Chapter 4: Gastrointestinal, Hepatic, and Nutritional Problems

Introduction

Good to Know

The **gastrointestinal system** digests food and absorbs the nutrients our bodies need to function properly.

This system is a complex group of cells organized as a long, hollow tube that begins at the mouth, continues through the esophagus, stomach, and intestines, and ends at the anus. The liver aids digestion by producing bile, which helps the body break down fats. The liver also clears some toxins from the body and synthesizes certain nutrients.

Both Fanconi anemia (FA) and medications used to treat the disease can cause gastrointestinal disorders, liver disease, and nutrition-related challenges. Many patients experience symptoms such as reduced appetite, nausea, abdominal pain, and diarrhea. Without proper treatment, these symptoms can interfere with daily living and create hurdles to healthy growth and development.

Concerns related to the gastrointestinal tract most commonly include:

- *Abnormalities of the gastrointestinal tract*
- *Gastrointestinal symptoms, including poor food intake, nausea, abdominal pain, and/or diarrhea*
- *Poor weight gain or malnutrition, often resulting from reduced food intake or difficulty absorbing nutrients from food*
- *Overweight or obesity*
- *Cancers of the gastrointestinal tract*
- *Liver disease*
- *Gastrointestinal-related complications of hematopoietic stem cell transplant (HSCT)*

The gastrointestinal clinical care team should include a **gastroenterologist** or **pediatric gastroenterologist** and, when needed, a **dietician**. This team should work in close collaboration with other FA specialists to provide comprehensive care. The involvement of multiple types of providers in the care of patients with FA introduces the risk that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

Gastrointestinal Tract Anatomic Abnormalities

Approximately 7% of patients with FA are born with anatomic (structural) abnormalities in the gastrointestinal tract [1]. The most common abnormalities include:

- ***Esophageal atresia (EA),*** in which the lower end of the esophagus—the tube that connects the mouth to the stomach—is incomplete or blocked and does not allow food to pass from the esophagus into the stomach.
- ***Esophageal atresia*** (see above) with ***tracheoesophageal fistula (TEF)***, an abnormal passage between the esophagus and the trachea, or windpipe, that may result in food from the esophagus crossing into the airways or air entering the esophagus.
- ***Duodenal atresia***, in which the entrance to the small intestine, or duodenum, is incomplete or blocked and does not allow the contents of the stomach to enter the intestines.
- ***Anorectal malformations***, a spectrum of disorders involving the rectum and anus. These malformations may include a blockage of the anus, a failure of the rectum to connect to the anus, or an abnormal passage between the rectum and another part of the body, such as the urinary tract or reproductive system.

Most anomalies are diagnosed and treated in early infancy, often before the diagnosis of FA. Although the gastrointestinal tract abnormalities may occur in isolation, they may also appear together with other birth defects, including the VACTERL spectrum of disorders—a group of abnormalities that are not necessarily related to each other, but tend to occur together. The term "VACTERL" is an acronym that stands for the following:

- ***V**ertebral defects*
- ***A**norectal malformations*
- ***C**ardiac abnormalities*
- ***T**racheo-Esophageal abnormalities*
- ***R**enal defects*
- ***L**imb defects*, such as extra fingers or toes, or abnormally formed forearms

Most patients with these anomalies do not have FA. However, because an early diagnosis of FA may help to prevent complications, all children exhibiting kidney and/or radial (referring to a bone in the forearm) abnormalities in addition to other disorders belonging to the VACTERL spectrum should be tested for FA [(2)] as described in *Chapter 2*.

Patients with FA may experience complications of these anatomic abnormalities and their surgical treatment throughout their lives. The long-term complications of these anomalies, described below, are similar in patients with and without FA.

Esophageal atresia and tracheoesophageal fistula
Esophageal atresia, with or without tracheoesophageal fistula (EA/TEF), is rarely diagnosed during pregnancy. Symptoms of EA/TEF in newborns may include excessive drooling, feeding intolerance or respiratory difficulties. Survival of EA/TEF is very good—more than 98% of EA/TEF infants who weigh more than 3 pounds 5 ounces (1500g) and lack major heart defects survive to childhood and beyond [(3)].

The severity of the EA/TEF defect and the quality of the repair determine the long-term complications the patient may experience. One form of EA/TEF, known as long gap atresia—characterized by a gap in the esophagus that spans a distance greater than 3 vertebrae of the spine—is difficult to repair and increases the risk that the esophagus will narrow, resulting in additional complications. A second, more severe form of EA/TEF is called ultra-long gap atresia, defined as a gap in the esophagus that spans 5 or more vertebrae. In this form of atresia, the esophageal segments are very short and it is likely that significant complications will occur. Therefore, these patients may require advanced surgical techniques, including reconstruction of the esophagus using tissue from the colon or stomach, or operations that induce esophageal growth. These procedures are associated with many complications, including leakage from the repaired esophagus connections, swallowing problems such as pain

with solid foods, frequent reflux, and vomiting. There may also be a long-term risk of colonic cancer in colon tissue used to reconstruct the esophagus. Experts continue to debate the preferred method for the treatment of ultra-long gap EA/TEF [3].

EA/TEF repair in infancy frequently leads to gastroesophageal reflux disease (GERD), difficulty swallowing, and breathing problems in adulthood [4]. Diagnosis and management of GERD, a condition in which the contents of the stomach leak backwards into the esophagus, is essential to reduce pain, bleeding, and narrowing of the esophagus; anti-reflux surgery is often necessary. Respiratory problems, including cough, pneumonia, and wheezing may suggest the need for bronchoscopy, a procedure that enables clinicians to look inside the airways. Recurrent TEF should be considered if pneumonia or pain develops after a period of relatively good health.

Duodenal atresia

Duodenal atresia occurs less frequently than EA/TEF. More than 50% of patients with duodenal atresia have other birth defects. Approximately 90% of infants survive the surgical repair of the intestines, and will grow normally and develop few symptoms. However, 12-15% of patients develop complications in the months and years after the surgery, including abdominal pain, delayed gastric emptying (slowed movement of food from the stomach to the intestines), peptic ulcer, megaduodenum (enlargement of the duodenum), reflux of fluids from the intestines into the stomach and esophagus, and blind loop syndrome—a condition in which food slows or stops moving through the intestine. Patients with duodenal atresia frequently experience slow movement of food through the digestive tract above the intestinal passage formed by surgery. Enlargement of the duodenum can occur up to 18 years after surgery and is associated with poor weight gain, vomiting, abdominal pain, and blind-loop syndrome, and usually requires additional surgery [5].

Anorectal malformations

Anorectal malformations are a spectrum of birth defects in which the gastrointestinal tract is closed off and not connected to the anus, or instead opens at an improper location, such as the skin, urinary tract, or reproductive system. The long-term outlook for patients with anorectal malformations varies and depends on the type of malformation, surgical technique used to repair the malformation, presence of additional disorders, ongoing medical care, and follow up. Management of these complications requires a multidisciplinary

approach. Long-term problems may include fecal incontinence, occasional soiling, and constipation with or without encopresis (involuntary leakage of stool) [6]. In most cases, bowel control can be restored with medication, although some patients may require a surgical procedure known as antegrade continence enema (ACE).

Gastrointestinal Symptoms

Many patients with FA experience gastrointestinal symptoms, including poor food intake, nausea, abdominal pain, and/or diarrhea. These symptoms cause significant discomfort and may contribute to poor weight gain in FA patients. During routine clinic visits, clinicians should encourage patients and their families to report gastrointestinal symptoms, as patients often do not spontaneously disclose these concerns.

- ***Poor food intake*** can result from many factors, including complications of anatomic gastrointestinal abnormalities (narrowing of the digestive tract or complications of repair), chronic inflammation and/or infection, medication side effects, or neurologic/behavioral problems.
- ***Nausea*** in patients with FA often results from infections (particularly urinary tract or sinus infections), delayed gastric emptying caused by infection, or medications. Nausea is usually temporary, resolving once the infection has been cured or the medication stopped. Psychological stress, anxiety, and depression can also lead to nausea and abdominal pain, and may worsen existing gastrointestinal complaints.

Good to Know

Opportunistic infections are caused by microorganisms that are normally controlled by a healthy immune system but can become harmful when the body's immune system is impaired and incapable of fighting off the infection.

Short bowel syndrome occurs when nutrients from food are not properly absorbed because a large segment of the small intestine is non-functional or has been surgically removed.

- ***Abdominal pain*** may also result from partial blockage of the digestive tract, which can be caused by complications of structural defects in the gastrointestinal system. Abdominal pain can also result from abnormal gastrointestinal motility, overgrowth of bacteria in the small intestine, or gallbladder disease.

- ***Diarrhea*** can occur for a variety of reasons, including opportunistic infection of the gastrointestinal tract, overgrowth of bacteria in the small intestine, medications, and short bowel syndrome. Constipation with accidental leakage of stool may be mistaken by some families for diarrhea.

Initial evaluation of gastrointestinal symptoms

In all cases, the initial evaluation of gastrointestinal symptoms in patients with FA begins with a history and physical exam. Most problems can be diagnosed at this level, without need for further study. If the patient has non-specific poor food intake, with or without nausea and abdominal pain, evaluation for evidence of an unobvious infection may be useful. Infection or systemic inflammation may be identified through laboratory studies, including urine culture, measurement of serum C-reactive protein, and red blood cell sedimentation rate. Patients with diarrhea should have stool examination for ova and parasites, giardia and cryptosporidia antigen, and other opportunistic agents. To diagnose suspected overgrowth of bacteria in the small intestine, hydrogen breath test or an experimental trial of the antibiotic metronidazole are recommended. Duodenal intubation to collect small intestinal juice for culture is impractical and not recommended for FA patients, who have both increased radiation sensitivity and increased risk for bleeding.

Limiting Radiation Exposure

Patients with FA are more sensitive to radiation than the general population. Therefore, physicians caring for a patient with FA should be judicious in the use of diagnostic tests that involve radiation, and should be in close contact with the pediatric radiologist when tests involving radiation exposure are warranted. The radiologist may help reduce exposure to diagnostic radiation by substituting imaging techniques that don't involve radiation exposure, such as ultrasound or magnetic resonance imaging (MRI).

If CT scans, a radiation-based imaging technique, are necessary, they should be limited to the area considered most important. Because pediatric and adult CT scan protocols differ in the amount of radiation used in each scan, care should be taken to use a pediatric-specific CT scanner managed by qualified pediatric radiologists who can minimize radiation exposure when radiographs are essential for pediatric patients. In some cases, digital radiographs may deliver less radiation than conventional techniques and are thus preferred.

As a general rule, studies involving radiation exposure should be avoided when possible, because patients with FA are more sensitive to radiation than the

general population. Radiographic imaging of the gastrointestinal tract should be reserved for patients with FA with compelling clinical evidence of bowel obstruction, whenever possible. Children with gastroesophageal reflux disease can be treated if they are old enough to reliably explain their symptoms. Alternatively, reflux can be diagnosed with a manometric-placed pH/impedance probe. Gastritis and other peptic diseases should be diagnosed by a procedure called endoscopy with biopsies without radiographic imaging. Peptic disorders should be treated with drugs known as proton pump inhibitors (e.g., omeprazole or lansoprazole at a dose of 1 mg/kg/day); H2-antagonists should be avoided because these drugs increase the risk of bone marrow suppression.

Evaluation of gastric emptying delay

Gastric emptying delay should be suspected in patients who experience nausea, feel full sooner than usual, and vomit food eaten several hours earlier. Some patients, however, may experience no symptoms. Delayed gastric emptying in the general population is commonly diagnosed using the nuclear medicine gastric emptying study, which involves radiation. To avoid radiation exposure in patients with FA, a gastric emptying study can be omitted and a trial of medication can be initiated, provided that the patient has classic symptoms, normal physical exam, and no evidence of obstruction in the digestive tract. Ultrasound-based diagnosis of delayed gastric emptying may be available at some clinics.

If the diagnosis of delayed gastric emptying is entertained, the patient should undergo dietary counseling with a dietitian to adjust meal content and frequency; small and frequent meals that restrict fats and nondigestible fibers while maintaining adequate caloric intake should be favored. A trial of medication that enhances gastrointestinal motility may be given, including erythromycin (5 mg/kg/dose, 3 times per day), or—in Canada and Europe—domperidone (0.25 – 0.5 mg/kg/dose 3 to 4 times per day; maximum daily dose of 2.4mg/kg or 80mg/day). Prior to prescribing, the physician must determine if the patient is on any medication that may interact adversely with the gastric emptying medication. For example, the azole group of medications (i.e., fluconazole, itraconazole, or ketoconazole), used to treat fungal infections are known to interact adversely with erythromycin. The use of metoclopramide is not recommended because of potentially dangerous side effects including irreversible tardive dyskinesia, a movement disorder characterized by repetitive and involuntary movements. Amoxicillin/clavulanic acid has been shown to improve small intestine motility and may be prescribed when the above

medications have failed or if a patient is not tolerating jejunal feeds (feeding directly into the small intestine) (20 mg/kg amoxicillin and 1 mg/kg clavulinate twice a day, with a maximum of 250 mg of amoxicillin 3 times a day) [8, 9].

Cases of delayed gastric emptying that do not improve with medication may require surgical procedures, such as endoscopic therapy with pyloric dilatation and botulinum toxin injection, jejunostomy, or gastro-jejunostomy. Before performing surgery, which could introduce further gastrointestinal complications, physicians should note that most cases of delayed gastric emptying in children that occur without an identifiable cause will resolve over time. Patients who report symptoms such as nausea or abdominal pain within 30 minutes of starting a meal might have impaired gastric accommodation, a condition in which the stomach fails to relax and accept food. These patients may benefit from treatment with the medication cyproheptadine, given 30 minutes before meals. In cases of severe, uncontrollable nausea without a detectable cause, a trial of the medication ondansetron may be warranted if there is no improvement with cyproheptadine or domperidone.

Poor Weight Gain

Good to Know

Growth curves allow physicians to monitor a child's growth over time in comparison with other children of the same age and gender.

These tools can track a child's progress using various measurements, including height, weight, and body mass index (BMI).

If a child's growth curve deviates from those of his healthy peers, physicians may search for an underlying health problem.

Parents of children with FA are often concerned about their child's poor weight gain and "picky eating." These two issues should be addressed separately. Approximately 60% of children with FA have short stature as part of the genetic disease. These children will also have proportionately lower weights. Parents should have a chance to discuss the pattern of their child's growth curves, particularly the changes in weight relative to height from birth to 2 years of age, and body mass index (BMI), a measure of body shape based on weight and height, after age 2. Parents should be encouraged to accept as normal a child whose weight is appropriate for their somewhat short height. Aggressively trying to increase the child's food intake will not increase their

height or overall health, and may create disordered eating or family problems with meals.

Children who are "picky eaters" and their families may benefit from behavioral therapies to increase the variety of foods eaten. These therapies have not been studied in patients with FA, but have been effective in other patient populations with poor food intake. For example, in patients with cystic fibrosis, behavioral modification has demonstrated long-term improvements in food intake [7].

Evaluating poor growth

Many children with FA experience poor growth. Weight and height should be measured at each clinical visit using methods appropriate for the age of the child and plotted on a graph called a growth curve (measurements of weight relative to height should be plotted for children less than 2 years of age, and measurements of body mass index (BMI) relative to age should be plotted for children more than 2 years of age).

Children with FA may be shorter than expected based on the genetic condition itself, the (non-FA related) genetics contributing to growth pattern in their families, the multiple hormonal abnormalities documented in these patients [10], or growth suppression due to inflammation associated with infection. Nevertheless, children with FA should have a normal weight-for-height or BMI for age. Evaluation by a pediatric endocrinologist may be needed for children with FA who exhibit poor growth.

Malnutrition, whether the result of poor food intake, high energy utilization, or excessive stool losses, initially results in a growth curve demonstrating low weight relative to height or low BMI relative to age. Attention must also be paid to children exhibiting weight loss or reduced growth rate. One study found that 22% of patients with FA were underweight, indicative of malnutrition [10]. The overall nutritional status of patients with FA can be determined during each routine physical exam by assessing muscle mass, skin and mucus membrane health, and energy and activity levels.

Poor food intake versus malabsorption

In patients with documented poor weight gain or weight loss, both poor food intake and/or diarrhea with malabsorption (poor absorption) of nutrients must be considered. Analysis of the patient's 3-day dietary record may indicate inadequate protein and calorie intake. Dietary counseling, with or without evaluation by a feeding specialist, may be enough to improve oral intake in

some patients; however, if food intake does not increase, counseling should be aimed at maximizing calories by addition of high calorie foods and liquid or powder supplements. Patients with FA may also have deficiencies in or increased need for specific vitamins and minerals, including folate and zinc. Even children with adequate weight-for-height may benefit from a daily vitamin-mineral supplement (generally, an iron-free supplement should be selected, and excessive doses of vitamins should be avoided, as discussed below). All patients should be screened for vitamin D deficiency at least once a year, preferably during the winter, by checking blood levels of the active form of vitamin D, known as 25-hydroxyvitamin D. If the level of 25-hydroxyvitamin D is less than 30, then supplementation with oral vitamin D once a week is indicated. Patients under 44 pounds (20 kg) should receive 8,000 IU once a week; those over 44 pounds (20 kg) should receive 50,000 IU once a week. Vitamin D levels should be rechecked after 8 weeks, and supplementation should continue until the 25-hydroxyvitamin D level is above 30.

Supplemental feeding

Supplemental feeding may be needed to achieve a healthy nutritional status in children who are persistently less than 85% of the expected weight for their height, who have a BMI that is persistently less than the 3rd percentile for their age, or who have failed to gain weight over a 3- to 6-month period. This strategy involves delivering a liquid food mixture directly into the bloodstream, stomach, or small intestine, thereby bypassing appetite and food interest. In this way, supplemental feeding allows the child to achieve normal growth to meet his/her genetic potential, have the energy to meet the demands of daily living, and store adequate nutritional reserves to face short-term malnourishment during acute illness.

Supplemental feeding via feeding tube, known as enteral supplementation, is preferable to supplementation by intravenous infusion, known as parenteral nutrition. Supplemental parenteral feeds require placement of a central catheter, which increases the risk of infection, metabolic disorders, and liver injury. Parenteral feedings should be limited to those patients unable to meet their needs with enteral nutrition.

Enteral supplementation may be delivered by feeding tubes inserted into the nose, such as a nasogastric tube or nasojejunal tube, or by a tube surgically inserted into the abdomen, known as a gastrostomy tube. In general, it is recommended that patients have a nasogastric or nasojejunal feeding trial

before proceeding to gastrostomy, thereby avoiding surgery unless absolutely necessary. Most patients tolerate nasal tubes well; the major objection, particularly among older children, is the unattractive nature of a visible tube in the nose. Nonetheless, for patients who need supplemental feedings for less than 3 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. It should be noted, however, that nasal tubes increase the risk of sinus infection. Furthermore, infants and neurologically impaired children may be at risk for dislodging the tube at night and inhaling the formula into the lungs. Nasojejunal tubes carry less risk of dislodgment than nasogastric tubes and, perhaps, less risk of gastroesophageal reflux of formula feedings. Dislodged tubes must be replaced by a radiologist using an X-ray-based imaging technique known as fluoroscopy.

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 which a small camera on the end of a thin, flexible tube is inserted into the gastrointestinal tract. In general, complications are limited to local irritation and/or infection, which can be treated with antibiotic ointments applied directly at the site of infection, rather than oral antibiotics that act on the whole body. Rarely, the gastrostomy tube can become dislodged, increasing the risk of infection. If the patient's platelet level is very low at the time of surgery, excessive bleeding is a risk. Unfortunately, many patients with FA have an abnormally low count of neutrophils, a type of white blood cell that helps defend the body against infections, resulting in a significantly elevated risk of infection at the gastrostomy tube site that may prevent placement of the tube.

To improve daytime appetite, supplemental feedings can be given over a period of 8-10 hours at night, using a high-calorie formula, if possible; patients may still refuse breakfast, but are generally hungry by lunch. Once an appropriate weight-for-height has been attained, it may be possible to reduce the number of days of the week supplementation is given. For example, older children appreciate not having to use supplemental feeds during sleepovers or group activities. In addition, parents usually do not need 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 nighttime feeds. Vomiting may also occur, particularly in the morning, and diarrhea can be a problem at night. Usually, a

dietitian or physician can make simple modifications to the therapy that will alleviate these symptoms. It is also advisable that patients monitor blood sugar levels regularly when on a high-calorie diet.

The preferred choice of enteral feeding methods may vary from patient to patient. Therefore, patients and their families must be educated about all of the available options. Importantly, the choice must not limit the child's social life—for example, even if supplemental 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 alleged appetite-stimulating side effects (e.g., cyproheptadine, megestrol acetate, and the atypical antipsychotic agents olanzapine and mirtazapine). Although these drugs were not originally formulated or prescribed as appetite stimulants, they have been used to try to prevent unwanted weight loss in patients with cancer, HIV/AIDS, and cystic fibrosis [11, 12]; however, none of these drugs has been tested in patients with FA. *The inclusion of this material in this chapter should not be construed as a recommendation.*

Before prescribing appetite stimulants, physicians must first investigate and appropriately manage diagnosable causes of poor appetite and inadequate growth. Appetite stimulants will not treat delayed gastric emptying, depression, chronic infection, or other treatable causes of inadequate weight gain and growth. It remains unclear whether any weight gained while taking appetite stimulants will be maintained after the medication has been stopped.

Cyproheptadine, an antihistamine used to treat allergic reactions, is a popular appetite stimulant because it has few side effects besides temporary sleepiness. In randomized, double-blind, placebo-controlled trials, the drug was well tolerated by patients with cancer or cystic fibrosis, but resulted in little or no weight gain [12, 13]. However, some physicians elect to try this medication before resorting to nasogastric or gastrostomy feedings. Patients may benefit from cyproheptadine, as it improves gastric accommodation to reduce retching [14].

Overweight and Obesity in FA

As in the general population, some patients with FA are overweight or obese. In one study, 27% of patients with FA were overweight or obese; furthermore,

these overweight or obese patients tended to also have diabetes [15]. Children who have a BMI greater than the 85th percentile and less than the 95th percentile for age are considered overweight, and those who have a BMI greater than the 95th percentile for age are considered obese. Both diagnoses must be confirmed by physical exam. Significant complications may result from overweight and obesity, including elevated levels of fat and cholesterol in the blood, diabetes, obstructive sleep disorder, and other aspects of metabolic syndrome—a combination of disorders that increase the risk of developing cardiovascular disease and diabetes. Some families may be surprised to find that a patient with FA may become overweight or obese after previous concerns with being underweight, but modification of lifestyle is essential.

While a full discussion of the management of overweight and obesity is beyond the scope of this chapter (see references [16-18] for a review), some useful starting points can be offered. Physicians should ask patients to keep a 6-day diary of diet and daily activity, both of which provide the foundation for counseling regarding dietary and exercise changes. Most families will require monthly counseling sessions for a time to insure achievement of appropriate weight. Psychological counseling may also help, especially if an eating disorder is suspected.

The obese patient should be assessed for the primary health consequences of obesity. At a minimum, measurements should include blood pressure using an appropriately sized cuff, fasting lipid profile, oral glucose tolerance with insulin levels, and blood levels of the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Obese patients with sleep disturbance or snoring will require a sleep study and may need an echocardiogram (a non-invasive imaging procedure that is used to assess heart function).

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.

Cancer Screening

Cancers of the gastrointestinal system are potential complications of FA. Only one case of colon cancer in a person with FA has been documented. Thus, the expert group preparing this review cannot recommend early colon cancer screening for patients with FA. Screening for esophageal carcinoma can be

done using an endoscope, a thin, flexible tube-like device used to look inside the body. Because esophageal cancers in patients with FA tend to be located in the upper part of the esophagus, an endoscope with a small diameter can be used with minimal sedation. Some experts recommend yearly ultrasound imaging of the liver to screen for liver tumors, even for the youngest patients.

Good to Know

Androgens are hormones produced in the body that stimulate the development of male sex characteristics, such as testes formation and sperm production.

Androgens can be used therapeutically to increase the production of blood cells.

Liver Disease

Liver disease in patients with FA is generally a complication of treatment. As a general rule, patients with liver disease should be referred to a gastroenterologist with expertise in liver disease. The following sections provide an overview of the most common liver-related problems that affect patients with FA.

Liver complications of androgens

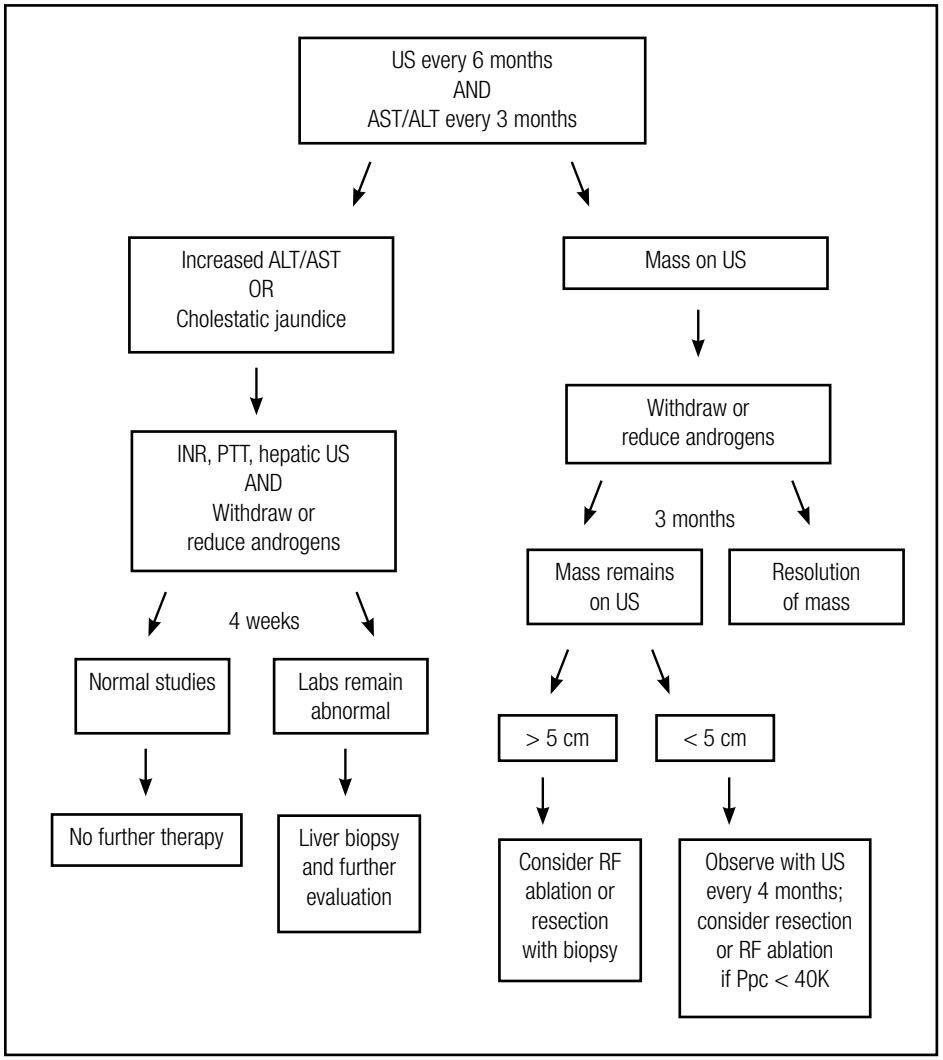
The androgenic steroids used to treat low blood cell counts in patients with FA can cause multiple liver complications, including a rare condition called peliosis hepatis, subcellular changes in liver cells called hepatocytes, and benign liver tumors known as hepatocellular adenomas [19]. One study of patients with FA found a 5-fold increase in liver enzyme levels—an indicator of liver injury—in patients with a history of androgen therapy compared with those without a history of androgen therapy; furthermore, 3 of the 20 patients treated with androgens developed liver tumors [20]. Thus, careful monitoring for hepatic complications of androgen therapy is essential. See Figure 1 for suggestions for managing liver complications in patients with FA on androgen therapy.

- ***Peliosis hepatis (PH)*** occurs when blood vessels in the liver called sinusoids become excessively dilated and form large blood-filled spaces, like cysts, that are scattered throughout the liver. This condition can occur with any dose of androgen therapy and at any time during treatment. Although many cases of PH are asymptomatic, symptoms may include abnormal enlargement of the liver, and pain and tenderness in the upper

right portion of the abdomen. This condition can be life-threatening if the sinusoids rupture. Patients with PH display normal levels of liver enzymes, bilirubin, and tests of liver function. This condition is best diagnosed via liver biopsy, although imaging techniques (e.g., ultrasound, angiography, and computed tomography) may reveal large lesions. Liver biopsy may be impossible in patients who have a high risk of bleeding. The lesions may regress after androgen therapy ends [19, 21].

- ***Nonspecific damage to the cells of the liver***, a potential consequence of androgen therapy, can lead to cholestatic jaundice—yellowing of the skin and eyes due to obstructed bile flow in the liver—or hypertransaminasemia—elevated levels of the liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST). There are case reports of liver cirrhosis in patients on continued androgen therapy [19]. Cessation of androgen therapy will usually lead to complete resolution of symptoms. However, if liver enzyme levels do not return to normal after androgen withdrawal, then liver biopsy may be indicated (see more information on androgens in *Chapter 3*).
- ***Hepatocellular adenomas*** can also result from androgen therapy. An adenoma is a benign tumor that does not invade surrounding tissue; however, it can rupture, leading to life-threatening bleeding. The risk of bleeding in hepatocellular adenomas is increased in patients with thrombocytopenia, a condition in which the blood has an abnormally low number of platelets, which help blood to clot. Patients with FA may develop hepatocellular adenomas rapidly, often within 3 months of beginning androgen therapy [21-23]. Hepatocellular adenomas are generally diagnosed by ultrasound. Contrast-enhanced CT scans and MRI are more sensitive than ultrasound in detecting hepatocellular adenomas. Hepatocellular adenomas may regress after cessation of androgen therapy, but if they persist, surgical removal or radiofrequency ablation may be necessary, particularly prior to hematopoietic stem cell transplantation (HSCT).

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



Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio; PPT, partial thromboplastin time; US, ultrasound; RF, radiofrequency; Ppc, platelet count

IMPORTANT NOTE: Despite the radiation exposure from CT, we strongly recommend that all patients receive both CT and MRI scans before hematopoietic stem cell transplantation (HSCT) if they have previously undergone androgen therapy [24].

- ***Hepatocellular carcinoma (HCC),*** or malignant liver cancer, is occasionally reported in association with androgen use. Some studies have suggested that patients with FA may have an increased risk for HCC resulting from androgen use. The HCC associated with androgen therapy is characterized by the absence of α-fetoprotein in the blood, distinguishing it from other forms of HCC [19]. Patients who develop HCC should discontinue androgen therapy.

Prevention and management of liver disease

General protective measures for patients with FA at risk of liver disease include screening, immunization, and avoidance of substances that may be toxic to the liver. Screening for liver disease includes measuring blood levels of the hepatocellular enzymes ALT and AST, and the biliary enzymes, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and 5′-nucleotidase. To screen for bile cell injury in children, measurements of GGT and 5′-nucleotidase are preferred over alkaline phosphatase, as alkaline phosphatase can be elevated by bone injury or bone growth.

Elevated levels of conjugated bilirubin reflect obstruction of bile flow in the liver or significant liver cell injury. Liver cell function can be investigated by testing how quickly the blood clots (e.g., international normalized ratio (INR) and measurements of albumin levels). A Doppler ultrasound may reveal the accumulation of fat or scar tissue, impaired blood flow, and obstruction of bile flow in the liver.

Patients with elevated liver enzyme levels should have a full evaluation of their liver by a hepatologist or pediatric hepatologist. The evaluation should include screening for the common causes of liver disease and iron overload disorder, a genetic condition in which the liver absorbs excessive amounts of iron from the diet (which might exacerbate iron overload from transfusions in patients with FA), and an assessment of the severity of liver disease. In some cases, liver biopsy may be required.

Patients should be immunized against varicella zoster virus (unless live virus vaccines are contraindicated), hepatitis A virus, and hepatitis B virus. The levels of antibodies against these viruses should be measured to insure that the patient has acquired immunity. Drugs that are toxic to the liver, including alcohol, should be avoided when possible. Levels of fat-soluble vitamins should be monitored on a yearly basis in patients with most forms of liver disease, particularly in cases where bile flow is reduced, known as cholestatic disease.

Gastrointestinal and liver complications of hematopoietic stem cell transplant (HSCT)

To treat the blood abnormalities associated with FA, many patients undergo hematopoietic stem cell transplantation, a procedure in which abnormal stem cells are replaced with healthy stem cells. Prior to HSCT, patients must undergo 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 who require supplemental feeding via a gastrostomy tube would ideally have it inserted at least 3 months prior to HSCT to insure complete healing of the insertion site. Infections or irritation at the insertion site should be treated prior to HSCT. In addition, diarrhea should be evaluated to detect opportunistic organisms, optimal nutritional status should be achieved, and the liver cell injury and/or function should be evaluated (see above) prior to the transplant. Patients who previously received androgens must be evaluated for adenomas with ultrasound, CT scan, and an MRI.

A review of the full spectrum of liver- and gastrointestinal-related complications of HSCT is beyond the scope of this work (for a recent review, see reference [25]). This section focuses on the complications that may occur during the first 100 days after HSCT.

While it is not clear that this remains the case with current regiments, historically patients with FA who undergo HSCT had an increased risk of graft-versus-host disease (GvHD), in which the transplanted cells regard the recipient's body as foreign and attack the body, damaging the intestines, skin, and liver [(26)]. FA patients who develop chronic GvHD after undergoing HSCT may experience diarrhea with poor absorption of nutrients from the diet, resulting in difficulty maintaining weight. Occasionally, the intestinal tract narrows, causing pain. Pancreatic insufficiency—a lack of digestive enzymes made by the pancreas that results in impaired food digestion—is uncommon, but should be considered in patients with poor absorption of fat.

Patients with chronic liver GvHD usually experience cholestasis (reduced bile flow) in the liver, with elevated levels of the liver enzymes ALT and AST. ALT and AST may increase rapidly if the patient has GvHD and as the doses of immune system-suppressing medications (given to patients to prevent immune rejection of the transplanted cells) are reduced. It is uncommon for patients to acquire chronic viral hepatitis from HSCT, but this should be considered if liver enzymes are increasing. If the diagnosis of chronic liver GvHD is

uncertain, liver biopsy is indicated. Chronic GvHD of the liver is treated with immune system-suppressing medications and ursodeoxycholic acid (20 mg/kg/day). Cholestasis may lead to poor absorption of the fat-soluble vitamins A, E, D, and K; therefore, levels of these vitamins should be monitored to determine whether vitamin supplementation is needed. Vitamin A, E, and D levels can be measured via blood tests, and vitamin K levels can be inferred by measuring the clotting tendency of blood using the PIVKA test or the INR test [27].

Perhaps most importantly, it should be noted that chronic GvHD increases the risk of squamous cell carcinoma in patients with FA [28]. Physicians participating in the long-term management of these patients must be aware of this risk.

Good to Know

Transferrin is a protein in the body that binds and transports iron in the blood. **Transferrin saturation** refers to the amount of iron carried by the transferrin protein in the blood. Saturation increases as the amount of iron in the body increases.

Ferritin is a protein that binds and stores iron. The levels of ferritin in the blood increase as the amount of iron in the body increases.

The **unsaturated iron binding capacity** test reveals the amount of transferrin that is not being used to transport iron. Binding capacity decreases as the amount of iron in the body increases.

Secondary iron overload

Many patients with FA require repeated red blood cell transfusions, which can lead to excessive iron accumulation in the body, a condition known as iron overload (discussed in detail in *Chapter 3*). A single transfusion unit of packed red blood cells contains 200-250 mg of elemental iron. The body is unable to excrete excess iron; thus, all iron obtained via transfusions must be deposited somewhere in the body. When tissue iron levels become too high, organ dysfunction ensues. The organs most commonly affected by iron overload include the liver, pancreas, and heart.

Patients with iron overload are generally asymptomatic; fatigue is the only commonly reported symptom. Patients often have an enlarged liver, which may be discovered by physical exam, and elevated blood levels of the liver enzyme aminotransferase. Cirrhosis is a rare but irreversible complication of iron overload; therefore, it is important to prevent liver fibrosis, the scarring process

that occurs in response to liver injury that can lead to cirrhosis. Fibrosis may occur earlier than usual in patients with viral hepatitis (particularly hepatitis C), non-alcoholic fatty liver disease, and/or alcohol abuse.

Diabetes, joint pain, and heart disease are common in patients with severe iron overload and liver disease. Heart disease may include cardiomyopathy (weakening and enlargement of the heart muscle), irregular heartbeats, or heart failure.

Patients receiving blood transfusions should be screened yearly for iron overload. Iron overload and its therapies are also discussed in *Chapter 3*. Screening is performed using blood tests to measure transferrin saturation, ferritin, and unsaturated iron binding capacity. A transferrin saturation measurement of greater than 45% or a transferrin saturation measurement of less than 45% with elevated levels of ferritin should prompt further testing and investigation into the patient's medical history.

The method of choice for estimating the levels of iron in the liver is a form of magnetic resonance imaging (MRI) called MRI T2*. MRI is non-invasive and may also detect cirrhosis or hepatocellular carcinoma. Patients with highly elevated blood levels of amino acids, obesity, or those suspected of chronic alcohol consumption may need a liver biopsy to detect liver disease or to determine the extent of liver injury due to other causes. A liver biopsy may assist in choice of therapy. Patients who develop iron overload at an early stage in their blood transfusion history or who have a family history of primary iron overload should undergo genetic testing for hemochromatosis, an inherited disorder that causes the body to absorb too much iron. Patients who test positive for inherited hemochromatosis may need to undergo HSCT earlier than other patients with FA.

Good to Know

Oxidative stress refers to the harmful effects of compounds called free radicals, which can damage cellular structures such as proteins and DNA.

Free radicals are naturally produced in the body as our cells use energy, and may be produced in response to environmental factors such as pollution.

Antioxidants are substances that neutralize free radicals.

Patients with iron overload should avoid vitamins or medications containing iron and vitamin C, but do not need to restrict their consumption of foods

containing iron and vitamin C. Phlebotomy (removal of blood), the mainstay of classic treatment of iron overload, is not an option for patients with FA who have not yet undergone HCST, but may be used after transplantation and recovery. Another treatment option for patients with FA who have undergone HCST is chelation therapy with drugs that bind iron and remove it from the body [29]. This is also discussed in detail in *Chapter 3.* The chelating agent deferasirox has been used in one study of children with FA and iron overload due to blood transfusions, leading to a significant reduction in ferritin levels; of the 39 children who received the drug, 3 developed renal toxicity and 3 developed liver toxicity [30]. Oral chelation should be chosen and monitored in consultation with a physician with some experience with these agents.

Nutrition as Therapy

Complementary and alternative therapies include any treatments and practices that have not been shown to be effective by evidence-based clinical studies. Complimentary therapies are used *in conjunction* with standard medical care, and alternative therapies are 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 multi-billion dollar industry that produces complementary/alternative nutritional regimes lacks federal regulation and has a clear incentive to promote its products regardless of the degree of evidence of the effectiveness of these products. Many complementary/alternative nutritional regimes and supplements are directly harmful or, by displacing standard medical therapy, indirectly harmful.

Some patients with FA might consider taking large doses of vitamins, antioxidants, or trace elements. Although studies suggest that it may be important to counteract oxidative stress in patients with FA [31], this research does not conclusively prove that supplementation with oral antioxidants changes the course of the disease. It remains unclear whether oral antioxidants even reach the intracellular site of oxidant stress in patients with FA. Some of these supplements may be toxic and some may promote tumor development. In particular, vitamins A, D, C, and niacin may be toxic in excess. Micronutrient supplementation to prevent cancer in patients without FA has shown supplementation may reduce cancer risk in populations with nutrient deficiency, but populations with healthy nutrient levels see no effect or, sometimes, increased cancer risk [32]. No therapy involving large doses of vitamins, antioxidants, or micronutrients has been shown to be effective in the treatment of FA using evidence-based criteria. Controlled clinical trials of

supplements are necessary to demonstrate effectiveness and limit the risk of toxicity.

Products containing supplemental iron, vitamins A (including b-carotene), C, and E, and omega-3 fatty acids may lead to health risks in patients with FA [33]. Products containing iron must be avoided to reduce the risk of exacerbating iron accumulation in the liver and other tissues. Vitamin C increases iron absorption; therefore, products containing vitamin C, such as multivitamins or fortified fruit juices/drinks should be avoided. In large studies, both vitamin A and vitamin E supplements have been associated with an *increased* risk of some cancers; therefore, they should be avoided until further study indicates otherwise. Large doses of omega-3 fatty acids, commonly found in fish oil supplements, can increase the risk of bleeding due to inactivation of platelets, blood cells that mediate blood clotting. Because patients with FA have reduced levels of platelets, products that impair platelet function should be avoided.

It is essential for physicians who manage patients with FA to become knowledgeable about complementary and alternative therapies, and question patients and families about their use of these therapies. Patients and their families often have the desire to control some aspect of the patient's care; in this respect, diet seems a harmless choice. Because patients with FA have significant nutritional problems that are often ignored, there is little to dissuade parents and patients from trying complementary and alternative therapies unless their physician becomes involved in these decisions. Establishing a non-judgmental, but candidly informative discussion of complementary and 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 website of the Office of Complementary and Alternative Medicine of the National Institutes of Health, available at: http://www.cancer.gov/occam, where there are several links to reliable information.

Chapter Committee

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