have adequate nutritional reserves to face short-term malnourishment during acute illness.

Enteral supplementation is preferable to parenteral supplementation in all practical cases. Supplemental parenteral feeds require placement of a central line, with increased risk of infection and metabolic disorders, including hepatic injury. Parenteral feedings should be limited to those patients unable to meet their needs enterally.

Enteral alimentation may be delivered by nasogastric tube, nasojejunal tube or gastrostomy tube. In general, it is recommended that patients have a nasogastric or nasojejunal feeding trial before proceeding to gastrostomy or gastro-jejunal tube placement. This prevents performing a surgical procedure unless it has a good chance of success. Most patients tolerate nasal tubes well. There is some risk of sinusitis with these tubes. Neurologically impaired children or infants may be at risk for dislodging the tube at night and aspiration of formula. There is less risk of dislodgment with the nasojejunal tube and, perhaps, less risk of gastroesophageal reflux of formula feedings but, when dislodged, the tube must be replaced by a radiologist with fluoroscopy. The major objection, particularly among older children, is the unattractive nature of a tube hanging out of the nose. Nonetheless, for patients anticipating supplemental feedings for less than three months, the nasal route is the best. Many children can be taught to place the tube at bedtime and remove it on awakening before going to school.

Gastrostomy tubes provide more permanent access to the gastrointestinal tract for administration of enteral feedings. Placement requires a brief surgical procedure, generally performed by endoscopy. In general, complications are limited to local irritation and/or infection, which can be treated with local antibiotics, rather than systemic ones. Rarely, disruption of tube site can occur, with the risk of peritonitis. If platelets are very low at placement, esophageal bleeding is a risk. Unfortunately, once FA patients become neutropenic, the risk of significant local infection at the gastrostomy tube site is increased and may prevent placement of the tube.

To reduce the impact on the daytime appetite, supplement feedings can be given at night, over 8-10 hours

using a high-calorie formula, if possible. Patients may still refuse breakfast, but are generally hungry by lunch. Once appropriate weight-for-height is attained, it may be possible to reduce the number of days of the week supplementation is given. In particular, older children appreciate not running their feeds during sleepovers or group activities. It is not usually necessary for parents to transport feeding equipment on short vacations if the child can eat during the day.

Some patients experience heartburn after starting enteral feeding supplementation, particularly with nocturnal feeds. Vomiting may occur, particularly in the morning. Diarrhea at night can be a problem. Usually, a dietitian or physician can implement simple modifications of the therapy that will alleviate these symptoms. It is also prudent to monitor blood glucose levels regularly when on a high-calorie diet.

While the choice of enteral feeding methods may seem obvious, patients and their family must be educated as to the options available. In particular, the choice must not limit the child's social situation—for example, even if feeds are likely to end after several months, a gastrostomy may be better accepted than a nasogastric tube by an image-conscious teenager.

Appetite Stimulants

Several medications have been suggested as appetite stimulants. None has been tested in FA populations; information is derived from their use in cancer, HIV/AIDS, and cystic fibrosis.^{7,8} The inclusion of this material in this chapter should not be construed as a recommendation. Prior to using such medications, diagnosable causes of failure to thrive and poor appetite must be first investigated and appropriately managed.

Appetite stimulants will not treat gastroparesis, depression, chronic infection or other treatable causes of failure to thrive. Of the medications studied in trials for appetite stimulation, megestrol acetate, cyproheptadine, and the atypical antipsychotic agents olanzapine and mirtazapine warrant brief discussion.

Megestrol acetate (MA) is a progestational agent used to stimulate appetite and increase weight. In a recent review of several randomized prospective studies, MA demonstrated modest increases in weight in approximate half of subjects receiving the drug. Although this represented twice as many subjects gaining weight on MA compared to placebo or other medications used as controls, the majority of weight gain was small. Side effects included reversible adrenal insufficiency, glucose intolerance, impotence, and, with long-term use, risk of thromboembolism.^{7,9}

Cyproheptadine (CH) is popular because of its minimal side effects (transient somnolence). It is an antihistamine with serotonin antagonist effects. In randomized, double-blind, placebo-controlled trials in cancer or cystic fibrosis, weight gains were modest to none, but the drug was well tolerated.^{8,10}

Atypical antipsychotic agents olanzapine and mirtazapine are associated with weight gain. Small trials both in cancer and in cystic fibrosis have been reported.^{7,8} Weight gain was modest and side effects are significant, and may include glucose and lipid dysregulation and liver enzyme elevation.

For each of the drugs discussed, maintenance of weight gain after medication has been stopped has not been demonstrated. At present, no medication is universally safe and effective for stimulating appetite and effecting

weight gain. Their use should be limited to clinical trials.

Overweight and Obesity in FA

As in the general population, overweight is being seen in patients with FA. In one study, 27% of patients examined were overweight or obese; diabetes was associated with overweight and obesity in this study.¹¹ Overweight is defined as BMI >85th percentile and <95th percentile for age. Obesity is defined as having a BMI >95th percentile for age. Both diagnoses must be confirmed by physical exam. Significant complications may result from overweight and obesity, including hyperlipidemia, diabetes, obstructive sleep disorder and other aspects of the metabolic syndrome. The impact of non-alcoholic steatohepatitis or liver disease during HSCT is unknown. It may surprise some families to face this issue after previous concerns with underweight, but modification of lifestyle is essential.

While a full discussion of the management of obesity is beyond the scope of this chapter (see this article for a review¹²), some useful starting points can be offered. We suggest starting with a 6-day diet diary and a review of daily activity. This provides the foundation for counseling regarding family change. Most families will require monthly counseling sessions for a time to insure achievement of appropriate weight. Psychological counseling may help, especially if an eating disorder is suspected.

Testing in the obese child for the primary consequent conditions of obesity should not be omitted. Minimal testing includes blood pressure measurement using an appropriate-sized cuff, fasting lipid profile, oral glucose tolerance tests with insulin levels, AST, and ALT.

Children with sleep disturbance or snoring will require a sleep study and may need an echocardiogram.

Management of overweight and obesity is a long-term process, requiring the commitment of the entire family for success. Patients should be urged to avoid fad diets and over-the-counter weight loss preparations and to focus on healthy lifestyle modifications.

Liver Disease

Liver disease in FA is generally a complication of treatment. As a general rule, referral to a pediatric gastroenterologist with expertise in hepatic disease is indicated. The following is an overview of the most common problems seen. Note that evaluation and management of iron overload is discussed in Chapter 3.

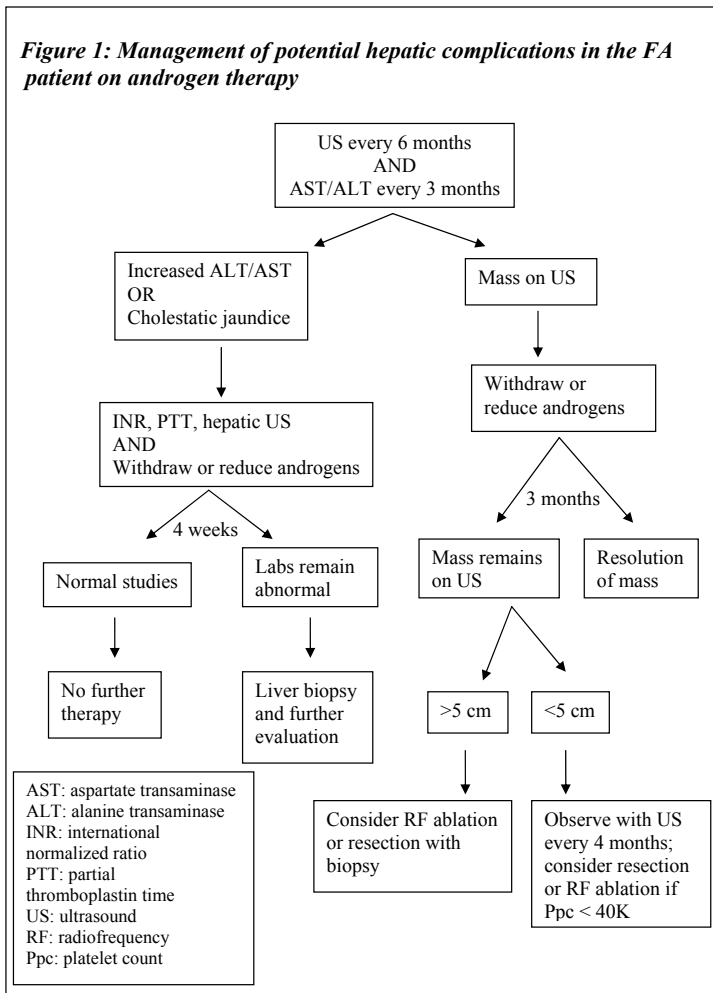
Hepatic complications of androgens

Androgenic steroids used to treat low blood counts in FA are associated with multiple hepatic complications, including peliosis hepatis, subcellular changes of hepatocytes, and hepatocellular adenomas.¹³ See Figure 1 for a proposal for managing liver complications in patients on androgens.

Peliosis hepatis (PH) is a cystic dilatation of the hepatic sinusoids. It is not dose-dependent and can occur at any time during treatment with androgens. These dilated areas fill with blood. Many cases are clinically silent. When symptomatic, patients present with hepatomegaly and right upper quadrant pain and tenderness. Liver enzymes, bilirubin, and hepatic function tests are normal. PH can be life-threatening if the sinusoids rupture. PH is best diagnosed by liver biopsy, although imaging (ultrasound, angiography, computed tomography) may demonstrate large lesions. The lesions may regress after withdrawal of androgens.^{13,14}

Androgens also damage hepatocytes nonspecifically. This may be manifest as cholestatic jaundice or hypertransaminasemia. Cessation of androgen therapy will usually lead to complete resolution. There are case reports of hepatic cirrhosis in patients on continued androgen therapy.¹³ If resolution of enzyme elevation does not occur after androgen withdrawal, biopsy is indicated.

Figure 1: Management of potential hepatic complications in the FA patient on androgen therapy



Hepatocellular adenomas are associated with androgen therapy. An adenoma is a benign tumor that does not invade surrounding tissue. It can, however, rupture, leading to life-threatening bleeding. FA patients may develop these tumors rapidly (within three months of beginning androgen therapy).¹⁴⁻¹⁶ Thrombocytopenia increases the risk of bleeding in hepatic adenomas. The tumor may regress after withdrawal of androgens. If persistent, surgical resection or radiofrequency ablation may be necessary, particularly prior to hematopoietic stem cell transplantation. Diagnosis is generally made by ultrasound. Both CT with IV enhancement and MRI with gadolinium enhancement are more sensitive than ultrasound. *Despite radiation exposure, we strongly recommend that all patients have BOTH a CT and an MRI before HSCT if they have been treated previously with androgens.*

Hepatocellular carcinoma (HCC) has been reported with androgen use. The occurrence is sporadic. Some studies have suggested that FA patients may be at increased risk for HCC resulting from androgen use. The HCC associated with androgens characteristically demonstrates no α -fetoprotein in serum, distinguishing it from non-androgenic associated HCC.¹³ Patients developing HCC should have androgen therapy discontinued.

Prevention and management of liver disease

General protective measures in children at risk for liver disease include screening, immunization, and avoidance of hepatotoxic agents. Screening for liver disease includes serum levels of hepatocellular enzymes (ALT and AST) and biliary enzymes (alkaline phosphatase, GGT, and 5'-nucleotidase). In children, GGT and 5'-nucleotidase are preferred over alkaline phosphatase to screen for biliary cell injury, as alkaline phosphatase can be elevated by bone injury or bone growth.

Elevated conjugated bilirubin levels reflect biliary obstruction or significant hepatocellular injury. Clotting studies (INR, PTT) and albumin are done to investigate hepatocellular function. Ultrasound with doppler gives information about the texture of the liver (suggestive of fatty infiltration or fibrosis), vascular compromise, and biliary obstruction.

Patients with elevated liver enzymes should have a full evaluation of their liver by a pediatric hepatologist. The evaluation would include screening for common causes of liver disease, iron overload, and assessment of the severity of liver disease. In some cases, liver biopsy may be required.

Patients should be immunized against hepatitis A and B. Titers should be performed to insure immunity. Hepatotoxic drugs, including alcohol, should be avoided when possible. Monitoring of fat-soluble vitamin levels on a yearly basis is indicated in most forms of liver disease.

Gastrointestinal and liver complications of HSCT

Prior to HSCT, patients require a complete gastrointestinal, liver, and nutritional evaluation. If undiagnosed chronic abdominal pain exists, endoscopy for detection of potential sources of bleeding or infection may be required. Patients requiring gastrostomy tube insertion must have it accomplished at least three months prior to HSCT, to insure complete site healing prior to cytoreduction. Site infections or irritation should be treated prior to HSCT. Any diarrhea should be evaluated, particularly to detect opportunistic organisms. Optimal nutritional status should be achieved prior to HSCT, although it is hoped that this would be accomplished well in advance of HSCT. Both the presence of liver cell injury and/or hepatic function should be evaluated ahead of transplant (see above). For patients

who have previously received androgens, evaluation for adenomas with ultrasound AND a CT AND an MRI is essential.

Review of the full spectrum of hepatic and gastrointestinal complications of HSCT is beyond the scope of this work. We will emphasize complications occurring after the first 100 days post-transplantation (generally after the patient has left the transplant center) and those issues unique to patients with FA.

Patients with FA who undergo HSCT are at increased risk of grade II-IV graft-versus-host disease.¹⁷ Both intestine and liver are involved in GvHD. Chronic GvHD will develop in a large number of FA patients after HSCT. Patients with chronic intestinal GvHD may experience diarrhea with malabsorption, resulting in difficulty maintaining weight. Occasionally, intestinal stricture will develop, causing pain. Pancreatic insufficiency is uncommon, but should be considered in patients with fat malabsorption.

Chronic GvHD increases the risk of squamous-cell carcinoma in FA patients.¹⁸ Physicians with long-term management of these patients must be aware of this risk.

Chronic hepatic GvHD is usually characterized by cholestasis, but rapid elevations of transaminases may occur as immunosuppression is tapered. Chronic viral hepatitis is an uncommon result of HSCT. If there is confusion about the diagnosis, liver biopsy is indicated. Chronic GvHD of the liver is treated with immunosuppression and ursodeoxycholic acid (20 mg/kg/day). Cholestasis may lead to malabsorption of fat-soluble vitamins and monitoring of vitamins A, E, D, and K (usually by monitoring INR) to allow appropriate supplementation.¹⁹

Nutrition as Therapy

Complementary therapies are those not supported by evidence-based clinical studies, used *in conjunction* with standard medical care. Alternative therapies are those not supported by evidence-based clinical studies, used *in place* of standard medical care. Many families view food and, by extension, dietary supplements, vitamins, and micronutrients, as “natural” and thus safe. The industry that produces complementary/alternative nutritional regimes and supplements is a multi-billion dollar industry without regulation, but with a clear incentive to promote their product regardless of the degree of evidence for effectiveness. Many complementary/alternative nutritional regimes and supplements are directly harmful or, by displacing standard medical therapy, indirectly harmful.

Patients with FA may consider megavitamin therapy and antioxidant or trace element supplementation. Patients may be aware that there is research regarding oxidant stress in FA.²⁰ Concerns about these therapies include the potential toxicities of some supplements and whether some supplements may promote tumor development. In particular, vitamins A, D, C, and niacin may be toxic in excess. No therapy using antioxidants, megavitamins, or micronutrients has been shown to be effective in treatment of FA using evidence-based criteria. Controlled trials of supplements are necessary to demonstrate efficacy and limit risk of toxicity.

Particular risk is associated with products containing supplements of iron, vitamins A, C, and E, and omega-3 fatty acids. Products containing iron must be avoided to reduce risk of exacerbating iron accumulation in liver and other tissues. Vitamin C potentiates iron absorption.

While foods containing vitamin C are not restricted, products containing vitamin C (multivitamins or fortified fruit juice/drinks) should be avoided. In large studies, both vitamin E and vitamin A supplements have been associated with *increased* risk of some cancers. Without further study, they should be avoided. Large doses of omega-3 fatty acids (fish oil) can increase risk of bleeding due to platelet inactivation. In this population with reduced levels of platelets, products that impair platelet function should be avoided.

It is essential that physicians managing children with FA become knowledgeable about complementary/alternative therapies. Patients and parents should be questioned about the use of these therapies. Patients and their families are frequently looking for some aspect of care to control; diet seems a harmless choice. Particularly since children with FA have significant nutritional problems that are often ignored, there is little to dissuade them, unless their physician becomes involved in these decisions. Establishing a non-judgmental, but candidly informative discussion of complementary/alternative therapies offers the physician a chance to educate parents about their choices. Physicians and families can access information about complementary/alternative nutritional therapies at the web site of the Office of Complementary and Alternative Medicine of the National Institutes of Health, <http://www.cancer.gov/occam>, where there are several links to reliable information.

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