

# Chapter 9

## Clinical Care of Fanconi Anemia Gastrointestinal Issues

### Introduction

Fanconi anemia (FA) and medications used to treat the disease can cause gastrointestinal disorders, liver disease, and nutrition-related challenges. Without proper treatment, these complications can interfere with daily living and create hurdles for healthy growth and development.

Concerns related to the gastrointestinal tract that affect patients with FA most commonly include:

- Anatomic 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 cell transplantation (HCT)

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.

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## Gastrointestinal Tract Anatomic Abnormalities

Approximately 7% of patients with FA are born with anatomic abnormalities in the gastrointestinal tract [1]. The most common abnormalities include esophageal atresia (EA), EA with tracheoesophageal fistula (TEF), duodenal atresia, and other anorectal malformations. 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. Gastrointestinal tract abnormalities may occur in isolation or appear with other birth defects, including the VACTERL-H spectrum of disorders (described in Chapter 2).

### Esophageal Atresia and Tracheoesophageal Fistula

Esophageal atresia, with or without tracheoesophageal fistula (EA/TEF), typically is diagnosed during pregnancy. Symptoms of EA/TEF in newborns may include excessive drooling, feeding intolerance, or respiratory difficulties. Infants with EA/TEF who weigh more than 3 pounds 5 ounces (1500 g) at birth and lack major heart defects have a 98% survival rate to childhood and beyond [2]. Recent guidelines for management of this condition have been published elsewhere and can be referred to for additional detail [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 three 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 five or more vertebrae. In this form of atresia, the esophageal segments are very short and it is likely that significant complications will occur. The best practices for treating ultra-long gap EA/TEF are still under debate [2]; however, 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 and swallowing problems such as pain with solid foods, frequent reflux, and vomiting. There also may be a long-term risk of cancer in colon tissue used to reconstruct the esophagus.

Repair of EA/TEF in infancy frequently leads to gastroesophageal reflux disease (GERD), difficulty swallowing, and breathing problems in adulthood [4]. Diagnosis and management of GERD is essential to reduce pain, bleeding, and narrowing of the esophagus. Anti-reflux surgery often is necessary to correct the complication. Respiratory problems, including cough, pneumonia, and wheezing, may suggest the need for bronchoscopy. 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, peptic ulcer, megaduodenum, reflux of fluids from the intestines into the stomach and esophagus, and blind loop syndrome. 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 and constipation with or without encopresis [6]. In most cases, bowel control can be restored with medication, although some patients may require an antegrade continence enema.

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## **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:** Can result from many factors, but often results from 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 also can lead to nausea and abdominal pain, and may worsen existing gastrointestinal complaints.
- **Abdominal Pain:** May result from partial blockage of the digestive tract, which can be caused by complications of structural defects in the gastrointestinal system. Abdominal pain also can 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 for diarrhea.

## Initial Evaluation of Gastrointestinal Symptoms

In all cases, the initial evaluation of gastrointestinal symptoms in FA patients begins with a medical 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.

## Evaluation of Gastroesophageal Reflux

A recent endoscopic study of eight patients with FA found evidence of reflux esophagitis in all at baseline, with five of the eight patients having moderate or severe disease [7]. All patients with moderate or severe disease were experiencing symptoms of reflux, including difficult swallowing. Age at initial endoscopy ranged from 10-39 years. Two individuals with the most severe esophagitis, including the child in the study, developed esophageal squamous cell carcinoma within two years. Best practice guidelines for evaluation and management of GERD in patients in the general population have been published for both

adults and children [8, 9]. For patients with FA, the symptoms of reflux must be queried at each visit. Common symptoms of reflux include heartburn, chest pain, abdominal pain at the midepigastic area, increased burping or hiccups, and dysphagia. From a strictly symptomatic standpoint, children with GERD can be treated without further testing if they are old enough to reliably explain their symptoms. Alternatively, reflux can be diagnosed in children with a manometric-placed pH/impedance probe. Treatment begins with proton pump inhibitors (e.g., omeprazole or lansoprazole at a dose of 1 mg/kg/day until adult doses are reached). H<sub>2</sub>-antagonists should be avoided because these drugs increase the risk of bone marrow suppression. However, a 2019 study suggests that yearly endoscopy, even in young children, must be considered in FA patients to allow early diagnosis of esophageal cancer [7] (see Chapter 5).

## Evaluation of Delayed Gastric Emptying

Delayed gastric emptying 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. The test most commonly used to diagnose delayed gastric emptying in the general population is the nuclear medicine gastric emptying study, which involves radiation. To avoid radiation exposure in FA patients, a gastric emptying study can be omitted and a trial of treatment 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 used when available.

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.

The first line of therapy for delayed gastric emptying is dietary. 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.

Gastrointestinal motility may be further enhanced by a trial of medication, such as erythromycin (5 mg/kg/dose, 3 times per day), or—in Canada and Europe—domperidone (0.25 – 0.5 mg/kg/dose, 3-4 times per day; maximum daily dose of 2.4 mg/kg or 80 mg/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 is known to interact adversely with erythromycin. The use of metoclopramide is not recommended because of potentially dangerous side effects including irreversible

tardive dyskinesia, a disorder characterized by repetitive and involuntary movements. The combined use of amoxicillin and clavulanic acid (20 mg/kg amoxicillin and 1 mg/kg clavulanate, 2 times per day, with a maximum of 250 mg of amoxicillin, 3 times per day) 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 [10, 11].

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.

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## 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 two years of age, and measurements of body mass index (BMI) relative to age should be plotted for children more than two 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, multiple hormonal abnormalities [12], 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 height/linear growth.

Malnutrition, whether the result of poor food intake, high energy utilization, or excessive stool loss, initially results in a growth curve demonstrating low weight relative to height or low BMI relative to age. Attention also must 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 [12]. 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 Weight Gain

Parents of children with FA often are 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 also will have proportionately lower weights. Medical providers should discuss with parents of FA

patients the pattern of their child's growth curves, particularly the changes in weight relative to height from birth to two years of age, and BMI after age two. 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 [12].

## **Poor Food Intake Versus Malabsorption**

In patients with documented poor weight gain or weight loss, both poor food intake and/or diarrhea with malabsorption 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 also may 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 on page 168).

## **Vitamin D Deficiency**

All patients with FA 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 in Children with Fanconi Anemia**

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 third percentile for their age, or who have failed to gain weight over a 3- to 6-month period. Supplemental feeding via feeding tube, known as enteral supplementation, is preferable to supplementation by intravenous infusion, known as parenteral nutrition. Supplemental parenteral nutrition requires 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 supplementation.

Enteral supplementation may be delivered by nasogastric, nasojejunal or gastrostomy tubes. It is recommended that patients with FA have a nasogastric or nasojejunal feeding trial before proceeding to gastrostomy. The nasal route is best for patients who require supplemental feedings for less than three months. Drawbacks of nasal tubes include increased risk of sinus infection and exposure to ionizing radiation during fluoroscopy used for tube placement.

Gastrostomy tubes provide more permanent access to the gastrointestinal tract for administration of enteral feedings. Complications of gastrostomy tubes are limited to local irritation and/or infection, potentially due to low neutrophil counts. In addition, if the patient's platelet level is very low at the time of surgery, excessive bleeding is a risk. Some patients experience heartburn after starting enteral feeding supplementation, particularly with nighttime feeds. Vomiting and diarrhea also may occur. 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.

## **Appetite Stimulants**

Before prescribing appetite stimulants, physicians must first investigate and appropriately manage diagnosable causes of poor appetite and inadequate growth in FA patients. 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.

Nonetheless, several medications have 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—and none has been tested in patients with FA—they have been used to try to prevent unwanted weight loss in patients with cancer, HIV/AIDS, and cystic fibrosis [13, 14].

Megestrol acetate has been shown to increase appetite and weight gain in small trials for relatively short periods [15]. It has a high potential for serious side effects, including adrenal insufficiency [16, 17]. While possibly suitable for situations where short-term treatment is needed (for example, during chemotherapy, palliation therapy), it is not recommended for individuals with FA, who may need long-term appetite stimulation.

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 [14, 18]. However, some physicians elect to try this medication before resorting to nasogastric or gastrostomy feedings. Patients may benefit from cyproheptadine, as it reduces retching [19].

Cannabinoids have been shown to reduce nausea and vomiting in many circumstances [20]. Although some patients try various forms of cannabinoids to stimulate appetite, use should be limited to investigational trials until more is learned.

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## Overweight and Obesity in Fanconi Anemia

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 also tended to have diabetes [21]. 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.

While a full discussion of the management of overweight and obesity is beyond the scope of this chapter (see references [22] and [23] for more information), modification of lifestyle is an essential starting point. 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 ensure achievement of appropriate weight. Psychological counseling also may help, especially if an eating disorder is suspected. Patients should be urged to avoid fad diets and over-the-counter weight loss preparations and to focus on healthy lifestyle modifications.

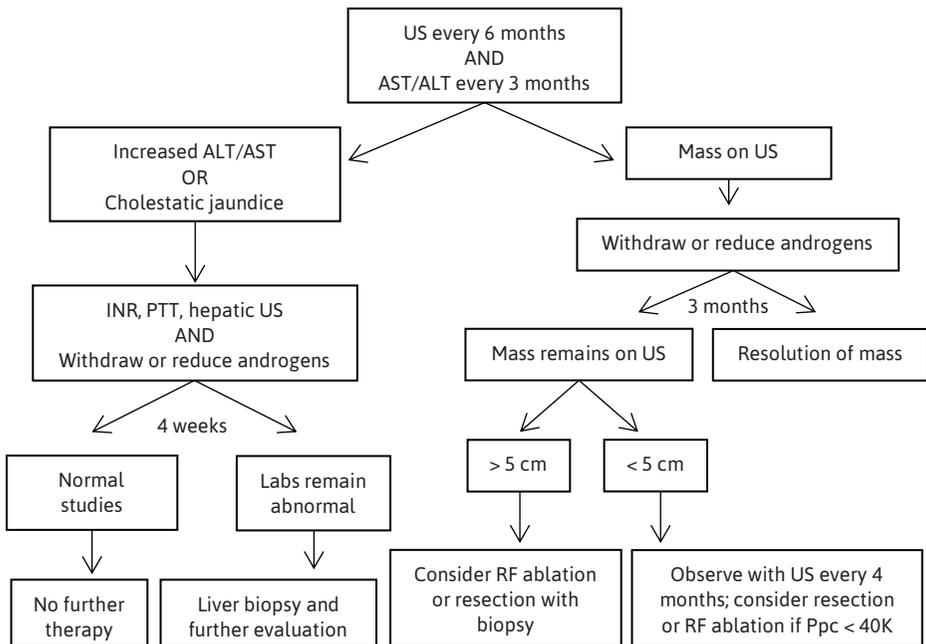
The obese patient should be assessed for the primary health consequences of obesity. At a minimum, measurements should include blood pressure using an appropriately sized cuff, fasting lipid profile, oral glucose tolerance with insulin levels, and blood levels of the liver enzymes aspartate aminotransferase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

# Liver Disease

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

## Liver Complications Associated with 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 [24]. 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, three of the 20 patients treated with androgens developed liver tumors [25]. Thus, careful monitoring for hepatic complications of androgen therapy is essential. Figure 1 provides a schematic for liver complication management strategies for FA patients on androgen therapy.



**Figure 1.** Management of potential hepatic complications in FA patients 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.

## **Peliosis Hepatis**

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 [18, 19].

## **Nonspecific Damage to the Cells of the Liver**

Androgen therapy can lead to cholestatic jaundice, hypertransaminasemia, or liver cirrhosis in patients on continued androgen therapy [18]. Cessation of androgen therapy usually will 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 Chapter 3 for more information on androgens).

## **Hepatocellular Adenomas**

Androgen therapy also can result in hepatocellular adenoma. An adenoma is a benign tumor that does not invade surrounding tissue; however, it can rupture, leading to life-threatening bleeding. There also is a risk of malignant transformation, particularly in some subsets of adenomas [26]. The risk of bleeding in hepatocellular adenomas is increased in patients with thrombocytopenia. Patients with FA may develop hepatocellular adenomas rapidly, often within 3 months of beginning androgen therapy [27-29]. Hepatocellular adenomas are generally diagnosed by ultrasound. Contrast-enhanced CT scans and MRI are more sensitive than ultrasound in detecting hepatocellular adenomas. Despite the radiation exposure from CT, it is strongly recommend that all patients receive both CT and MRI scans before hematopoietic cell transplantation (HCT) if they have previously undergone androgen therapy [30]. Hepatocellular adenomas may regress after cessation of androgen therapy, but if they persist, surgical removal or radiofrequency ablation may be necessary, particularly prior to HCT.

## **Hepatocellular Carcinoma**

Hepatocellular carcinoma (HCC), or malignant liver cancer, is reported occasionally 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  $\alpha$ -fetoprotein in the blood,

distinguishing it from other forms of HCC [18]. 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/or 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 and ultrasound examination may reveal the accumulation of fat or scar tissue, impaired blood flow, and obstruction of bile flow in the liver.

Patients with elevated liver enzymes should have a full evaluation of their liver by a hepatologist or pediatric hepatologist. In some cases, liver biopsy may be required to assess severity of liver disease.

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 of cholestatic disease.

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## **Gastrointestinal and Liver Complications of Hematopoietic Cell Transplantation**

To treat the blood abnormalities associated with Fanconi anemia (FA), many patients undergo hematopoietic cell transplantation (HCT), a procedure in which abnormal stem cells are replaced with healthy stem cells. Prior to HCT, 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 three months prior to HCT to ensure complete healing of the insertion site. Infections or irritation at the insertion site should be treated prior to HCT. 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 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 HCT is beyond the scope of this work (for a recent review, see [31]).

Historically, patients with FA who undergo HCT had an increased risk of graft-versus-host disease (GvHD) (see Chapter 3), in which the transplanted cells regard the recipient's body as foreign and attack the body, damaging the intestines, skin, and liver [32]. Patients with FA who develop chronic GvHD after undergoing HCT 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 is uncommon, but should be considered in patients with poor absorption of fat.

Patients with chronic liver GvHD typically experience cholestasis in the liver, with elevated levels of the liver enzymes ALT and AST. Both enzymes may increase rapidly if the patient has GvHD and as the doses of immune system-suppressing medications are reduced. It is uncommon for patients to acquire chronic viral hepatitis from HCT, 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, D, E, and K; therefore, levels of these vitamins should be monitored to determine whether vitamin supplementation is needed. Levels of vitamins A, D, and E can be measured via blood tests, and vitamin K levels can be inferred by measuring the clotting tendency of blood [33].

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## **Gastrointestinal System Cancer Screening**

Cancers of the gastrointestinal system are potential complications of Fanconi anemia (FA). Only one case of colon cancer in a person with FA has been documented in the literature to date; however, reports from FA adults who attended the Fanconi Anemia Research Fund's annual meeting in 2019 revealed that several adults in the FA community have been diagnosed with colon cancer. The Fanconi Anemia Research Fund is currently evaluating whether colon cancer screening is warranted. Patients with FA are at increased risk for esophageal cancer (see Chapters 4 and 5) and screening guidelines are discussed in Chapter 5. As mentioned on page 164, ultrasound imaging is recommended to screen for hepatocellular carcinoma for patients taking androgens.

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## Supplementation Risks and Benefits

Currently, no evidence-based studies have shown that large doses of vitamins, antioxidants, or other micronutrients are effective at treating FA. However, it has been shown that products containing supplemental iron, vitamins A (including beta carotene), C, and E, and omega-3 fatty acids may lead to health risks in patients with FA [34]. Large doses of omega-3 fatty acids, commonly found in fish oil supplements, can increase the risk of bleeding due to inactivation of platelets. Because patients with FA have reduced levels of platelets, products that impair platelet function should be avoided. In addition, vitamins A, C, D, and niacin may be toxic in excess.

Micronutrient supplementation to prevent cancer in patients in the general population has shown supplementation may reduce cancer risk in populations with nutrient deficiency, but populations with healthy nutrient levels see no effect or, in some cases, increased cancer risk [35]. In addition, large studies in the general population have shown that both vitamin A and vitamin E supplements are associated with an increased risk of some cancers; therefore, FA patients should avoid additional supplementation with these vitamins until further study indicates otherwise.

Counteracting oxidative damage by using antioxidants may be important for patients with FA [36]; however, research has not conclusively proven that supplementation with oral antioxidants changes the course of the disease. Currently, an ongoing clinical trial at the University of Cincinnati is examining whether oral delivery of quercetin, a naturally occurring flavonoid, reduces reactive oxygen species and DNA damage in cells of patients with FA. Interim results of the phase II prospective squamous cell carcinoma (SCC) chemoprevention study show that oral quercetin led to improved surrogate markers of genomic instability/DNA damage in buccal mucosal cells from the patients and no adverse events have been reported [37]. The preliminary results from the trial are encouraging; however, it is too early to confirm whether quercetin supplementation decreases risk of SCC in FA patients.



## Summary

Patients with Fanconi anemia (FA) experience gastrointestinal symptoms such as reduced appetite, nausea, abdominal pain, and diarrhea. These symptoms, in conjunction with anatomical abnormalities of the gastrointestinal tract, can lead to poor weight gain or malnutrition, or in some cases patients being overweight or obese. Common treatments for FA, including hematopoietic cell transplantation (HCT) can cause severe gastrointestinal complications including liver disease, graft-versus-host disease (GvHD), and potentially cancer. Gastrointestinal abnormalities are typically diagnosed and treated via surgery in infancy; however, a comprehensive physical exam is necessary to adequately evaluate gastrointestinal symptom root causes. Similarly, assessment of poor growth should be evaluated in the context of poor intake versus malabsorption issues. Patients with FA who are treated with androgens should be monitored for liver disease and development of hepatocellular carcinoma; prevention of liver disease should include screening and avoidance of substances that cause liver toxicity. Comprehensive and integrated clinical care that adequately addresses gastrointestinal issues for patients with FA is necessary to promote healthy growth, development, and high quality of life.

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Sarah Jane Schwarzenberg, MD

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