Fanconi Anemia

Guidelines for Diagnosis and Management

Third Edition • 2008

Fanconi Anemia: Guidelines for Diagnosis and Management • Third Edition • 2008

Fanconi Anemia Research Fund, Inc.

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These guidelines for the clinical care of Fanconi anemia (FA) were developed at a conference held April 10-11, 2008 in Chicago, Illinois. We owe a tremendous debt of gratitude to Eva Guinan, MD, for serving as moderator of the conference, as she did for the consensus conferences for the first two editions, and for her skill in helping the participants arrive at consensus.

We would like to thank all the participants for donating their time and expertise to develop these guidelines. The names and contact information of all participants appear in the Appendix.

These guidelines are posted on our website and are available from:

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The Fanconi Anemia Research Fund, Inc., was founded in 1989 to provide support to FA families and to raise money for scientific research. The Fund publishes a newsletter twice a year, sponsors an annual family meeting, and provides resource identification and counseling support to families. To aid research into FA, the Fund gives grants to scientists and sponsors scientific conferences, including an annual scientific symposium.

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Introduction

This edition of guidelines for the care of patients with Fanconi anemia is the result of a Consensus Conference held by the Fanconi Anemia Research Fund in Chicago, Illinois on April 11 and 12, 2008. It is intended as a complete replacement for earlier versions published in 1999 and 2003. Our audience is physicians who provide primary care for FA patients, and patients and families who wish to secure optimal treatment through medical understanding, consultation and appropriate referral.

These guidelines begin with a comprehensive checklist for physicians and medical specialists and diagnostic criteria. Subsequent chapters examine more specific issues faced by the FA patient. The guidelines conclude with important psychosocial considerations that bear upon the well-being of the patient and extended family.

Where possible, the guidelines rely on evidence-based medicine. Where adequate data are lacking because of limitations of numbers, time frame or present knowledge, the consensus of expert opinion underlies the recommendations. All chapters have been peer-reviewed and speak to the state of best practices as of the date of each chapter. To avoid being excessively prescriptive, the title of this book has been changed deliberately from "Standards" to "Guidelines." From the discussions at the Consensus Conference, the authors realize that a more robust clinical database must be developed to gather additional evidence upon which to base recommendations.

FA-related science has advanced significantly in the five years since the last publication in 2003:

- At least 13 FA genes now have been identified. The understanding of interactions among molecular pathways has become increasingly complex and sophisticated. Genotype determination and mutation analysis for each patient bear directly on the appropriateness of some treatment choices.
- Phenotypic and genotypic predictors of the natural history and outcome of the disease are beginning to emerge.
- The identification of *BRCA2* and other FA genes linked to breast cancer susceptibility has brought an influx of new scientific talent and interest to the field of FA research. The relevance of these findings to heterozygotes is being evaluated.
- The introduction of fludarabine (Fludara) into FA hematopoietic stem cell transplantation protocols has continued to produce dramatic improvements in patient outcomes. As a consequence, stem cell transplantation from unrelated or mismatched donors is a realistic treatment option for increasing numbers of FA patients.
- A growing cohort of post-transplant adult FA survivors presents new medical surveillance and treatment issues.
- The availability of preimplantation genetic diagnosis (PGD) for FA and for HLA determination provides a potential parental choice for securing an HLA-matched umbilical cord stem cell transplantation.

- Evaluation of adult FA patients reveals a striking and ominous incidence of squamous cell carcinomas (SCC), especially of the head and neck and gynecological tract. This underscores the need for continuous monitoring and more effective treatment options throughout the patient's lifetime.

General Considerations

The Consensus Conference was guided by the following general considerations that form the underlying basis for more specific recommendations.

FA is a very rare genetic disorder.

- Accuracy in diagnosis is crucial and requires sophisticated expertise.
- The mode of inheritance is important for further genetic testing of siblings; finding matched donors; identification of genotype for purpose of predicting onset of symptoms and consequences; family planning (including PGD); and genetic counseling to the family.
- Expertise in FA treatment is highly specialized and to date is concentrated only in a few, critically important centers. Many patients do not have access to such expertise locally, but the use of referral networks and provider cooperation should help provide adequate care.

FA is a complex and chronic disorder.

- Well-orchestrated multidisciplinary care across several medical and surgical specialties is typically required for adequate monitoring and treatment.

- Clinical trials or at least the collection of longitudinal data are required to inform treatment choices for patients with FA in the future.

FA must be considered a multi-system disease.

- The name of the disorder, Fanconi anemia, may disserve patients since hematologic manifestations of FA are not the sole (or even the most important) problem for many patients.
- The FA phenotype is quite variable and leads to misdiagnosis and failure of diagnosis. Patient monitoring must include hearing evaluation, assessment of endocrine system and GI tract issues, and long-term cancer surveillance.
- For the majority of patients, hematopoietic stem cell transplantation is the ultimate therapy for marrow dysfunction. Consequently, early involvement with a major transplant center experienced in FA transplants and with a multidisciplinary consultation team is optimal.

FA is a cancer-prone disorder.

- Close monitoring, especially for the high incidence of SCC, is a special consideration throughout the FA patient's lifetime, even post-transplant.
- The intrinsic genetic instability of the FA patient means that exposure to ionizing radiation, environmental carcinogens and chemotherapeutic agents could pose special risks to the patient. Consequently, diagnostic x-ray exposure and some otherwise routine medical tests or agents may themselves pose undesirable risks.

FA is a psychosocially demanding disorder.

- The pressures on the patients, parents and siblings over an extended time can be overwhelming, particularly where there are multiple affected family members.
- Patients, families and providers must be sensitive to issues of expense, the sophistication and availability of medical and family counseling, and the significant and continuing emotional trauma resulting from this diagnosis.

The underlying diagnosis and the many drugs often necessary for treatment may put FA patients at particular risk for hazardous pharmaceutical cross-reactions.

- The family and primary physician must continuously coordinate and monitor prescribed and over-the-counter medications taken by a patient.

The authors recognize that a significant proportion of affected families seek out and utilize "alternative" medicine.

- We accept this approach but at the same time ask families to be open in discussing what they are doing. Effective therapies may emerge and need to be shared. However, we also caution that unforeseen toxicities and drug interactions need to be identified.

We commend these guidelines in the profound hope that they will better serve the lives of patients afflicted with this serious and life-threatening disorder. We welcome comments that may inform future improvements in care and treatment.

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Chapter 1

Clinical Management Checklist

Fanconi anemia is a complex disease that can affect many systems of the body. Patients are at risk for bone marrow failure, leukemia, and squamous cell carcinoma. They also can be affected by other facets of the disease, such as endocrine, gastrointestinal or radial ray abnormalities.

This checklist, a compendium of suggestions from many of the authors of the handbook, is not all inclusive and does not take the place of reading the comprehensive information in the book. Many of the tests and procedures mentioned will not be appropriate for every individual patient nor does the checklist present an exhaustive list of possible tests or treatments that each FA patient should undergo. Rather, it should be used at the discretion of the patient's physician and should be specifically tailored to the needs of the patient.

Diagnostic Testing

- If FA is suspected, the patient should be referred to a hematologist to arrange for a diepoxybutane (DEB) or mitomycin C (MMC) chromosome fragility test of blood lymphocytes at a clinically-certified laboratory with expertise in FA diagnostic testing. The Fanconi Anemia Research Fund website (www.fanconi.org) provides a listing of such testing centers.
- If diagnostic test results of blood are not conclusive and there is a high probability of FA, skin fibroblasts should be obtained for more

complete testing. If the result remains inconclusive, additional diagnostic testing is available and described in this book.
- All children suspected of having the congenital anatomic abnormalities referred to as VACTERL should be tested for Fanconi anemia.
- All full siblings of the FA patient, regardless of whether they show physical signs or symptoms, must be tested to rule out FA.

Complete History and Physical

Patients diagnosed with FA should undergo a complete work-up and physical examination, which include the following:

- Family history, including consanguinity and history of prior family members with anemia, physical abnormalities or cancer.
- Past medical history, including an assessment of prior blood counts, congenital malformations, and medications used.
- Hematologic assessment, including a complete blood count and differential, and a bone marrow aspiration, biopsy, and cytogenetic evaluation.
- Hepatic assessment, including liver enzymes and total bilirubin.
- Renal assessment, including serum electrolytes and creatinine, and ultrasound to rule out renal dysplasia, hydronephrosis, and/or bladder anomalies.
- Urologic examination to assess for genitourinary (GU) reflux, urinary tract infections, and GU malformations. If a renal abnormality is found in a female, the patient should be assessed for reproductive tract malformations.

- Endocrine evaluation, including thyroid function, serum glucose and/or glucose tolerance, lipid assessment, and bone mineral density.
- Ear and hearing examination to assess for hearing loss and/or structural abnormalities of the ears.
- Eye examination by an ophthalmologist, if clinically indicated.
- Examination for head and neck cancer by an otolaryngologist (ear, nose, and throat specialist), beginning at age ten.
- Gynecological examination (see page 22).
- Examinations by other specialists, depending on the individual needs of the patient.

Complementation Group Assignment

- Identification of the complementation group can guide medical management of the FA patient and help the family determine cancer risk in patients and in carriers. It can also guide family planning efforts and may be important for prospective gene therapy trials. Complementation group typing is available through FA-specialized laboratories.
- Genes not currently identifiable by complementation group testing include *FANCD1/BRCA2*, *D2*, *I*, *M*, and *N*. Mutation analysis is necessary to classify individuals into one of these five groups.

Mutation Analysis

- Mutation analysis determines and/or confirms the initial complementation group result and is also used to perform other genetic tests, such as carrier testing or prenatal testing. Mutation

analysis is available at certain FA-specialized diagnostic laboratories.

Genetic Counseling

- At diagnosis, the FA patient and family should be referred to a genetic counselor, who can explain the genetic testing process, clarify the mode of inheritance of FA, and provide reproductive counseling.

Medical Management after Diagnosis

The care of most FA patients should be coordinated by a hematologist with expertise in Fanconi anemia, in conjunction with the patient's local family physician. See Chapter 3 for a thorough discussion of ongoing hematological care.

Bone Marrow Failure

Most Fanconi anemia patients develop bone marrow failure, but the age of onset is variable, even among affected siblings. Patients with or without marrow involvement should be monitored by a hematologist with experience in managing FA patients.

- **Cytopenias:** Cytopenias in FA patients warrant a thorough hematologic work-up to rule out additional treatable causes other than primary bone marrow failure.
- **Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML):** Patients are at high risk of developing MDS and AML. They should be monitored closely to assess possible onset of MDS or frank leukemia and to identify the presence of cytogenetic abnormalities that may warrant immediate intervention.

    - Bone marrow aspiration with or without biopsy should be done annually to allow comparison of marrow to patient's previous specimens. See Chapter 3 for an individualized schedule for clinical monitoring of bone marrow and timing of referral for discussion with a transplant center.
- **HLA typing:** Early high-resolution HLA typing of the patient and immediate family members is recommended to assess the availability of potential bone marrow donors, should a transplant be necessary. *To allow for the most appropriate medical plan, a donor search—if there is no identified sibling donor—should be initiated well before the need for transfusions or development of MDS or AML.*

Blood Transfusions and Iron Overload

- **Transfusions:**
    - High transfusion burden may adversely affect transplant outcomes. Family members should not be used as blood donors for the patient. Timely consideration of transplant is recommended if transfusions are required.
- **For patients who receive transfusions:**
    - Patients who receive multiple transfusions of red blood cells are at risk for accumulating toxic levels of iron. The liver, heart, and endocrine organs are primary sites of iron accumulation, and end-organ damage may result (e.g., hepatic cirrhosis, heart failure, endocrine dysfunction). For an extensive

discussion of the management of iron overload, refer to Chapter 3.
    - Referral to a pediatric gastroenterologist or hematologist with expertise in iron toxicity is indicated for monitoring of iron overload.
- **For patients post-transplant:**
    - If a patient has received a significant number of red blood cell transfusions, an assessment of total body iron should be performed no later than one year after transplant.
    - Depending on the result, monthly phlebotomy or chronic iron chelation may be necessary.

Polypharmacy

The involvement of multiple subspecialists introduces the risk that medications prescribed by one physician will interact adversely with those prescribed by another or that the use of non-prescription drugs may interact adversely with prescribed medication. All subspecialists must communicate with the primary physician—usually the hematologist—to coordinate care, and the patient should identify all prescription and non-prescription drugs used for each provider.

Radiation Exposure

Because FA patients have increased sensitivity to radiation, the primary FA physician involved in managing the patient should consult the family and other doctors of the patient to reduce exposure to diagnostic radiation as much as possible.

Hand and/or Arm Abnormalities

Patients with hand or arm abnormalities should be assessed at diagnosis by an orthopedic surgeon with experience in congenital limb differences and with a *Certificate of Added Qualification in Hand Surgery*. Early referral (in the first few months of life) of the patient to an orthopedic upper extremity specialist is highly recommended to obtain the best possible result if surgery is required.

Recommended management by the orthopedic surgeon includes:

If the patient has not been assessed for a possible diagnosis of FA:

- Consider and/or rule out the diagnosis of Fanconi anemia if patient presents with radial ray or thumb abnormalities or other characteristic features of FA (see Chapters 2 and 5).

If the patient has FA:

- Consult with patient's primary physician/hematologist.
- Assess for musculoskeletal problems.
- Assess for thumb anomalies.
- Assess for forearm anomalies.
- The physician should provide emotional support to the patient and family through open discussions about the patient's psychological adjustment to his/her hand or arm anomalies.

Ear and Hearing Abnormalities

FA patients should be examined by an otolaryngologist (ear, nose and throat specialist) at diagnosis to assess for possible hearing loss or structural abnormalities of

the eardrums and/or middle ear bones. If the patient has hearing loss or structural abnormalities, follow-up should include:

- **At diagnosis:**
  - An assessment from an audiologist to determine whether an amplification system will be useful (for children as young as four months).
  - Possible surgical intervention to improve hearing.
  - Contact with the school district regarding early intervention services provided by the Individuals with Disabilities Education Act (from birth through age 21).
  - Speech and language therapy, if needed.
- **Medical management after diagnosis:**
  - If an FA patient receives potentially ototoxic drugs, such as intravenous antibiotics, iron-chelating agents, and chemotherapy drugs used during hematopoietic stem cell transplant, the patient's auditory function should be monitored with serial audiograms.

Gastrointestinal and Hepatic Issues

Patients with gastrointestinal or hepatic issues should be seen by a pediatric gastroenterologist.

Gastrointestinal issues: Approximately 7% of FA patients have gastrointestinal tract abnormalities and many have gastrointestinal symptoms, such as poor oral intake, nausea, abdominal pain, and/or diarrhea. *These problems may affect nutrition in FA patients.* The physician should ask the patient and family about gastrointestinal symptoms during routine clinic visits, since it

is common for a patient not to disclose these concerns spontaneously.

Hepatic complications of androgens: Androgenic steroids used to treat low blood counts in FA are associated with multiple hepatic complications. Liver enzymes should be monitored every six months in patients receiving androgens, and a yearly liver ultrasound is recommended.

Endocrinology Issues

Many children and adults with Fanconi anemia have endocrine problems, including growth hormone deficiency, hypothyroidism, pubertal delay, diabetes or osteopenia/osteoporosis. To ensure optimal care, the FA patient should consult with a pediatric endocrinologist (with experience in growth and puberty), as well as other sub-specialists as indicated.

- **Baseline and ongoing evaluation:** At diagnosis and annually, each FA patient should receive a thorough baseline endocrine evaluation.
- **Growth:**
    - Nutritional and medical causes for poor growth should be identified as early as possible for optimal treatment.
    - Growth in children with FA should be followed clinically. Height should be plotted on a growth chart.
    - If child is small for his or her age, obtain a bone age x-ray.
- **Puberty:**
    - Delayed onset of puberty should be followed by at least annual physical examinations to evaluate stage of puberty.

    - After age 12, pubertal hormone concentrations should be obtained every two years as needed to assess pubertal progression.
- **Glucose tolerance:**
    - A two-hour oral glucose tolerance test (OGTT) with insulin levels should be obtained every two years or yearly if the results are not normal.
- **Diet and exercise:** All persons diagnosed with FA—regardless of OGTT results—should get regular exercise and follow a healthful diet that ensures adequate caloric consumption and follows the guidelines of the American Diabetes Association.

Osteopenia and Osteoporosis

FA patients are at risk for osteopenia and osteoporosis. For patients who have not undergone a transplant, a screening DXA scan should be obtained at age 14, with follow-up as needed. Factors such as transplant (bone marrow, peripheral blood cell or umbilical cord blood) may increase the risk of osteopenia; therefore, a DXA scan should be obtained one year post-transplant, with ongoing monitoring as needed. Independent of transplantation, premature menopause is a high-risk factor. Gynecological experts who treat adult FA women recommend a DXA scan every two years or as clinically indicated. Recent studies suggest that FA men as well as women may be at risk.

Gynecologic Issues

Fanconi anemia patients may experience a variety of gynecologic issues, including structural abnormalities, delayed puberty, decreased fertility, early menopause,

and a high risk of squamous cell carcinoma of the lower genital tract, which includes cervical, vaginal, vulvar, and anal cancers.

- **Gynecologic Examinations:**
    - Beginning at age 13, obtain annual examinations by a gynecologist for visual inspection of the external genitalia.
    - Comprehensive annual gynecologic exams with cervical cytology testing (Pap smears) should begin at age 18 and include discussion of STDs and contraception.
    - Colposcopy and biopsy should be done if lesions are noted on inspection or if the cervical cytology test is abnormal.
- **HPV vaccination:** Obtain an HPV vaccination series beginning at age nine for prevention of HPV-associated cancers. The safety and immunogenicity of HPV vaccination in FA men and women has yet to be determined.
- **Reproductive tract anomalies:** Assess for reproductive tract anomalies if patient is known to have kidney anomalies.
- **Breast cancer:** Breast cancer surveillance should begin by the early 20s and include annual breast exams. Screening mammograms should be initiated by age 25 or if a mass is detected.
- **Pregnancy:**
    - Discuss childbearing options before transplant, since the transplant may affect future fertility.
    - The patient should not take androgens during pregnancy.

    - While pregnancy for women with FA is not life-threatening, the pregnancy should be considered high risk and be co-managed by a maternal/fetal medicine specialist and a hematologist.
- **Menopause:** FA patients usually go through premature menopause. Thus, the physician should consider the post-menopausal health risks of osteoporosis, cardiovascular disease, breast cancer, and the management of hot flashes.

Squamous Cell Cancer of the Head and Neck

Fanconi anemia patients are at extremely high risk of acquiring squamous cell carcinoma of the head and neck (HNSCC). Proper prevention, surveillance, and treatment of HNSCC are essential.

If the patient with HNSCC has not been assessed for a possible diagnosis of FA:

- Testing for FA should be considered in younger SCC patients (<40 years of age), especially if they have atypical findings (e.g., borderline anemia, macrocytic red cells, mild thrombocytopenia) or an atypical response to cytotoxic treatment.

For a patient with a diagnosis of FA:

- **Prevention:**
    - Beginning at age ten, obtain a thorough examination twice a year from an ear, nose and throat specialist, oral surgeon or other doctor experienced in head and neck cancer detection and familiar with Fanconi anemia. The exam should

include the nasopharynx, oropharynx, hypopharynx, and larynx.
    - Maintain good oral hygiene.
    - Avoid all alcohol, including mouthwashes that contain alcohol, and avoid tobacco use, including second-hand smoke.
    - Consider an HPV vaccination, beginning at age nine for both boys and girls, to possibly prevent squamous cell carcinoma associated with the HPV virus (see Chapter 13).
- **Treatment and surveillance:**
    - Suspicious lesions should be biopsied immediately. If a premalignant lesion is found, examinations should increase to every two to three months, at the physician's discretion. Malignant lesions must be treated immediately.
    - Aggressive monitoring by the surgeon is an absolute must for those already treated for head and neck cancer.
    - Those already treated for head and neck cancer should obtain an annual chest x-ray.

Dental Care

- **Regular dental examinations:** All FA patients should have regular dental examinations by a dental practitioner versed in FA cancer risks. The examination should include a thorough screening for possible oral cancer.
- **Post-transplant:** Because of the risk of bacteremia, patients should not have dental cleaning, extraction or other invasive procedures

performed until at least one year after transplantation.

Dermatology

Patients with suspicious nevi or other abnormal skin lesions should be examined by a dermatologist. All FA patients should limit sun exposure and wear sunscreen to reduce the risk of skin cancer and, in those post-transplant, to reduce the risk of cutaneous chronic GvHD.

Malignancy Surveillance

FA patients are at extraordinary risk for malignancy at an early age and require lifelong surveillance, regardless of whether they have undergone a transplant.

- A subset of FA patients is at even higher risk of malignancy, including those with *FANCD1/BRCA2* mutations and those who develop GvHD after transplantation.
- Patients with biallelic *FANCD1/BRCA2* mutations require at least annual brain MRIs to assess for the development of medulloblastoma. Renal ultrasounds should be performed at least annually in these high-risk individuals to assess for Wilms tumors.

Hematopoietic Stem Cell Transplantation (HSCT)

HSCT is currently the best therapy available to cure the FA patient of marrow aplasia, to prevent progression to MDS or AML, or cure existing MDS or AML.

In a patient not diagnosed with FA:

- **Unexplained cytopenia:** In patients with

unexplained cytopenias, consider the diagnosis of Fanconi anemia before proceeding to transplant.

For patients diagnosed with FA:

- **Selection of transplant center:** FA transplants are complex. Consensus of physicians participating in the development of these guidelines is that, if a local transplant center has performed fewer than five transplants for FA, strong consideration should be given to refer the patient to a transplant center with greater experience in FA transplants.
- **Confirm diagnosis:** For FA patients, the FA diagnosis must be confirmed before proceeding to transplant.
- **Suitability for and timing of transplant:** The exact timing and therapeutic plan may vary depending upon the hematopoietic cell source (marrow versus peripheral blood versus cord blood), degree of donor and patient HLA mismatch, age of patient, presence of specific end-organ dysfunction, the stage of the disease (aplastic anemia versus MDS versus acute leukemia), infection status, institutional preferences, and personal factors such as school or employment.
- **Future fertility:** Discuss childbearing options before transplant, because the transplant may affect future fertility.
- **HLA typing:**
    - The pre-transplant evaluation must confirm the HLA typing by high-resolution Class I and Class II testing in both the donor and recipient at the lab utilized by the center performing the transplant.

- The related donor must be tested to rule out Fanconi anemia.

Post-Transplant Care

- **Schedule of post-transplant clinical examinations:** See Table 2 in Chapter 11 (*Late Effects in Fanconi Anemia Patients Post-transplant*) for schedule of post-transplant clinical examinations.
- **Early complications:** Watch for early complications of transplant, such as GvHD, graft failure, organ toxicity, and infections. Provide close follow-up of rashes, diarrhea, liver enzymes, and blood counts, with testing for viruses and monitoring of drug levels.
- **Late complications:**
  - Monitor for chronic GvHD, organ toxicity (cardiac, pulmonary, renal) or endocrinopathies (diabetes, hypothyroidism, gonadal dysfunction), osteoporosis, avascular necrosis, and cancer, particularly HNSCC.
- **Infectious disease prophylaxis post-HSCT (yeast/fungal; viral; protozoal):**
  - Most transplant centers will expect the patient to remain near the facility for a minimum of 100 days, the highest risk period for the development of the immunologic complications (i.e., graft rejection, GvHD, and opportunistic infection) associated with transplantation. Prophylactic antibiotic regimens commonly used after HSCT are outlined in Chapter 10 (*Unrelated Donor HSCT*).

- **Immune reconstitution and immunizations post-transplant:**
    - Screen for immune reconstitution one year after transplant.
    - The primary care physician should discuss the exact timing of immunizations with the patient's transplant physician.
    - All patients and their family household members should receive the influenza vaccine on an annual basis. Only the intramuscular formulation should be administered because intranasal influenza vaccine contains live virus, which puts the patient at risk of becoming ill.
- **Hematology:** After transplantation, the patient's transplant physician will decide how often blood counts and bone marrow (BM) tests are needed.
    - In general, BM aspirates and biopsies are performed several times during the first year after transplant. The pattern thereafter varies widely by transplant center.
    - Subsequent BM examinations are warranted if the patient has mixed chimerism, remains transfusion dependent, or if there are concerns about low peripheral blood counts.
- **Ophthalmology post-transplant:** The three major ocular complications after transplantation are cataracts, dry eyes (usually associated with GvHD), and retinopathy.
    - All patients should undergo an ophthalmology evaluation one year after HSCT.
    - Patients with signs or symptoms of chronic GvHD should have a Schirmers' test performed to screen for decreased tear production.

    - Any change in visual acuity should be assessed immediately.

Novel Treatments

- If the patient does not qualify for currently available treatment for FA, contact a major medical center with an FA comprehensive care center to determine if and where novel treatments may be available on a clinical trial basis.
- The Family Support Coordinator at the Fanconi Anemia Research Fund can assist the patient in locating possible clinical trials.

Prenatal Screening and Preimplantation Genetic Diagnosis

Families wishing to have additional children may be interested in pursuing prenatal screening or preimplantation genetic diagnosis. The physician should refer such families for appropriate medical and genetic counseling.

Transition to Adult Medical Care

Patients with Fanconi anemia usually are diagnosed in childhood, and their medical care is managed in the pediatric medical system. As patients reach adulthood, the physician and patient must develop a plan for a seamless transition to adult medical care that includes the following:

- Sufficient time for the transition to adult care, with time to educate the FA adolescent and family about the transition and to locate appropriate adult medical resources.
- The adult medical care selected should provide for surveillance and treatment of all aspects of

the disease, including:

- Preventive health care.
- Hematological consultations. If transplanted, ongoing evaluation may be necessary. If not already transplanted, possible transplantation can be discussed with experts in transplantation of FA adults.
- Continuation of rigorous cancer prevention and surveillance, especially of head and neck and gynecological SCC.
- Vascular and cardiac disease.
- Endocrinopathies, such as abnormal thyroid function, diabetes mellitus, reduced fertility, and osteoporosis.
- Treatment-related late effects, such as cataracts, iron overload or the effects of iron-chelation therapy.
- HPV vaccination or re-vaccination for possible prevention of SCC.
- Gynecological consultations for continued rigorous cancer prevention and surveillance, menses and menopause management, and fertility issues.

Quality of Life Issues for Adult FA Patients

FA adult patients may need assistance with educational, vocational, workplace, community or family relationships. Patients may have neurocognitive deficits, anxiety, depression, social withdrawal, difficulty with re-entry into society or school after transplant or cancer treatment, and insurance problems. Programs to address these needs will be available in many communities. Additionally, the Family Support Coordinator of the Fanconi Anemia Research Fund can provide assistance

in locating resources to address psychosocial or medical issues.

Acknowledgement

We extend our sincere gratitude to Margaret MacMillan, MD, University of Minnesota, for her expertise and leadership in chairing the discussion of the Clinical Management Checklist at the Consensus Conference in Chicago in April, 2008.

Chapter 2

Diagnostic Evaluation of FA

Blanche P. Alter, MD, MPH, FAAP

Definition of Fanconi Anemia

Fanconi anemia is an autosomal recessive disorder associated with a very high frequency of bone marrow failure, leukemia, and squamous cell carcinoma. FA has many other manifestations including, but not restricted to, severe birth defects,[1,2] chromosomal instability, and a defect in DNA repair. Thirteen genes have been identified as of 2008; a few otherwise typical FA patients do not have mutations in the known genes and, thus, more genes await discovery.

The Importance of Early Diagnosis

Early diagnosis of FA permits the exclusion of other diseases and precludes inappropriate management of hematologic disease (aplastic anemia [AA], myelodysplastic syndrome [MDS], acute myeloid leukemia [AML]), and permits appropriate consideration of stem cell transplant, androgens, hematopoietic growth factors or supportive care (see later chapters). Surgical intervention for orthopedic, renal or other anomalies is also optimized if the diagnosis of FA is known. For example, surgeries might be accelerated in order to be completed before the development of significant cytopenias. Physicians can offer targeted cancer surveillance and early, aggressive surgery for solid tumors. Experts can discuss realistic prognoses. Genetic counseling is imperative, because of the 25% risk of FA in each subsequent pregnancy. Opportunities must be provided for family

planning, prenatal diagnosis, and even preimplantation genetic diagnosis.

Index of Suspicion

Physical appearance

The most frequent characteristic birth defects in FA, in descending frequency from approximately 50 to 20 percent, include skin hyperpigmentation and *café au lait* spots; short stature; abnormal thumbs and radii; abnormal head, eyes, kidneys, and ears. These data are from 1,865 case reports in the literature (Alter, unpublished) and are biased by under- and over-reporting because cases in the literature tend to focus on the unusual or more sensational findings. Additional specific types of anomalies in Fanconi anemia patients are listed below. Although these types of anomalies may be present in many other syndromes, FA should be "ruled in" or "ruled out" in patients with these findings. However, at least 25% of known FA patients have few or none of these features.[2]

Examples of Anomalies in Fanconi Anemia[1]

Anomalies are listed in approximate order of frequency within each category, as follows:

Skin: Generalized hyperpigmentation; *café au lait* spots, hypopigmented areas
Microsomia: Short stature
Upper Limbs:

- ***Thumbs:*** Absent or hypoplastic, bifid, rudimentary, attached by a thread, triphalangeal
- ***Radii:*** Absent or hypoplastic (only with abnormal thumbs), absent or weak pulse
- ***Hands:*** Hypoplastic thenar eminence, absent first metacarpal
- ***Ulnae:*** Dysplastic

Gonads:

Males: Hypogenitalia, undescended testes, hypospadias, micropenis

Females: Hypogenitalia, bicornuate uterus, abnormal menses

Other Skeletal:

Head and face: Microcephaly, micrognathia, triangular

Neck: Sprengel, Klippel-Fiel

Spine: Spina bifida, scoliosis, abnormal ribs

Eyes: Small, close-set, strabismus, epicanthal folds, cataracts, astigmatism

Ears: Deaf (usually conductive), abnormal shape, atresia, abnormal middle ear

Renal: Ectopic or pelvic, abnormal, horseshoe, hypoplastic or dysplastic, absent, hydronephrosis or hydroureter

Gastrointestinal: Atresia (esophagus, duodenum, jejunum) imperforate anus, tracheoesophageal fistula

Lower Limbs:

Feet: Toe syndactyly, abnormal toes

Legs: Congenital hip dislocation

Cardiopulmonary: Various structural congenital heart defects.

For a complete listing of possible anomalies in FA, see Young NS, Alter BP. *Aplastic Anemia: Acquired and Inherited*. Philadelphia, PA: WB Saunders; 1994.

Hematology

Patients with FA may present with AA, MDS, AML, single cytopenias without another explanation (such as antibodies) or macrocytic red cells without another explanation (e.g., vitamin B12 or folate deficiency). We recommend that FA be considered in all children and young adults with unexplained cytopenias. It is

absolutely imperative to test for FA if a stem cell transplant is planned.

Table 1: Cancer in Patients with FA, Not Transplanted, 1927-2007*

Type of Cancer	Male	Female	Not Stated	Total	Median Age in FA (Range)	Median Age for Sporadic Cancers†
Leukemia:						
Acute myeloid leukemia (AML)	68	59	12	139	13 (0.1-50)	67
Acute leukemia, unspecified	3	9	0	12	14 (9-24)	
Acute lymphoid leukemia (ALL)	3	3	0	6	5 (1-10)	13
Chronic myelomonocytic leukemia (CMML)	0	3	1	4	16 (11, 20)	NA
Solid Tumors:						
Head and neck	15	21	0	36	27 (13-46)	62
Esophagus	3	9	0	12	27 (20-50)	69
Vulva	-	17	-	17	26 (14-38)	68
Cervix	-	6	-	6	24 (22, 25)	48
Breast	0	7	0	7	37 (26-45)	61
Brain	8	11	4	23	3 (0.5-11)	10
Renal Wilms	9	4	3	16	1(0.5-5)	5†
Renal carcinoma	0	1	0	1	36	65
Neuroblastoma	4	1	2	7	0.7 (0.2-1.4)	0.5†
Lung	3	0	0	3	29 (23-34)	70
Stomach	2	0	1	3	28 (21, 35)	71
Lymphoma	1	1	0	2	1.4 (0.3, 2.5)	67
Colon	0	1	0	1	21	71
Retinoblastoma	0	1	0	1	0.3	0.5†
Osteosarcoma	0	1	0	1	7	15†
Bladder	1	0	0	1	38	73
Dermatofibroma	0	1	0	1	20	56
Liver Tumors:						
Adenoma	7	8	0	15	11 (8-48)	NA
Carcinoma	18	10	0	28	14 (5-50)	65

*Data from 1,865 literature cases. 161 patients with leukemia; 11 also had a solid tumor. 181 solid tumors in 166 patients. Twenty-three had 2-4 solid tumors. A hyphen (-) indicates that the cancer type is not possible in males. Ages are in years. If the number of ages is fewer than the number of patients, some data missing. NA=not available. †Median ages for sporadic cancers in pediatric patients where available. Ages for sporadic cancers from SEER. (Alter, unpublished)

The relative risk of AML in FA patients compared to the general population is ~800-fold, and the median age in reported cases is 13 years, with a range from <1 to 50 years of age (Table 1).[3,4] The frequency of MDS is unknown, and the temporal relation between MDS and AML is not clear. However, FA should be considered in patients who are children or young adults and have either diagnosis.

Aplastic anemia is usually the first adverse event in patients with FA, occurring at a median age of around 8-10 years and reaching a plateau by the 20s. Leukemia develops primarily in teenagers and young adults, and solid tumors begin to appear in the 20s and do not level off.[5,6]

Solid Tumors

Patients with FA are at a particularly high risk (hundreds- to thousands-fold) of developing specific solid tumors at unusually young ages, including head, neck, esophageal, and gynecological squamous cell carcinomas, as well as liver tumors (Table 1).[3,4] The risk of head and neck squamous cell carcinomas is even higher in patients who have received a bone marrow transplant.[7] Approximately 25% of reported FA patients with the FA types of cancers were not aware that they had FA until they developed cancer (and sometimes complications from the treatment).[3] This highlights our concern that older FA patients may be significantly underdiagnosed.

Miscellaneous Conditions

Experts must test for FA if spontaneous chromosome breaks are found during studies for prenatal or postnatal evaluation of genetic conditions (see below). FA should be considered in patients with AML or solid tumors

with excessive sensitivity to chemotherapy or radiotherapy or who are atypically young and lack the usual risk factors for their cancers. Patients with androgen-responsive or ATG/cyclosporine A-non-responsive "acquired" aplastic anemia might have FA. FA should also be considered in individuals with macrocytic red cells and/or increased levels of fetal hemoglobin (Hb F) who do not have a hemoglobinopathy; in males (and perhaps females) with unexplained infertility; and in young patients with liver tumors without the usual viral or alcohol risk factors.

Table 2 outlines the hierarchy of indications for testing for FA, listing those in whom the FA work-up should definitely be done, as well as those in whom it should be highly considered. This table is not restrictive, but rather, is a guide.

Table 2: Indications for Testing for Fanconi Anemia*

Definite:

- Sibling with FA
- Aplastic anemia
- Characteristic birth defects, particularly one or more of abnormal radii and/or thumbs; renal structural anomalies; microophthalmia; microcephaly; *café au lait* spots; features of VACTERL-H such as tracheo-esophageal fistula, imperforate anus, and others (see earlier listing).
- Spontaneous chromosome breaks
- Primary MDS (at a young age)
- Primary AML (at a young age)
- Unusual sensitivity to chemo- or radiotherapy
- Cancer typical of FA at an atypical age, such as HNSCC <50 years old, cervical <30 years old,

anal/vulvar <40 years old (see Table 1)
- Family history consistent with FA or with cancer (e.g., breast cancer)

Consider:

- Single cytopenias
- Macrocytosis unexplained by B12 or folate deficiency
- Liver tumors without alcohol or hepatitis
- Premature ovarian failure <30 years old
- Diminished ovarian reserve <30 years old
- Brain tumor <5 years old
- Wilms tumor <4 years old
- Increased Hb F not otherwise explained
- Male (or female) infertility
- Liver adenomas or hepatomas without alcohol or hepatitis

*Note: Combinations of features are particularly strong indications for testing.

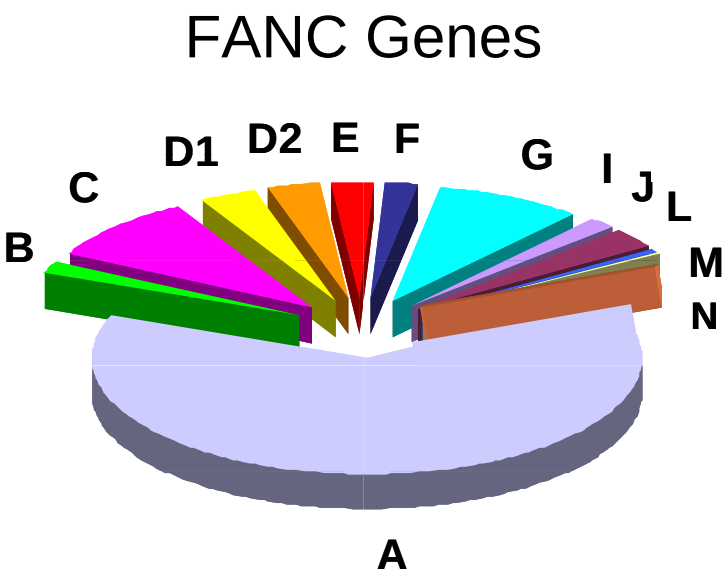


Figure 1: Relative frequency of the FA complementation groups (genes). Modified from Joenje, et al.[8]

FA Genes and DNA Damage Response Pathway

There are currently at least 13 known FA genes (Figure 1 and Table 3).[8]

Table 3: FA Genes and Gene Products

Gene	Locus	Genomic DNA kB	cDNA kB	No. of Exons	Protein kD	Amino Acids	Muta-tions	% of Patients	Genetics
FANCA	16q24.3	80	5.5	43	163	1455	~100	~70	AR
FANCB	Xp22.31	30	2.8	10	95	859	4	rare	XLR
FANCC	9q22.3	219	4.6	14	63	558	10	~10	AR
FANCD1 (BRCA2)	13q12.3	70	11.4	27	380	3418	-	rare	AR
FANCD2	3p25.3	75	5	44	162	1451	5	rare	AR
FANCE	6p21.3	15	2.5	10	60	536	3	rare	AR
FANCF	11p15	3	1.3	1	42	374	6	rare	AR
FANCG (*XRCC9*)	9p13	6	2.5	14	70	622	18	~10	AR
FANCI (KIAA1794)	15q25-26	73	4.5	38	150	1328	~12	rare	AR
FANCJ (BACH1/BRIP1)	17q22.3	180	4.5	20	150	1249	15	rare	AR
FANCL (PHF9/POG)	2p16.1	82	1.7	14	43	375	1	rare	AR
FANCM (Hef)	14q21.3	250	6.5	22	250	2014	1	rare	AR
FANCN (PALB2)	16p12.1	38	3.5	13	130	1186	15	rare	AR

The protein products of eight genes form a complex which permits ubiquitination of the FANCD2 protein, which in turn interacts with downstream FA gene products in the FA/BRCA DNA repair pathway (Figure 2). Three FA genes are associated with breast cancer in heterozygotes: *FANCD1/BRCA2*, *FANCJ/BRIP1*, and *FANCN/PALB2*.[9]

Laboratory Test Methods to Diagnose FA

Anyone who suspects FA should refer the patient to a hematologist and/or geneticist, who can arrange for an FA test to be performed by a clinically-certified laboratory with the appropriate expertise in FA testing. The specific test may vary by locale. The first test should

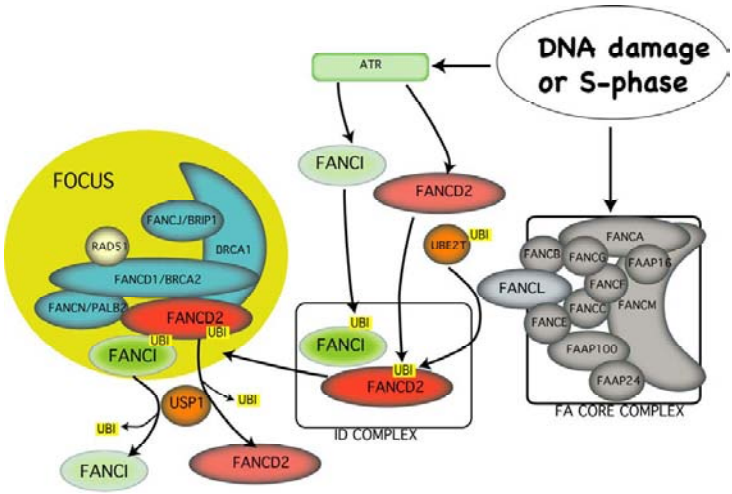


Figure 2: DNA damage response pathway, linking the FA and BRCA pathways. From Grompe and van de Vrugt.[9]

be used as a screening/diagnostic test. If it is positive, the physician should make the appropriate referrals. If it is negative and the level of suspicion of FA is low, no further studies are indicated. If it is negative but the suspicion level is high, then one or more of the next tier of tests should be done. If those are negative and the patient does appear to have an inherited bone marrow failure syndrome, then other disorders must be considered, such as dyskeratosis congenita, Shwachman-Diamond syndrome or Diamond-Blackfan anemia, and specific testing should be performed for each.[1,2,10]

Chromosome breaks in T-lymphocytes

The classical diagnostic test involves detection of chromosomal breakage or aberrations (breaks, gaps, rearrangements, radials, exchanges, endoreduplications) in peripheral blood cells after culture with a T-cell mitogen and a DNA clastogenic (cross-linking) agent, such as diepoxybutane (DEB) or mitomycin C (MMC). Data

are reported as aberrations per cell, as well as percent of cells with aberrations, usually for 20 to 100 cells. The test is most reliable if there is a low concentration of clastogen, which does not produce aberrations in normal controls, as well as a high concentration, which leads to a few abnormal control cells and thus indicates that the reagent is working. There are rare disorders, such as Nijmegen breakage or Roberts syndromes, in which chromosome breakage is positive with DEB or MMC and, yet, the patient does not have FA. If the blood result is normal but FA is still suspected, then a skin biopsy should be done to provide fibroblasts for chromosome breakage analysis in order to evaluate for somatic mosaicism.

The existence of mosaicism may complicate the FA diagnosis when chromosome breakage tests are used. The percent of cells with aberrations may be more useful than the breaks per cell, because patients with hematopoietic somatic mosaicism (the simultaneous presence of both normal and FA cells in the blood) may have only a few cells with breaks, and the average number of breaks per cell may fall into the normal range. Mosaicism is difficult to diagnose and even to define. Expert hematologists and cytogeneticists define it as a condition in which the peripheral blood lymphocyte breakage is "normal," while skin fibroblasts show clastogen-induced increased breakage. Approximately 10-20% of patients with FA have this result. However, the diagnostic percent of "normal" cells in the blood ranges from "a few," to 20, to 50, to 100%, depending on the laboratory. Low-level mosaicism may develop into high-level mosaicism, and this may be associated with "spontaneous" hematologic improvement. However, the mosaicism measured is in T-lymphocytes, which are long-lived and may not reflect myeloid hematopoiesis.

Final proof requires molecular demonstration of reverse mutation by molecular analyses from myeloid blood cells compared with fibroblasts.

Flow cytometry

Flow cytometry examines cell cycle kinetics and can detect the proportion of cells that are arrested at G2/M after culture with a clastogen such as nitrogen mustard. In contrast with the 100 cells examined microscopically for aberrations, flow cytometry examines thousands of cells and is less labor-intensive and subjective, but it does require sophisticated instrumentation. This test is usually done in a specialized laboratory and is not used nearly as widely as the chromosome breakage assay. Flow cytometry may give a false negative result in FA patients with MDS or AML; experience is limited.

Fibroblasts

Fibroblast cultures are useful for patients who might have hematopoietic somatic mosaicism, for patients following successful bone marrow transplant or for prenatal diagnosis (using chorionic villus cells or amniotic fluid cells). These cells can be used for chromosome breakage analyses or flow cytometry. FA cells often grow poorly, which might provide the first clue that the patient may have FA.

D2 Western blots

Following DNA damage, the complex of upstream FA gene products (A, B, C, E, F, G, I, L) leads to ubiquitination of the product of *FANCD2*, forming a longer protein (D2-L), which can be distinguished from the shorter non-ubiquitinated form (D2-S) on a Western blot with a D2-specific antibody.[11] This relatively inexpensive assay may be useful for screening patients for whom FA is in the differential diagnosis, such as those with radial ray anomalies, short stature, hypogonadism

or *café au lait* spots or for population-based FA incidence studies; however, it is usually only a research tool. FA patients whose gene defect is downstream of *FANCD2* will not be detected with a D2 Western blot.

Complementation analysis

Patient lymphocytes, EBV-lymphoblasts or fibroblasts can be cultured with retroviruses which introduce known normal FANC genes into the patient's cells, leading to correction of the FA cellular phenotype (chromosome breaks or poor growth in the presence of a clastogen). This test is limited to the availability of cloned DNA from known FA genotypes and is performed in a very limited number of primarily research laboratories.

Mutation testing

Determination of the specific mutation in FA genes is complicated and is done in laboratories with specific expertise. It requires sophisticated methods and involves DNA amplification, sequencing, and detection of large deletions. Many laboratories rely on knowing the complementation group before sequencing, while in some contexts targeted sequencing of candidate genes is more appropriate. One center goes directly to gene sequencing for patients in whom chromosome breakage testing indicates FA: *FANCA* by multiplex ligation-dependent probe amplification (MLPA) for large deletions and full sequencing; *FANCB* by MLPA and full sequencing, if indicated; *FANCC, E, F, G* by denaturing high performance liquid chromatography (DHPLC) and sequencing; *FANCD2* by Western blot; *FANCD2* sequencing if D2 bands are absent; *FANCL* and *FANCM* sequencing if only D2-S is seen; *FANCD1/BRCA2* sequencing, if indicated; *FANCJ/BRIP1* and *FANCN/PALB2* sequencing; and finally *NBS1* and

ESCO2 sequencing for Nijmegen breakage and Roberts syndromes.[12] Mutation testing is used to confirm known cases and for family studies to determine affected or carrier status. Genetic counseling should be included in these processes, because of the complicated explanations and support needed for the families.

Importance of Gene and Mutation Information

Current

The majority of patients worldwide are in the *FANCA* group, in which several hundred mutations have been documented. However, there are several populations in which there is a founder effect, leading to a limited number of specific mutations that can be targeted for genetic diagnoses. These include Ashkenazi Jewish *FANCC* IVS4+4 A>T or *FANCD1/BRCA2* 6174delT; non-Ashkenazi Jewish Moroccan *FANCA* 2172-2173insG or *FANCA* 4275delT; Tunisian *FANCA* 890-893del; Indian *FANCA* 2574C>G (S858R); Israeli Arabs *FANCA* del ex 6-31, *FANCA* IVS 42-2A>C, and *FANCG* IVS4+3A>G; Japanese *FANCC* IVS4+4 A>T; Afrikaner *FANCA* del ex 12-31 and *FANCA* del ex 11-17; Brazil *FANCA* 3788-3790del; Spanish Gypsy *FANCA* 295C>T; and Sub-Saharan African Black *FANCG* 637-643delTACCGCC. Patients from those specific groups can be tested initially for those mutations, and premarital and prenatal testing are possible.

In families in which the proband's mutation is known, mutation testing of family members permits accurate diagnosis of homozygotes and heterozygotes, leading to appropriate medical management and focused genetic counseling. Premarital screening, prenatal diagnosis, and preimplantation genetic diagnosis can be performed. Potential bone marrow transplant donors, such

as siblings who are phenotypically and hematologically "normal," can be accurately genotyped, so that undiagnosed homozygotes will not be used as donors. Patients genotyped as FA who are clinically well can be monitored closely for potential development of aplastic anemia, MDS, leukemia or solid tumors.

We are just beginning to learn about genotype/phenotype correlations. The most severe physical findings, including in some cases features of VACTERL-H syndrome (**V**ertebral anomalies, anal **A**tresia, **C**ardiac anomalies, **T**racheo-esophageal fistula, **E**sophageal atresia, **R**enal anomalies, radial **L**imb anomalies, plus **H**ydrocephalus), were reported more frequently in those with mutations in *FANCC* IVS4+4 A>T, *FANCD1/BRCA2*, *FANCD2*, *FANCG*, *FANCI*, and *FANCN/PALB2*. Early onset aplastic anemia was most common in some patients with *FANCA*, *FANCC* IVS4, *FANCG*, and *FANCI*. Leukemia particularly characterizes *FANCD1/BRCA2* and *FANCN/PALB2*, and the rates of specific solid tumors (medulloblastoma and Wilms tumor) were also extremely high in those with mutations in those two genes. In general, null mutations which produce no protein are more severe than hypomorphic mutations.[13]

Future

Future research is focused on determination of more specific genotype/phenotype outcome correlations, in order to better inform a patient or family with a specific mutation about the risks associated with that mutation. However, since FA gene mutations occur in a milieu of other genes and the environment, this will never be a perfect prediction. Gene-gene, gene-environment, and epigenetic modifiers will continue to challenge physicians and their patients.

References

1. Young NS, Alter BP. *Aplastic Anemia: Acquired and Inherited*. Philadelphia, PA: WB Saunders; 1994.

2. Alter BP. Inherited bone marrow failure syndromes. Nathan DG, Orkin SH, Look AT, Ginsburg D, eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 6th ed. Philadelphia, PA: WB Saunders; 2003: 280-365.

3. Alter BP. Cancer in Fanconi anemia, 1927-2001. *Cancer* 2003; **97**: 425-440.

4. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi anemia. *Blood* 2003; **101**: 822-826.

5. Rosenberg PS, Huang Z-G, Alter BP. Individualized risks of first adverse events in patients with Fanconi anemia. *Blood* 2004; **104**: 350-355.

6. Rosenberg PS, Alter BP, Ebell W. Cancer risks in Fanconi anemia: experience of the German Fanconi Anemia (GEFA) Registry. *Haematologica* 2007; **93**: 511-517.

7. Rosenberg PS, Socie G, Alter BP, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. *Blood* 2005; **105**: 67-73.

8. Joenje H, Oostra AB, Zwaan CM, Pals G. Fanconi anemia. *Hereditary Cancer Syndromes* 2006.

9. Grompe M, van de Vrugt HJ. The Fanconi family adds a fraternal twin. *Developmental Cell* 2007; **12**: 661-662.

10. Alter BP. Diagnosis, genetics, and management of inherited bone marrow failure syndromes. *Hematology: American Society of Hematology Education Program Book 2007*; **2007**: 29-39.

11. Shimamura A, de Oca RM, Svenson JL, et al. A novel diagnostic screen for defects in the Fanconi anemia pathway. *Blood* 2002; **100**: 4649-4654.

12. Ameziane N, Errami A, Leveille F, et al. Genetic subtyping of Fanconi anemia by comprehensive mutation screening. *Human Mutation* 2008; **29**: 159-166.

13. Faivre L, Guardiola P, Lewis C, et al. Association of complementation group and mutation type with clinical outcome in Fanconi anemia. *Blood* 2000; **96**: 4064-4070.

Chapter 3

Treatment of Hematologic Abnormalities in Fanconi Anemia

Akiko Shimamura, MD, PhD

Hematologic Abnormalities in FA

Patients with FA generally develop some degree of marrow dysfunction, ranging from mild asymptomatic cytopenias in any lineage to severe aplastic anemia, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The absence of marrow failure, however, does not rule out the diagnosis of FA. Most patients with FA will have macrocytosis (high MCV for age) in infancy or childhood.

The time of onset of bone marrow failure is highly variable, even among siblings. Approximately 3/4 of FA patients develop evidence of marrow failure ranging from mild to severe within the first decade of life.[1] Rarely, marrow failure from FA can present in infants and adults. Despite the potentially misleading nomenclature, patients with FA can develop neutropenia and thrombocytopenia as well as anemia. Indeed, thrombocytopenia is commonly the presenting cytopenia.

Cytopenias in FA patients warrant a thorough hematologic work-up to rule out additional treatable causes of cytopenias other than primary bone marrow failure, acquired or inherited. Red cell folate, B12 levels, and urine methylmalonic acid levels should be assessed to rule out nutritional causes of megaloblastic anemias. Absence of red cell macrocytosis may be a manifestation of concurrent iron deficiency or thalassemia trait.

Red cell antibody testing to assess for autoimmune hemolytic anemia should be considered where clinically indicated.

Marrow suppression secondary to infection should be considered. Effects of potentially myelosuppressive medications (e.g., antibiotics such as Bactrim or macrolides or H2-blockers such as cimetidine) should be evaluated.

Marrow cellularity is best evaluated by bone marrow biopsy. Marrow cellularity must be interpreted in the context of the peripheral blood counts, since marrow cellularity may be patchy and subject to sampling variation. Following trends in marrow cellularity and peripheral blood counts over time is helpful. Therapeutic intervention should not be based on marrow cellularity alone in the absence of clinically significant peripheral cytopenias or evidence of a myelodysplastic or malignant process.

Patients with FA are at high risk of developing MDS and AML.[2] Patients with the *FANCD1/BRCA2* or *FANCN* subtypes are at particularly high risk of developing AML or solid tumors at a very young age and warrant close clinical monitoring (see Chapter 2). Many different AML subtypes have been described in FA patients. Acute lymphocytic leukemia (ALL) is rare in FA patients.

The bone marrow cellular morphology often appears dysplastic in FA patients. Marrow dysplastic features, such as nuclear/cytoplasmic dysynchrony, hypolobulated megakaryocytes, and binucleated erythroid cells, are often seen in patients with FA and must be distinguished from MDS syndrome. Baseline marrow dysplasia is commonly associated with the pediatric

marrow failure syndromes and is not necessarily a harbinger of impending AML. The distinction between marrows with dysplastic but stable features versus MDS associated with imminent progression to acute leukemia is often challenging in patients with marrow failure syndromes. Marrow dysplasia warrants careful evaluation by a hematopathologist with expertise in these rare syndromes.

Significance of Clonal Abnormalities

In FA patients, the relationship between clonal cytogenetic abnormalities and progression to leukemia is not always clear in a marrow without accompanying morphologic evidence of MDS.

Many isolated cytogenetic clones of unclear clinical significance have been observed to come and go without apparent progression to leukemia in many FA patients and have persisted without adverse consequences for more than a dozen years in some cases.[3] Nonetheless, findings of cytogenetic abnormalities commonly associated with MDS (e.g., monosomy 7) warrant careful evaluation and referral to a transplant center experienced in the treatment of FA patients. The most common cytogenetic abnormalities observed to date in FA patients involve chromosomes 1, 3, 4 or 7 (John Wagner, MD, University of Minnesota, personal communication).

One center reported a striking association between chromosome 3q26q29 amplifications (partial trisomies and tetrasomies) and rapid progression to MDS or AML.[4] This cytogenetic abnormality was detectable in marrow cells and, with lower sensitivity, in peripheral blood cells in 18 out of 53 FA patients studied. In 8 of the 18 patients with 3q26q29 amplification,

monosomy 7 was also noted in the 3q clone. Thirteen of the 18 patients with 3q amplifications developed MDS or AML. Clinical testing for chromosome 3q abnormalities is available using fluorescent *in situ* hybridization (FISH) probes for this chromosomal region. All reported cases of chromosome 3 amplifications were detectable as extraneous chromosomal material by G-banding. However, the identity of the duplicated chromosomal material was not always apparent by G-banding alone and required confirmation by FISH, spectral karyotyping (SKY), or comparative genomic hybridization (CGH). Given the poor prognosis of the patients with 3q amplifications in this study, it is recommended that patients with a 3q cytogenetic clone undergo evaluation for a possible hematopoietic stem cell transplant with close monitoring of the peripheral blood counts and bone marrow. Whether all FA patients with a 3q cytogenetic clone are at high risk for progression to AML is currently unclear. Therapeutic decisions must be made on an individualized basis in consultation with a physician experienced in the care of FA patients.

Definition of Bone Marrow Failure

Bone marrow failure is clinically manifested by blood counts that are below age-appropriate norms due to decreased effective marrow hematopoiesis. While many patients progress to frank aplastic anemia, others may remain at mildly abnormal levels indefinitely. Clinical surveillance and therapeutic management are guided by the severity of the cytopenias, the stability of the blood counts, the presence of morphologic and cytogenetic marrow abnormalities, and potentially high-risk genotypes such as *FANCC* IVS 4; *FANCD1/BRCA2* or *FANCN* mutations.

Bone marrow failure was classified by the participants of the consensus conference into three broad categories, depending upon the degree of cytopenia(s) (Table 1). These definitions are more than semantic; they also define points at which different clinical management options should be considered.

Table 1: Severity of Bone Marrow Failure

	Mild	**Moderate**	**Severe**
ANC	<1,500/mm^3	<1,000/mm^3	<500/mm^3
Platelets	150,000-50,000/mm^3	<50,000/mm^3	<30,000/mm^3
Hb	≥8 g/dl*	<8 g/dl	<8 g/dl

*Less than norm for age but >8 g/dl

Importantly, to meet these criteria for marrow failure, the cytopenias must be persistent and not secondary to another treatable cause, such as infection, medications, peripheral blood cell destruction/loss or nutritional deficiencies.

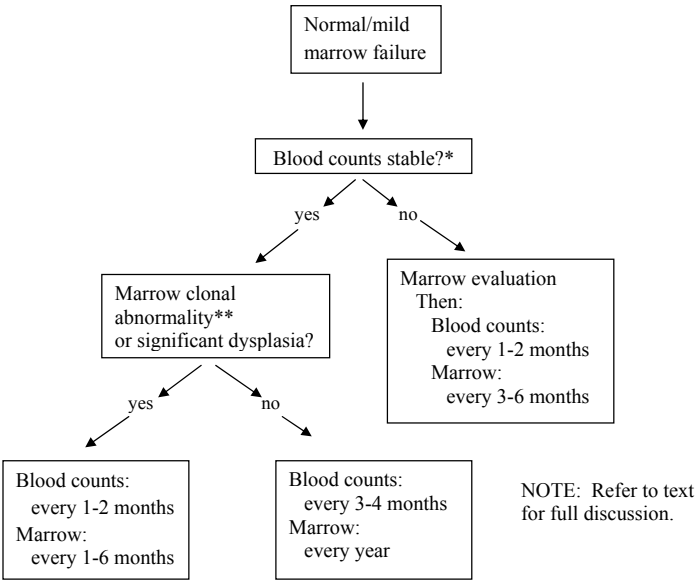
Clinical Monitoring of Bone Marrow Failure

Current guidelines for monitoring bone marrow failure are summarized below. These recommendations may be modified as new data become available, and patients are urged to consult with a hematologist with expertise in FA. Testing should be individualized as indicated.

At a minimum, bone marrow examination should consist of an aspirate to assess cytology and cytogenetics with G-banding and FISH (where available) for abnormalities associated with MDS. A bone marrow trephine biopsy provides valuable information regarding marrow architecture and cellularity. Periodic monitoring is important to assess the significance of a clonal

cytogenetic abnormality and the onset of MDS or frank leukemia and to identify the presence of cytogenetic abnormalities that may demand immediate intervention. Annual evaluation of the bone marrow allows for comparison of a patient's marrow to previous specimens from the same patient. The availability of serial marrow specimens facilitates assessment of the progression of that patient's marrow and allows for more informed decisions about the significance of a clonal abnormality. Recommendations for clinical monitoring are summarized below (Table 2):

Table 2: Clinical Monitoring of Bone Marrow Failure



*Persistent drop or rise in blood counts without apparent cause warrants bone marrow evaluation.
**Specific clonal abnormalities may warrant immediate treatment intervention or closer monitoring.

1. Blood counts stable in the normal to mild marrow failure range AND clonal cytogenetic abnormalities absent

For patients with normal blood counts and no cytogenetic clonal marrow abnormalities, the recommendation is a complete blood count with differential white blood cell count at least every 3-4 months and a bone marrow with cytogenetics at least yearly. A similar monitoring regimen is recommended for patients with mildly abnormal, but stable, blood counts without any associated clonal marrow abnormalities.

2. Blood counts stable in the normal to mild marrow failure range AND clonal cytogenetic abnormalities present

For patients with a cytogenetic clonal marrow abnormality (in the absence of morphologic MDS) together with normal or mildly low, but stable, blood counts, increased frequency of surveillance blood counts and bone marrow exams should be considered, as indicated by the patient's clinical status, to monitor for progression to MDS or leukemia. It would be reasonable to examine the blood counts every 1-2 months and the bone marrow every 1-6 months initially to determine if the blood counts are stable or progressively changing. If the blood counts are stable, then the frequency of bone marrow exams may be decreased. Appropriate plans for stem cell transplantation should be in place, as adverse changes may evolve rapidly.

3. Blood counts falling or rising

Patients with progressively changing blood counts without a clinically apparent underlying cause (e.g., transient response to an acute infection or suppression secondary to medication) require evaluation with

a complete blood count and bone marrow exam with cytogenetics. Such patients warrant continued close monitoring with complete blood counts every 1-2 months and a marrow exam with cytogenetics every 1-6 months. Appropriate plans for intervention should be in place, as adverse changes may evolve rapidly.

Treatment Options for Bone Marrow Failure

Available treatments for marrow failure in FA patients are described below. The risks and benefits of each treatment are discussed. A suggested treatment algorithm is presented under "Management Guidelines for Bone Marrow Failure."

Hematopoietic stem cell transplant

Hematopoietic stem cell transplant is the only current curative treatment for bone marrow failure, although it does not cure other non-hematopoietic complications of FA. FA patients, with their underlying defect in DNA repair, experience undue toxicity from the chemotherapy and radiation used in standard transplant conditioning regimens. Excellent results have been achieved using modified transplant regimens for matched sibling donor transplants. Currently available alternate donor regimens appear to have markedly improved results so far compared to past regimens, representing a new opportunity for patients. These regimens for alternate donor transplant will continue to evolve over the coming years and need to be discussed on an individualized basis with a physician experienced in transplants for FA patients.

Since the best transplant outcomes are associated with young patients who have not yet developed medical complications from their bone marrow failure, patients and families who opt to pursue transplantation are

generally encouraged to proceed early in the course of the disease. However, issues regarding timing of transplant are complicated by the up-front risk of transplant-related mortality and the unknown long-term side effects of transplant in FA patients. Since it is currently not possible to predict which patients will progress to severe marrow failure, transplantation prior to the development of significant marrow failure may unnecessarily subject a subset of patients to both early and late transplant-related morbidity and mortality. Potential long-term transplant-related risks such as increased risk of solid tumor development remain to be ascertained. For example, one study identified GvHD as a risk factor for oral squamous cell carcinoma in FA patients. An ongoing dialogue with an FA transplant specialist should be initiated early after the diagnosis of FA.

Androgens

Androgens have been widely used for the treatment of cytopenias in FA. The effects of androgens are most pronounced in the red cells and platelets, but neutrophil counts may also improve.[5,6] The mechanism(s) whereby androgens raise blood counts is currently unclear. The advantages of androgens include the low risk of therapy-related mortality and the long history of experience with their use; their side effects have been well documented. The major potential side effects associated with androgen therapy are listed in Table 3. About half of all patients treated will respond to androgen therapy, and a subset of those who initially respond may become refractory over time. An additional significant risk is that androgens do not prevent progression to AML that, once developed, creates a significantly higher transplant risk. For patients for whom hematopoietic stem cell transplant is indicated, delay in going to transplant may increase transplant-associated risks.

Table 3: Possible Side Effects of Androgens

- Virilization (including acne, facial hair growth/scalp hair loss, deepening of voice, pubic hair, enlargement of penis or clitoris)
- Growth spurt followed by premature closure of epiphyses and adult short stature
- Hyperactivity and behavioral changes
- Cholestatic jaundice or transaminitis
- Hepatic adenoma or hepatoma, hepatocellular carcinoma
- Peliosis hepatis
- Hypertension

The major effect of androgen therapy is to increase the hemoglobin, though it can also improve the platelet count. Androgen therapy should be considered when the patient's hemoglobin drops below 8 g/dl or the platelet count falls below 30,000/mm^3. Since there is no evidence that androgens can forestall bone marrow failure, treatment is initiated when cytopenias drop to clinically significant levels but before the marrow becomes completely devoid of hematopoietic stem cells for androgens to stimulate.

The standard recommended androgen is oxymetholone, with a starting dose of 2-5 mg/kg/day rounded to the nearest 1/4 tablet (50 mg tablets are available in the United States, while 10 mg tablets are available in many countries in Europe). If the patient responds to the initial dose with a stabilization of or increase in the hemoglobin level, the daily dose may be tapered in 1/2 tablet decrements after 3 months. Thereafter, a reasonable taper schedule might involve gradually decreasing the androgen dose at 2-4 month intervals.

If, in the absence of other causes of cytopenias (such as viral or bacterial infection), no response is seen after 3-4 months, oxymetholone should be discontinued, although there are anecdotal reports of patients responding after 6 or more months. Studies of the optimal initial dosing of oxymetholone are lacking. Improvements in hemoglobin are seen earlier than platelet responses to androgens. The family should be counseled about the possible side effects of androgen therapy and the child, especially teenagers, should be forewarned about them. Every effort should be made to minimize the side effects by tapering the dose whenever possible. Aggressive acne treatment with topical benzoyl peroxide and topical antibiotics (clindamycin or erythromycin) may make the treatment more tolerable. Androgens should not be withheld from female patients.

Since the masculinizing side effects of oxymetholone are particularly troublesome in girls and women, some female patients have been treated with a different androgen, danazol, which is hypothesized to produce fewer of these side effects. The comparative efficacy of danazol versus oxymetholone to treat marrow failure in FA patients is unknown. It has not been established whether, dose for dose, danazol is as effective and, at the same time, less masculinizing than oxymetholone. A clinical trial using another androgen, oxandrolone, in FA patients has been ongoing. Clinical trials comparing efficacy and side effects of different androgens are currently being developed.

The use of low dose (5-10 mg every other day) prednisone in an attempt to attenuate the premature epiphyseal closure by androgens has been advocated by some physicians. There are no data to support any sparing of androgen toxicity with the use of low dose prednisone. Furthermore, prednisone therapy carries a risk of

additional bone toxicities, such as avascular necrosis or osteoporosis.

Monitoring for liver tumors and liver function test (LFT) abnormalities should be performed regularly while a patient is taking androgens. Blood tests for LFTs are recommended every 3-6 months, and a liver ultrasound is recommended every 6-12 months. Unfortunately, transaminases do not always correlate with the degree of liver inflammation on liver biopsy. If liver transaminases increase to 3-5 times above normal, the androgen dose can be tapered until the blood tests improve. Androgen-associated liver adenomas can resolve after androgens are discontinued, but some may persist even years after androgens are stopped. If screening tests raise a concern for adenocarcinoma, a liver biopsy (generally performed as an open procedure to minimize bleeding risk) should be considered.

Cytokines

Studies have demonstrated that G-CSF[7] or GM-CSF[8] can improve the neutrophil counts in FA patients. Treatment with G-CSF or GM-CSF should be considered if the neutropenia is associated with recurrent or serious infections, particularly if the neutrophil counts persistently fall below 500/mm^3 or fail to rise in response to infection. A few patients have also shown improvements in hemoglobin or platelet counts while on G-CSF or GM-CSF therapy. No comparative trials of G-versus GM-CSF are available in FA patients.

G-CSF is typically started at a dose of 5 μg/kg/day. In one published study on G-CSF,[7] no FA patient required a higher dose to maintain an ANC >1,000/mm^3. Patients have been maintained on lower doses given less frequently (e.g., every other day or 2-3 times per week),

and the dose should be tapered to the lowest effective dose. The recommended starting dose of GM-CSF is 250 μg/m^2/day. Patient responses to doses as low as 5 μg/m^2/day have been seen. Treatment should generally be discontinued if the neutrophil count fails to improve after eight weeks of G-CSF or GM-CSF therapy. Recently, long-acting preparations of G-CSF have become available. These formulations offer the advantage of decreased injection frequency (a particularly appealing prospect for thrombocytopenic patients). However, there is no experience with their use in FA patients.

A bone marrow aspirate/biopsy with cytogenetics is recommended prior to the initiation of cytokine treatment, given the theoretical risk of stimulating growth of a leukemic clone. It is reasonable to monitor the bone marrow morphology and cytogenetics every six months while patients are treated with cytokines. There are currently no studies demonstrating a causal relationship between cytokine therapy and leukemogenesis. In the setting of a compelling clinical indication for cytokine therapy, there is no literature to mandate withholding cytokines from patients with clonal abnormalities. The use of hematopoietic cytokines in this situation should be pursued in consultation with experts in the care of FA patients.

Investigational protocols

For those patients who fail to respond to androgens or cytokines and have no acceptable transplant donor or pose an unacceptably high transplant risk, investigational protocols for new therapies may be considered (see Chapter 12).

Management Guidelines for Bone Marrow Failure

Since FA is a rare disease, prospective randomized trials comparing different treatment approaches are not available to guide therapeutic decisions. For this reason, the risks and benefits of available treatment options need to be discussed with hematologists experienced with FA. A suggested **treatment algorithm** is presented below.

At the time of diagnosis of Fanconi anemia:

- Refer to a hematologist with expertise in FA for medical monitoring and management.
- Patients with any degree of bone marrow failure should be referred to a transplant center with expertise in FA to initiate a discussion of available treatment options and to assess available potential transplant options. Early discussion with a transplant expert is recommended to allow families the option of initiating the procedure at an optimal time for the patient. If the patient has no hematologic abnormalities at the time of diagnosis, it is reasonable to defer referral to a transplant center. Early high resolution HLA typing of the patient and immediate family members is recommended to assess the availability of potential bone marrow donors.
- Some families wishing to have additional children may be interested in pursuing prenatal screening or preimplantation genetic diagnosis (PGD) (see Chapters 9, 10, and 15). Such families should be referred for appropriate medical counseling.

Normal blood counts or mild marrow failure:

- Monitor blood counts and bone marrow as described earlier under "Clinical Monitoring of Bone Marrow Failure" until further therapeutic intervention is warranted. Since transplant risk is lowest in young patients prior to the development of complications from marrow failure, a few physicians have proposed that transplants might be offered to young FA patients with normal blood counts prior to the potential development of marrow failure. This suggestion for "preemptive transplantation" is highly controversial since some patients who might never progress to significant marrow failure would be unnecessarily subjected to both early and late mortality risk and potential morbidity associated with transplant. Research is ongoing to elucidate risk factors that identify a subset of FA patients who might benefit from very early transplant. A careful discussion with a hematologist and transplant physician is warranted for families interested in this investigational approach.

Moderate marrow failure:

- For eligible candidates with an HLA-identical sibling, consider allogeneic stem cell transplant; otherwise, continue monitoring if the patient is asymptomatic.

- For patients lacking an HLA-identical sibling, consultation with a transplant center to plan for a possible future unrelated donor transplant (see "Severe marrow failure" below) is recommended. Management would include high-resolution HLA typing and a preliminary *World Book* search through the National Marrow

Donor Program for a free, preliminary screen of potential HLA-matched donors. Selection of a donor requires additional confirmatory testing as well as determination of donor availability. This stage accrues a substantial charge and is not undertaken until active plans for transplant are underway. Information regarding the number of potential donors available is helpful in estimating the time likely required to complete a full donor search if the marrow failure progresses.

- For patients who do not wish to proceed to transplant or who have risk factors conferring a high transplant risk, androgens are indicated if the Hb falls below 8g/dl.

Severe marrow failure:

- Consider unrelated donor hematopoietic stem cell transplant for eligible candidates.
- Consider androgens/cytokines for patients with risk factors conferring a high transplant risk or who do not wish to proceed to transplant.

Severe marrow failure unresponsive to androgens/ cytokines and high transplant risks:

- Consider investigational protocols.

MDS or AML: No standard effective therapy has been established for FA patients with MDS or AML. Treatment options include:

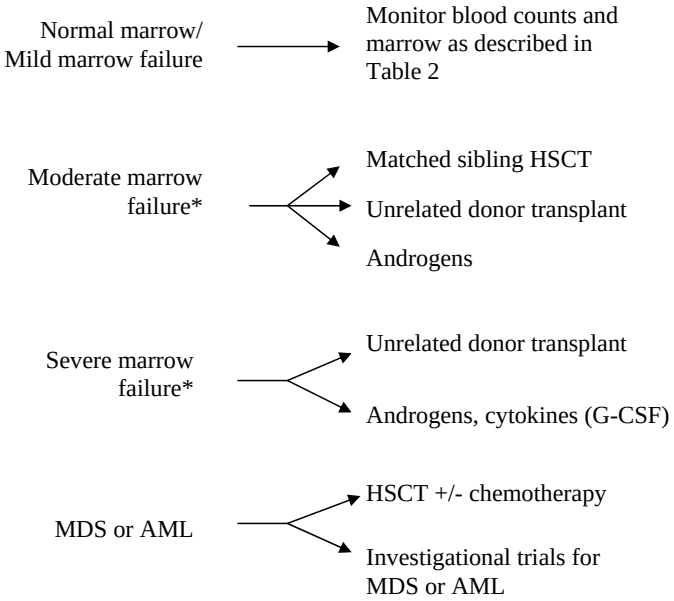
- Chemotherapy: This treatment should be undertaken by centers experienced with FA. Since myelosuppression by chemotherapy may be severe, prolonged or even irreversible in FA patients, back-up plans for potential stem cell rescue should be considered

- Hematopoietic stem cell transplant with or without prior induction chemotherapy.
- Phase I/II trials for MDS or AML.

Published reports of chemotherapy regimens for AML in FA patients are sparse and limited by the lack of longitudinal follow-up. It remains unclear whether pre-transplant chemotherapy improves or worsens outcomes.

These recommendations are summarized in Table 4.

Table 4: Marrow Failure Algorithm



*These represent nodal points at which discussion of the risks and benefits of the therapeutic options should be initiated. Refer to text for full discussion.

Supportive Care

Anemia

The onset of anemia in patients with FA is insidious. Close monitoring of the hemoglobin is necessary, as outlined above, so that treatment may be instituted before transfusion with packed red blood cells is required. Treatment for anemia should be considered when the patient's hemoglobin consistently falls below 8g/dl. The hemoglobin level at which treatment is started should be modified upward for patients who live at high altitude, where the normal range for hemoglobin levels is higher. When treatment is anticipated, it should be initiated under the care of a hematologist. As discussed above, treatment options for anemia consist of bone marrow transplant or androgens. Many FA patients will require red blood cell transfusions. The standard of care for patients with FA is to transfuse patients only when they are clearly symptomatic with tachypnea, tachycardia or a decreased activity level. *High transfusion burden may adversely affect transplant outcomes, so timely consideration of transplant is recommended.*

Some physicians advocate a more aggressive and regularly scheduled transfusion program to maintain as normal a quality of life as possible for patients with bone marrow failure. These physicians reason that the patient should maximize the benefit of transfusion therapy. Using the latter approach, a patient would be transfused to maintain a minimal trough hemoglobin of 7-8 g/dl. A post-transfusion hemoglobin level of 10-12 g/dl is generally sufficient to allow for normal activity, growth, and development in children. Clinical adequacy of the transfusion regimen must be continuously assessed. In the end, the program which best contributes to the patient's quality of life—infrequent visits to the doctor,

but a lower hematocrit trough, or more frequent visits to maintain a higher hemoglobin—is a decision to be made by the patient, the patient's family, and the treating hematologist.

All patients should receive red blood cells that have been leuko-depleted. The most widely used and effective method is to use a leuko-depletion filter. Irradiated blood products should be used to avoid transfusion-associated graft-versus-host disease. Some centers use only CMV-negative red blood cells, while others accept leuko-depletion as an alternative to CMV-negative products. Extended antigen matching may be important for patients in certain racial groups, where minor antigen mismatch is more commonly encountered. Directed donation is not encouraged, especially for family members. *The use of family members as directed donors may cause alloimmunization to an antigen that would increase the risk of graft rejection after sibling donor hematopoietic stem cell transplant.*

Secondary iron overload

Each mL of transfused packed red cells contains approximately 0.7 mg of iron. Since the human body lacks mechanisms to actively eliminate excess iron, patients who receive multiple red blood cell transfusions are at risk for accumulating toxic levels of iron overload. The liver is a primary site of iron accumulation, and hepatic fibrosis and cirrhosis may result. Iron deposition in the myocardium may cause dysrhythmias and cardiac failure. Cardiac decompensation may be sudden and acute despite regular monitoring with electrocardiograms and measurements of cardiac function. Recent data in the thalassemia population suggests that T2* MRI may be a better modality to follow cardiac function and cardiac siderosis in patients with

significant iron overload. Iron also targets endocrine organs such as the pituitary, pancreas, thyroid, and parathyroid (Table 5).

Table 5: Clinical Complications of Iron Overload

Liver disease with fibrosis and cirrhosis	
Cardiac failure, arrhythmias	
Hypopituitarism:	central hypogonadism
	growth hormone deficiency
	central hypothyroidism
Poor growth	
Diabetes mellitus	
Primary hypothyroidism	
Primary hypogonadism	
Hypoparathyroidism	

While ferritin levels are often followed as a convenient marker for total body iron load, their interpretation is complicated by additional factors such as acute or chronic inflammation and infection or hepatitis. In addition, ferritin fails to correlate with iron stores in some patients. Ferritin levels may be useful to monitor trends in total body iron over time. The gold standard for the measurement of total body iron has been a liver biopsy; however, hepatic iron distribution may be uneven, particularly with cirrhosis and, thus, liver biopsies may be limited by sampling error. Elevated liver iron >15mg/g dry weight is associated with a high risk of cardiac toxicity.[9] Liver iron levels between 7-15 mg/g dry weight are associated with an elevated risk of iron toxicity. Bleeding or infection as possible complications of the surgical biopsy procedure are of heightened concern in patients who are thrombocytopenic or neutropenic. Magnetic susceptometry using a

superconducting quantum interference device (SQUID) offers a non-invasive measurement of liver iron, but availability is limited (two centers in the US and two centers in Europe). Recently, MRI R2 and T2* imaging parameters of the liver and heart have been used to measure iron load.[10] Since the correlation between liver iron and cardiac toxicity is not perfect, the ability to measure directly cardiac iron together with the left ventricular ejection fraction has generated considerable clinical interest, and experience with this modality to measure cardiac iron is growing.

Guidelines for the institution of iron chelation therapy in bone marrow failure patients are based on those established for thalassemia patients, with the caveat that thalassemia patients who undergo accelerated, albeit ineffective, erythropoiesis, often have concomitant increases in iron absorption and are transfused to the point of suppressing endogenous hematopoiesis. Total red cell volumes transfused, particularly for infants and small children, as well as total body iron status as reflected in liver iron, cardiac iron, and ferritin levels must be carefully monitored. Iron overload may be prevented or treated with chelation therapy. The optimal time to initiate chelation therapy has not been clearly determined. As a general guide, chelation is considered when the total red cell volume transfused reaches 200mL/kg (roughly corresponds to a total of 12-18 red cell transfusions) or the liver iron reaches 7mg/g dry weight. Chronically transfused patients heading to a hematopoietic stem cell transplant may also benefit from total body iron measurements and chelation therapy to reduce iron levels. In situations where liver iron measurements are not clinically available, a serum ferritin persistently greater than 1,500 without other apparent etiologies has been used as a surrogate, albeit imperfect (see prior discussion), marker.

Chelation must be titrated to reduce or prevent iron accumulation while avoiding excessive dosing of chelator relative to total body iron levels. The risk of side effects increases as the dose of chelator exceeds body iron stores. The goal liver iron level is typically between 3-7 mg iron/g dry weight. Two chelators are currently clinically available in the U.S.: deferoxamine (Desferal) and deferasirox (ICL670 or Exjade). Deferiprone (L1) is not licensed for clinical use in the U.S. Features of each chelator are summarized in Table 6.

Table 6: Iron Chelation Therapies

Drug	Route	Toxicities	Advantages	Disadvantages	Monitoring
Deferasirox (ICL670, Exjade)	PO	GI Rash Renal Transaminitis Neutropenia	Convenience (PO) Low toxicity to date	Relatively new Limited long-term experience	Creatinine (monthly) Creatinine clearance ALT monthly Liver iron annually Cardiac iron and cardiac function annually (after age 10)
Deferoxamine (Desferal)	SQ, IV	Skin irritation Hearing impairment Decreased vision Skeletal abnormalities Infection risk (Yersinia)	Well-defined toxicity profile Efficacy Treatment of cardiac iron overload	Inconvenience Poor compliance Infection and bleeding risks with SQ infusions if neutropenic or thrombocytopenic	Annual auditory and visual testing Liver iron annually Cardiac iron and cardiac function annually (after age 10)
Deferiprone (L1)	PO	Neutropenia Arthritis Hepatic fibrosis	Convenience (PO) May enhance cardiac iron chelation	Possible lower efficacy Toxicity profile Not approved in U.S.	Regular CBC with differential ALT (monthly) Liver iron annually Cardiac iron and cardiac function annually (after age 10)

Experience with deferoxamine therapy is extensive and its efficacy in treating iron overload is well established. Although generally effective, its use is complicated by the need for parenteral infusion (subcutaneously or intravenously). Furthermore, deferoxamine must be administered over prolonged periods of time since only a small proportion of total body iron is available for chelation at any given moment and the half-life of deferoxamine is short. Subcutaneous infusions pose risks of bleeding or infection in patients with thrombocytopenia or neutropenia. Side effects of deferoxamine include loss of hearing or vision, particularly when desferoxamine doses are high relative to iron stores. Immediate cessation of deferoxamine and medical evaluation is warranted if such symptoms arise. Deferoxamine therapy is associated with an increased risk of *Yersinia enterocolitica* infection, and the drug should be stopped for unexplained fevers pending the results of blood cultures and infection work-up. Side effects and monitoring guidelines are summarized in Table 6.

Given the disadvantages of a parenterally administered drug, deferasirox offers an attractive alternative for iron chelation. Deferasirox is conveniently administered orally once a day as a slurry on an empty stomach. Clinical experience with deferasirox is limited, but short- and long-term side effects reported to date are generally mild. Renal toxicity, gastrointestinal symptoms, skin rash, and elevated ALT have been reported. Optimal dosing of deferasirox is still under investigation. Patients who continue to have unacceptable iron levels on deferasirox despite dose escalation may benefit from switching back to deferoxamine until goal iron levels have been achieved.

Deferiprone (L1) is currently not licensed for clinical use in the U.S. Studies suggest that deferiprone may be more efficient than deferoxamine at removing cardiac iron. Its utility is limited by its side effects, which include agranulocytosis, arthritis, and hepatic fibrosis.

For patients with severe iron overload or with cardiac functional compromise (arrhythmias or failing left ventricular function), continuous high dose (e.g., 50 mg/kg/day) intravenous deferoxamine infusion has been shown to reduce dysrhythmias and to improve left ventricular function.[11]

There is no demonstrated role for the use of erythropoietin to treat anemia in FA patients in the absence of erythropoietin deficiency (e.g., in association with renal failure).

Thrombocytopenia

Bone marrow transplant should be considered when the platelet counts fall below 50,000/mm^3. If transplant is not pursued, then thrombocytopenia should be treated with androgens as the platelet count declines to 30,000/mm^3. As noted above, a longer trial of oxymetholone, up to six months, is required before treatment is discontinued for lack of a platelet response.

Platelet transfusion is indicated in patients with severe bruising, bleeding or undergoing invasive procedures. The strict use of a numeric trigger for transfusion is probably not necessary. Single donor apheresis platelets should be provided in an effort to decrease the risk of alloimmunization and to decrease the risk of infection from exposure to multiple donors. Studies of the use of leukocyte depletion filters to decrease the risk of infection with CMV and alloimmunization may result in the return to the use of random donor platelets in the future.

Transfused platelets should be leuko-depleted and irradiated.

Amicar (epsilon aminocaproic acid) may be used as an adjunct to platelet transfusion in the patient with mucosal bleeding. The drug is given at a dose of 50-100 mg/kg every six hours, with a maximum dose of around 12 grams/day. A loading dose of 200 mg/kg may be considered. Amicar is usually administered for several days until the clot is stabilized. Amicar is generally contraindicated in patients with hematuria.

Additional factors that increase bleeding risk should be minimized. Drugs that inhibit platelet function, such as aspirin or non-steroidal anti-inflammatory drugs (e.g., ibuprofen), should be avoided. A soft toothbrush should be used. Stool softeners should be administered if constipation poses a risk of GI mucosal trauma. Activities carrying a high risk of significant trauma (particularly to the head or trunk) should be avoided.

Neutropenia

Patients with mild neutropenia are often asymptomatic. Treatment with G-CSF or GM-CSF as described earlier may be considered if the patient is having neutropenia-related infectious complications with neutrophil counts <1,000/mm^3. G-CSF may also be considered for patients with a history of recurrent or severe infections. Patients with fever and neutropenia should have a thorough examination and cultures, and should receive broad spectrum antibiotics until the cultures are found to be negative and the fever resolves. Precautions to minimize the risk of infections from endogenous bacterial flora should be instituted according to local guidelines. There is no demonstrated role for the general use of prophylactic antibiotics in FA patients, and

such practices may lead to increased risks of fungal infections and antibiotic resistance.

Sedation and analgesia for invasive procedures
Given the need for frequent evaluation of the bone marrow, adequate sedation and analgesia should be offered to every patient undergoing bone marrow aspiration and biopsy. The use of local anesthetic alone may not be sufficient to alleviate the anxiety and pain that is associated with frequent, repeated bone marrow aspirations. The use of intravenous propofol, fentanyl and midazolam, or similar regimens used in accordance with the guidelines established by the American Academy of Pediatrics, is strongly recommended. Such regimens may make it easier for families and patients to accept a yearly bone marrow examination as a routine part of the care for FA.

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References

1. Butturini A, Gale RP, Verlander PC, Adler-Brecher B, Gillio A, Auerbach AD. Hematologic abnormalities in Fanconi anemia: an International Fanconi Anemia Registry study. *Blood* 1994; **84**: 1650-1655.

2. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi anemia. *Blood* 2003; **101**: 822-826.

3. Alter BP, Caruso JP, Drachtman RA, Uchida R, Velagaleti GVN, Elghetany MT. Fanconi anemia: myelodysplasia as a predictor of outcome. *Cancer Genetics and Cytogenetics* 2000; **117**: 125-131.

4. Tonnies H, Huber S, Kuhl JS, Gerlach A, Ebell W, Neitzel H. Clonal chromosomal aberrations in bone marrow cells of Fanconi anemia patients: gains of the chromosomal segment 3q26q29 as an adverse risk factor. *Blood* 2003; **101**: 3872-3874.

5. Shahidi N, Diamond L. Testosterone-induced remission in aplastic anemia of both acquired and congenital types. Further observations in 24 cases. *New England Journal of Medicine* 1961; **264**: 953.

6. Diamond LK, Shahidi NT. Treatment of aplastic anemia in children. *Seminars in Hematology* 1967; **4**: 278-288.

7. Rackoff WR, Orazi A, Robinson CA, et al. Prolonged administration of granulocyte colony-stimulating factor (filgrastim) to patients with Fanconi anemia: a pilot study. *Blood* 1996; **88**: 1588-1593.

8. Guinan EC, Lopez KD, Huhn RD, Felser JM, Nathan DG. Evaluation of granulocyte-macrophage colony-stimulating factor for treatment of pancytopenia in children with Fanconi anemia. *Journal of Pediatrics* 1994; **124**: 144.

9. Brittenham GM, Griffith PM, Nienhuis AW, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. *New England Journal of Medicine* 1994; **331**: 567-573.

10. Wood JC. Magnetic resonance imaging measurement of iron overload. *Current Opinion in Hematology* 2007; **14**: 183-190.

11. Davis BA, Porter JB. Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk beta-thalassemia. *Blood* 2000; **95**: 1229-1236.

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, anal **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 anastamotic 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 nonspecific 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 review[12]), 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

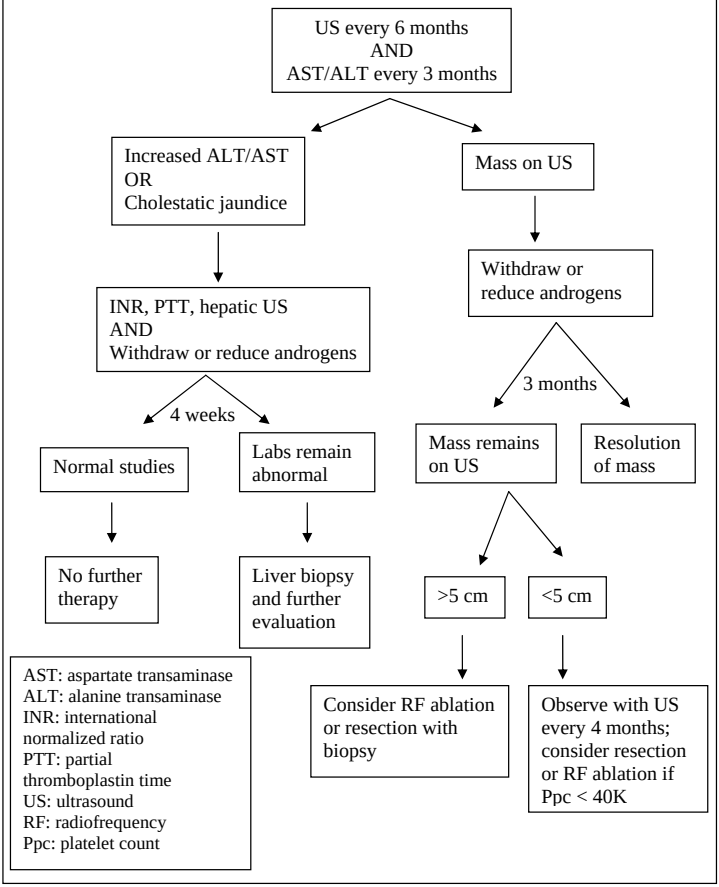
Liver disease in FA is generally a complication of treatment. As a general rule, referral to a pediatric gastroenterologist with expertise in hepatic disease is indicated. The following is an overview of the most common problems seen. Note that evaluation and management of iron overload is discussed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

References

1. Alter BP. Inherited bone marrow failure syndromes. Nathan DG, Orkin SH, Ginsburg D, Look AT, eds. *Hematology of Infancy and Childhood*. 6th ed. Philadelphia, PA: Harcourt Health Sciences; 2003.

2. Kovesi T, Rubin S. Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. *Chest* 2004; **126**(3): 915-925.

3. Escobar MA, Ladd AP, Grosfeld J, et al. Duodenal atresia and stenosis: long-term follow-up over 30 years. *Journal of Pediatric Surgery* 2004; **39**(6): 867-71.

4. Pena A, Hong A. Advances in the management of anorectal malformations. *American Journal of Surgery* 2000; **180**(5): 370-376.

5. Levitt MA, Pena A. Outcomes from the correction of anorectal malformations. *Current Opinion in Pediatrics* 2005; **17**(3): 394-401.

6. Wajnrajch MP, Gertner JM, Huma Z, et al. Evaluation of growth and hormonal status in patients referred to the International Fanconi Anemia Registry. *Pediatrics* 2001; **107**(4): 744-754.

7. Mattox TW. Treatment of unintentional weight loss in patients with cancer. *Nutrition in Clinical Practice* 2005; **20**(4): 400-410.

8. Nasr SZ, Drury D. Appetite stimulants use in cystic fibrosis. *Pediatric Pulmonology* 2008; **43**(3): 209-219.

9. Pascual Lopez A, Roque i Figuls M, Urrutia Cuchi G, et al. Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. *Journal of Pain and Symptom Management* 2004; **27**(4): 360-369.

10. Kardinal CG, Loprinzi CL, Schaid DJ, et al. A controlled trial of cyproheptadine in cancer patients with anorexia and/or cachexia. *Cancer* 1990; **65**(12): 2657-2662.

11. Giri N, Batista DL, Alter BP, Stratakis CA. Endocrine abnormalities in patients with Fanconi anemia. *Journal of Clinical Endocrinology and Metabolism* 2007; **92**(7): 2624-2631.

12. Dietz WH, Robinson TN. Clinical practice. Overweight children and adolescents. *New England Journal of Medicine* 2005; **352**(20): 2100-2109.

13. Soe KL, Soe M, Gluud C. Liver pathology associated with the use of anabolic-androgenic steroids. *Liver* 1992; **12**(2): 73-79.

14. Westaby D, Portmann B, Williams R. Androgen related primary hepatic tumors in non-Fanconi patients. *Cancer* 1983; **51**(10): 1947-1952.

15. Touraine RL, Bertrand Y, Foray P, Gilly J, Philippe N. Hepatic tumours during androgen therapy in Fanconi anaemia. *European Journal of Pediatrics* 1993; **152**(8): 691-693.

16. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. *American Journal of Hematology* 2004; **77**(3): 257-267.

17. Guardiola P, Socie G, Li X, et al. Acute graft-versus-host disease in patients with Fanconi anemia or acquired aplastic anemia undergoing bone marrow transplantation from HLA-identical sibling donors: risk factors and influence on outcome. *Blood* 2004; **103**(1): 73-77.

18. Gluckman E, Wagner JE. Hematopoietic stem cell transplantation in childhood inherited bone marrow failure syndrome. *Bone Marrow Transplantation* 2008; **41**: 127-132.

19. McDonald GB. Review article: management of hepatic disease following haematopoietic cell transplant. *Alimentary Pharmacology and Therapeutics* 2006; **24**(3): 441-452.

20. Pagano G, Korkina LG. Prospects for nutritional interventions in the clinical management of Fanconi anemia. *Cancer Causes and Control* 2000; **11**(10): 881-889.

Chapter 5

Hand and Arm Differences in FA

Scott H. Kozin, MD

Introduction

Children with Fanconi anemia often have upper extremity anomalies (a.k.a. differences). Approximately 50% of FA children have skeletal anomalies, and about 70% of these are upper extremity anomalies. The most common problems affect the thumb and radial border of the forearm. This section will describe the upper extremity problems in children with FA, including diagnosis, management, and outcome. The specific treatment rendered must be individualized to each child and family. The decision process is multi-factorial and requires participation from the family, physician, and physical therapist.

Initial Evaluation

Early referral (within the first few months) to an upper extremity specialist is recommended for children with congenital limb differences. The evaluating physician should be comfortable with and proficient in the diagnosis and management of congenital limb differences. These qualities especially are important for FA children who require coordinated care among multiple specialists. Many physicians who care for adult limb problems are not comfortable treating children. Referral to an orthopedic hand surgeon specializing in pediatrics, with a *Certificate of Added Qualification in Hand Surgery*, is recommended.

The early referral and assessment establish a doctor-patient relationship with the child and family. In addition, the evaluation and discussion answer many of the questions that parents may have about limb differences in respect to cause, treatment, and expectations. Parents often seek information via the internet, which can be a compendium of misinformation. Furthermore, many children with upper extremity limb problems require early therapy, which can be instituted after the initial assessment.

Limb evaluation often occurs prior to the diagnosis of FA. The precise indication for a chromosomal breakage test or other diagnostic test for FA in children with limb anomalies is still evolving. Testing every child with isolated thumb or hand abnormalities should be considered. We recommend a chromosomal breakage test on all children with deficiencies of the thumb and radial border of the forearm. Additional findings, such as abnormal skin pigmentation (*café au lait spots*), growth retardation, and microcephaly, add to the suspicion of FA.

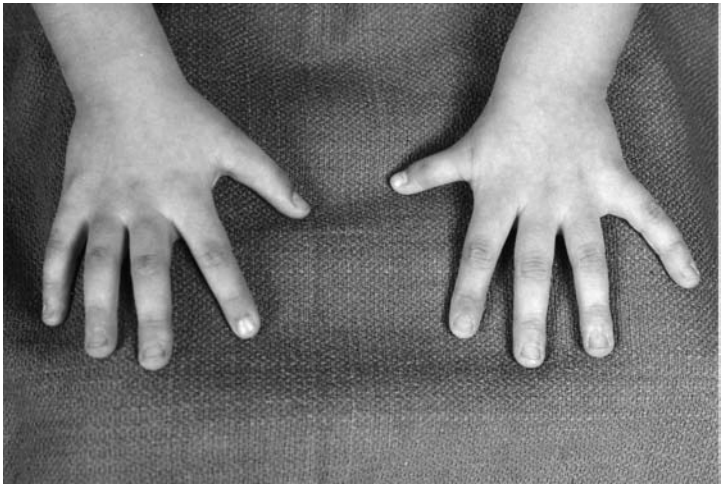
Table 1: Classification of Thumb Hypoplasia

Type	Findings	Treatment
I	Minor generalized hypoplasia	Augmentation
II	A. Absence of intrinsic thenar muscles B. First web space narrowing C. Ulnar collateral ligament (UCL) insufficiency	A. Opponensplasty B. First-web release. C. UCL reconstruction
III	Similar findings as Type II plus extrinsic muscle and tendon abnormalities Skeletal deficiency A. Stable carpometacarpal joint B. Unstable carpometacarpal joint	A. Reconstruction B. Pollicization
IV	*Pouce flottant* or floating thumb	Pollicization
V	Absence	Pollicization

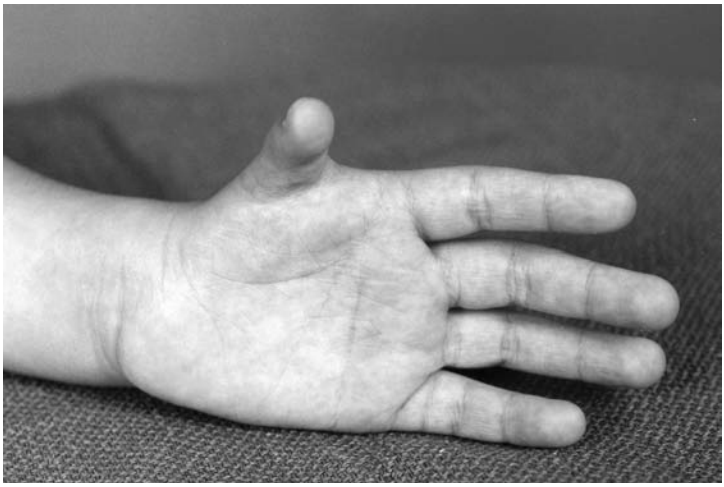
Adapted from James et al.

Anomalies (Differences)

The most common abnormalities in FA children affect the thumb and may or may not include the radial border of the forearm. The thumb may be smaller (hypoplasia) or absent. Similarly, the radius may be shortened (hypoplasia or deficiency) or absent.



Figures 1A and 1B: Six-year-old child with left thumb hypoplasia. A Type II deficiency is apparent with thumb-index web space narrowing and absence of the thenar muscles.



Thumb

Underdeveloped thumbs display a spectrum of deficiency and have been classified into five types. These types guide treatment recommendations (Table 1).

The degree of hypoplasia and absence is variable and not consistent among FA children. This creates multiple treatment algorithms that vary with the extent of involvement.

A Type 1 deficiency represents mild thumb hypoplasia without discrete absence of structures. This mild deficiency may go unrecognized. A Type II deficiency is more involved and characterized by thumb-index web space narrowing, thenar muscle absence, and instability of the metacarpophalangeal joint (Figures 1A and B).

Type III hypoplasia possesses similar anomalies associated with a Type II deformity, plus additional skeletal and musculotendinous abnormalities. Type III anomalies are divided into III-A and III-B, dependent upon the presence or absence of a stable carpometacarpal joint. Type IV deficiency represents a severe expression of thumb hypoplasia and denotes a *pouce flottant* (floating thumb) or residual digit (Figure 2).

Type V is noted by complete absence of the thumb (Figure 3).

Hypoplastic, floating, and absent thumbs
The main distinction between a thumb that can be reconstructed and a thumb that requires ablation (i.e., removal) is the presence or absence of a carpometacarpal joint. An unstable carpometacarpal joint negates the possibility of thumb reconstruction and is best treated by ablation and pollicization. The clinical differentiation between Types III-A and III-B can be difficult. The

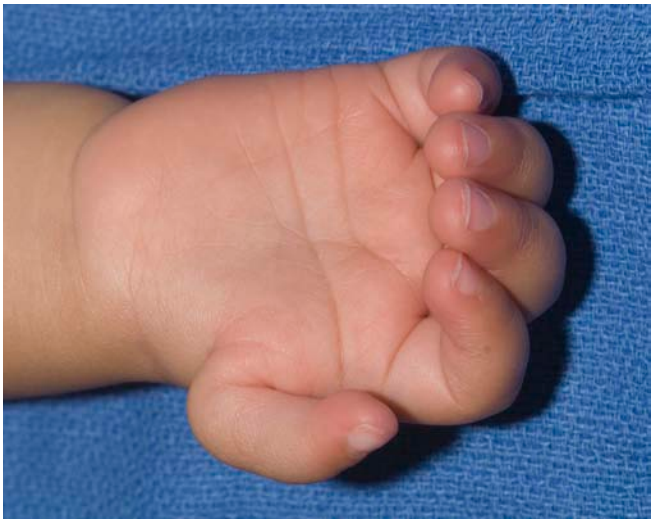


Figure 2: One-year-old with a right Type IV thumb deficiency attached to the radial side of the hand, also known as a pouce flouttant *(floating thumb). (Courtesy of Shriners Hospital for Children, Philadelphia)*

Figure 3: Six-year-old with complete absence or Type V deficiency of his right thumb. (Courtesy of Shriners Hospital for Children, Philadelphia)

child often helps discriminate between these types by pattern of usage. An unstable thumb (Type III-B) is not incorporated into pinch and grasp. Prehension or pinch develops between the index and long digits, and the index finger tends to rotate out of the palm to resemble a thumb position. In equivocal cases, the decision is further complicated by the delayed ossification of the bones at the base of the thumb (trapezium and trapezoid), which do not ossify until four to six years of age. The decision to ablate a hypoplastic thumb without a base is often a difficult process for parents and caregivers. Discussions with the surgeon and conversations with families who have made similar decisions are often helpful.

A thumb that is slightly smaller than the normal thumb (Types I, II, and III-A) can be reconstructed, or augmented, by tendon transfers to improve its motion and use. Thumb reconstruction in Types II and III-A requires addressing all deficient elements. The tight web space is corrected by opening the space between the thumb and index finger. The metacarpophalangeal joint instability is corrected by ulnar collateral ligament reconstruction. The deficient thenar muscles are supplanted by a tendon and/or muscle transfer from the ring or small finger to the thumb (Figure 4). This tendon transfer improves active motion and enhances function. There is negligible effect on the donor digit.

A thumb without a stable base (Types III-B, IV, and V) is removed, and the index finger moved to the thumb position. The index is moved with its nerves, arteries, tendons, and muscles. This procedure is known as a pollicization. The time to perform pollicization remains controversial, with a trend toward early surgery (6 months to 1 year of age), prior to the normal

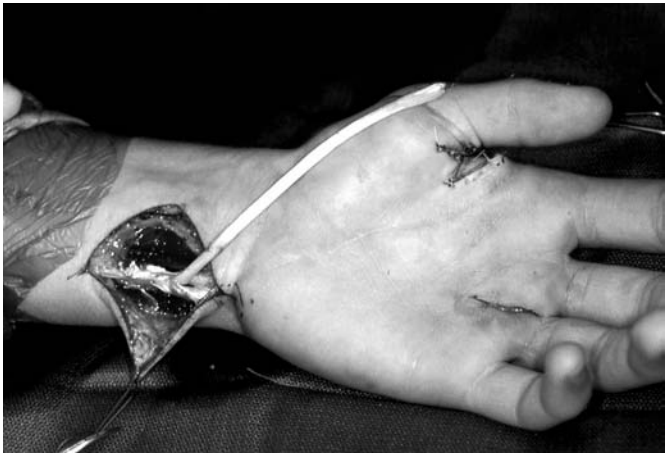


Figure 4: A tendon transfer from the ring finger to the hypoplastic thumb to augment motion and compensate for the lack of thenar muscles.

development of oppositional or fine pinch (usually about 15 months of age). This early intervention takes advantage of the growing brain and its plasticity to adjust to the new thumb. In addition, early surgery avoids the development of compensatory side-to-side pinch pattern between adjacent fingers. Currently, the procedure is performed somewhere between 6 months and 2 years of age, dependent upon the health status of the child, degree of forearm deficiency, and surgeon preference.

A concomitant forearm deformity usually takes precedence for treatment, which delays index finger pollicization. Pollicization requires meticulous surgical technique because the index finger must be shortened, rotated, and reconstructed with the surrounding muscles to give the appearance and function of a thumb (Figure 5). The surgeon should be familiar and experienced with this procedure.

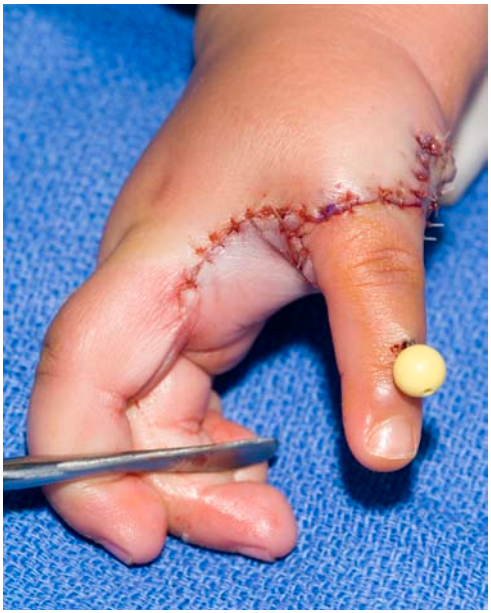


Figure 5: Pollicization requires meticulous surgical technique to give the appearance and function of a thumb. (Courtesy of Shriners Hospital for Children, Philadelphia)

The results after pollicization are directly related to the status of the index finger prior to surgery. A stiff index finger will provide a stable thumb for gross grasp, but fine pinch is unlikely. In contrast, a mobile index finger transferred to the thumb position can provide stability for grasp and mobility for fine pinch (Figure 6). Early good results after pollicization have been shown to persist into adulthood.

Other thumb anomalies

Although hypoplasia is the most common thumb anomaly in FA children, other abnormalities have been reported. The thumb can possess an extra bone (a.k.a. triphalangeal thumb) or can be duplicated. The exact prevalence of these anomalies is unknown.

Figure 6: Three-year-old child following right index finger pollicization with satisfactory appearance and function including grasping large and small objects. (Courtesy of Shriners Hospital for Children, Philadelphia)

Triphalangeal thumb

A triphalangeal thumb has an extra phalanx of variable size and shape. A small extra phalanx that is normally shaped can be treated without surgery (Figure 7).

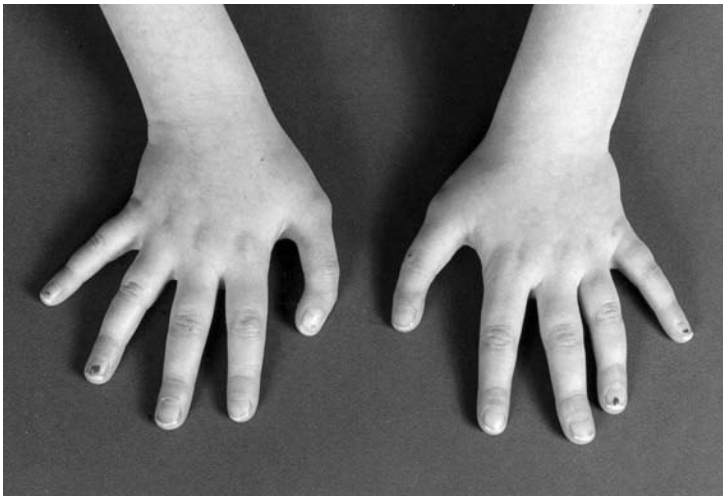


Figure 7: Nine-year-old child with bilateral triphalangeal thumbs that are slightly angulated and longer than a normal thumb.

The thumb must be monitored for alignment and length until skeletal maturity. A wedge-shaped extra phalanx causes deviation of the thumb, and treatment is recommended. A small bone is excised and the adjacent ligaments are reconstructed. A large and wedge-shaped extra phalanx produces deviation and excessive length. Simple excision of the phalanx is not recommended as post-operative instability is common. Fusion of the abnormal phalanx with an adjacent phalanx along with removal of a wedge of bone is a better option. This procedure eliminates the extra joint, shortens the digit, and realigns the thumb.

Thumb duplication

Duplication of the thumb (pre-axial polydactyly) can be partial or complete and has been classified into various types depending on the degree of skeletal replication (Figure 8 and Table 2). In this classification, the extent of duplication is defined by whether the components are attached proximally (bifid) or completely separated (duplicated).

Figure 8: One-year-old child with a duplicated right thumb prior to surgical correction. (Courtesy of Shriners Hospital for Children, Philadelphia)

Thumb duplication involves more than the bony elements, since the parts may share common nails, tendons, ligaments, joints, and neurovascular structures. Treatment requires using portions of each component to construct a properly aligned and functional thumb. This decision is not always straightforward and requires careful examination. The soft tissues from the ablated thumb are used to augment the retained thumb, including the collateral ligament and muscles. Articular surface modification via osteotomy or joint recontouring and tendon realignment are necessary to optimize thumb function. Irrespective of treatment, the reconstructed thumb will be smaller than a normal thumb and usually will lack some motion.

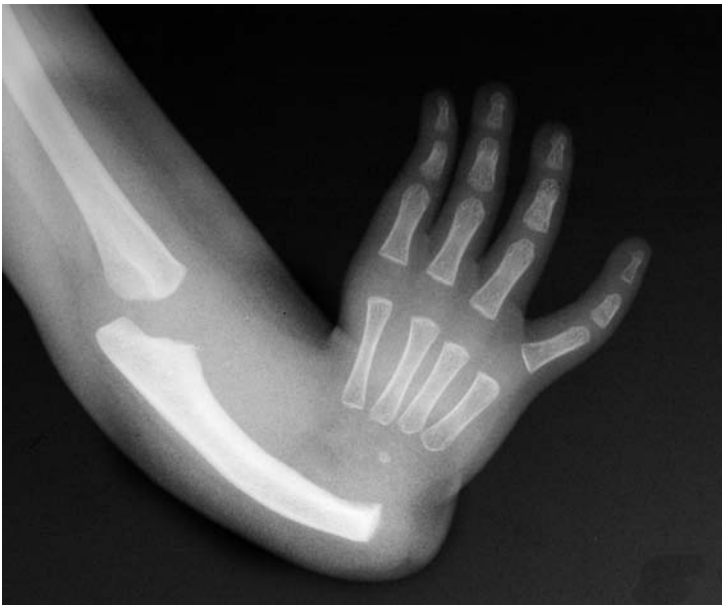
Table 2: Classification of Duplicated Thumbs

Type	**Duplicated Elements**
I	Bifid distal phalanx
II	Duplicated distal phalanx
III	Bifid proximal phalanx
IV	Duplicated proximal phalanx*
V	Bifid metacarpal phalanx
VI	Duplicated metacarpal phalanx
VII	Triphalangeal component

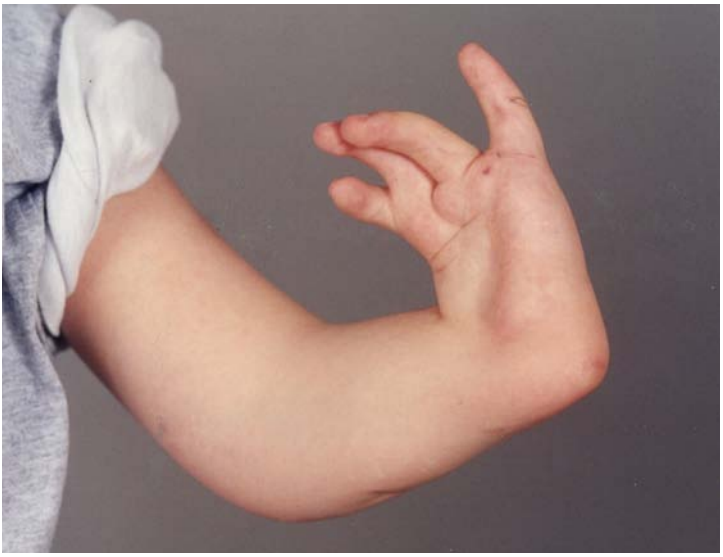
***** Most common type
Adapted from Wassel et al.

Radial Deficiency

The radius can be slightly smaller, considerably smaller, or absent. The severity of radial deficiency is graded from I through IV, and based on x-ray interpretation (Table 3). Ossification of the radius is delayed in radial deficiency, and the differentiation between total and partial absence (Types III and IV) cannot be established until approximately three years of age. Complete



Figures 9A and 9B: X-ray and clinical picture of an eight-year-old child with complete absence of the left radius and a perpendicular alignment between the hand and forearm. (Courtesy of Shriners Hospital for Children, Philadelphia)



absence of the radius (Type IV) is the most common variant, and the hand develops a perpendicular relationship with the forearm (Figure 9A and B). In FA children, complete absence of the radius typically occurs in conjunction with thumb absence.

Table 3: Classification of Radial Deficiency

Type	X-ray findings	Clinical Features
I Short radius	Distal radial epiphysis delayed in appearance. Normal proximal radial epiphysis. Mild shortening of radius without ulna bowing.	Minor radial deviation of the hand. Thumb hypoplasia is the prominent clinical feature requiring treatment.
II Hypoplastic	Distal and proximal epiphysis present. Abnormal growth in both epiphyses. Ulna thickened, shortened, and bowed.	Miniature radius. Moderate radial deviation of the hand.
III Partial absence	Partial absence (distal, middle, proximal) of radius. Distal 1/3-2/3 absence most common. Ulna thickened, shortened, and bowed.	Severe radial deviation of the hand.
IV Total absence	No radius present. Ulna thickened, shortened, and bowed.	Most common type. Severe radial deviation of the hand.

Because ossification of the radius is delayed in radial deficiency, the differentiation between total partial absence (Types III and IV) cannot be established until approximately three years of age.
Centralization is indicated for Types II, III, and IV.
Adapted from Bayne and Klug.

A Type I deficiency is the mildest expression characterized by mild radial shortening of the radius without considerable bowing of the ulna. Although minor radial deviation of the hand is apparent, considerable thumb hypoplasia may be evident. A Type II deficiency presents with a miniature radius with growth plate abnormalities and moderate deviation of the wrist. A Type III deficiency is partial absence of the radius, most

commonly the distal portion, and severe wrist radial deviation. Complete absence of the radius is a Type IV deformity and is the most common variant.

In complete absence of the radius (Type IV), the humerus may or may not be shorter than expected and the elbow is often lacking motion, primarily in flexion. The forearm is always shorter as the ulna is approximately 60% of the normal length at birth. This length discrepancy persists throughout the growth period. The ulna is thickened and often bowed toward the absent radius. Forearm rotation is absent in partial or complete aplasia of the radius, although some rotation is evident through the carpus. The wrist is positioned in a variable amount of radial deviation. The carpal bones are delayed in ossification with the scaphoid and trapezium often absent or hypoplastic. The index and long fingers can be stiff and slender with limited-motion joints. The ring and small digits are less affected and often have better motion.

The neurovascular structures are also aberrant because the radial artery and nerve often are absent. The ulnar nerve and artery are normal. An enlarged median nerve substitutes for the absent radial nerve and supplies a large dorsal branch for sensation to the radial aspect of the hand. This branch is positioned in the fold between the wrist and forearm, and knowledge of this subcutaneous location is critical during surgery along the radial aspect of the wrist.

Goals, indications, and contraindications for treatment

The basic goals of treatment are to:

1) correct the radial deviation of the wrist;
2) balance the wrist on the forearm;

3) maintain wrist and finger motion;
4) promote growth of the forearm;
5) improve the function of the extremity.

Slight shortening of the radius (Type I deficiency) requires continued stretching and may need a tendon transfer to re-balance the wrist. This treatment is relatively straightforward. Partial or complete absence is more common (Types II, III, and IV) and is more difficult to treat. The wrist assumes a position of severe radial deviation, which shortens an already undersized forearm, places the extrinsic flexor and extensor tendons at an unfavorable angle, and creates functional deficits. The functional impairment is far greater in bilateral than in unilateral cases. The digital abnormalities also require consideration during formulation of a treatment plan, as stiff fingers and a deficient thumb will hamper prehension and create additional functional impediment.

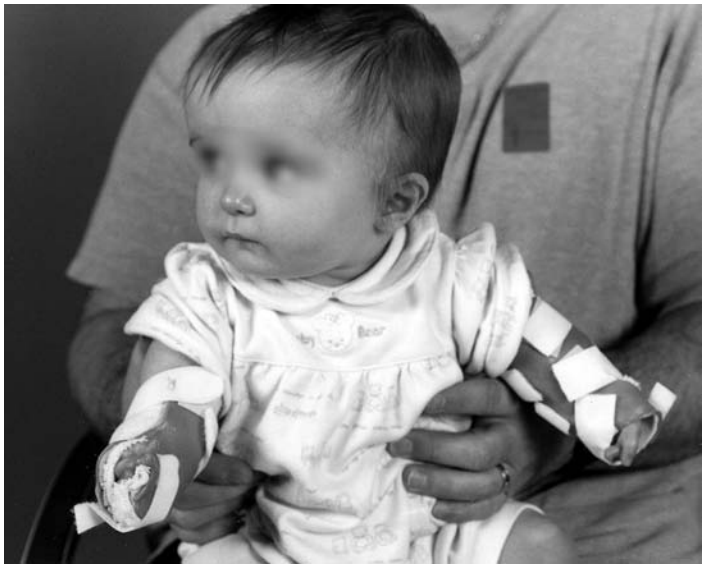
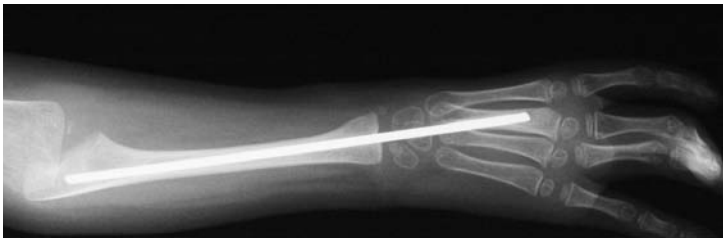


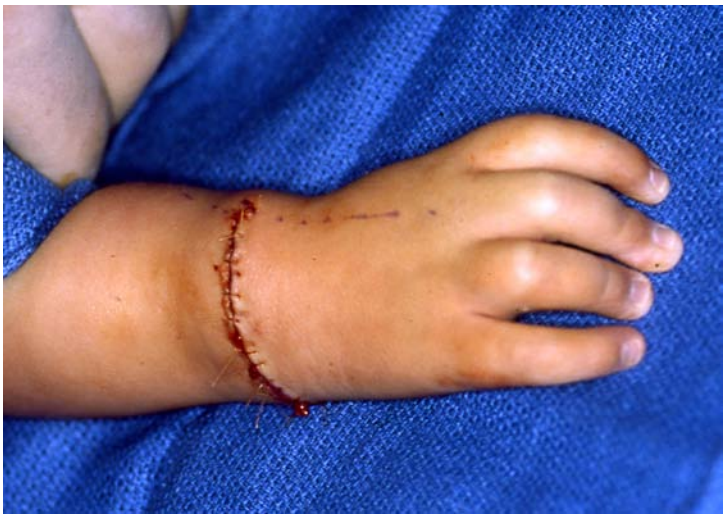
Figure 10: Bilateral upper extremity splints fabricated to maintain wrists in straight alignment.

The radial deviation deformity is treated by a combination of non-operative and operative management that begins shortly after birth. The initial treatment for the absent radius is stretching, both by the therapist and the caregiver. Stretching is usually recommended every diaper change and is important to the overall success of treatment. Fabrication of a splint is difficult in the newborn with a shortened forearm, and is usually delayed until the forearm is long enough to accommodate a splint (Figure 10). Splints are used to maintain the hand in a straight alignment. If no treatment is rendered, the hand will develop a fixed perpendicular relationship to the forearm.

Surgical treatment for Types II, III, and IV deficiencies involves placing the wrist on top of the ulna, which is the only substantial bone within the forearm. The procedure is known as a "centralization" or "radialization." Centralization remains the principal procedure to realign the carpus onto the distal ulna. Contraindications for surgical intervention are mild deformity with adequate support for the hand (Type 1) and an elbow extension contracture that prevents the hand from reaching the mouth. In these children, the radial deviation of the wrist facilitates hand to mouth function and straightening would further impair this motion. Another contraindication to centralization is adults who have adjusted to their deformity.

The procedure is typically performed at about one year of age, and the initial correction is impressive. Unfortunately, the ability to maintain the correction and prevent recurrence has not been completely solved. Centralization is performed by release of the tight aberrant radial musculotendinous units and anomalous contracted fibrous bands to allow passive correction of the over the end of the ulna (Figure 11A and B).





Figures 11A and 11B: X-ray and clinical appearance after centralization with positioning of the carpus onto the distal ulna. (Courtesy of Shriners Hospital for Children, Philadelphia)

The carpus is then reduced onto the distal ulna for centralization. In severe cases, adequate reduction cannot be obtained and alternative measures are necessary. Surgical options include carpectomy, limited shaving of the distal ulna epiphysis or application of an external fixator followed by post-operative distraction and delayed formal centralization. In fact, many cases of radial deficiency with rigid deformity are treated with preliminary soft tissue distraction (i.e., external fixation) prior to centralization to stretch the tight radial

structures and facilitate carpal reduction.

After the carpus is placed on the end of the ulna, the soft tissues are balanced by tightening of the capsule and by a tendon transfer to redirect the deviating forces. The wrist is held in position by a Kirschner wire. An ulnar bow greater than 30 degrees requires a concomitant wedge osteotomy at the apex of the deformity to correct the angulation. The Kirschner wire is removed eight to twelve weeks after surgery. A splint is made and removed for exercises, with gradual weaning from the splint. A nighttime splint regimen is encouraged until skeletal maturity.

Numerous technical modifications have been proposed to maintain alignment of the wrist position (Figure 12). These include over-correction of the carpus, additional tendon transfer, and prolonged Kirschner wire fixation. Even microvascular free toe transfer to support the radial side of the wrist with a growing part has been advocated. The toe proximal phalanx is fused to the base of the second metacarpal and the proximal metatarsal affixed to the side of the distal ulna.

Unfortunately, no method reliably and permanently corrects the radial deviation, balances the wrist, and allows continued growth of the forearm. Currently, the maintenance of the carpus on the end of the ulna without sacrificing wrist mobility or stunting forearm growth remains a daunting task. Recurrence after centralization is the most common source of failure, and the cause appears multifactorial. Operative causes include the inability to obtain complete correction at surgery, inadequate radial soft tissue release, and failure to balance the radial force. Postoperative reasons consist of premature Kirschner wire removal, poor postoperative splint use, and the natural tendency for the shortened forearm

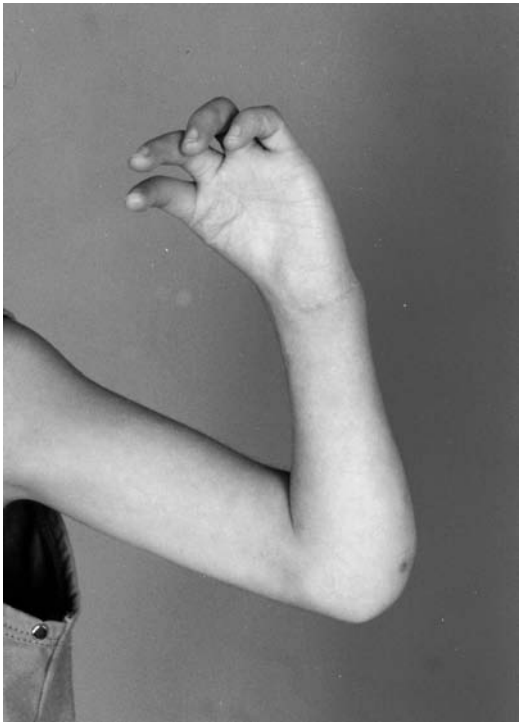


Figure 12: Eight-year-old child after centralization of the left wrist to realign the carpus over the end of the ulna and straighten the forearm segment.

and hand to deviate in a radial direction for hand to mouth use.

The management of recurrent deformity must be individualized to each patient and his/her specific deformity. The indications for a revision procedure have yet to be clearly defined. Similarly, the indications for forearm lengthening to overcome the inherent shortening have yet to be delineated. Surgery is offered to patients and family interested in correction of the deformity and willing to comply with an arduous postoperative course. Lengthening or distraction osteogenesis via an external fixator (e.g., Ilizarov device) is usually part of

Figure 13: Four-year-old child with recurrent deformity of the left wrist treated with distraction histiogenesis using an Ilizarov device to stretch the taut soft tissue structures.

the treatment regimen, and preoperative education is critical (Figure 13).

This sophisticated form of treatment introduces additional complications that require discussion prior to surgery, such as pin tract infection, fracture of the regenerated bone, and digital stiffness. On occasion, adolescents with shortened forearms may want their arms longer to improve appearance and function. Lengthening of the ulna can be performed using an external fixator and gradual distraction. However, this forearm lengthening is laborious and can require extended periods of time in the device waiting for bony consolidation (Figure 14).

Figure 14: Adolescent undergoing simultaneous bilateral forearm lengthening to increase arm lengths. (Courtesy of Shriners Hospital for Children, Philadelphia)

Ultimately, fusion of the ulnocarpal joint may be contemplated in certain instances to keep the wrist straight. Wrist fusion results in a permanent loss of wrist mobility. Careful assessment of hand usage and compensatory motion is mandatory prior to this procedure. A functional evaluation by a therapist is a valuable preoperative tool. Painstaking measures should be taken to ensure that wrist fusion will not result in loss of function.

Emotional Issues

Parents of children born with congenital anomalies are extremely concerned about peer pressure and taunting. The physician should acknowledge this probability and encourage parental support during these times. Literature is available to help children and families explain their child's limb anomalies, although parental discussions are the mainstay to understanding. School age playmates are keenly aware of congenital limb

differences, which will be a source of discussion and possible teasing. As congenitally different children grow, they develop inward and outward coping mechanisms to handle their anomalies. The physician should play an active role and serve as part of the child's support system with open discussions regarding the limb differences, including asking questions about peer discourse. These conversations are often insightful and revealing to both the physician and family. Difficulties with peer pressure may require counseling to promote emotional development.

Transition of Pediatric FA Patients to Adult FA Patients

Fortunately, many children with FA are living and prospering as adults. Usually all hand surgery has been completed and regular follow-up is not necessary. However, occasional evaluation is recommended to assess for any developing problems. Many pediatric facilities do not treat adults, and transition to an adult practice is necessary. Patients should ask their pediatric hand surgeon for recommendations for care. Referral to a hand surgeon with a *Certificate of Added Qualification in Hand Surgery* is recommended.

References

Hypoplastic thumb

Clark DI, Chell J, Davis TR. Pollicization of the index finger. A 27-year follow-up study. *The Journal of Bone and Joint Surgery* 1998; **80B**: 631-635.

Graham TJ, Louis DS. A comprehensive approach to surgical management of the type IIIA hypoplastic thumb. *Journal of Hand Surgery* 1998; **23A**: 3-13.

Lister G. Reconstruction of the hypoplastic thumb. *Clinical Orthopaedics and Related Research* 1985; **195**: 52-65.

Kozin SH, Weiss AA, Weber JB, Betz RR, Clancy M, Steel H. Index finger pollicization for congenital aplasia or hypoplasia of the thumb. *Journal of Hand Surgery* 1992; **17A**: 880-884.

Manske PR, McCarroll HR Jr, James MA. Type III-A hypoplastic thumb. *Journal of Hand Surgery* 1995; **20A**: 246-253.

Thumb duplication

Cohen MS. Thumb duplication. *Hand Clinics* 1998; **14**:17-27.

Dobyns JH, Lipscomb PR, Cooney WP. Management of thumb duplication. *Clinical Orthopaedics and Related Research* 1985; **195**: 26-44.

Ezaki MB. Radial polydactyly. *Hand Clinics* 1990; **6**: 577-588.

Wassel HD. The results of surgery for polydactyly of the thumb. A review. *Clinical Orthopaedics and Related Research* 1969; **125:** 175-193.

Radial deficiency

Bayne LG, Klug MS. Long-term review of the surgical treatment of radial deficiencies. *Journal of Hand Surgery* 1987; **12**: 169-179.

Bora FW Jr, Osterman AL, Kaneda RR, Esterhai J. Radial club-hand deformity. Long-term follow-up. *Journal of Bone and Joint Surgery* 1981; **63A**: 741-745.

Damore E, Kozin SH, Thoder JJ, Porter S. The recurrence of deformity after surgical centralization for radial clubhand. *Journal of Hand Surgery* 2000; **25A**: 745-751.

Goldfarb CA, Klepps SJ, Daily LA, Manske PR. Functional outcome after centralization for radius dysplasia. *Journal of Hand Surgery* 2002; **27A**: 27: 118-124.

Goldfarb CA, Murtha YM, Gordon JE, Manske PR. Soft-tissue

distraction with a ring external fixator before centralization for radial longitudinal deficiency. *Journal of Hand Surgery* 2006; **31**: 952-959.

Goldfarb CA, Wall L, Manske PR. Radial longitudinal deficiency: the incidence of associated medical and musculoskeletal conditions. *Journal of Hand Surgery* 2006; **31**: 1176-1182.

Heikel HV. Aplasia and hypoplasia of the radius. Studies on 64 cases and on epiphyseal transplantation in rabbits with the imitated defect. *Acta Orthopaedica Scandinavica, Supplementum* 1959; **39**: 1-155.

James MA, McCarroll HR, Manske PR. The spectrum of radial longitudinal deficiency: a modified classification. *Journal of Hand Surgery* 1999; **24A**: 1145-1155.

Lourie GM, Lins RE. Radial longitudinal deficiency. A review and update. *Hand Clinics* 1998; **14**: 85-99.

McCarroll HR. Congenital anomalies: a 25-year overview. *Journal of Hand Surgery* 2000; **25A**: 1007-1037.

Nanchahal J, Tonkin MA. Pre-operative distraction lengthening for radial longitudinal deficiency. *Journal of Hand Surgery* 1996; **21B**: 103-107.

Taghinia AH, Al-Sheikh AA, Upton J. Preoperative soft-tissue distraction for radial longitudinal deficiency: an analysis of indications and outcomes. *Plastic and Reconstructive Surgery* 2007; **120**: 1305-1312.

Vilkki SK. Distraction and microvascular epiphysis transfer for radial clubhand. *Journal of Hand Surgery* 1998; **23B**: 445-452.

Psychological issues

Bradbury E. Psychological issues for children and their parents. Buck-Gramcko D, ed. *Congenital Malformations of the Hand and Forearm*. London: Churchill Livingstone; 1998; 48-56.

Chapter 6

Gynecologic and Fertility Issues in Female FA Patients

Pamela Stratton, MD, Rahel Ghebre, MD, and Jill Huppert, MD, MPH

Congenital Genital Tract Anomalies

FA patients have not been studied sufficiently to determine if they are at increased risk for congenital genital tract anomalies. In fetal development, the genital tract and renal system are interlinked. Since renal anomalies have been documented in FA patients,[1] those with identified renal or lower gastrointestinal tract anomalies should undergo screening for congenital malformations of the genital tract such as unicornuate or bicornuate uterus or ovarian atresia. In other populations, the rate of renal anomalies in those with genital tract anomalies is 30%.[2]

Menses and Fertility

Females with Fanconi anemia have a shortened reproductive life and are probably less fertile than the general population. They usually do not begin menstruating until their mid-teens, may have infrequent, irregular menses, and are often menopausal by their thirties.[3] These characteristics may be related to the effect of mutations in FA genes, since FA animal models also have hypogonadism and impaired fertility[4] or they may be related to low body weight or chronic disease.[5] Endocrine problems, such as thyroid and hypothalamic dysfunction, which may alter the menstrual cycle should be considered (see Chapter 7). Infrequent

menstrual cycles experienced by FA patients could also result from taking androgens to improve hematopoiesis.

Pubertal Delay

Pubertal delay should be considered in patients who do not have breast buds by age 13, or by age 14 if they have low body weight. In the general population, 90% of women begin menses by age 16 or 3 years after breast buds.[6] While pubertal delay might result from low body mass index or chronic disease, young women with late menarche should be evaluated for hypothalamic dysfunction.[5,6] If puberty is delayed or does not occur, patients may need hormonal supplementation to optimize their growth and develop secondary sex characteristics (see Chapter 7).

Gynecologic Surveillance

General gynecologic examination

FA patients are at extraordinarily high risk for vulvar cancer, as well as cervical and anal cancers. Therefore, we recommend that all FA patients receive an annual gynecologic exam, beginning at 13, for visual inspection of the external genitalia. These patients should be followed by a gynecologist familiar with FA and with experience in treating patients with lower genital tract neoplasia.

For non-sexually active women, a comprehensive pelvic exam should be considered at age 18, three years earlier than recommended for non-FA patients.

For sexually experienced women, the gynecologic examination should be comprehensive and include cervical cytology testing and careful inspection of the vagina and cervix during a speculum examination. The use of colposcopy in inspecting these areas should be

initiated only after abnormal cytology or squamous intraepithelial lesions have been identified. Any visually abnormal areas should be biopsied to exclude dysplasia or cancer.

FA patients should be counseled on sexually transmitted diseases (STD) and human papillomavirus (HPV) prevention, and be encouraged to receive the HPV vaccination with Gardasil®.[7] Gardasil® is the only currently available vaccine that helps protect against four types of HPV: two types that cause 70% of cervical cancer, and two more types that cause 90% of genital warts.

Hormonal contraception

Hormonal contraception is not contraindicated in FA patients. The physician should discuss contraception and safe sex practices with these patients and screen for sexually transmitted diseases.[8] Patients who are prescribed hormonal contraception to regulate their menses or are given androgens to help stimulate the bone marrow may have normal menses.

Possible effects of androgen use

While the regular use of androgens may be contraceptive, if pregnancy does occur, androgens should be discontinued immediately. Androgen use during pregnancy can masculinize a female fetus.

Evaluation and treatment of abnormal uterine bleeding

The evaluation of heavy bleeding in women with FA should include a complete blood count and assessment of hemodynamic status. Pregnancy should be excluded. Heavy or prolonged menstrual bleeding may occur when patients are thrombocytopenic; infrequent ovulation may contribute to prolonged uterine bleeding. Measures to improve the hematologic status should be

instituted, including transfusions of platelets and red cells, as well as the use of hormonal treatments.

Excessive menstrual bleeding, as in other thrombocytopenic and gynecologic conditions, can be treated with hormonal therapy.[9,10] Options include daily monophasic combined oral contraceptives (estrogen and progestin pills that do not vary in dosage over the cycle) taken continuously, skipping the placebo pills. Oral contraceptive pills containing at least 30 mcg of ethinyl estradiol should be used, as a slightly higher dosage of estrogen minimizes the risk of breakthrough bleeding. During an acute bleeding episode, treatment can begin with two or three tablets of oral contraceptives daily, tapered quickly to one pill a day. Megestrol acetate, medroxyprogesterone acetate or other oral progestins may also be used. Long-acting progestins may be effective. Leuprolide acetate, a gonadotropin releasing hormone (GnRH) agonist, given as a 3.75 mg injection monthly (or 11.25 mg every three months), has been used in other thrombocytopenic populations. Use of a GnRH agonist for more than six months increases the risk of bone loss, a particular problem observed in women with Fanconi anemia, regardless of hormone use (see Chapter 7).[3,11] Therefore, use of GnRH for longer periods may be coupled with additional estrogen and progestin therapy to minimize bone loss.

If these measures fail, non-hematologic reasons for excessive menstrual bleeding should be considered. A transvaginal sonogram is helpful in determining endometrial thickness, the presence of polyps or fibroids in the endometrial cavity, and ovarian activity. The endometrium should be sampled to assess for abnormalities, such as endometrial hyperplasia. Surgical treatment of any endometrial or uterine abnormalities may be indicated.

Cancer Risk

Increased risk of lower genital tract squamous cell carcinoma

A high rate of lower genital tract squamous cell carcinoma, which includes cervical, vaginal, vulvar, and anal cancers, has been reported in women with FA. The median ages of cervical or vulvar cancer in FA women are very young, 25 and 27 respectively, significantly younger than expected in the general population (age 47 for cervical cancer and 72 for vulvar cancer).[12,13] The young ages for these cancers in FA patients translates into a relative risk of 4,000-fold higher for vulvar cancer and 200-fold higher for cervical cancer compared to the general population.[12,14]

The high risk for early vulvar cancer provides the rationale for instituting gynecologic care at a young age. Screening for genital tract neoplasia which includes cytology testing and visual inspection of the vulva and vagina should be part of the clinical care for FA patients, as outlined in the earlier section subtitled "General gynecologic examination." Colposcopy should be done when any abnormal areas are seen on visual inspection or if a cervical cytology test is abnormal. Any suspicious lesions should be biopsied. Any woman with a history of dysplasia or squamous intraepithelial lesions should have twice yearly gynecologic exams to assess for recurrence.

Surgical treatment of dysplastic lesions in FA patients is preferable, as these patients have significant adverse effects from chemotherapy and radiation. They are at increased risk of bone marrow failure with chemotherapy and, as FA is a DNA repair defect, there is a theoretical risk of toxicity with radiation.[15] Because treatment of cancer in FA patients can be complicated,

surgical treatment of lesions should be considered, and consultation with a hematologist experienced with FA should be obtained prior to instituting radiation or chemotherapy.

Human papillomavirus immunization

In two recent studies on a small number of vulvar SCC tumors in FA patients, the tumors tested positive for HPV.[16,17] Because of the increased risk of genital tract neoplasia in women with FA and head and neck cancer in both men and women with FA, it may be reasonable to consider HPV vaccination for both male and female FA patients at age nine. It is unknown whether FA patients mount the usual immune response to the vaccine. While the vaccine will not treat existing HPV disease, it may prevent the acquisition of some other subtypes. As the HPV vaccine does not prevent all genital tract cancers and the efficacy of this vaccine in FA is not known, vaccinated FA patients should continue regular screening.

Breast cancer surveillance

Breast cancer surveillance should begin by the early 20s and include annual breast exams. Screening mammograms should be initiated if a mass is detected or by age 25. The risk of breast cancer in FA does not appear to be excessive, although a few cases have been reported to date.[18] A few FA patients have acquired breast cancer at a median age of 37 years, compared to a median age of 61 in the non-FA population (see Chapter 2). To avoid radiation, magnetic resonance imaging may be considered. However, breast magnetic resonance imaging, while very sensitive, is non-specific and has a high false positive rate. Thus, it is usually considered to be an adjunct to mammography.[19]

Gynecologic Issues Related to Hematopoietic Stem Cell Transplantation

Many FA patients undergo hematopoietic stem cell transplantation during childhood or adolescence and may develop gynecologic problems as a result. Factors that influence post-transplantation fertility and ovarian function include total body irradiation, prescribed drugs, age, and relation of puberty to age at transplant.[18] When patients are transplanted prior to puberty, their ovarian function may be spared. After menarche, transplantation may result in ovarian failure.[18]

If the transplant will occur after puberty, patients may wish to preserve their ovarian function. However, there is no definitive way to protect the ovaries during the transplantation process at this time. In other populations, gonadotropin releasing hormone agonists, like leuprolide acetate, have been used to attempt to preserve ovarian function with limited success.[20,21] Clinical studies using these or other agents called GnRH antagonists are underway.

For girls or women who are menstruating prior to transplant, menstrual suppression can decrease the risk of anemia, blood loss, and transfusions, and can be accomplished by continuous combined oral contraceptives, depo-medroxyprogesterone acetate or leuprolide.[9,10]

The gynecologist should discuss childbearing options with adolescents and young adults prior to transplant. This may be especially challenging with an adolescent patient, since it is unlikely that the patient has considered future childbearing. If pregnancy is desired in the future and the young woman is old enough to participate in this discussion, the use of assisted reproductive technologies prior to transplant should

be considered.[22,23] A higher viability and subsequent success rate has been noted in embryo cryopreservation compared to oocyte cryopreservation. Oocyte or ovarian tissue cryopreservation are both experimental and should occur in the context of a research protocol. For those FA patients who have undergone transplantation prior to considering childbearing, donor oocytes may be an option if they decide to have children. There may be additional concerns regarding the ability of a radiated uterus to carry a pregnancy, as damage to the uterine vasculature from radiation may affect implantation and placental physiology.[24-26]

Some pregnancies have been reported after stem cell transplantation in patients with FA who have not taken any additional hormones or undergone assisted reproductive technologies.[27]

Fertility

Although young women with FA may be less fertile than the general population, they are able to have children. Because of hypogonadism and menstrual irregularities, FA patients may not ovulate monthly, and the fertile time of the month may be difficult to predict. However, a uterine anomaly or ovarian dysfunction in an FA patient may affect the ability to become pregnant or carry a pregnancy to term. The actual fertility rate in FA is unknown. From case reports of those patients who have given birth, most did so in their 20s, with few pregnancies after age 30. In one reported patient series by Alter et al, 29% of women over age 16 who were not taking androgens conceived, suggesting decreased fertility.[28] When those taking androgens were included, the overall pregnancy rate was 15%.

Pregnancy-related complications

Pregnancy for women with FA should be considered high risk and should be co-managed with a maternal/fetal medicine specialist and a hematologist to monitor for pregnancy complications and worsening hematologic status. In the Alter series, FA patients had a higher risk of pregnancy-related complications, such as preeclampsia, eclampsia, and spontaneous abortions, when compared to the general population. The caesarean section rate in this series was 25%, perhaps because the small stature of FA patients may mean they have small pelvises and a higher rate of failure to progress in labor.[28]

Pregnancy in women with FA does not appear to be life-threatening. Although others report that women with acquired aplastic anemia had pregnancy-related mortality of nearly 50%, no deaths occurred among the FA women in the above series.[28] However, the hematologic status of the mother worsened in more than 50% of the FA pregnancies, requiring transfusions for anemia and/or thrombocytopenia.

Menopause

FA patients usually go through premature menopause (age less than 40). Thus, the physician should consider the post-menopausal health risks of osteoporosis, cardiovascular disease, breast cancer, and the management of hot flashes. The results from the Women's Health Initiative Study suggest that post-menopausal hormonal replacement in the general population protects against bone loss, is associated with a slightly increased risk of breast cancer, and an increased risk of heart attack, stroke, and thromboembolic disease.[29]

For women with FA, there are no data regarding the use of hormone replacement. For those patients who go through menopause at a very early age, the physician can reasonably consider giving hormone replacement of estrogen and progestin (such as monophasic oral contraceptive pills or prempro containing 0.625 premarin and 2.5 mg provera or similar hormonal treatment) until the age of 50. Estrogens are useful in preventing hot flashes and providing a sense of well-being.

Osteoporosis

It is especially important to protect post-menopausal FA women against bone loss, which is common in these patients.[3] Osteoporosis treatment options are plentiful, including biphosphonates (Fosamax or Actonel) which prevent bone resorption, and hormones (estrogen or raloxifene) which build bone. Most post-menopausal women with FA would benefit from taking 1,500 mg of calcium a day, vitamin D supplementation, and a biphosphonate like Fosamax (70 mg tablet once weekly) or Actonel (35 mg once weekly). Even if osteoporosis medications are instituted, women with FA should be monitored for osteoporosis with DXA (dual energy X-ray absorptiometry) scans every two years or as clinically indicated (see Chapter 7).

Cardiovascular Risk

The cardiovascular risk for patients with FA may not be high, but the physician should consider an individual patient's family history. Lipids, insulin resistance (see Chapter 7), and blood pressure should be monitored as part of a cardiovascular risk assessment, with special attention paid to the effects of androgens on lipids. In those with documented cardiovascular risk factors, hormone replacement therapy may be contraindicated.

Future Research Directions

1. Defining osteoporosis risk in FA women.
2. Defining the risk of congenital reproductive tract anomalies in FA women.
3. Fertility preservation for patients undergoing stem cell transplantation.
4. The safety and immunogenicity of HPV vaccination in FA men and women.
5. Improving diagnosis and treatment of genital tract dysplasias before cancer arises.

References

1. Faivre L, Portnoi MF, Pals G, et al. Should chromosome breakage studies be performed in patients with VACTERL association? *American Journal of Medical Genetics* 2005; **137**(1): 55-58.

2. Oppelt P, von Have M, Paulsen M, et al. Female genital malformations and their associated abnormalities. *Fertility and Sterility* 2007; **87**(2): 335-342.

3. Giri N, Batista DL, Alter BP, Stratakis CA. Endocrine abnormalities in patients with Fanconi anemia. *Journal of Clinical Endocrinology and Metabolism* 2007; **92**(7): 2624-2631.

4. Koomen M, Cheng NC, van de Vrugt HJ, et al. Reduced fertility and hypersensitivity to mitomycin C characterize Fancg/Xrcc9 null mice. *Human Molecular Genetics* 2002; **11**(3): 273-281.

5. Genazzani AD, Ricchieri F, Lanzoni C, Strucchi C, Jasonni VM. Diagnostic and therapeutic approach to hypothalamic amenorrhea. *Annals of the New York Academy of Sciences* 2006; **1092**: 103-113.

6. Hoffman B, Bradshaw KD. Delayed puberty and amenorrhea. *Seminars in Reproductive Medicine* 2003; **21**(4): 353-362.

7. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *New England Journal of Medicine* 2007; **356**(19): 1928-1943.

8. ACOG Committee Opinion No. 357: Primary and preventive care: periodic assessments. *Obstetrics and Gynecology* 2006; **108**(6): 1615-1622.

9. Levens ED, Scheinberg P, DeCherney AH. Severe menorrhagia associated with thrombocytopenia. *Obstetrics and Gynecology* 2007; **110**(4): 913-917.

10. Meirow D, Rabinovici J, Katz D, Or R, Shufaro Y, Ben-Yehuda D. Prevention of severe menorrhagia in oncology patients with treatment-induced thrombocytopenia by luteinizing hormone-releasing hormone agonist and depo-medroxyprogesterone acetate. *Cancer* 2006; **107**(7): 1634-1641.

11. Scialli AR, Jestila KJ, Simon JA. Leuprolide acetate and bone mineral density measured by quantitative digitized radiography. *Fertility and Sterility* 1993; **59**(3): 674-676.

12. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi anemia. *Blood* 2003; **101**(3): 822-826.

13. Alter BP. Cancer in Fanconi anemia, 1927-2001. *Cancer* 2003; **97**(2): 425-440.

14. Rosenberg PS, Alter BP, Ebell W. Cancer risks in Fanconi anemia: findings from the German Fanconi Anemia Registry. *Haematologica* 2008; **93**(4): 511-517.

15. Alter BP. Radiosensitivity in Fanconi's anemia patients. *Radiotherapy and Oncology* 2002; **62**(3): 345-347.

16. Kutler DI, Wreesmann VB, Goberdhan A, et al. Human papillomavirus DNA and p53 polymorphisms in squamous cell carcinomas from Fanconi anemia patients. *Journal of the National Cancer Institute* 2003; **95**(22): 1718-1721.

17. Van Zeeburg HJ, Snijders PJ, Wu T, et al. Clinical and molecular characteristics of squamous cell carcinomas from Fanconi anemia patients. *Journal of the National Cancer Institute* 2008; **100**(22): 1649-1653.

18. Chemaitilly W, Mertens AC, Mitby P, et al. Acute ovarian failure in the childhood cancer survivor study. *Journal of Clinical Endocrinology and Metabolism* 2006; **91**(5): 1723-1728.

19. Robson M, Offit K. Clinical practice. Management of an inherited predisposition to breast cancer. *The New England Journal of Medicine* 2007; **357**(2): 154-162.

20. Waxman JH, Ahmed R, Smith D, et al. Failure to preserve fertility in patients with Hodgkin's disease. *Cancer Chemotherapy and Pharmacology* 1987; **19**(2): 159-162.

21. Pereyra Pacheco B, Mendez Ribas JM, Milone G, et al. Use of GnRH analogs for functional protection of the ovary and preservation of fertility during cancer treatment in adolescents: a preliminary report. *Gynecologic Oncology* 2001; **81**(3): 391-397.

22. Davis M. Fertility considerations for female adolescent and young adult patients following cancer therapy: a guide for counseling patients and their families. *Clinical Journal of Oncology Nursing* 2006; **10**(2): 213-219.

23. Fallat ME, Hutter J. Preservation of fertility in pediatric and adolescent patients with cancer. *Pediatrics* 2008; **121**(5): e1461-1469.

24. Critchley HO, Bath LE, Wallace WH. Radiation damage to the uterus — review of the effects of treatment of childhood cancer. *Human Fertility (Cambridge, England)* 2002; **5**(2): 61-66.

25. Critchley HO, Wallace WH. Impact of cancer treatment on uterine function. *Journal of the National Cancer Institute - Monographs* 2005; (34): 64-68.

26. Edgar AB, Wallace WH. Pregnancy in women who had cancer in childhood. *European Journal of Cancer* 2007; **43**(13): 1890-1894.

27. Goi K, Sugita K, Nakamura M, et al. Natural pregnancy and delivery after allogeneic bone marrow transplantation in a Fanconi anaemia patient. *British Journal of Haematology* 2006; **135**(3): 410-411.

28. Alter BP, Frissora CL, Halperin DS, et al. Fanconi's anaemia and pregnancy. *British Journal of Haematology* 1991; **77**(3): 410-418.

29. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association* 2002; **288**(3): 321-333.

Chapter 7

Endocrine Disorders in Fanconi Anemia

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Introduction

Many children and adults with Fanconi anemia have endocrine problems. These include short stature, growth hormone (GH) deficiency, hypothyroidism, pubertal delay or related abnormalities, osteopenia or osteoporosis, and abnormal glucose or insulin metabolism (leading to impaired glucose tolerance or diabetes mellitus). Both the basic underlying condition of FA and its treatment (hematopoietic cell transplantation [HSCT]) may have effects on the endocrine systems of FA patients.

For these reasons, a thorough baseline and annual endocrine evaluation should be performed in every person with FA. The endocrine clinical care team should include a dietician, pediatric endocrinologist (with experience in growth and puberty), and a reproductive endocrinologist (with experience in children and fertility) or a pediatric gynecologist.

Until recently, only one medical journal article existed on endocrine function in FA patients (New York group [NY][1]), but now three additional centers have each published articles on the subject (National Institutes of Health [NIH][2]; Cincinnati Children's Hospital Medical Center [CCHMC][3-6]; and the University of Minnesota [U. of M.].[7,8]) Over 80% of FA individuals in all reports have had at least one abnormal endocrine test result (Tables 3 and 4).

Height

Height is a major clinical focus of the pediatric endocrinologist, the parent, and the child with FA. The average height for persons with FA is -2.1 standard deviation units (SD). SD units are a way of expressing divergence from average. For instance, 2.5% of the normal population have heights more than 2 SD above average, and 2.5% of the normal population have heights shorter than 2 SD (-2 SD) below average. The average height in FA of -2.1 SD is about equivalent to 150 cm (4 feet, 11 inches) in women and 161 cm (5 feet, 3.5 inches) in men (Table 1). About half of FA patients are shorter than the 2.5 percentile or -2 SD, including some children with FA who are extremely small for their age (average height of the short group, -3.5 SD).[1-6] However, almost half of individuals with FA have height within the normal range. Thus, some FA children have no problems related to height, with about 10% having heights above the average for the general population.

Effect of hormone deficiencies on height

FA patients with hormone deficiencies have a shorter height. Those with growth hormone (GH) insufficiency have an average height of -2.7 SD, and those with hypothyroidism -3.0 SD, while those with no demonstrable endocrinopathy have an average height of -2.0 SD.[1] FA children who have untreated GH deficiency or hypothyroidism will achieve an even shorter adult height. However, short stature in FA cannot fully be explained on the basis of endocrinopathy alone. Occasionally, significant short stature is seen in FA even with no detectable hormone deficiencies. As a result, hormonal replacement therapy is unlikely to normalize growth completely.

Effect of FA mutation on height

A particular mutation is a strong predictor of short stature, providing genetic evidence for a hormone-independent effect of FA on height. In the subset of patients with the IVS4 mutation of *FANCC*, average height was -4.3 SD, markedly reduced compared to FA children not in that subset (p=0.002).[1]

Table 1: Stature in Children with Fanconi Anemia

	Total Group		**Short Cohort**		**Normal Height Cohort**	
	Mean HtSD (N)*	**Range**	**Mean HtSD (N)**	**Range**	**Mean HtSD (N)**	**Range**
NY[1]	-2.4 (54)	-6.3 to +0.8	-3.5 (31)		-0.8 (23)	
NIH[2]	-1.9 (45)	-7.8 to +0.8	-3.8 (23)		-0.1 (22)	
CCHMC[3-6]	-2.0 (63)	-4.8 to +0.8	-2.9 (31)		-0.6 (32)	
Overall	-2.1 (162)	-7.8 to +0.8	-3.4 (85)	-7.8 to -2.0	-0.5 (77)	-1.9 to +0.8
Equivalent adult height:						
Women				115 to 151 cm 3 ft 8 in to 4 ft 11 in		151.5 to 170 cm 4 ft 11.5 in to 5 ft 7 in
Men				121 to 162 cm 4 ft 0 in to 5 ft 3.5 in		162.5 to 183 cm 5 ft 4 in to 6 ft 0 in

Parental height

The average height of parents of children with FA tends to be near the middle of the normal range. Parents' height can be expressed as target height, which is the average of the parents' height percentiles.

Effect of birth weight on height

Average birth weight in infants with FA is approximately 1.8 SD below the mean; i.e., at the lower end of

the normal range. Approximately 40% of FA children are born small for gestational age (SGA). In the general population, about 90% of children who were born SGA gradually catch up to the normal range for height. However, in the CCHMC patient group, 80% of the children with FA who were born SGA had height below -2 SD, while only 20% had normal height.

Clinical observations of growth rate

Growth in children with FA should be followed clinically. Accurate height by stadiometer measurement is important, and height should be plotted on a growth chart. Not all individuals with FA experience growth failure. When growth velocity and stature decline below expectations relative to the family background, appropriate endocrine evaluation should be performed. Nutritional and medical causes for poor growth should be identified in children as early as possible (Table 2).

Estimates of adult height based on bone age (BA) measurements may lead to over-optimistic height predictions. Androgens and corticosteroids may alter growth, advance BA or impair adult height. Adult height predictions should be re-evaluated after a decrease in the growth velocity or following initiation of androgen therapy and after HSCT.[9,10]

Bone maturation

Height prediction algorithms make use of information about the amount of delay in bone maturation. Height measurement and a radiograph of the patient's left hand and wrist should be obtained every two years in short children or every year in a child receiving androgen therapy.

If BA is like that of a younger child, height prediction may suggest that adult height will be normal. This expectation assumes that there will be continued

Table 2: Endocrine Screening in Fanconi Anemia (for therapy, see text)

	Annual Screening	**Detailed testing**
Thyroid hormone	Height, weight 0800h TSH, FT4	Bone age x-ray every 2 years if the child is small or puberty is early or late.
Growth hormone	Height, weight IGF-I (if over age 4 years), IGFBP3 if growth rate slow	Arginine, clonidine stimulation test MRI pituitary if peak GH <10 Bone age x-ray every 2 years
Glucose and insulin	One-hour post-prandial glucose and insulin; After HSCT, HgbA1c may be useful	2h oral glucose tolerance test with insulin levels every 2 years (yearly if not normal)
Puberty, gonadal function	Pubertal staging	LH, FSH, estradiol or testosterone every 2 years after age 12 years DXA (see next line)
Bone mineral	DXA every 5 years starting at age 14 year or one year after BMT Repeat in one year if Z-score below -1 SD for age and height.	
Cortisol	0800h cortisol	ACTH stimulation testing if AM cortisol is <18

healthy growth, optimal nutrition, normal hormone secretion, and normal timing of puberty. These assumptions are not necessarily correct in FA patients. In adolescents with FA, GH secretory ability may decline with advancement of puberty, leading to a decrease in predicted adult height, as BA may proceed more rapidly than growth. Initiation of androgen therapy requires re-evaluation of adult height prediction, as BA may proceed more rapidly. Finally, the process of HSCT itself may contribute to growth failure. Growth rate needs to be followed closely and, if appropriate, short stature should be treated early.

Table 3: Endocrinopathies in Children and Adolescents (ages ≤16 years) with Fanconi Anemia.

Center (reference)	N	Weight	Low Thyroid %	Low Growth Hormone %	Abnormal Glucose/ Insulin %	Abnormal Puberty %	Low Bone Mineral %
NY[1]	47	-1.3±0.2 SD	36%	44%	25% hyperglycemia; high insulin 72%	NA	NA
NIH [2]	19	22% failure to thrive; 27% high weight for height	38%	38% (N=8) MRI: midline defect 17% (N=24)	27% hyperglycemia; high insulin 20%; dyslipidemia 29%	Males: 64% small gonads Females: delayed menarche 28% (N=7).	NA
CCHMC[3-6]	58	24% Body Mass Index (BMI) ≤ -2SD; 33% BMI ≥ +2SD	62%	33% (N=30); small pituitary 45% (N=11)	46% hyperglycemia; high insulin 34% (N=39)	Males: 86% small gonads (N=22). Females: delay 14% (N=7).	NA
U of M[7-8]	12						Low bone mineral density in 52% of 49 children after HSCT

Weight and Nutrition

As mentioned above, the average birth weight in infants with FA is approximately 1.8 SD below the mean; i.e., at the lower end of the normal range. Approximately 40% of FA children are born small for gestational age.

Nutritional and gastroenterological problems are common in at least a quarter of FA patients and may contribute to poor linear growth. In children with FA, weight is generally below average for the general population (-1.5 SD), but is significantly better than the height, indicating that inadequate caloric intake is not sufficient to explain the height deficit. About one-quarter of children with FA have low weight for height (sometimes called failure to thrive), while about

one-quarter to one-third are relatively overweight for their height (Table 3).[1-6] Of note, this frequency of relative overweight is similar to trends being observed in the general population.

Some children may have a smaller than expected appetite; others may experience malabsorption. In addition, illness can raise caloric requirements or metabolism. Children who secrete inadequate insulin do not make use of all of the calories that they eat, and many have elevated blood sugars and lose glucose in their urine. Thus, insulin deficiency can contribute to poor weight gain in childhood.

Alternatively, excess weight gain or glucocorticoid therapy (which can occur during stem cell transplant) can worsen glucose intolerance by making the body require higher insulin levels from a sluggish pancreas. As a result, persons with FA may develop overt diabetes.

Healthy dietary intake should be encouraged, including sufficient calcium and vitamin D and avoiding concentrated sweets, in order to normalize serum glucose and to optimize growth and bone mineral.

Hypothyroidism

Many children with FA have serum thyroid hormone levels that are not fully normal, such as borderline low thyroxine (T4) or free T4 (FT4) or borderline high thyroid stimulating hormone (TSH) (especially in diagnostic samples drawn first thing in the morning) (Tables 3 and 4).[1,2,5] This combination of test results is consistent with mild hypothyroidism. Mild hypothyroidism can occur either because of limited thyroid production by the thyroid gland (primary hypothyroidism) or because of limited TSH production centrally by the pituitary (central hypothyroidism). Forty to 63% of individuals

with FA have thyroid function tests that are borderline for primary hypothyroidism.

One study described reduced thyroid hormone binding in persons with FA.[1] Although reduced thyroid hormone binding is not usually clinically significant, it can make total T4 levels appear low and lead to a false diagnosis of hypothyroidism. Thyroid hormone binding globulin (TBG)-bound T4 (but not other bound forms) was lowest in individuals receiving androgen therapy.[1]

Thyroid treatment was compared to placebo in short children with FA who have TSH >3 mU/L or FT4 in the lowest third of the normal range, whether or not TSH is high.[5] Eight children with FA were treated for seven months with thyroid hormone, compared to seven months with placebo. Children grew significantly better on thyroid hormone than during placebo, and parents felt that their children did better during the thyroid hormone phase.[5] Thus, it is likely that treatment of such children with thyroid hormone will improve their growth.

There is controversy about use of TSH >3 mU/L as a diagnostic criterion for mild hypothyroidism. Among endocrinologists who treat adults, this criterion has been acknowledged as defining the upper limit of TSH in healthy individuals, but treatment is not usually started unless TSH is persistently 10 mU/L or higher.[11-13] Among pediatric endocrinologists, some use a similar approach, while others feel that mild TSH elevation provides an opportunity to treat a short child to achieve potential benefit.[14] Although the thyroid treatment study was conducted in a small number of FA children, children with FA who have small stature and borderline thyroid function tests may benefit from thyroid hormone therapy.[5]

Thyroid function evaluation and treatment

Thyroid function should be evaluated by obtaining an early morning (e.g., 8 am) blood sample for free T4 and a TSH level. All FA patients should undergo screening for hypothyroidism every 6 to 12 months. Abnormal thyroid hormone binding is common; thus, a low total T4 may be misleading. TSH levels above 3 mU/L may indicate mild hypothyroidism.[5]

Hypothyroidism should be treated promptly. Thyroid hormone treatment can improve growth rate. Replacement therapy for hypothyroidism is according to usual dosing for age. Thyroid hormone replacement treatment should be initiated as in non-FA patients—based on low thyroid hormone levels, especially if the TSH is above 3 mU/L at 8 am or FT4 is 1.0 ng/dL or below. An initial dose in a child age 4 to 13 years can be 3 mcg/kg daily, with monthly levels and dose adjustment until the treatment target is achieved. Initial dose in adults is about 1.5 mcg/kg or 100 mcg/m^2. Target for thyroid hormone therapy should be TSH of 0.5 to 2 mU/L in the case of primary hypothyroidism. If the problem is a hypothalamic-pituitary deficiency (low night TSH secretion or central hypothyroidism), target for therapy is a free T4 just above the middle of the normal range.

Growth Hormone Deficiency

Growth hormone deficiency (GHD) has been described in case reports of a few patients with FA.[15-19] About 54% of the subjects tested (under age 20 years) failed to produce GH in response to clonidine stimulation, while 72% failed to raise GH levels in response to arginine stimulation.[1] Timing of peak GH response to stimulation tests was somewhat delayed. GH secretory dynamics are often not normal in FA children during spontaneous overnight GH secretion studies. Taken together,

these test results are consistent with a "hypoactive hypothalamus," leading to "partial" GH deficiency or, alternatively, neurosecretory GH deficiency. GH and insulin-like growth factor I (IGF-I) values are not as severely affected as is height.

Magnetic resonance imaging (MRI) of the brain and pituitary suggest that the pituitary is small in children with FA compared to that of age-matched children without FA.[3] In addition, four of seven FA patients with GHD in a study at the National Institutes of Health had midline brain anomalies on MRI, and one had pituitary stalk interruption syndrome (PSIS).[2] Five patients with FA and PSIS were previously reported, suggesting that PSIS is a diagnostic marker of GHD and severe growth failure.[18]

If growth rate remains slow during thyroid therapy and with improved glucose control, further endocrine evaluation is indicated. Growth velocity may worsen with time and, therefore, longitudinal follow-up is necessary. Screening can be performed by drawing a blood sample for IGF-I and IGFBP3. If both are normal, growth hormone stimulation testing is not necessary. If IGF-I and IGFBP3 values are below -1 SDS for age, evaluation should include standard GH stimulation testing and thyroid function. Evaluation of GH secretory ability in a slowly growing child can be done utilizing clonidine (150 mcg/m^2, maximum dose 300 mcg) and arginine (0.5 gm/kg, maximum dose 20 gm). GH peak is considered normal if 10mcg/L or greater. If GH peak is normal, GH therapy is not indicated in FA children before HSCT even if they meet other FDA-approved indications for GH therapy, such as SGA birth or "idiopathic short stature." Such treatment may be considered in a patient who has had HSCT.

Treatment for growth hormone deficiency

Similar to hypothyroidism, GH deficiency can cause poor growth and can be treated with exogenous GH treatment. Physicians should counsel FA families as to the risks and benefits of therapy. Therapy should be discontinued immediately if routine hematological examination reveals clonal hematopoietic stem cell proliferation.

A short child with FA should be treated with GH if GH deficiency has been unequivocally documented. Treatment with GH prior to HSCT, or in the absence of GH deficiency, is controversial. There is not full consensus among endocrinologists familiar with FA regarding safety of GH therapy prior to or after HSCT. There may be better growth response to GH therapy before use of glucocorticoid therapy than during glucocorticoid therapy. If GH therapy is used in FA patients, doses should probably be titrated to achieve IGF-I concentrations in the mid-normal range for age. As a separate issue, current recommendations are to temporarily discontinue GH therapy during critical illness.[20]

The issue of use of GH therapy in FA subjects raises medical dilemmas. FA patients are at an increased risk of malignancy, including head and neck and gynecological cancers, and are at ~800-fold greater risk of developing acute myelogenous leukemia (AML).[21-23] Thus, FA patients have a lifelong cancer risk even if their bone marrow has been corrected by HSCT. It is not known whether GH therapy could increase these risks.

The incidence of leukemia development in GH-treated patients who do not have predisposing risk factors is not thought to be different from that of the general population.[24-27] Indeed, some authors have postulated that patients who developed leukemia after GH therapy

may have been FA patients with short stature and no other abnormalities.[23] The limited available data do not suggest that GH-treated FA persons are at higher risk of AML (or other malignancies) than are FA patients not treated with GH.

Patient registries have provided useful safety and efficacy data on the use of GH in the general population and in cancer survivors, but include few subjects with the diagnosis of FA.[28-34] Growth rate during GH therapy in FA patients is improved, but not to the extent seen in the non-FA patient. Families should be counseled regarding predicted adult heights, the effects on growth rate of the available treatment modalities, and the potential risks and benefits of GH treatment—with the tempering statement that there is a paucity of clinical data regarding long-term safety of GH therapy in FA patients.

Abnormal Glucose or Insulin Metabolism

Glucose elevation/delayed insulin secretion
Diabetes mellitus occurs more commonly in FA patients than in the general population.[35] In the general population, children with diabetes usually have insulin deficiency. However, in children with FA, insulin levels are usually elevated. Insulin elevation could occur because of resistance to insulin or because of delayed insulin secretion. In FA, there is a relatively high incidence of impaired glucose tolerance, elevated insulin levels, and overt diabetes mellitus. Both androgen therapy and HSCT have been associated with insulin resistance.[30,37] However, glucose intolerance and limited rapid insulin response to food predate either treatment and are inherent features of FA.[4]

Using the World Health Organization criteria, approximately 8% of persons with FA were diabetic, while an additional 27 to 46% had impaired glucose tolerance (Tables 3 and 4).[1,2,4] In addition, up to 72% of persons with FA showed elevated insulin levels by one to two hours after eating. Insulin levels were low at 10 to 45 minutes after oral glucose, suggesting slow initial insulin secretion, while high insulin levels occurred by 60 to 120 minutes.[4] Similar impaired first-phase insulin secretion has been found at the University of Minnesota after HSCT in children with FA.[7] Although the elevated insulin levels could suggest the possibility of insulin resistance, analysis was more consistent with beta cell dysfunction and sluggish insulin release.[4]

Evaluation for abnormal glucose or insulin metabolism

All FA patients should be tested for abnormalities of glucose and insulin homeostasis upon diagnosis and, thereafter, at least annually. Screening of glucose tolerance can be performed with one post-prandial glucose and insulin. The practice of obtaining only serum glucose values or relying on fasting values should be avoided. Measuring glucose values only will fail to identify those subjects in the "early, pre-diabetic" stage. This, therefore, mandates measuring insulin levels. Fasting glucose and insulin levels are often normal, while post-prandial levels may be elevated. The aim of identifying both glucose and insulin level abnormalities is to intervene optimally. Glycosylated hemoglobin (HbA1c) and fructosamine levels may be deceptively normal and are of no use in FA patients prior to HSCT. HgbA1c may be more useful after HSCT.

More detailed annual evaluation should consist of a two-hour oral glucose tolerance test (OGTT,

1.75 gm/kg, maximum dose 75 gm), with serum samples for both glucose and insulin levels obtained every 30 minutes. FA patients with normal OGTT response should be assessed every two years and annually in those with mildly abnormal tests. The prevalence of diabetes mellitus in this population is age and disease progression-dependent, and the majority of FA patients may be at risk.

Beta-cell injury in the FA population may result from damage from excessive reactive oxygen species (ROS). β-cells are susceptible to oxidative damage by ROS in FA persons because of low levels of anti-oxidant enzyme mRNA, protein, and activity of superoxide dismutases, catalase and glutathione peroxidase.[38,39] FA proteins are directly involved with the machinery of cellular defense and the modulation of oxidative stress.[40] Thus, it is possible that impaired early insulin secretion in patients with FA may result from damage from enhanced ROS action on the β-cell.

Medications known to alter glucose metabolism in FA

Several medications used in the treatment of FA are known to alter glucose metabolism, most importantly androgens and corticosteroids. Androgen treatment can lead to significant rise in both glucose and insulin levels.[1] Glucocorticoids may also alter glycemic control. The guidelines regarding glucocorticoid use in FA should be the same as in any other subject; i.e., use the minimum necessary. Pharmacological doses of corticosteroids (as used in transplant patients) commonly lead to hyperglycemia that should be treated in a standard fashion with insulin.

Diabetes treatment: insulin and glucose

FA individuals with low insulin levels and glucose above 200 at 30 minutes after oral glucose load may

need treatment using appropriate insulin regimens involving long-acting basal insulin and short-acting insulin at the time of meals, as in the general population. A serum insulin concentration less than or equal to 44 mcIU/mL (300 pmol/L) at 30 min on the OGTT would be below 2 SD of values seen in normal individuals. In persons with normal fasting glucose but abnormal oral glucose tolerance test results (impaired glucose tolerance) or patients with deficient early insulin secretion, administration of short-acting insulin with meals may be more beneficial than metformin. Since most children with FA have normal fasting glucose, it is not necessary to treat them with long-acting basal insulin.

If post-prandial glucose is consistently above 180 mg/dL, insulin therapy at mealtime (carbohydrate coverage) using short-acting insulin may be considered. A good starting dose is short-acting insulin, 0.5 unit for each 15g of carbohydrate, just before eating. Both child and parent need to know how to check blood sugar. Blood sugars should be checked two hours after the start of each meal initially. If blood sugar after eating remains over 180mg/dL, insulin dose should be increased to 1 unit for 25g of carbohydrate, then 1 unit for 20g, and so on. The goal for insulin therapy is a post-prandial glucose of 90 to 150 mg/dL without hypoglycemia. The American Diabetes Association guidelines for blood glucose control in type 1 diabetes suggest the following finger stick glucose ranges: for toddlers and preschoolers, 100-180 mg/dL before meals and 110-200mg/dL at bedtime; for school age (6-12 years), 90-180 before meals and 100-180 at bedtime; and for adolescents and young adults (13-19 years), 90-130 before meals and 90-150 at bedtime.

Insulin therapy during HSCT

During HSCT, most children with FA require insulin therapy. A regimen similar to that described above may be utilized while the child is able to eat. Additional basal insulin may be required using a long-acting insulin (24 h duration), starting at 0.3 unit per kilogram once daily. If the child is not eating, long-acting insulin can be used alone or short-acting insulin can be given in an intravenous infusion or in the hyperalimentation.

Isolated hyperinsulinemia

Some practitioners have begun treating otherwise normal children and adolescents with FA who have isolated hyperinsulinemia (i.e., without glucose impairment) with oral agents, such as metformin. In cases where the FA individual is overweight, metformin may be the better first choice. Such use in FA should be accompanied by increased surveillance, as potential risk for side effects is not known.

Diet

All persons diagnosed with FA—regardless of OGTT results—should be placed on a healthful diet that avoids concentrated sweets and excessive sugar intake, following the guidelines of the American Diabetes Association. It should be emphasized that this recommendation applies only to concentrated sweets (e.g., juices, soda, and candy) and not all forms of carbohydrate. It is important to ensure adequate caloric consumption and regular exercise.

Dyslipidemia, Obesity, and Metabolic Syndrome

Of the 29 patients with FA who have had lipid studies reported, 55% had dyslipidemia: elevated LDL in 21%, low HDL in 31%, and elevated triglycerides in 10%.[2]

Abnormal lipid profile was associated with glucose intolerance and was observed in 40% of patients with hyperglycemia or insulin resistance. Of those with diabetes, 75% were overweight or obese. FA adults who had diabetes were overweight or obese compared with those without these metabolic abnormalities. Metabolic syndrome (overweight/obesity, dyslipidemia, and insulin resistance) was diagnosed in 21% of the adults with FA, while 12 of 24 children tested had at least one metabolic abnormality: four with insulin resistance; one with diabetes; and seven with dyslipidemia.

Cortisol Sufficiency

Cortisol sufficiency should be evaluated in young FA children who have poor growth and who require major surgery because of the possibility of central hypothalamic dysfunction, even in the absence of a detectible midline central nervous system defect.[3,15] If cortisol and ACTH adequacy have not been assessed, hydrocortisone stress dosing (50 to 100 mg/m^2 intravenous or intramuscular) should be provided for major surgical procedures.

Most FA patients have had normal circadian cortisol levels and normal responses to ACTH administration testing.

Multiple Hormonal Deficiencies

If multiple hormonal deficiencies are found and hypothalamic or other central causes are suspected, a brain MRI should be obtained with emphasis on the pituitary-hypothalamic area.

Puberty

Early onset of puberty
Children and adolescents with FA often have abnormally timed puberty (see Chapter 6). If puberty starts too early, it may progress quickly, thus limiting the number of years that a child can grow.

In the boy or girl with FA who has early onset of puberty at a short height (or before age 11), therapy to delay puberty can allow additional time to grow. Use of Lupron Depot therapy can be used to delay puberty for four years to achieve an average of a 4 to 5 cm increase in adult height.[41]

Delayed puberty
More commonly, boys and girls with FA appear to enter puberty late. Delay can be defined as no signs of puberty in a 12- to 13-year-old girl or a 13- to 14-year-old boy, or no menstrual period in a 14- to 16-year-old girl or by three years after onset of breast buds. Testing of the pubertal axis should be undertaken when delayed pubertal development is noted.

While clinically well-recognized, the cause of delayed puberty in FA is not at all understood. There may be blunted and/or prolonged gonadotropin (primarily luteinizing hormone [LH]) responses to stimulation, suggesting hypothalamic-pituitary dysregulation.

Delayed onset of puberty and pubertal progression should be followed by at least annual physical examination to evaluate stage of puberty. Pubertal hormone concentrations (LH, FSH, estradiol or testosterone) can be useful in adolescent children who are not progressing normally or in adults with symptoms of hypogonadism.

Treatment for delayed puberty in boys

In a boy with no signs of puberty by age 14, low dose testosterone therapy can be initiated, again taking into account height and ability to grow. Injectable testosterone can be given at 45 mg per m^2 monthly for three to six months, with observation for pubertal progression during the following six months.

For long-term low-dose therapy in a short adolescent boy with diagnosed gonadal deficiency, one alternative to injections is topical testosterone gel with an initial dose of 1.25g daily, titrated to achieve reasonable serum levels for age and height. Initial goal might be a testosterone of 50 ng/dL, similar to levels observed in a boy in early puberty.

For mid-pubertal boys, a level of 100-200 ng/dL might be appropriate; for later puberty, a level of 300-350 ng/dL; and for adults a level of 450 to 800 ng/dL is appropriate. Low-dose testosterone dosing can be maintained for several years while the boy grows taller.

If the boy is short for his age, rapid increase in testosterone dose should be avoided. When acceptable adult height is achieved, adult testosterone dosing can be used for sex steroid replacement.

Not every adult man with FA will require testosterone therapy. The decision to treat should be based on clinical evidence of rate of puberty, energy level, physician examination, and laboratory results (testosterone, LH, FSH). Testosterone production or therapy in an adult affects not only bone mineral, but also energy, stamina, muscle development, self esteem, and ability to be appropriately assertive.

Treatment for delayed puberty in girls

In a girl with FA who has no signs of puberty by age 13, low-dose estrogen therapy should be started under the care of the pediatric endocrinologist or adolescent gynecologist, taking into account height and ability to grow[42] (see Chapter 6). The reason to use estrogen therapy in a girl with delay is for medical benefit: to decrease cardiac risk factors, increase BMD, optimize growth rate, and to optimize breast development. One possible low-dose approach is to use a half tablet of conjugated estrogen daily (Premarin, 0.3 mg tablets).

In FA girls who are tall enough to expect to reach adequate adult height, the estrogen dose should be slowly increased every 6 months or so until the full replacement dose of Premarin, 1.25 mg daily, is being taken. Progesterone (Provera, 10 mg by mouth daily for 10 days) should be added when breakthrough bleeding occurs or after two years of estrogen replacement.

In FA girls who are short for age, rapid increase in estrogen dose should be avoided. Low-dose estrogen therapy can be continued for several years while the girl grows taller. When spotting occurs, oral progesterone can be given for ten days, then low-dose estrogen can be resumed. When acceptable adult height is achieved, birth control pills can be used for estrogen and progesterone replacement. Standard birth control pills provide a simple way to give estrogen and progesterone in a monthly pattern. Daily doses of estrogen in these pills range from 20 to 50 mcg of estradiol. The lower end of this range is adequate for the medical benefits (and for birth control), especially in a small adult.

Therapy is not indicated if a girl has normal pubertal development or is having normal menstrual cycles unless there is evidence of ovarian hormone deficiency.

Genital Tract Abnormalities

Developmental anomalies of the genital tract are more frequent in FA patients than in the general population. Boys may be born with cryptorchidism and hypospadias. Many boys with FA have small testes for their age and pubertal status, most likely reflecting reduced Sertoli cell mass and spermatogenesis. Girls with FA may be at higher risk for a unicornuate uterus or hemiuteri.[43] Chemotherapy and radiation therapy, usually given in preparation for HSCT, may also result in gonadal failure.

Fertility

Fertility in FA patients is often impaired, with males often being infertile and females having premature menopause and a significantly abbreviated window of fertility. Infertility in men with FA is at least in part due to a reduced sperm count; on the other hand, in some rare cases fertility has been documented.[43] A specific endocrine basis for the decreased fertility has not yet been identified except for after HSCT, when it can be due to radiation and chemotherapy.

Cryopreservation of embryos or sperm
Cryopreservation of embryos or sperm is being investigated as a reproductive option. Contraception should always be utilized when pregnancy is not desired (see Chapter 6).

Bone Mineral Density

Evaluation of bone mineral density (BMD) in FA has been reported in two studies. All but one of 13 adults with FA were found to have osteopenia or osteoporosis, compared to normal for gender and age.[2] In 49 children (12 with FA), 52% had reduced BMD at 1 year

after HSCT.[8] The effects of HSCT on BMD in children with FA were similar to the bone mineral effects in other children after HSCT. On average, BMD Z-score declined 0.5 SD units during the first six months after HSCT.[8] Longer follow-up will be worthwhile to observe whether BMD declines further or recovers over a longer period of time. These findings point out the importance of intake of adequate dietary calcium and vitamin D.

Dual energy absorptiometry (DXA) evaluation
DXA evaluation of bone mineral density should be performed every five years, beginning at about one year after HSCT and/or beginning at about age 14 if there has been no HSCT. Subsequent yearly studies are indicated if bone mineral is low for height age.

Interpretation of DXA results
Of note, interpretation of BMD studies by DXA will overestimate the incidence of osteopenia in persons with small stature. A DXA estimate of BMD is two-dimensional, and bone thickness is influenced by statural height and, thus, bone size. Interpretation should be adjusted for bone size (such as adjustment for height age or bone age). DXA results should be expressed as Z-score for age (not T-score, which compares BMD to DXA results in young adults).

Bone therapy
Among other dietary recommendations, it is important to maintain adequate dietary intake of calcium and vitamin D to offer opportunity for normal growth and normal mineralization of bone.

- Elemental calcium recommendations: 500 mg daily in a young child; 1,000 to 1,500 mg in an adolescent; and 1,500 mg in an adult.

- Vitamin D recommendations: 400 units daily in a young child; 800 to 1,000 units in an adolescent or adult.

More aggressive intervention with calcium and vitamin D replacement is indicated if BMD is low for height.

Bisphosphonates (oral or intravenous) have been used safely in children with Osteogenesis Imperfecta and in growing children with osteopenia and fractures. Treatment with bisphosphonates may be considered if the child has sustained two or more low-impact fractures and a DXA result is lower than -1.5 SD (after adjustment for height age). Oral bisphosphonates may worsen esophageal reflux. Treatment for any hormone deficiency, especially for pubertal delay, can be beneficial for bone mineralization.

Adults with Fanconi Anemia

Adults with FA must be monitored for a variety of endocrinopathies, including hypogonadism, thyroid function, diabetes mellitus, hyperlipidemia, reduced fertility, and bone mineral density.

Endocrine function

Endocrine function in FA adults has not been well described. Each of the publications of endocrine function in FA patients has included some adults (Table 4). The total number of adults with FA who have had endocrine results reported has been small.[1,2,4,5] Early intervention and therapy may improve quality of life. Treatment of endocrine issues in adults with FA should be monitored by endocrinologists who care for adults, with attention to thyroid status, glucose tolerance, lipid abnormality, gonadal function, and bone mineral density.

Table 4: Endocrinopathies in Adults (ages >16y) with Fanconi Anemia.

Center (Reference)	N	Adult Height	Low Thyroid %	Low Growth Hormone %	Abnormal Glucose/ Insulin %	Abnormal Gonadal Function %	Low Bone Mineral Density %
NY[1]	7	NA	NA (results not separately provided for adults)	NA	NA	NA	NA
NIH[2]	26	42% shorter than -2SD	57%	57% (N=7)	38% hyperglycemia; high insulin 27%; metabolic syndrome 21%.	Males: 43% hypogonadism (N=7) Females: 77% premature ovarian failure (N=13)	92% (N=13) low bone mineral
CCHMC[3-6]	5	60% shorter than -2SD	80%	33% (N=3)	2 diabetic	Males: 80% hypogonadism Females: NA	NA

Medications and Treatments That Affect Endocrine Function

Androgen therapy

Androgen therapy can improve growth rate along with improving blood counts, but can lead to faster maturation of bones, leading to a shorter period available for childhood growth (see Chapter 3). Criteria for androgen use in FA patients with hematological deterioration should be determined by the hematologist or transplanter because of the potential effects on future HSCT. Androgen use may result in virilization of children, in both males and females. While growth rate often improves during androgen therapy, the skeletal advancement often outstrips the gain in height. The child treated with androgen can appear to be growing quite well, but potential adult height may decline. Prior to beginning androgen therapy, a BA x-ray should be

performed. The impact of androgen therapy on height and maturation should be discussed with the family. During androgen therapy, the BA should be reassessed every six months.

Multiple transfusion therapy

Multiple transfusion therapy can affect endocrine function through the mechanism of iron overload (see Chapter 3). Iron deposition in endocrine glands can affect testicular function, contribute to development of diabetes, and can lead to primary hypothyroidism, hypoparathyroidism or pituitary dysfunction.

Hematological cell transplant

Transplantation is associated with a state of illness. Illness is not an optimal time to assess any hormone concentrations, as thyroid levels, growth, gonadal function, nutrition, and glucose regulation are often altered in illness (see Chapter 9 and 10). For example:

- Cytoxan has a known dose-related effect on gonadal function in both males and females.
- Glucocorticoids can lead to elevation in appetite, weight gain, insulin resistance, and hyperglycemia, even to the extent of requiring insulin therapy.
- Metaclopromide raises prolactin. This can lead to galactorrhea or fluid from the breasts, and alteration of thyroid function or pubertal development.
- Anticonvulsant therapy can lead to alteration of thyroid function or thyroid dose requirement. Some anticonvulsants, such as Valproate, can lead to weight gain and altered ovarian function.

After HSCT, additional hormone alterations may be evident as a consequence of the transplantation process. HSCT regimens may result in transient or persistent growth failure due to health alteration, GH deficiency, primary hypothyroidism, gonadal failure or other hormone deficiencies. Most common late effects of HSCT are primary hypothyroidism, partial gonadal failure, and osteopenia. Persons with FA appear to have underlying risk for these endocrinopathies even before HSCT, as well as for hyperglycemia.

Summary

Patients with FA are usually shorter than the general population and shorter than their parent-derived target heights, with average height being just below the third percentile. However, many FA patients are not short. Children with FA frequently have reduced GH secretion, hypothyroidism, and abnormal glucose homeostasis with deficient beta cell secretion of insulin and/or insulin resistance, which may further compromise their growth. In addition, puberty and fertility may not be normal, and bone mineral accrual may be delayed.

Etiology of endocrinopathies in FA is unclear. Hypothyroidism is generally accompanied by elevated TSH levels and, therefore, appears to be of thyroidal (i.e., peripheral) origin, although hypothalamic-pituitary dysregulation leading to abnormal central TSH release may also be present. Hyperglycemia/hyperinsulinemia is generally considered to be related to pancreatic beta cell dysfunction. In contrast, GH insufficiency is probably of hypothalamic or pituitary (i.e., central) origin. Thus, there is not currently a single unifying cause for all of these endocrinopathies. It is possible that endocrine secretory cells are damaged by excessive reactive oxygen species, with inadequate repair mechanisms in FA.

With the recent increased success of hematopoietic stem cell transplantation in curing the hematological complications of Fanconi anemia, the long-term effects of FA are now of greater importance.[8,11] With the prospect of a significantly extended lifespan, we must prepare to treat the previously considered "secondary problems" of non-hematological conditions and to address quality of life issues, such as adult height. The endocrinologist should be involved in initiating and supervising endocrine therapy. Treatment regimens must always be specific for the individual subject. Individuals with FA should be followed for the most common endocrine abnormalities, including growth failure, insulin insufficiency/hyperinsulinemia/glucose intolerance, and hypothyroidism.

Attention to endocrine issues may permit the individual with FA to have the energy and stamina to better enjoy his or her life. Overall treatment philosophy is to ensure an optimal quality of life.

References

1. Wajnrajch MP, Gertner JM, Huma Z, et al. Evaluation of growth and hormonal status in patients referred to the International Fanconi Anemia Registry. *Pediatrics* 2001; **107**: 744-754.

2. Giri N, Batista DL, Alter BP, Stratakis CA. Endocrine abnormalities in patients with Fanconi anemia. *Journal of Clinical Endocrinology and Metabolism* 2007; **92**: 2624-2631.

3. Sherafat-Kazemzadeh R, Mehta SN, Care MM, Kim MO, Williams DA, Rose SR. Small pituitary size in children with Fanconi anemia. *Pediatric Blood and Cancer* 2007; **49**: 166-170.

4. Elder D, D'Alessio DA, Eyal O, et al. Abnormalities in glucose tolerance are common in children with Fanconi anemia and associated with impaired insulin secretion. *Pediatric Blood and Cancer* 2008; **51**: 256-260.

5. Eyal O, Blum S, Mueller R, Smith F, Rose SR. Improved growth velocity during thyroid hormone therapy in children with Fanconi anemia who have borderline thyroid function. *Pediatric Blood and Cancer* 2008; **51**: 652-656.

6. Wadwa RP, Rose SR, Eaton ME, and the Fanconi Anemia Comprehensive Care Center. Endocrine effects of Fanconi anemia. *Pediatric Research* 2003; **52**: 437A.

7. Polgreen LE, MacMillan ML, Wagner JE, Moran A, Petryk A. Impaired first-phase insulin secretion in children with Fanconi anemia after hematopoietic cell transplantation. 2008; (submitted).

8. Petryk A, Bergemann TL, Polga KM, et al. Prospective study of changes in bone mineral density and turnover in children after hematopoietic cell transplantation. *Journal of Clinical Endocrinology and Metabolism* 2006; **91**: 899-905.

9. Gluckman E, Auerbach AD, Horowitz MM, et al. Bone marrow transplantation for Fanconi anemia. *Blood* 1995; **86**: 2856-2862.

10. Wagner JE, Davies SM, Auerbach AD. Hematopoietic cell transplantation in the treatment of Fanconi anemia. Forman SJ, Thomas, ED, eds. *Hematopoietic Cell Transplantation*. Malden, MA: Blackwell Science, Inc: 1998.

11. Spencer CA, Hollowell JG, Kararosyan M, Braverman LE. National Health and Nutrition Examination Survey III thyroid-stimulating hormone (TSH)-thyroperoxidase antibody relationships demonstrate that TSH upper reference limits may be skewed by occult thyroid dysfunction. *Journal of Clinical Endocrinology and Metabolism* 2007; **92**: 4236-4240.

12. Baloch Z, Carayon P, Conte-Devolx B, et al. Guidelines Committee, National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 2003; **13**: 3-126.

13. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. *Journal of Clinical Endocrinology and Metabolism* 2005; **90**: 5483-5488.

14. Rose SR. TSH above 3 is not usually normal. *The Endocrinologist* 2006; **16**: July-August.

15. Aynsley-Green A, Zachmann M, Werder EA, Illig R, Prader A. Endocrine studies in Fanconi's anemia. *Archives of Disease in Childhood* 1978; **53**: 126-131.

16. Zachmann M, Illig R, Prader A. Fanconi's anemia with isolated growth hormone deficiency. *Journal of Pediatrics* 1972; **80**: 159-160.

17. Nordon UZ, Humbert JR, MacGillivray MH, Fitzpatrick JE. Fanconi's anemia with growth hormone deficiency. *American Journal of Diseases of Children* 1979; **133**: 291-293.

18. Dupuis-Girod S, Gluckman E, Souberbielle JC, Brauner R. Growth hormone deficiency caused by pituitary stalk interruption in Fanconi's anemia. *Journal of Pediatrics* 2001; **138**: 129-133.

19. Potchedly C, Collipp PJ, Wolman SR, Suwansirikul S, Rezvani I. Fanconi's anemia with growth hormone deficiency. *Journal of Pediatrics* 1971; **79**: 93-96.

20. Wilson TA, Rose SR, Cohen P, et al. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. *Journal of Pediatrics* 2003; **143**: 415-421.

21. Swift M. Fanconi's anaemia in the genetics of neoplasia. *Nature* 1971; **230**: 370.

22. Auerbach AD, Allen RG. Leukemia and preleukemia in Fanconi anemia patients: a review of the literature and report of the International Fanconi Anemia Registry. *Cancer Genetics and Cytogenetics* 1991; **51**: 1-12.

23. Butturini A, Gale RP, Verlander PC, et al. Hematologic abnormalities in Fanconi anemia: an International Fanconi Anemia Registry study. *Blood* 1994; **84**: 1650-1655.

24. Stahnke N. Leukemia in growth-hormone-treated patients: an update, 1992. *Hormone Research* 1992; **38**: 56-62.

25. Blethen SL, Allen DB, Graves D, et al. Safety of recombinant deoxyribonucleic acid-derived growth hormone: The National Cooperative Growth Study Experience. *Journal of Clinical Endocrinology and Metabolism* 1996; **81**: 1704-1710.

26. Taback SP, Dean HJ. Mortality in Canadian children with growth hormone (GH) deficiency receiving GH therapy 1967-1992. The Canadian Growth Hormone Advisory Committee. *Journal of Clinical Endocrinology and Metabolism* 1996; **81**: 1693-1696.

27. MacGillivray MH, Blethen SL, Buchlis JG, et al. Current dosing of growth hormone in children with growth hormone deficiency: how physiologic? *Pediatrics* 1998; **102**: 527-530.

28. Darendeliler F, Karagiannis G, Wilton P. Headache, idiopathic intracranial hypertension and slipped capital femoral epiphysis during growth hormone treatment: a safety update from the KIGS database. *Hormone Research* 2007; **68** Suppl 5: 41-47.

29. Kemp SF, Kuntze J, Attie KM, et al. Efficacy and safety results of long-term growth hormone treatment of idiopathic short stature. *Journal of Clinical Endocrinology and Metabolism* 2005; **90**: 5247-5253.

30. Quigley CA, Gill AM, Crowe BJ, et al. Safety of growth hormone treatment in pediatric patients with idiopathic short stature. *Journal of Clinical Endocrinology and Metabolism* 2005; **90**: 5188-5196.

31. Bowlby DA, Rapaport R. Safety and efficacy of growth hormone therapy in childhood. *Pediatric Endocrinology Reviews* 2004; **2** Suppl 1: 68-77.

32. Harris M, Hofman PL, Cutfield WS. Growth hormone treatment in children: review of safety and efficacy. *Paediatric Drugs* 2004; **6**: 93-106.

33. Gibney J, Johannsson G. Safety of growth hormone replacement therapy in adults. *Expert Opinion on Drug Safety* 2004; **3**: 305-316.

34. Ergun-Longmire B, Mertens AC, Mitby P, et al. Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. *Journal of Clinical Endocrinology and Metabolism* 2006; **91**: 3494-3498.

35. Morrell D, Chase CL, Kupper LL, Swift M. Diabetes mellitus in ataxia-telangiectasia, Fanconi, xeroderma pigmentosum, common variable immune deficiency, and severe combined immune deficiency families. *Diabetes* 1986; **35**: 143-147.

36. Woodard TL, Burghen GA, Kitabchi AE, Wilimas JA. Glucose intolerance and insulin resistance in aplastic anemia treated with oxymetholone. *Journal of Clinical Endocrinology and Metabolism* 1981; **53**: 905-908.

37. Wilson DM, Frane JW, Sherman B, et al. Carbohydrate and lipid metabolism in Turner syndrome: effect of therapy with growth hormone, oxandrolone and a combination of both. *Journal of Pediatrics* 1988; **112**: 210-217.

38. Lenzen S, Drinkgern J, Tiedge M. Low antioxidant enzyme gene expression in pancreatic islets compared with various other mouse tissues. *Free Radical Biology and Medicine* 1996; **20**: 463-466.

39. Sigfrid LA, Cunningham JM, Beeharry N, et al. Antioxidant enzyme activity and mRNA expression in the islets of Langerhans from the BB/S rat model of type 1 diabetes and an insulin-producing cell line. *Journal of Molecular Medicine (Berlin, Germany)* 2004; **82**: 325-335.

40. Pagano G, Youssoufian H. Fanconi anaemia proteins: major roles in cell protection against oxidative damage. *Bioessays* 2003; **25**: 589-595.

41. Yanovski JA, Rose SR, Municchi G, et al. Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. *New England Journal of Medicine* 2003; **348**: 908-17.

42. Rose SR. Induction of puberty in female hypogonadism. *The Endocrinologist* 1996; **6**: 439-442.

43. Alter BP, Frissora CL, Halpérin DS, et al. Fanconi's anaemia and pregnancy. *British Journal of Haematology* 1991; **77**: 410-418.

Chapter 8

Hearing and Ear Abnormalities in Fanconi Anemia

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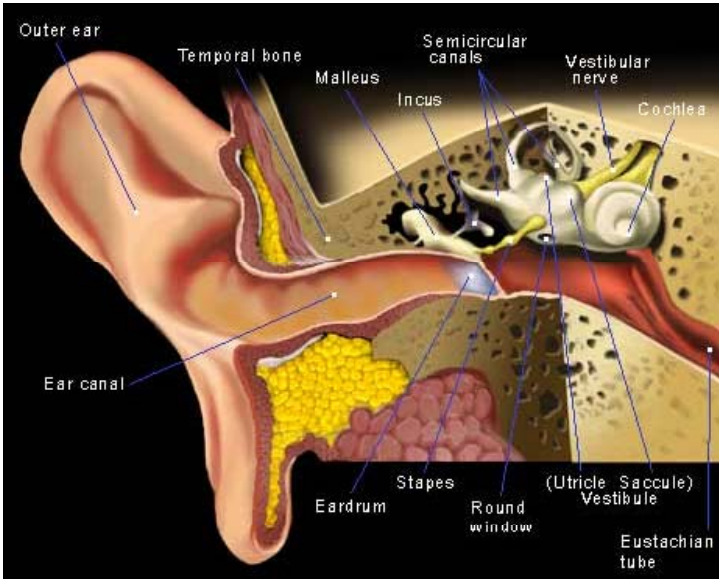
Introduction

In 1927, Guido Fanconi, MD, noticed an association between ear anomalies and FA. In a 1993 review of 370 patients with FA, hearing loss was documented in 11.3% of cases and ear malformations in 14.9%.[1] However, detailed ear manifestations in FA have not been well described in the literature. This chapter will describe normal anatomy and function of the ear, types and degree of hearing loss, the common physical and audiologic findings among the patients with FA, and potential rehabilitation and treatment options for their hearing loss.

Anatomy and Function of the Ear

The ear is made up of three main sections: the outer, the middle, and the inner ear (Figure 1). The two main portions of the outer ear are the pinna and the ear canal. The middle ear consists of the eardrum (tympanic membrane) and three tiny bones called ossicles: malleus (hammer), incus (anvil) and stapes (stirrup). The malleus bone attaches to the eardrum and bridges the gap between the eardrum, the other two ossicles, and the inner ear. The hearing part of the inner ear consists of a snail shell-like cochlea and is filled with several canals of fluids.

Figure 1: Anatomy of Ear



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Sound waves enter the ear canal and vibrate the eardrum like a real drum. These vibrations reach the three tiny ossicles and amplify the sound. Once the sound waves reach the inner ear, the fluid within the cochlea moves and stimulates thousands of tiny hair cells. These hair cells then transform the sound vibrations into electrical impulses, which travel along the auditory nerve from the cochlea to the brain. The brain then translates these signals and allows us to comprehend speech and surrounding sounds.

Types and Degree of Hearing Loss

In general, there are three main types of hearing loss: conductive, sensorineural, and mixed (combined conductive and sensorineural). Conductive hearing loss (CHL) is commonly caused by problems in the outer and/or middle ear, which prevent the sounds from

reaching the inner ear. This is most often due to a middle ear infection, excessive wax accumulation, and/or a hole in the eardrum. Uncommonly, this can also happen if the middle ear tiny bones are malformed or if their movements are restricted from abnormal scar tissue formation.

Sensorineural hearing loss (SNHL) occurs when the hair cells in the inner ear are damaged and unable to transform sound waves into the electrical signals. This type of hearing loss is commonly caused by the aging process, excessive loud noise exposure, and certain drugs, such as particular chemotherapy agents or intravenous antibiotics. If the auditory nerve from the inner ear becomes damaged or is absent, this can prevent sound signals from reaching the brain.

Sounds can be characterized as loud or soft, and high-pitched or low-pitched. Subsequently, hearing loss can be described in terms of the loss of auditory perception in variable degrees of intensity and ranges of pitches. An audiologist performs a hearing test to determine the degree, type and pattern of hearing loss. There are several types of measurement methods, including behavior audiologic tests, otoacoustic emission tests, and brainstem-evoked auditory response tests (BAER). The age and ability of a patient to cooperate will determine which methods are appropriate. In very young children, several tests are often required to characterize clearly their hearing loss.

Hearing loss is classified according to severity in terms of *decibels hearing level* (dB HL; measuring unit for sound intensity): mild hearing loss (> 25-40 dB HL); moderate hearing loss (> 40-70 dB HL); severe hearing loss (> 70-90 dB HL); and profound hearing loss (> 90 dB HL). When there is a mild to moderate hearing

loss, it is difficult to understand normal daily speech conversation, especially in the presence of background noise. When there is a moderate to severe hearing loss, speech must be very loud to be understood. For those with profound hearing loss, communication is very difficult, even with hearing aid amplification.

Ear and Hearing Presentations in Fanconi Anemia

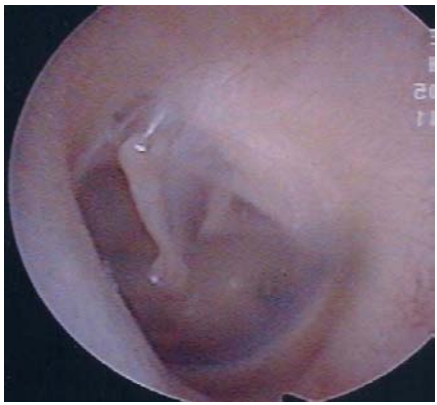
Only a few scattered case reports describing ear manifestations are currently found in the medical literature on Fanconi anemia. In order to systematically examine and define the ear manifestations in FA, a prospective study of twenty FA patients was conducted at the National Institutes of Health, Bethesda, MD, as part of a prospective inherited bone marrow failure syndrome study.[2] Patient ages ranged from 5 to 41 years. Four patients were excluded because either their audiogram and/or temporal bones computerized tomography were not available. Out of the remaining 32 ears in 16 patients, five ears in four FA patients were excluded from the data analysis because of surgical alteration of the congenital status of the ear. Thus, the results reflect the data obtained from 27 ears (16 patients). All patients underwent comprehensive audiologic and otolaryngologic evaluation, including microscopic ear examination.

Microscopic examination of the 27 eardrums revealed abnormally formed eardrums in 17 cases (63%), and one case of an undeveloped, absent ear canal (aural atresia). The abnormal eardrum findings include a smaller eardrum, shorter and abnormally placed malleus within the eardrum, and the presence of abnormal bony islands under the eardrum (Figure 2). Hearing loss was detected in 14 of 27 ears (53%) while normal hearing

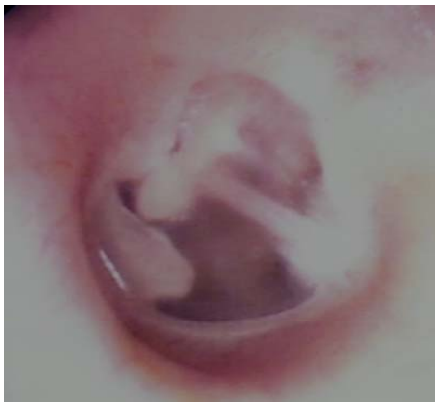
was documented in the remaining 13 ears. The majority of hearing loss was mild, and the most common types of hearing losses were conductive hearing loss (9 cases, 65%), followed by sensorineural hearing loss (3 cases, 21%) and mixed hearing loss (2 cases, 14%). These findings suggest that over half of individuals with FA have a mild conductive hearing loss, probably due to an abnormally developed eardrum and/or ossicles in the middle ear space.

Figure 2:

Normal eardrum



Abnormal eardrum in FA patient



In summary, hearing loss, mostly conductive, is present in greater than 50% of our FA cohort ears. Congenital abnormalities in the tympanic membrane and middle ear ossicles were found in 67%. This incidence of hearing loss and congenital ear malformation is much higher than previously reported. This study suggests that these features characteristic of FA can occur even when hearing is normal or slightly reduced.

Consequences of Hearing Loss

Children use their hearing to develop speech, language, communication skills, and to facilitate learning. Children with a mild hearing loss (25-40 dB HL) have difficulty hearing faint and distant speech. Vowel sounds can be heard clearly, but voiceless consonants (e.g., "s," "f," and "th") can be difficult to hear. School-age students with mild hearing loss have difficulty when functioning in a regular classroom with normally present background noises.[3] Children with moderate hearing loss (41-55 dB HL) miss much of normal conversation. These children may have difficulty learning vocabulary, grammar, and other aspects of verbal communication. Even children with unilateral hearing loss (one ear with normal hearing and other other with at least a mild permanent hearing loss) can be affected. If listening takes place in a consistently noisy environment, their academic potential and social interaction can be compromised.

Early Identification and Intervention for Hearing-Impaired Children

Once hearing loss is identified or suspected, the child should undergo comprehensive medical ear and audiologic evaluation. The earlier the hearing loss is identified and intervention initiated, the less serious the

permanent effects. Often hearing-impaired children require some form of special education or services including:

1) Favorable seating in the class;
2) Amplification systems;
3) Possible surgical intervention to improve hearing deficits;
4) Regular speech and language therapy from a specialist.

The Individuals with Disabilities Education Act (IDEA) mandates that children who have hearing loss receive appropriate early intervention programs from birth to age three and throughout the school years (ages 3-21).[4] Hearing impairment is defined by IDEA as "an impairment in hearing, whether permanent or fluctuating, that adversely affects a child's educational performance." Early intervention services for children are often family-centered and involve multidisciplinary services.

Hearing Amplification

Hearing aids

An audiologist and early intervention team should evaluate the aural amplification needs of hearing-impaired children. Infants as young as four weeks old can be fitted with amplification such as hearing aids and assistive listening devices (ALD). Hearing aids can be beneficial for all types of hearing loss (conductive, senorineural or mixed hearing loss).

Several types of hearing aids are available. Hearing aids differ in design (analog versus digital), size (smaller completely-in-the-ear canal versus larger behind-the-ear), the amount of amplification, and availability of special features. They also have common components that include:

1) A microphone to pick up sound;
2) A processor to make the sound louder;
3) A receiver to deliver the amplified sound into the ear.

The behind-the-ear (BTE) hearing aid is the type of hearing aid most commonly used in children. It can accommodate a wide variety of hearing losses and can be adjusted for different degrees of amplification. It is easier to handle and can be monitored by the child and caretakers. The ear mold, a plastic piece that fits the ear and holds the hearing aid on the ear, can be detached and easily remade as the child grows. The hearing aid is often equipped with a direct audio input capability that can be used with other listening devices.

Assistive listening devices

An assistive listening device can provide excellent help to hearing impaired individuals to function better in daily communication situations. ALDs may be used alone or in combination with hearing aids. These devices provide extra help in specific listening situations, such as in noisy backgrounds (e.g., school classrooms, restaurants, movie theaters, conferences). The most commonly utilized ALDs are based on frequency modulation (FM) systems, like a radio. The personal FM system consists of a transmitter microphone used by the speaker and a receiver used by the listener. For example, this device allows the voice of a teacher, who is wearing a microphone, to be heard more clearly over the background noises of a classroom by a student with an FM receiver.

Surgical Management of Hearing Loss in FA

Middle ear surgery

When the middle ear bones are malformed and unable to vibrate normally, the sound wave cannot be amplified

and transferred to the cochlea; this leads to conductive hearing loss. In FA cases, several possible causes for the inefficient sound transmission through the ossicles include fusion of the malleus to the bony island under a bony eardrum, scarring around the stapes, or an absent ear canal. Sometimes, a portion of the ossicles may miss sound transmission to the inner ear. These causes of conductive hearing loss can sometimes be corrected surgically. Sensorineural hearing loss from the inner ear or auditory nerve damage cannot be restored by ear surgery.

During a middle ear bone surgery to restore normal sound transmission (also called ossicular chain reconstruction), the bony and fibrous tissue restricting ossicular movements is corrected or the immobile ossicle(s) replaced with a middle ear bone prosthesis. Prostheses are commonly composed of artificial bone (hydroxyapatitie), titanium or other biocompatible composite materials. Middle ear bone surgery can be done using either local anesthesia sedation or general anesthesia and typically takes about one to three hours.

When thinking about a middle ear surgery, an ear specialist (also known as an otologist) and the patient and family must consider multiple factors and other treatment options, such as hearing aids. Individuals with serious medical conditions such as heart problems, bleeding tendencies, and high susceptibility for infection from significant bone marrow failure, are probably better candidates for hearing aid trials. Middle ear bone surgery is usually recommended after the age of seven when patients are less susceptible to frequent ear infections.

Middle ear bone surgeries (not specific to FA) typically improve conductive hearing loss in 75% to 90% of the

surgeries.[5] The potential complications associated with ear surgeries are uncommon but include:

1) Further hearing loss or no hearing improvement (in <10% to 20% of surgeries). Total deafness is extremely uncommon;

2) Injury to the facial nerve that runs through the ear, which can cause facial paralysis. This is extremely uncommon, and a facial nerve monitor is typically used during ear surgery to minimize risk;

3) Altered taste on the side of the tongue, which can last for a couple months; and

4) Persistent post-operative dizziness or ringing in the ears, but both are quite uncommon.

Implantable BAHA hearing device

Bone-anchored hearing aids (BAHA) are very useful for those with conductive hearing loss from ossicular chain problems or a congenitally undeveloped ear canal when conventional hearing aids cannot be used, or for those individuals who are not good candidates for traditional middle ear surgery.[6] BAHA works by transmitting sound vibration through the skull and the inner ear, bypassing the external auditory canal and middle ear. It has been used since 1977 in Europe and was approved in the United States in 1996 as a treatment for conductive and mixed hearing losses.

In the BAHA system, a titanium implant is placed during a short surgical procedure and allowed to integrate with the skull bone for three months. A sound processor attached to the titanium implant produces sound vibrations through the skull and inner ear that stimulate the inner ear nerve fibers.

Hearing and Ear Screening for FA Family Members

When a patient is diagnosed with FA, his or her siblings must also be tested to rule out FA. More than 50% of the individuals with FA have hearing loss and abnormal eardrums and middle ear bones. If a sibling does not test positive for FA via a chromosomal breakage test but has classic FA-related ear and hearing findings, the hematologist may wish to rule out FA with further genetic tests, including a clastogen-induced chromosomal breakage test in skin fibroblasts. Approximately 10% to 20% of FA patients with somatic mosaicism may have normal peripheral blood chromosomal breakage tests.[7] In the absence of obvious clinical presentations like absent thumbs and aplastic anemia, a diagnosis of FA is often delayed. Early detection and diagnois of FA means prompt early surveillance, appropriate timely treatment, and eventually improved overall prognosis.

Regular Periodic Auditory Monitoring

FA patients are predisposed to recurrent infections from neutropenia, multiple blood transfusions for severe anemia, and solid organ and hematologic malignancies. Consequently, they are more likely to receive ototoxic intravenous antibiotics (e.g., aminoglycoside), iron-chelating agents (e.g., desferoxamine), and chemotherapy agents (e.g., cisplatin). While they are exposed to these ototoxic agents, their auditory function should be closely monitored with serial audiograms.

Conclusions

1) Congenital hearing loss and eardrum and middle ear malformations are more commonly associated with FA than previously reported.

2) All patients with FA should undergo comprehensive ear examination and audiologic evaluation by an otolaryngologist and audiologist, respectively, who are familiar with FA.

3) FA-related hearing problems can often be successfully treated with either appropriate amplification and/or surgical correction.

Useful Resources for Hearing Impaired

Alexander Graham Bell Association for the
Deaf and Hard of Hearing
3417 Volta Place, NW
Washington, DC 20007
202-337-5220; 202-337-5221 (TTY)
info@agbell.org

American Academy of Audiology
11730 Plaza America Drive, Suite 300
Reston, VA 20190
800-AAA-2336 (V)

American Academy of Otolaryngology-HNS
One Prince Street
Alexandria, VA 22314
703-836-444 (V)
www.entnet.org

American Speech-Language-Hearing Association
10801 Rockville Pike
Rockville, MD 20852
301-897-5700 (V/TTY)
800-638-8255 (V/TTY)

National Institute on Deafness and Other Communication Disorders Information Clearinghouse
1 Communication Avenue
Bethesda, MD 20892-3456
800-241-1044; 800-241-1055 (TTY)
nidcdinfo@nidcd.nih.gov

Self Help for Hard of Hearing People (SHHH)
7910 Woodmont Avenue, Suite 1200
Bethesda, MD 20814
301-657-2248; 301-657-2249 (TTY)
info@hearingloss.org

References

1. Giampietro PF, Adler-Brecher B, Verlander PC, et al. The need for more accurate and timely diagnosis in Fanconi anemia. *Pediatrics* 1993; **91**: 1116-1120.

2. Kim HJ, Brewer CC, Zalewski C. Otologic manifestations in Fanconi anemia. The Triologic Society Meeting. Combined Otolaryngology Spring Meeting. Chicago, IL, 2006.

3. Roberts JE, Wallace IF, Brackett D. *Pediatric Otology and Neurotology*. Lalwani AK, Grundfast KM, eds, Philadelphia, PA, Lippincott-Raven Publishers; 1998.

4. The Individuals with Disabilities Education Act (IDEA) 1997. http://www.ed.gov/offices/OSERS/Policy/IDEA/the_law.html

5. Krueger WW, Feghali JG, Shelton C, et al. Preliminary ossiculoplasty results using the Kurz titanium prosthesis. *Otology and Neurotology* 2002; **23**: 836-839.

6. Tjellstrom A, Hankansson B, Granstrom G. Bone-anchored hearing aids: current status in adults and children. *Otolaryngolic Clinics of North America* 2001; **34**: 337-364.

7. Soulier J, Leblanc TL, Larghero J, et al. Detection of somatic mosaicism and classification of Fanconi anemia patients by analysis of the FA/BRCA pathway. *Blood* 2005; **105**: 1329-1336.

Chapter 9

Matched Sibling Donor Hematopoietic Stem Cell Transplantation

Farid Boulad, MD

Matched sibling donor (MSD) transplantation for Fanconi anemia is currently the best therapy available to cure the FA patient of marrow aplasia, to prevent progression to myelodysplasia or leukemia or cure the myelodysplasia or leukemia if they are already present.

Overview

In the early 1980s, the use of high-dose cyclophosphamide and radiation in preparative stem cell transplant regimens for FA patients from matched sibling donors often resulted in excessive organ toxicity and death in the early post-transplant period. Eliane Gluckman, MD, Hôpital St. Louis in Paris, showed that the extreme hypersensitivity of FA patients to high dose alkylator therapy or irradiation was an inherent aspect of the disease.[1] The use of low doses of cyclophosphamide (20-40 mg/kg) combined with 400-600 cGy of thoraco-abdominal or total body irradiation resulted in reduced toxicity, substantially improved the outcome for the FA patients transplanted from HLA-matched donors, and became the standard of care cytoreductive regimen for FA patients transplanted from matched sibling donors.

In the 20 years since, and through collaborations sponsored by the Fanconi Anemia Research Fund and the IBMTR/ABMTR,[2] physicians from a number of hospitals with expertise in FA transplants have been working

on developing protocols to reduce the toxic effects of standard chemotherapy and radiation preparative regimens, while enhancing engraftment and reducing graft-versus-host disease (GvHD). The collaborations are critical because of the small numbers of FA patients undergoing transplantation.

Results of Transplants from Matched Sibling Donors

Research into the most effective protocol for MSD transplants for FA patients is ongoing. Several centers around the world, including Hôpital St. Louis (France); IRCCS Gaslini and IRCCS Policlinico, San Pavia (Italy); University of Paraná (Brazil); Hadassah Hospital (Israel); Charité Hospital (Germany); Tokai University (Japan); and, in the U.S., the University of Minnesota; Cincinnati Children's Hospital Medical Center; Hackensack University; and Memorial Sloan-Kettering have been active in transplantation of patients with Fanconi anemia. Early results of transplants of FA patients from matched sibling donors are encouraging (Tables 1 and 2).

Outcomes for several large series of patients with FA who have received transplants from matched sibling donors have been published, comprising a total of approximately 250 patients. Results of earlier studies were associated with a disease-free survival rate of 64%. Recently, data from several centers reflect very encouraging outcomes of 81-93%. These results are similar to those obtained in non-FA patients with non-malignant hematologic disorders, such as idiopathic severe aplastic anemia or the hemoglobinopathies (thalassemia and sickle cell disease), for which hematopoietic stem cell transplants represent the standard of care therapeutic approach when HLA-matched sibling donors are identified.

Table 1: HSCT for Fanconi Anemia from Matched Related Donors – TBI-based Cytoreductive Regimens

Author(s); Year	**Socie, Gluckman; France 2007**	**Ayas; Saudi Arabia 2001**	**Dufour; Italy 2001**	**Harris; Cincinnati 2007**
N	**50**	**19**	**27**	**35**
Age	11 (4-26)	9 (3-15)	6 (2.4-13)	7.6 (3-23)
Diagnosis	AA 43 MDS 7	AA	AA 25 MDS 2	AA 30 MDS/ AML 5
Cytoreduction	CY 20-40 TAI 500 hATG 120	CY 20 TAI 400 hATG 160	22 pts w/ TBI/TAI 500 CY 20; 5 pts w/ CY 120	CY 20 TAI 400 hATG 120
GvHD Prophylaxis	CSA	CSA 13; CSA/MTX 6; hATG 120 19	CSA/MTX (26); MTX (1)	CSA/ Steroid ATG 120
Graft	BM 46 Cord 4	BM	BM 26 Cord 1	BM 32 Cord 3
Graft Failure	4/49	2/19 (late)	8%	2/35
Mortality	18: 1 Rejection; 7 GvHD; 4 Secondary malignancy; 6 Other	5: 1 Sepsis; 1 Bleeding; 2 CMV; 1 AML	18.5% (Overall and Treatment-related mortality (TRM)	11% 2 TRM; 1 Leukemia; 1 Secondary malignancy
Disease-Free Survival	**64%** 32/50	**74%** 14/19	**81.5%**	**89%** 29/35

Cytoreductive regimens used in these published studies have mainly included:

- Total lymphoid irradiation, Cyclophosphamide (CY) and ATG (France, Italy and Cincinnati);
- Fludarabine (Flu), Cyclophosphamide, and ATG (Israel, Japan, Italy and Minnesota);
- Cyclophosphamide alone (Brazil).

Table 2: HSCT for Fanconi Anemia from Matched Related Donors – Non-TBI-based Cytoreductive Regimens

Author(s); Year	**Bonfim, Pasquini; Brazil 2007**	**Bitan, Slavin; Israel 2007**	**Yabe, M, Yabe, H; Japan 2008**	**Ebell; Germany; Personal Communi-cation**	**Gillio; New Jersey; Personal Communi-cation**	**Wagner, MacMillan; Minnesota 2006**
N	**43**	**5**	**5**	**2**	**3**	**11**
Age	9 (5-29)	12 (9-31)	8 (6-17)	?	?	9.5 (4-22)
Diagnosis	AA	AA 3 AML 2	AA	AA	AA	AA 10 MDS 1
Cyto-reduction	CY 60	CY 10 Flu 180 fATG 40	CY 40 Flu 150 rATG 5	Bu 2 Flu 180 fATG 60	CY Flu ATG	CY 20 Flu 175 ATG 150
GvHD Prophy-laxis	CSA/ MTX	ATG/ Campath CSA	CSA or CSA/ MTX	OKT3 CSA	CSA/ Steroid ATG	CSA/ Steroid
Graft	BM	BM 3 Cord 1 PBSC 1	BM	BM PBSC	BM	BM 8 Cord 3
T-cell Depletion	None	None	None	None	None	Yes: 8 of 11
Graft Failure	5/43	0	0	0	0	1/11
GvHD Acute >Grade 2 Chronic	Acute 17%; Chronic 28%	Acute 1; Chronic 1	None	?	None	Chronic 1
Mortality	6% 2 Rejection; 1 TRM	0%	0%	1/2	0%	2 of 11: 1 Leukemia; 1 GvHD
Disease-Free Survival	40/43	**5/5**	**5/5**	1/2	**3/3**	9/11

The combination of these cytoreductive regimens, followed by unmodified marrow grafts used by most centers, was associated with a risk of primary or secondary graft failure of 5-10%. Graft-versus-host disease prophylaxis included mostly cyclosporine (CSA), either alone or with steroids. A few centers used other agents, including methotrexate (MTX), ATG, OKT3 or Campath. With such regimens in the largest series, the risk of acute GvHD varied from as low as 8% (using CSA/ MTX) to as high as 55% (using CSA alone).

One center, the University of Minnesota, used the CY/Flu/ATG cytoreductive approach followed by T-cell depleted marrow grafts, resulting in minimal graft failure or GvHD.

Physicians who transplant FA patients continue to test research protocols to find more effective transplantation methods. The reader is urged to contact the FA specialists listed in the Appendix for their most current protocols.

The consensus of the physicians who participated in the development of these guidelines is as follows: if the local transplant center has performed fewer than five transplants for FA, strong consideration should be given for referral to a transplant center with greater experience in transplants for FA. FA patients often experience complications which are not routine in other transplants, such as a marked increased risk in organ toxicity (mucositis, GI toxicity, hemorrhagic cystitis), infections, graft failure, GvHD and the development of glucose intolerance requiring insulin therapy.

Proceeding to Transplant

Definitive diagnosis
An FA patient being considered for a matched sibling donor BMT must first have a definitive diagnosis of FA (see Chapter 2).

Patients with a proven diagnosis of FA who have a matched sibling donor are all potential candidates for transplant. The indication and timing of the transplant are sometimes controversial and depend on several factors including (1) the patient's hematologic status; (2) the patient's age and overall clinical condition; (3) the transplant center and experience, as well as the

transplant physician's recommendation; and (4) the parental or adult patient's decision.

The decision-making process in the timing of transplantation is difficult and must include multiple factors:

- The vast majority of patients will progress to aplastic anemia and/or MDS/AML without transplant.
- Transplants for FA using matched sibling donors have a very good chance of success, at 85-90% in FA-specialized transplant centers;
- However, transplants are associated with a risk of peritransplant mortality of 10-15% and a risk of chronic GvHD for a "minimum" of 12% (with unmodified transplants);
- In general, results of transplants are better for patients with aplastic anemia than with MDS/AML;
- Results of transplants are generally better for patients who are younger, partly due to a lower risk of GvHD; and
- The patient's overall vital organ status, such as renal or hepatic function, influences the transplant outcome.

In addition to these factors, the following are relative and absolute indications for transplantation of FA patients from matched sibling donors based on patients' hematologic status and age:

Absolute indications

- Severe aplastic anemia and transfusion dependence. In this case, no trial of androgens prior to proceeding to BMT.

- High-risk myelodysplastic syndrome; i.e., refractory anemia with high-risk chromosomal abnormalities (involving chromosomes 3 or 7) or marrow blast count >5%.
- Acute myelogenous leukemia.

Relative indications

- Moderate isolated cytopenias or moderate aplastic anemia with evidence of progression towards transfusion dependence.
- Low-risk myelodysplastic syndrome; i.e., refractory anemia with no chromosomal abnormalities or low-risk chromosomal abnormalities.

Definitions of the Transplant Indications

Significant cytopenia

Platelet count <50,000, or hemoglobin <8 gm/dl, or transfusion dependence, or an ANC <1000 represent significant cytopenias. Any single cytopenia is reason enough to proceed to transplant in a patient with FA who has a matched sibling donor available. A patient with an ANC >1000 who has frequent severe infections is also eligible for early transplant.

Age over ten years

Univariate statistical data show that the outcome of transplant in general and for FA in particular is worse for those patients over age ten. However, the more important factors are probably the degree of cytopenia, the intercurrent development of serious infections, the number of prior transfusions, the prior use of androgens, and the presence of clones or dysplasia, all of which increase with age and are probably responsible for much of this increased risk. Thus, age over ten is not an absolute indication for immediate MSD BMT, but

should be considered in the final equation. If the patient has acceptable counts and is generally healthy on no medications, including androgens, transplant can probably be safely delayed.

Evidence of a clone, MDS or leukemia

Patients with FA may develop cytogenetic clones. These clones may disappear or be replaced by some other clone on a subsequent bone marrow test done just a few months later. The danger signs which should lead to transplantation include a clone which is steadily increasing in percentage, or a clone involving chromosome 7 or showing a gain in the 3q26q29 segment. Data suggest that such patients have a higher risk of progression to MDS or AML.

Myelodysplasia is a hard call in aplastic-appearing marrows of FA patients. Mild dysplasia is often seen, but significant multilineage dysplasia should prompt consideration for transplant. It is advisable to have bone marrow smears reviewed by physicians at a center with extensive experience in FA patients. Patients with FA who have developed advanced MDS or leukemia clearly need immediate referral for transplant. The goal is to proceed to transplant before definite advanced MDS or leukemia develops.

Occasionally, patients do progress quickly into advanced MDS or leukemia, making it necessary to transplant them at once. This is a very difficult situation which is best left in the hands of a center with extensive experience in FA. Some centers use an induction protocol prior to transplant, with a regimen specifically modified for FA patients. Patients are first administered a mild course of chemotherapy to get them into remission. Two to three weeks later, patients begin preparative therapy for a bone marrow transplant. Other centers

proceed directly to transplant using a total body irradiation or busulfan based regimen.

Organ Function Parameters

Patients should have adequate renal function (GFR >50 ml/min/1.73 m^2), cardiac function (shortening fraction >27%), and liver function (bilirubin <2 mg/dl, SGOT/ SGPT <5x normal). If pulmonary function testing can be performed, those patients with a DLCO <50% normal or an FEV1 <60% of normal may be at increased risk of pulmonary failure post-transplant. These guidelines assume that the patient will be treated with a low-intensity preparative regimen.

Transplants in patients with relatively poor organ function can be successful, but should be performed in a specialized center with extensive experience in FA transplants.

Androgen and Cytokine Therapy Prior to Transplant

FA patients are sometimes treated with androgens (see Chapter 3). This treatment is known to affect liver function adversely and is associated with other significant side effects. Experts generally recommend that an FA patient not receive androgens if the patient has a matched sibling donor available.

Before starting androgen therapy in an FA patient, the physician should first obtain family HLA typing to see if a matched sibling donor is available. Subsequently, the physician should speak to a transplant center experienced in FA transplants about the current recommendations relative to androgens and their later adverse effects on transplant outcomes.

Use of cytokines such as G-CSF is discussed elsewhere in this publication (see Chapter 3). There is no evidence that prior use of cytokines increases the risk of a later transplant. Thus, the use of cytokines, especially G-CSF for a low ANC, provided the marrow has been tested and shows no evidence of a clone or dysplasia, is acceptable. However, if the patient does not respond to the cytokine, the patient should proceed to transplant. Currently there is no generally available platelet-stimulating cytokine available with acceptable toxicity levels for children with FA.

The Transplant

Definition of matched sibling donor
Only those FA patients with a full genotypic sibling match are, in general, eligible for the low-dose regimens utilized for matched sibling BMT. Thus, patients with relatives who are full 6/6, 8/8 or 10/10 matches, but not genotypic matches, should not be treated on a matched sibling protocol, but should rather be treated on a regimen suited for an unrelated donor. This recommendation is based on the higher risk of GvHD and graft rejection in these phenotypically matched but not genotypically matched donor-recipient pairs.

To ensure that the donor does not have FA, DEB or MMC testing of the donor's peripheral blood lymphocytes must be performed. Some physicians recommend that the donors undergo mutation testing or have DEB or MMC testing done on skin fibroblasts to be certain that the donor does not have FA. Such FA-undiagnosed donors may have negative DEB or MMC testing due to high levels of mosaicism in peripheral blood lymphocytes, meaning that a large percentage of peripheral blood lymphocytes may have undergone reversion by

reciprocal recombination and may not show alkylator sensitivity above normal. Most of these undiagnosed patients will still have an elevated MCV on the CBC, the earliest sign of marrow dysfunction in FA. Thus, many physicians consider that a donor who is clearly DEB or MMC normal and has a normal MCV on the CBC is an acceptable donor for a sibling matched by HLA typing. If a potential donor is shown to be an FA carrier by mutation analysis, (i.e., has one abnormal copy of the FA gene and one normal copy), that person is acceptable as a donor for a MSD transplant. There is currently no evidence that a carrier has any increased risk of marrow failure, leukemia or other cancers, although studies at the NIH and The Rockefeller University are investigating this question.

Pre-transplant Evaluation

Patient

The pre-transplant evaluation should confirm the HLA typing by high-resolution Class I and Class II testing in both the donor and recipient at the lab utilized by the center to perform the transplant.

The patient should undergo a pre-transplant bone marrow evaluation including an aspirate and biopsy, cytogenetics, FISH for 7 and for 3q27 (or by comparative genomic hybridization [CGH] to rule out a 3q26q29 gain), and an evaluation to rule out MDS or leukemia, including flow cytometry if necessary.

Blood studies should include a CBC and differential, and a comprehensive metabolic panel. A ferritin level should be obtained and, if elevated (especially if >2000), consideration should be given to a quantitative evaluation for hemosiderosis (MRI liver or liver biopsy). Patients with elevated ferritin levels should

possibly be treated with iron chelation therapy for a period of time to reduce the iron deposition in the liver prior to transplant.

Patients should be closely evaluated to look for evidence of active infection. Standard testing would include serology for CMV, EBV, HSV, VZV and the hepatitis viruses. Most centers perform PCR testing on blood for CMV or EBV if the serologies are positive. Some centers perform CT scanning of the head, sinuses, chest, abdomen, and pelvis to look for occult fungal infections, since aspergillosis is one of the more common causes of death in FA BMT recipients.

Donor

Prior to proceeding to transplant, all matched sibling donors should be evaluated for FA. This should include a medical history, physical examination including height percentiles, skin examination, and detailed examination of the extremities. Blood work should include a CBC for evaluation of counts and MCV. Testing for Fanconi anemia should be performed as discussed above (see Chapter 2).

Stem Cell Grafts

The usual accepted stem cell source for a sibling donor transplant is bone marrow, as most of the available data published in the medical literature have been obtained using marrow grafts.

Cord blood from a full sibling is equally effective, although the number of sibling donor cord blood transplants reported in the registries is low. The engraftment rate, the incidence of GvHD, and the overall survival are favorable in these patients.

Peripheral blood stem cells (PBSC) are generally not

used in MSD FA transplants for two reasons: first, most donors are children and apheresis of a young donor is difficult and more risky, often requiring placement of an apheresis catheter; and second, when centers do not use T-cell depletion, there appears to be a higher risk of chronic GvHD in the PBSC transplants. Depending on the donor's age and whether there will be T-cell depletion of the graft, the PBSC collection and transplant could be a valid alternative as a stem cell source. However, this undertaking should be part of a clinical trial.

Cytoreduction

Low doses of cyclophosphamide (20-40 mg/kg) combined with 400-600 cGy of thoraco-abdominal or total body irradiation were the standard of care cytoreductive regimen for FA patients transplanted from matched sibling donors, as pioneered by Dr. Eliane Gluckman. Results of transplants using this approach represent almost half of the transplanted FA patients by three of the major transplant groups published in the literature. The Paris group, the Italian AIEOP/GITMO group, and the Cincinnati group used a cytoreduction that included TAI or TBI (400 or 500 cGy) and cyclophosphamide (20 mg/kg for aplastic anemia or 40 g/kg for MDS/AML). All three groups used unmodified grafts. Overall, risks of graft rejection and acute toxicity were within acceptable range.

However, recently, a number of investigators have eliminated the use of radiation in the preparative regimen in FA patients because of a fear of the later development of secondary cancers, especially squamous cell carcinomas (SCC) of the head and neck or the genitourinary tract. FA patients are at a much higher risk of developing SCC, at a higher frequency and at an earlier age than patients without FA. Radiation may further

increase or accelerate this risk. Additionally, radiation can be associated with other late effects such as endocrine dysfunction with delayed growth, hypothyroidism, and gonadal dysfunction.

Three non-TBI regimens have been used for transplantation of FA patients from matched sibling donors. For several years, the Curitiba (Brazil) group has pioneered a cyclophosphamide-only protocol, and established a dose de-escalation trial. The most recent results (2007) report on 43 patients who received cyclophosphamide at 15 mg/kg/day x 4 to a total of 60 mg/kg followed by unmodified marrow grafts. Here as well, risks of graft rejection and acute toxicity were within acceptable range.

Several other FA transplants groups used a cyclophosphamide/fludarabine/ATG approach, followed by unmodified marrow grafts, with one alternative cytoreduction including busulfan/fludarabine/ATG. Although these represent a smaller patient series (15 pts/5 centers), there appear to be acceptable risks of graft rejection and toxicity. Finally, the Minnesota group has been pioneering the cyclophosphamide/fludarabine/ATG cytoreductive regimen BUT followed by T-cell depleted grafts with very promising results.

Recently, one transplant group from Tunisia used a low-dose busulfan/cyclophosphamide approach with ATG, and a CSA/MTX GvHD prophylaxis approach. This regimen was associated with an 18% risk of graft rejection and, therefore, should not be a recommended approach for cytoreduction of FA patients.

GvHD and Graft Rejection Prophylaxis and Treatment

FA patients who have received a BMT may be at increased risk of SCC, compared to those FA patients who have not received a BMT. One factor associated with this increased risk is the development of acute and/or chronic GvHD, especially in the younger patients. The use of radiation appears to be a secondary cause of cancer. Thus, the primary emphasis today should be on the prevention of acute and chronic GvHD.

The initial standard approach used by the Paris group included the sole use of cyclosporine (CSA) with unmodified marrow grafts. Other approaches to prevention of acute and chronic GvHD have included the use of different combinations of cyclosporine and methotrexate (MTX), cyclosporine and steroids with or without the addition of ATG in the preparative therapy, also using unmodified transplants. With such regimens, in the largest series the risk of acute GvHD was 55% (CSA alone); 36% (CSA or CSA/MTX); 23% (CSA/steroids/ATG); 17% (CSA/MTX); and 8% (CSA/MTX). Thus, more aggressive GvHD prophylaxis using the standard cyclosporine/methotrexate combination appears to be associated with a decreased/acceptable rate of acute GvHD. However, there are pros and cons for the different combinations. The addition of methotrexate may result in a slower rate of engraftment, increased risk of mucositis, and possibly liver dysfunction. It should not be used for cord blood transplants. The addition of ATG and/or steroids, on the other hand, may result in increased risks of infections.

Using these approaches, the risk of chronic GvHD varied from 12% to 70% in the different series. However,

in the case of chronic GvHD, there did not appear to be a suppression combination regimen that produced superior outcomes.

The use of T-cell depletion of the donor stem cell source has become more and more the standard approach for the transplant of FA patients from unrelated donors, and has been associated with low risks of GvHD. This approach, in general, is associated with the lowest risks of GvHD in transplants of non-FA patients. Therefore, to eliminate the risks of GvHD and the subsequent increased risk of secondary malignancies, the use of T-cell depletion in transplants of HLA-matched siblings should continue to be studied as part of a trial at a BMT center of excellence for the treatment of FA.

Post-transplant Evaluation

Transplant Complications

Early complications

Early post-transplant complications include (1) graft rejection, (2) graft-versus-host disease, (3) organ toxicity, and (4) infections. FA patients appear to be more at risk for these complications, compared to non-FA patients. The physician must follow FA patients post-transplant carefully and aggressively, including close follow-up of (1) clinical status (rashes, diarrhea, liver enzymes); (2) blood counts; (3) aggressive monitoring of infections with PCR or antigenemia testing for viruses (CMV, EBV, adenovirus) or fungi (galactomanann and b-D-Glucan), and appropriate monitoring of anti-microbial levels (voriconazole, ganciclovir, etc.).

Late complications

Physicians must provide follow-up of patients with FA by monitoring their blood counts for secondary

leukemia and screening for oral and urogenital cancers. Additionally, patients must be monitored for chronic GvHD and for other post-transplant late effects such as organ toxicity (cardiac, pulmonary, renal) or endocrinopathies (diabetes, hypothyroidism, gonadal dysfunction).

Finally, the previously transfused patient must be monitored for hemochromatosis by measures of ferritin and by T2-MRI or SQUID testing for more accurate iron quantitation. Patients with iron overload will need to be treated accordingly. The preferred approach remains the use of periodic phlebotomy for a usual period of one year.

Mixed chimerism status

The physician must follow the chimerism status of patients post-transplant. Rarely, mixed chimerism may exist with the presence of a certain percentage of host cells. Often, mixed chimerism is associated with the absence of any other issues. Rarely, it can be associated with a decrease in blood counts and need more careful attention. Regardless of blood counts, the presence of mixed chimerism could be associated with an increased risk of host-derived leukemia and MDS.

PGD and IVF

Preimplantation genetic diagnosis (PGD) coupled with *in vitro* fertilization (IVF) is an option for families who have a child with FA without a matched sibling donor. If the mother is fertile, the family may consider PGD/IVF to select a fertilized egg which is both FA-negative and an HLA match for their FA-affected child. At the time of delivery, the cord blood can be collected and utilized for the matched sibling donor transplant. More details can be found in the Genetic Counseling chapter.

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References

1. Berger R, Bernheim A, Gluckman E, et al. In vitro effect of cyclophosphamide metabolites on chromosomes of Fanconi anaemia patients. *British Journal of Haematology* 1980; **45**: 565-568.

2. International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry.

3. Neto JZ, de Medeiros CR, Bitencourt MA, et al. Bone marrow transplantation for Fanconi anemia, decreasing the cyclophosphamide dose without irradiation. *Program, Fifteenth Annual Fanconi Anemia Research Fund Scientific Symposium* 2003; 35.

4. MacMillan ML, Tan PL, Auerbach AD, et al. Uniform engraftment and survival after fludarabine-based regimen without radiation in Fanconi anemia patients undergoing genotypically identical donor hematopoietic cell transplantation. *Program, Fifteenth Annual Fanconi Anemia Research Fund Scientific Symposium* 2003; 33.

5. Gluckman E, Auerbach AD, Horowitz MM, et al. Bone marrow transplantation for Fanconi anemia. *Blood* 1995; **86**(7): 2856-2862.

6. Kutler DI, Auerbach AD, Satagopan J, et al. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. *Archives of Otolaryngology-Head Neck Surgery* 2003; **129**: 106-112.

7. Guardiola P, Socie G, Li X, et al. Acute graft-versus-host disease in patients with Fanconi anemia or acquired aplastic anemia undergoing bone marrow transplantation from HLA identical sibling donors: risk factors and influence on outcome. *Blood* 2004; **103**(1): 73-77.

8. Tönnies H, Huber S, Kühl JS, et al. Clonal chromosomal aberrations in bone marrow cells of Fanconi anemia patients: gains of the chromosomal segment 3q26q29 as an adverse risk factor. *Blood* 2003; **101**: 3872-3874.

9. Socie G, Devergie A, Girinski T, et al. Transplantation for Fanconi's anaemia: long-term follow-up of fifty patients transplanted from a sibling donor after low-dose cyclophosphamide and thoraco-abdominal irradiation for conditioning. *British Journal of Haematology* 1998; **103**: 249–255

10. Dufour C, Rondelli R, Locatelli F, et al. Stem cell transplantation from HLA-matched related donor for Fanconi's anaemia: a retrospective review of the multicentric Italian experience on behalf of Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP)-Gruppo Italiano Trapianto di Midollo Osseo (GITMO). *British Journal of Haematology* 2001; **112**: 796-805.

11. Tan PL, Wagner JE, Auerbach AD, Defor TE, Slungaard A, Macmillan ML. Successful engraftment without radiation after fludarabine-based regimen in Fanconi anemia patients undergoing genotypically identical donor hematopoietic cell transplantation. *Pediatric Blood Cancer* 2006; **46**: 630–636.

12. Bonfim CM, de Medeiros CR, Bitencourt MA, et al. HLA-matched related donor hematopoietic cell transplantation in 43 patients with Fanconi anemia conditioned with 60 mg/kg of cyclophosphamide. *Biology of Blood and Marrow Transplantation* 2007; **13**: 1455-1460.

13. Farzin A, Davies SM, Smith FO, et al. Matched sibling donor haematopoietic stem cell transplantation in Fanconi anaemia: an update of the Cincinnati Children's experience. *British Journal of Haematology* 2007; **136**(4): 633-640.

14. Grewal SS, Kahn JP, MacMillan ML, Ramsay NK, Wagner JE. Successful hematopoietic stem cell transplantation for Fanconi anemia from an unaffected HLA genotypically-identical sibling selected using preimplantation genetic diagnosis. *Blood* 2004; **103**(3): 1147-1151.

Chapter 10

Unrelated Donor Hematopoietic Stem Cell Transplantation

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Introduction

As of June 2008, allogeneic hematopoietic cell transplantation (HSCT) remains the only treatment that can correct the hematologic complications common to most patients with Fanconi anemia. HSCT from HLA-identical sibling donors is generally associated with an excellent outcome (i.e., survival rates in excess of 85% for children less than 10 years of age and 65% for children and adults together).[1,2] HSCT from alternate (i.e., HLA-mismatched related or unrelated) donors, however, is relatively more complex and challenging. It is associated with a higher risk of complications, with survival rates lower than that observed with HLA-matched sibling donors, although significantly better than survival rates of five years ago. For these reasons, it is recommended that HSCT from alternate donors be performed at selected transplant centers experienced in the care of FA patients, in the use of alternate donor HSCT, and in clinical trials which are specifically designed to address the high risks of regimen-related toxicity and infection unique to this patient population.

Overview

The general experience with alternate donor transplantation for the treatment of FA has been detailed

elsewhere.[1-9] From these institutional and registry studies, four important findings emerge: 1) survival rates at three years after alternate donor HSCT range between 40-75%; 2) regimen-related toxicity and infection are the primary reasons for treatment failure; 3) risk factors for best outcome after alternative donor HSCT are: age <10 years; recipient cytomegalovirus (CMV) seronegativity; history of fewer than 20 blood product exposures; and use of fludarbine in the preparative regimen; and 4) results with HLA 5-6/6 matched unrelated donor umbilical cord blood are similar to that observed with bone marrow.

Compared to the 2003 edition of this handbook, survival outcomes are significantly better, due to 1) safer and more effective pre-transplant cytoreductive therapies; 2) improved supportive care measures; 3) better methods of HLA-matching between the patient and donor; and 4) earlier referral for HSCT prior to the onset of myelodysplastic syndrome (MDS), acute leukemia and/or systemic infection (Table 1).

Indications for Alternate Donor Hematopoietic Stem Cell Transplant

With improved outcomes, the indications for alternate donor HSCT are increasingly similar to those described for sibling donor HSCT (Chapters 3 and 9). For some patients considered to be at an exceptional risk of transplant-related mortality (e.g., those with severe organ dysfunction, age ≥35 years, pre-existing malignancy or systemic infection), alternative treatment options, such as use of hematopoietic growth factor therapy and androgens, may be appropriate.

If the patient develops persistent and severe cytopenia (i.e., hemoglobin [Hgb] <8 g/dL; absolute neutrophil count [ANC] <500/mm^3; and/or platelets [PLT]

Table 1: Observations since the 2003 Edition

- Transplantation using HLA-mismatched related or HLA-matched/mismatched unrelated donors should be performed at transplant centers that specialize in Fanconi anemia transplants and perform five or more such transplants a year.
- Umbilical blood transplantation is an acceptable alternative, if HLA 8/8 matched marrow is not available.
- Transplantation should be considered prior to the administration of blood products. Data document reduced survival after transplant in recipients of ≥20 blood product exposures.
- Other risk factors adversely affecting survival after unrelated transplant potentially include HLA mismatch, prior exposure to androgens, and number of congenital malformations ≥3.
- Fludarabine, in combination with cyclophosphamide and total body radiation, represents a new standard of care in the setting of unrelated HSCT. It is associated with an increased incidence of engraftment and survival in recipients of umbilical cord blood, peripheral blood stem cells or marrow and appears to reduce the deleterious effect of T-cell mosaicism.

<20,000/mm^3) or evidence of MDS or leukemia, the patient should be offered the option of alternate donor HSCT, provided the patient has adequate organ function and controlled infection (Table 2). Earlier transplantation may be considered for patients with specific mutations deemed to be particularly high risk for rapid progression to MDS or leukemia and markedly shortened survival (e.g., breast cancer [*BRCA*] gene mutations).[10,11]

Table 2: Eligibility for Alternate Donor HSCT

- Severe cytopenia (Hgb <8 g/dL, ANC <500/mm^3, PLT <20,000/mm^3)
- MDS or leukemia
- High risk mutation (e.g**.,** *BRCA2*)
- Absence of an HLA-A, B, DRB1-identical sibling donor

Referral to a transplant center

Transplant centers with valuable areas of expertise exist in many countries. Some centers might be limited to adult transplants or to the use of autologous (patient's own marrow) versus both autologous and allogeneic (another person's marrow). While most transplant centers are experienced in the treatment of leukemia, few have experience with FA.

Table 3: Transplant Center Interview Questions

1. How many allogeneic FA transplants has your center performed? How many in children? How many in adults? How many have survived beyond one year?
2. How many unrelated donor transplants on FA patients has your center performed in the prior calendar year?
3. What specific preparatory therapy does your center recommend? (Obtain the doses of each therapy.)
4. What is your center's long-term follow-up plan for transplanted patients with FA; e.g., growth and development late effects?

To determine the experience of a transplant center being considered, the physician or patient should ask the questions listed in Table 3.

Referring doctors and insurance companies may have associations with transplant centers, often based on experience with patients with leukemia. Proximity to home is a factor that may not be appropriate for the patient with FA, if specific FA expertise is not locally available.

Patients and families should note that they or their advocate can often negotiate with the insurance company concerning where a transplant is performed. A transplant center's experience in FA and the use of alternative donors can change an insurer's preference and allow the development of individual contracts, even when the transplant center is "out of network" or not considered one of the insurer's "Centers of Excellence." Note: "Center of Excellence" is the designation for a center with an existing negotiated contract and is not related to a center's expertise. As a rule, a family should not accept a denial from an insurance carrier without asking a transplant center expert in FA transplants to negotiate with the carrier.

Assessment

An evaluation at an FA transplant center will address the following elements (Table 4).

Past medical history
FA is a genetically and phenotypically heterogeneous disorder, often accompanied by multiple congenital malformations, growth failure, learning disabilities, etc. Congenital malformations may range from none to many and may involve any of the major organ systems.

Table 4: Required Elements of the History to be Prepared Prior to Going to the Transplant Center

- Reason for FA testing.
- Date of diagnosis.
- Results of DEB and MMC tests, including evidence of somatic mosaicism (i.e., presence of DEB/MMC-resistant cells).
- Results of complementation group or mutation analysis (including *BRCA2* testing for those with early onset of leukemia [age <6 years] or negative complementation group testing results).
- List of congenital malformations and treatments (e.g., kidneys, gut, liver, bladder, heart, lungs, limbs).
- Gynecological (females) and sexual history (males and females).
- Chronic pain and management.
- Nutritional assessment.
- Documentation of endocrine status. Consider the use of growth hormone therapy prior to the use of agents such as TBI and steroids that could interfere with later therapy.
- List of medications and responses to treatments (e.g., androgens, steroids, hematopoietic growth factors, chemotherapy, radiotherapy, hormonal replacement) and alternative therapies (complementary medicine).
- Transfusions (e.g., number of red cell or platelet exposures).
- Known alloimmunization.
- Details of prior infections (organism, antibiotic sensitivities, sites, response to treatment, history of prophylaxis).
- History of cancer (site, treatment).

Because certain malformations and treatments may interfere with HSCT, the physician must take a complete medical history, including evaluating these malformations and prior or ongoing treatments. All infectious disease complications, prior use of androgens, prior history of hepatic adenomata, and cancer must be carefully detailed, as these complications may affect the design of the treatment plan for transplantation. The history must detail any past surgeries (e.g., tracheoesophageal fistula, duodenal atresia, ureteral reflux); medical treatments (e.g., metoclopramide and ranitidine for gastroesophageal reflux, Bactrim prophylaxis for ureteral reflux); and general issues (immunizations, allergies, use of vitamins, iron supplements, and herbal remedies).

Family medical history

The family medical history is extremely important. Without exception, all siblings, regardless of phenotype and HLA match, must be tested for FA. It has been repeatedly shown that siblings who appear to be completely healthy and without any manifestation suggestive of FA may still have FA. Further, it is important to determine if there are full siblings who are no longer living with the family or, because of donor compatibility issues, if the child with FA is adopted.

Social history

Behavioral, school and work performance issues should be reviewed. Alcohol and smoking (cigarette and cannabis) exposure should be determined, because of cancer risk and risk of infection in the early transplant period. Additionally, the physician should inquire about the use of other drugs which potentially could interfere with liver function or metabolism rates of drugs used in the transplant setting.

Concurrent medications
Use of complementary medications should be assessed by the transplant team. Some agents, like echinacea, believed to help the immune system and prevent colds, flu and infections, may cause rashes and diarrhea (similar to symptoms of graft-versus-host disease). Others, like ginkgo, believed to treat asthma and bronchitis as well as improve memory, may cause bleeding problems. St. John's wort, believed to treat anxiety and depression, may interfere with the metabolism of cyclosporine A, an important drug used in the early transplant period. A summary of published results of various complementary medications and potential side effects can be found at http://nccam.nih.gov.

Physical examination
Prior to HSCT, the physician will assess potential factors that may alter the risk or plan of transplant therapy. Careful attention will be paid to the oropharyngeal area (precancerous lesions, infection, dental health); ears (hearing); nose and sinuses (infection); respiratory system (infection, reactive airway disease); and urogenital system (infection, bladder anomalies, cervical/vulvar precancerous/cancerous lesions). The general examination should carefully document pre-existing cutaneous changes (e.g., *café au lait* spots, areas of hyper- or hypopigmentation, nail abnormalities, nevi, and lesions characteristic of squamous cell carcinoma or melanoma), heart sounds/murmurs, liver and spleen size, and scars from prior surgeries.

Donor Identification: HLA Typing and Donor Search Process

Principles of the donor search
Physicians should pursue an extended family and/or

unrelated donor search well before the development of severe marrow failure, transfusion dependence, MDS or AML, so that delays are minimized when HSCT is required. According to the National Marrow Donor Program (NMDP), the average time from search initiation to HSCT is approximately 3-4 months[12]; therefore, a search should be initiated well before the need for transfusions or development of leukemia. In general practice, the NMDP will allow the transplant center to "reserve" a donor for several months without having received a request for a marrow harvest or peripheral blood stem cell collection date. After that time, the NMDP will request more specific information as to the proposed timing of the transplant procedure. In some cases, the NMDP and medical director of the Collection Center will permit an exception and allow the donor to be kept on "reserve" without a specific date. This is decided on a case by case basis. It is important to recognize that a donor on "reserve" may still appear on other patient searches so, although uncommon, it is possible that a patient with urgent need could request that donor, in which case the NMDP will work to seek an equitable solution. Note: A donor may not be reserved for years in the hope that the "perfect" donor will be available in the future. Also, it is not generally possible to collect marrow and store it for the future.

A search should be performed with urgency if the patient has advanced bone marrow failure, necessitating scheduled transfusions or hematopoietic growth factor therapy, or if the patient shows evidence of MDS or acute leukemia. The search should include both adult volunteer and cord blood donor registries. While use of adult volunteers has generally been the preferred source, urgency and lack of allele level HLA-matched

adult volunteer donors have resulted in a growing utilization of cord blood units for FA.

For alternate donors (any donor other than an HLA-matched sibling), high resolution typing at HLA-A, B, C, and DRB1 of the patient must be obtained. Most transplant centers will require confirmatory HLA-typing at their institution if HLA-typing was performed elsewhere originally. HLA-typing results are typically available within 7-10 business days.

A search of the marrow and cord blood registries requires submission of the patient's HLA type and, in the case of umbilical cord blood (UCB), the patient's weight. A preliminary search can be performed by any physician at no cost. A formal search and the pursuit of a potential donor, however, must be performed by a transplant center with the consent of the patient (age ≥18 years) or parent/legal guardian (for patients <18 years). A formal search will result in charges, so the patient should obtain insurance approval prior to the initiation of the search. The cost will vary depending on the number of donors identified and evaluated.

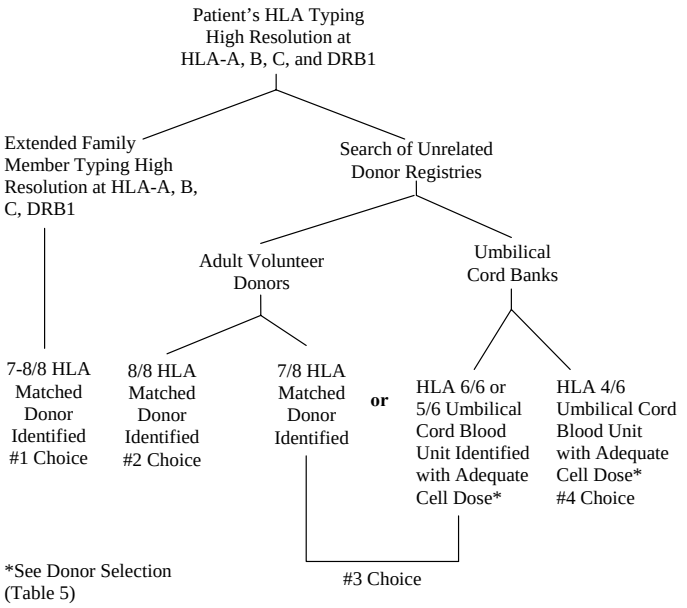
Note: Even if a formal search has been initiated by a transplant center, the patient is not obligated to have a transplant at that center or have a transplant at all. Transfer of the search only requires notification of the National Marrow Donor Program or other coordinating center (varies on country) and a newly signed consent from the patient or family.

The search process is summarized in Figure 1.

Donor selection

For non-FA patients, we recommend that an antigen HLA-mismatched related donor be chosen over a

Figure 1: Donor Search Process



HLA-matched unrelated donor. Based on the general experience with non-FA patients, donor priority accepted by major FA transplant centers is shown in Table 5.

In some circumstances, greater degrees of HLA disparity might be considered acceptable. In the context of a transplant center phase I–II trial, related marrow donors mismatched at 2 or 3 antigens and unrelated umbilical cord blood donors mismatched at 3 antigens might also be used as a source of hematopoietic stem cells for transplantation.

Because of proven effect on transplant outcome, other factors are considered in the selection of an alternate donor, such as age of donor, CMV serostatus, female parity (i.e., number of pregnancies), and sex match

Table 5: Donor Selection: Prioritization of HSC Alternate Donors

Marrow or Peripheral Blood Stem Cells

- Relative (other than sibling) matched at 8 of 8 HLA-A, B, C and DRB1 alleles
- Relative (including sibling) matched at 7 of 8 HLA-A, B, C and DRB1 alleles
- Unrelated adult volunteer donor matched at 8 of 8 HLA-A, B, C and DRB1 alleles
- Unrelated umbilical cord blood unit matched at 6 of 6 HLA-A and B (antigen level) and DRB1 (allele level), cell dose $\geq 2.5 \times 10^7$ nucleated cells/kg recipient body weight

Umbilical Cord Blood or Unrelated Adult Volunteer

- Unrelated umbilical cord blood unit matched at 5 of 6 HLA-A and B (antigen level) and DRB1 (allele level), cell dose $\geq 3.0 \times 10^7$ nucleated cells/kg recipient body weight or unrelated adult volunteer donor matched at 7 of 8 HLA-A, B, C and DRB1 alleles

Unrelated Cord Blood or Haploidentical Relative

- Unrelated umbilical cord blood unit matched at 4 of 6 HLA-A and B (antigen level) and DRB1 (allele level), cell dose $\geq 4.0 \times 10^7$ nucleated cells/kg recipient body weight or 4-6/8 haploidentical donor or co-infusion of two partially HLA-matched cord blood units

between the donor and patient. Effect of donor age on transplant outcome is under investigation, with new data suggesting lack of effect. Factors included in choice of the cord blood unit may include cord blood bank track record and ability to confirm unit identity.

No data exist to indicate whether one stem cell source (8/8 marrow versus 8/8 peripheral blood versus 6/6 or 5/6 umbilical cord blood) is better or worse than another. Data in other patient populations (e.g.,

leukemia) suggest that when compared to bone marrow, there is greater risk of graft failure and slower recovery with cord blood and greater risk of chronic GvHD with unmodified peripheral blood. Recent data suggest that 6/6 or 5/6 HLA-matched cord blood results are similar to those with 8/8 HLA-matched marrow. Currently, the vast majority of FA patients have received marrow. There is relatively less experience using cord blood and peripheral blood to draw conclusions about the best stem cell source.

While UCB clearly extends the availability of HSCT to those lacking an 8/8 HLA-matched adult volunteer donor, it is not yet known whether a 6/6 matched cord blood is superior. Data thus far suggest a better outcome with 6/6 matched cord blood but larger patient numbers are required before a recommendation can be made.

Exclusion criteria

Alternate donor HSCT is not the appropriate treatment for all patients. While exclusion criteria may differ among transplant centers, usually patients will be considered ineligible for transplant if the transplant evaluation indicates that the patient has:

- Active uncontrolled infection
- HIV seropositivity
- Active extramedullary leukemia
- History of epithelial malignant solid tumors within two years of HSCT
- Severe end-organ dysfunction (variable)
- Karnofsky performance status <70% or Lansky status <50%.
- Pregnancy

Table 6: Laboratory Evaluations to Determine Eligibility for Alternate Donor HSCT

Diagnosis

- Confirmatory diepoxybutane (DEB) or mitomycin C (MMC) chromosome fragility test (if mosaic, test skin fibroblasts)

Complementation Group and Genotype

- Determination of complementation group and genotype (desirable but not required)

Hematologic

- Complete blood count and differential
- Bone marrow aspiration and biopsy with cytogenetic evaluation

Hepatic

- Liver enzymes, total bilirubin
- Ultrasound (to determine presence of adenomata, liver size)
- Abdominal CT (as indicated)

Renal / Bladder

- Serum electrolytes and creatinine
- 24-hour creatinine clearance or glomerular filtration rate (GFR)
- Ultrasound (to determine presence of renal dysplasia, hydronephrosis, abnormal bladder)

Cardiac

- Electrocardiogram (EKG)
- Echocardiogram with left ventricular ejection fraction (heart function)

Infectious Disease

- Chest radiograph
- Chest CT with high resolution inspiratory/expiratory films to rule out occult infection is performed at some centers.
- Sinus CT to rule out infection
- Panorex to rule out major dental problems

Cancer Evaluation (patients with biallelic *BRCA2* mutations)

- Abdominal CT (to rule out kidney cancer)
- MRI of the head (to rule out brain cancer)

Transplant Therapy

Once the patient and donor meet the transplant center's eligibility criteria, the patient will be scheduled for the transplant admission. The exact timing and therapeutic plan may vary depending upon the hematopoietic stem cell source (marrow versus peripheral blood versus cord blood), degree of donor and patient HLA mismatch, age of patient, presence of specific end-organ dysfunction, the stage of the disease (aplastic anemia versus MDS versus acute leukemia), institutional preferences, and other personal factors (school, employment, etc).

Preparative therapy

The pre-transplant (or preparative) therapy most often used in 2008 in the United States consists of fludarabine (FLU), cyclophosphamide (CY), and total body irradiation (TBI). The purpose of the preparative therapy is to destroy the diseased marrow and to suppress the patient's immune system so that the hematopoietic stem cells from the donor have less chance of being rejected. Pre-transplant therapy in FA patients is significantly reduced compared to transplant patients without FA, due to the unique hypersensitivity to alkylating agents and irradiation of FA patients. While lower dose therapy in FA recipients of sibling donor HSCT has been successful, such therapy is not sufficient in recipients of alternate donor HSCT due to high risk of graft rejection. The side effects of FLU, CY, and TBI are outlined in Table 7.

Graft-versus-host disease (GvHD) prophylaxis

GvHD results when the immune system of the donor recognizes the patient as "foreign" and tries to reject the foreign tissues. GvHD occurs after HSCT because the donor immune system is transplanted along with the hematopoietic stem cells responsible for marrow

Table 7: Preparative Therapy Side Effects

Total Body Irradiation

- Sterility
- Fluid retention
- Temporary painful swelling of the parotid gland (located in the jaw area), as in mumps
- Lung scarring
- Hair loss
- Sores in the mouth
- Nausea, vomiting, and diarrhea
- Fever
- Dry skin and darkening of the skin
- Cataracts
- Hormone deficiencies (such as low thyroid hormone levels)
- Cancer

Cyclophosphamide

- Hemorrhagic cystitis (bleeding from the urinary bladder), which sometimes can be prevented by intravenous fluid and with the drug Mesna.
- Heart muscle injury
- Nausea, vomiting, and diarrhea
- Fluid retention
- Sores in the mouth
- Hair loss
- Skin rash
- Sterility

Fludarabine

- Infection
- Nausea, vomiting, and diarrhea
- Confusion, coma, rapidly progressive brain injury
- Kidney insufficiency and failure
- Mouth Sores

recovery and reconstitution of the blood cells. While GvHD can occur in all patients undergoing an

allogeneic HSCT, it is particularly common and severe after alternate donor HSCT because of the greater degree of HLA disparity. The signs and symptoms of acute and chronic GvHD are described in Table 8.

Table 8: Manifestations of GvHD

Acute GvHD

- Skin (maculopapular rash to generalized erythroderma to desquamation and bullae)
- Liver (hyperbilirubinemia)
- Gastrointestinal system (secretory diarrhea, abdominal pain, ileus, hemorrhage, nausea/vomiting)
- Pancytopenia
- Ocular (photophobia, hemorrhagic conjunctivitis, pseudomembrane formation, and lagophthalmos)
- Fever

Chronic GvHD

- Skin (lichen planus, scleroderma, maculopapular rash, hyperkeratosis, hair and nail loss)
- Liver (cholestasis, absent bile duct syndrome, cirrhosis, portal hypertension, hepatic failure)
- Gastrointestinal system (dysphagia, failure to thrive, aperistalsis, malabsorption syndrome)
- Obliterative bronchiolitis (restrictive/obstructive airway disease)
- Sicca Syndrome (keratoconjunctivitis sicca with burning, photophobia, irritation, pain; oral dryness, pain, lichenoid lesions, gingival atrophy, dental caries)
- Vaginitis, vaginal dryness/strictures
- Pancytopenia; eosinophilia
- Serositis (pleural, pericardial, joint effusions)
- Myofasciitis

Just as novel pre-transplant therapies are being evaluated in FA patients undergoing alternate donor HSCT, so are novel GvHD prophylactic regimens. Today, it is clear that T-cell depletion reduces the risk of acute

and chronic GvHD after alternate donor HSCT, and it appears to have improved disease-free survival in patients with FA.

Regardless of the source of hematopoietic cells, most patients receive cyclosporine A or tacrolimus for 6–12 months after HSCT to reduce the risk of GvHD. The side effects of GvHD prevention strategies are shown in Table 9.

Table 9: GvHD Prevention Therapy Side Effects

T-Cell Depletion

- Graft failure
- Slow immune recovery and infection

Cyclosporine A/Tacrolimus

- Poor kidney function or failure (dialysis)
- Blood chemistry imbalances (low potassium and magnesium)
- Swelling of gums
- Excess body hair growth
- High blood pressure
- Bleeding problems
- Neurological side effects (seizures, coma, confusion, tingling/burning sensations, involuntary shaking of extremities)
- Infection

Methylprednisolone

- Infection
- Mood swings
- High blood sugar (requiring insulin)
- High blood pressure
- Avascular necrosis of long bones (damage to hip, knees, and shoulder bones most commonly)

Regardless of the prophylactic approach used, GvHD can still occur. The more severe the GvHD (e.g., grade 3-4 disease), the higher the risk of death, mostly due to opportunistic infection. If GvHD occurs, the mainstay

of treatment is methylprednisolone. Other agents successfully used in the management of acute and chronic GvHD include antithymocyte globulin (ATG), mycophenolate mofetil (MMF), thalidomide, and psoralens with ultraviolet light (PUVA). PUVA is **not** recommended, however, as it may be particularly toxic in FA patients.

Infectious Disease Prophylaxis

Infectious complications after alternate donor HSCT are a major problem for FA as well as non-FA patients, but may be a greater risk in FA patients due to: 1) the unique sensitivity of FA patients to chemoradiotherapy; 2) the resultant breakdown of mucosal barriers after treatment; 3) the extensive period of neutropenia; and 4) considerable transfusion exposure prior to HSCT and the resultant exposure to infectious agents.

For these reasons, strategies are needed to prevent infection in the early period after alternate donor HSCT and to hasten immune recovery. Prophylactic antibiotic regimens commonly used after HSCT are outlined in Table 10.

Table 10: Common Infection Prevention Strategies

Yeast/Fungal Infections

- Fluconazole (systemic yeast)
- Nystatin (oral yeast)
- Vorizonazole (yeast and filamentous fungus)
- Amphotericin-based agents (yeast and filamentous fungus)

Viral Infections

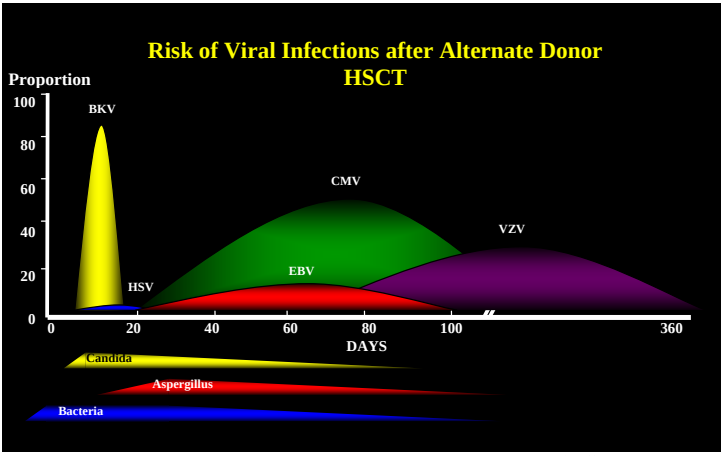
- Acyclovir (herpes simplex)
- Ganciclovir (cytomegalovirus)

Protozoal Infections

- Bactrim/Septra (pneumocystis)

The length of infection prophylaxis therapy depends upon the degree of immunosuppression, absolute CD4 T-cell level, development of acute or chronic GvHD, and development of infectious complications. In Figure 2, the timing of common viral, bacterial and fungal infections (if they occur) are shown:

Figure 2: Risk of Viral Infections after Alternate Donor HSCT



BKV: BK virus EBV: Epstein-Barr virus VZV: Varicella zoster virus
HSV: Herpes simplex virus CMV: Cytomegalovirus

Late Effects

All recipients of chemoradiotherapy and allogeneic HSCT are subject to late effects that are not necessarily peculiar to patients with FA. These include late graft failure, recurrent acute and chronic GvHD, and the effects of prolonged steroid therapy, such as hypertension, hyperglycemia, and aseptic necrosis of bone. Other late effects such as short stature and sterility have not been formally evaluated in patients with FA since these are pre-existing problems in most FA patients. As survival improves for FA patients after HSCT, greater research is now being focused on reducing the risk of

late effects, such as malignancy, sterility or endocrinopathies, to improve quality of life.

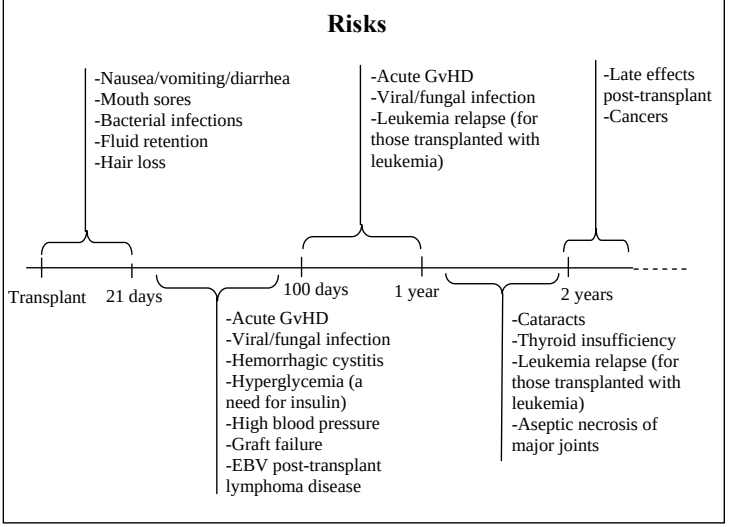
FA patients have an extremely high incidence of squamous cell carcinoma (SCC).[13-17] Some studies support a conclusion that the SCC risk may be higher after HSCT (sibling or unrelated donor), although the factors responsible for this (if verified) are unclear. Studies suggest that development of chronic GvHD or its therapy (e.g., azithioprine) may be the relevant risk factor. Because of this association between cancer and GvHD, use of T-cell depletion (the best approach for reducing GvHD risk) has been incorporated into most protocols. Furthermore, as irradiation is a known risk factor for cancer in general, strategies to eliminate or reduce the dose of radiation are being explored. Although there is no proven method of cancer prevention in FA, recognition of the problem and close monitoring of the head and neck region in particular (such as with frequent dental and ENT evaluations) are important strategies toward reducing the morbidity and mortality associated with this late effect. Linkage of head and neck cancer to the HPV virus has led to a general recommendation that both males and females with FA receive the HPV vaccine (Gardasil). The timing of infections after alternate donor HSCT is summarized in Figure 3.

Other Issues

Collection of autologous stem cells

Although not uniformly performed, the collection of autologous hematopoietic stem cells prior to transplant has been recommended for patients at high risk of graft failure after unrelated donor HSCT. In many instances, patients with FA have very poor marrow cellularity, preventing this option. However, earlier consultation with patients (when their marrow has greater cellularity)

Figure 3: Timing of Infections after Alternate Donor HSCT



regarding the future need for transplantation has led to renewed consideration of this option. It is unknown whether the infusion of autologous hematopoietic stem cells collected at an earlier time would benefit patients as a method of rescue after graft rejection or as a source of hematopoietic stem cells for future gene therapy or multipotent adult stem cells for treatment of organs other than the bone marrow. The transplant team should consider the need for collecting autologous hematopoietic cells.

Exposure to infection post-HSCT

Most transplant centers will expect the patient to remain near the facility for a minimum of 100 days. While major complications can occur after this period, the first 100 days are considered the highest risk period for the development of the immunologic complications (i.e., graft rejection, GvHD, and opportunistic infection) associated with alternate donor HSCT. During the

initial hospitalization for the transplant procedure, all patients are kept in a single occupancy room equipped with a high-efficiency air filtration system to reduce exposure to infectious agents. Once the marrow has recovered sufficiently, patients are allowed out of their hospital rooms unless intercurrent problems prevent this. After discharge, patients are expected to avoid crowded enclosed spaces and to wear masks in an attempt to reduce exposure to viral, bacterial, and fungal pathogens.

Alternatives to Unrelated Donor HSCT

Recent cloning of the FA genes has provided new insights into the molecular basis of FA and has made new opportunities available for better care of FA patients. For example, knowledge of the complementation group or mutation not only allows the physician to predict the course of the disease in some cases,[1] it permits the potential use of gene therapy and preimplantation genetic diagnosis (PGD). While gene correction of stem cells is not yet a clinical reality, PGD in combination with *in vitro* fertilization allows couples at high risk of having children with FA to have additional children free of the disease. In addition, PGD can be used to select those embryos that are HLA-matched with the child affected with the disease.[18-20] While there are ethical issues regarding the use of PGD and embryo selection, it is nonetheless a strategy that is being considered by many couples.

Remaining Challenges

Substantial improvement has been made in the survival of FA patients undergoing alternate donor HSCT, but challenges and questions remain. These include: 1) the optimal timing of alternate donor HSCT; 2) the impact

of androgens on survival after HSCT; 3) the selection of stem cell source (marrow versus peripheral blood versus umbilical cord blood); 4) the optimal pre-transplant and GvHD therapies; 5) the effect of the mosaic phenotype on the natural history of the disease; and 6) the role of radiation and chronic GvHD on the risk of malignancy later in life.

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References

1. Wagner JE, MacMillan M, Auerbach AD. Hematopoietic Cell Transplantation for Fanconi Anemia. Blume KG, Forman SJ, Appelbaum FR, eds., Thomas' *Hematopoietic Cell Transplantation*. Oxford, UK: Blackwell Publishing Ltd.; 2008.

2. Gluckman E, Auerbach AD, Horowitz MM, et al. Bone marrow transplantation for Fanconi anemia. *Blood* 1995; **86**: 2856-2862.

3. Ebell W. Transplant results and observations from our transplant expert in Germany. *FA Family Newsletter* 2002; **32**: 5.

4. de Mederios CR, Bitencourt MA, Zanis-Neto J, et al. Allogeneic hematopoietic stem cell transplantation from an alternative stem cell source in Fanconi anemia patients: analysis of 47 patients from a single institution. *Brazilian Journal of Medicine and Biological Research* 2006; **39**: 1297-1304.

5. Guardiola P, Pasquini R, Dokal I, et al. Outcome of 69 allogeneic cell transplantations in patients for Fanconi anemia using HLA-matched unrelated donors: a study on behalf of the European Group for Blood and Marrow Transplantation. *Blood* 2000; **95**: 422-429.

6. MacMillan ML, Auerbach AD, Davies SM, et al. Haematopoietic cell transplantation in patients with Fanconi anemia using alternate donors: results of a total body irradiation dose escalation trial. *British Journal of Haematology* 2000; **109**: 121-129.

7. Wagner JE, Eapen M, MacMillan ML, et al. Unrelated donor bone marrow transplantation for the treatment of Fanconi anemia. *Blood* 2007; **109**: 2256-2262.

8. Gluckman E, Rocha V, Ionescu I, et al. Results of unrelated cord blood transplant in Fanconi anemia patients: risk of analysis for engraftment and survival. *Biology of Blood and Marrow Transplantation*. 2007; **13**: 1073-1082.

9. Chaudhury S, Auerbach AD, Kernan NA, et al. Fludarabine-based cytoreductive regimen and T-cell depleted grafts from alternative donors for the treatment of high risk patients with Fanconi anemia. *British Journal of Haematology* 2008; **140**: 644-655.

10. Kutler DI, Singh B, Satagopan J, et al. A 20-year perspective of the International Fanconi Anemia Registry (IFAR). *Blood* 2003; **101**: 1249-1256.

11. Wagner JE, Tolar J, Levran O, et al. Germline mutations in BRCA2: shared susceptibility to breast cancer, early onset leukemia and Fanconi anemia. *Blood* 2004; **103**: 3226-3229.

12. Dodson KL, Coppo PA, Confer DL, The National Marrow Donor Program: improving access to hematopoietic stem cell transplantation. *Clinical Transplants* 1999; 121-127.

13. Alter BP. Diagnosis, genetics, and management of inherited bone marrow failure syndromes. *Hematology* 2007; 29-39.

14. Kutler DI, Auerbach AD, Satagopan J, et al. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. *Archives of Otolaryngology* 2003: **129**: 106-112.

15. Rosenberg, PS, Green MH, Alter BP. Cancer incidence in persons with Fanconi's anemia. *Blood* 2003; **101**: 822-826.

16. Deeg JH, Socie G, Schoch G, et al. Malignancies after marrow transplantation for aplastic anemia and Fanconi anemia: a joint Seattle and Paris analysis of results in 700 patients. *Blood* 1996; **87**: 386-392.

17. Socie G, Devergie A, Girinski T, et al. Transplantation of Fanconi's anemia: a long-term follow-up of fifty patients transplanted from a sibling donor after low dose cyclophosphamide and thoraco-abdominal irradiation for conditioning. *British Journal of Haematology* 1998; **103**: 249-255.

18. Verlinsky Y, Rechitsky S, Schoolcraft W, Strom C, Kuliev A. Preimplantation diagnosis for Fanconi anemia combined with HLA matching. *Journal of the American Medical Association* 2001; **285**: 3130-3133.

19. Verlinsky Y, Kuliev A, eds. *An Atlas of Pre-implantation Genetic Diagnosis*, New York: Parthenon; 2000: 92.

20. Grewal SS, MacMillan ML, Kahn JP, Ramsay NKC, Wagner JE. Successful hematopoietic stem cell transplantation for Fanconi anemia from an unaffected HLA genotypically-identical sibling selected using preimplantation genetic diagnosis. *Blood* 2004; **103**: 1147-1151.

Chapter 11

Late Effects in Fanconi Anemia Patients Post-Transplant

Margaret L. MacMillan, MD, K. Scott Baker, MD, and John E. Wagner, MD

Introduction

A greater proportion of FA patients are now surviving into adulthood, largely due to major advances in the field of hematopoietic stem cell transplantation (HSCT), particularly donor selection, preparative therapy, graft-versus-host-disease (GvHD) prophylaxis, and supportive care measures. The medical community is now faced with the challenge of optimizing long-term care for these patients through early intervention to prevent late effects. Early intervention must include systematically evaluating FA patients to understand the issues they may face in the future.

Overview

No published studies exist that specifically address late effects in FA patients. However, studies conducted in other populations of patients are instructive, particularly those for patients who have undergone treatment for cancer or have had a HSCT. Guidelines for following childhood cancer survivors have been developed by the Children's Oncology Group (available on-line at http://www.survivorshipguidelines.org) and can serve as a foundation for developing a long-term follow-up plan for transplanted FA patients, based on the specific chemotherapy agents and radiation to which they were exposed. In addition, the European Group for Blood

and Marrow Transplantation (EBMT), the Center for International Blood and Marrow Transplant Research (CIBMTR) and the American Society of Blood and Marrow Transplantation (ASBMT) recently developed joint recommendations, which include suggested screening and preventive practices for adult HSCT survivors. Many of these recommendations also apply to FA children after HSCT.[1]

Long-term follow-up in FA patients is considerably more complex than for those patients with acquired illnesses later in life. FA patients need lifelong follow-up, including ongoing assessment of adverse effects on physical and mental health, quality of life, growth, development, education, and employment.

As shown in Table 1, the etiology of late effects can be attributed to the underlying diagnosis of FA as well as to the treatment the individual patient has received.

The goal of long-term follow-up is to develop and implement strategies to prevent harmful late effects. Thus, treatment protocols are being modified, where possible, to reduce radiation exposure and to eliminate GvHD, as both play important roles in the development of late effects after HSCT. To assess a patient's exposure to possible late effects, the physician should consider mediating and moderating factors, including the patient's current age, family history, genotype, comorbidities (especially chronic GvHD), past treatments, and environmental issues, and must provide vigilant screening for early detection of late effects. Patients should be encouraged to lead a healthy lifestyle, which should include a healthy diet, regular exercise, avoidance of alcohol, smoking and second-hand smoke, limited sun exposure and use of sunscreen. The physician

Table 1: Etiology of Late Effects

Related to Fanconi Anemia

- Congenital anomalies: GI tract, heart, kidney, urinary, dental
- Endocrine abnormalities: diabetes, GH deficiency, hypothyroidism
- Reproductive issues: infertility, high-risk pregnancy, early menopause
- Nutritional issues: GI tract anomalies, poor oral intake
- Neurological issues: vision, hearing
- Musculoskeletal issues: hand and arm anomalies, hip dysplasia
- High risk of malignancy
- Genotype/phenotype correlation (*BRCA2*)
- Psychosocial impact of chronic illness

Related to Treatment

- Multiple transfusions: iron overload
- Androgens: liver toxicity, masculinization
- Bone marrow transplant (BMT): toxicity of chemotherapy and radiation, acute and chronic GvHD

should educate the primary caregivers and the families about the risks for late effects and preventative strategies.

Long-Term Follow-up Evaluations

A guideline for long-term follow-up of FA patients is outlined in Table 2 at the conclusion of the chapter. It is written primarily for patients who are at least one year post-transplant and is intended only to guide the physician; it must be tailored to the individual FA patient. The FA patient's primary physician must

discuss planned follow-up with the other physicians involved in the individual's care, including hematologists, bone marrow transplant physicians, and all other subspecialists.

In addition, this guideline can serve as a framework for FA patients who have not yet had a transplant, as these patients have a myriad of potential health issues.

History and physical examination

One of the most important aspects of long-term care of FA patients is a thorough history and physical examination, performed at least annually. Each patient needs a primary care provider to orchestrate the comprehensive care of the patient, obtain consultation when necessary, and ensure appropriate implementation and follow-up.

Hematology

After transplantation, the patient's transplant physician will decide how often bone marrow (BM) tests are needed. In general, BM aspirates and biopsies are performed several times during the first year after transplant and then again at two years after transplant. Subsequent BM examinations are warranted if the patient has mixed chimerism, remains transfusion dependent or if there are concerns about low peripheral blood counts.

Iron overload

An assessment of total body iron should be performed one year after transplant, as most patients have received a significant number of red blood cell transfusions. Repeated serum ferritin levels may be helpful to monitor a trend, but ferritin is an inaccurate measure of iron burden. Liver biopsy or newer non-invasive magnetic resonance imaging measurements are much more sensitive and specific. Depending on the result, monthly phlebotomy or iron chelation may be necessary. For an

extensive discussion of the management of iron overload, refer to Chapter 3.

Endocrine

Endocrine issues are common in FA patients and require lifelong endocrine evaluation and follow-up.[2] After HSCT, additional endocrinopathies may develop, including hypothyroidism, growth hormone deficiency, gonadal dysfunction, osteoporosis, and infertility.[3] Post-transplant, all patients should receive the endocrine evaluation as outlined in Table 2 as a minimum and undergo annual lifelong endocrine evaluations. Particular attention to age, stage of pubertal development and growth is important to determine timing and extent of the endocrine assessment for the individual.

HSCT can induce osteopenia, osteoporosis, and avascular necrosis of the bone, each of which can be accelerated by cumulative doses of glucocorticoids. A Dual Energy X-ray Absorptiometry (DXA) scan should be performed at one year after transplant. For children <5 years of age, normal comparative values are not available, but the DXA scan can still be used to look for changes over time in these individuals. If the initial DXA scan is abnormal, the decision regarding treatment (vitamin D, calcium, bisphosphonates or other agents) and when to perform follow-up DXA scans should be decided in consultation with the patient's endocrinologist.

Growth and development

Growth and development need to be assessed at least annually. A formal neuropsychology evaluation should be performed for patients at risk, particularly those transplanted before the age of three years.[1,4] Early intervention to assist in identified problems is mandatory to optimize the patient's development. Although most FA

patients are petite and relatively picky eaters, if growth is suboptimal, both endocrine and nutritional evaluations should be performed to identify potential etiologies. Therapy with growth hormone may be indicated in some patients.

Organ function

Patients with FA may have organ dysfunction stemming from congenital anomalies or from treatments, including the conditioning regimen used in transplantation. Additional late complications after HSCT may arise from chronic GvHD, infections, immune deficiency, and from medications to treat these complications.[4-6] Therefore, although all patients require an evaluation at one year after transplantation, as outlined in Table 2, the severity and duration of the organ dysfunction will dictate the follow-up, which needs to be determined in consultation with the patients' subspecialists. Further details of specific potential organ dysfunction can be found in the medical literature.[1,4,5]

Metabolic syndrome

Metabolic syndrome is a constellation of central obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension, and is associated with an increased risk for Type 2 diabetes mellitus and atherosclerotic cardiovascular disease. BMT survivors have a higher age and body mass index-adjusted risk of diabetes and hypertension, potentially leading to a higher than expected risk of cardiovascular events with age.[7,8] Although there are no data to determine the exact risk of metabolic syndrome in FA patients, the risk may be significant as FA patients are inherently more prone to diabetes. Therefore, all FA patients must be monitored for early indications of metabolic syndrome and be encouraged to follow a healthy diet and exercise regimen.

Immunology

Infections remain a major cause of morbidity and mortality in FA patients after HSCT. Immune reconstitution is a gradual process after HSCT; most patients achieve immune recovery 1-2 years after HSCT. However, immune recovery is markedly delayed in patients with GvHD or those receiving immunosuppressive therapy.

At one year after transplant, screening for immune reconstitution should include measuring T-cell subsets and immunoglobulin levels. The primary care physician should discuss the exact timing of starting the immunizations with the patient's transplant physician. If the patient has no active GvHD and is off all immunosuppressive medications, inactive immunizations should be administered starting one year after HSCT, with live virus vaccines delayed until two years after transplant. In addition, all patients and their family household members should receive the influenza vaccine on an annual basis. Only the intramuscular formulation should be administered as intranasal influenza vaccine contains live virus and puts the patient at risk of becoming ill. HPV vaccination should be given to all FA patients beginning at age nine.

Malignancy surveillance

FA patients are at an extraordinary risk for malignancy at an early age and require lifelong surveillance regardless of whether they have undergone a transplant.[9-11] A subset of FA patients are at even higher risk of malignancy, including those with *BRCA2* mutations[12] and those who develop GvHD[13,14] after transplantation.

Oropharyngeal screening should occur every six months (Chapter 13) after transplant, regardless of the age of the patient. Because of the risk of bacteremia, patients should not have dental cleaning, extraction or

other invasive procedures performed until at least one year after transplantation.

Gynecological examinations and screening for malignancy should occur at least annually once females are 13 years of age (Chapter 6). Breast cancer screening should be initiated by 25 years of age.

Earlier and/or more frequent malignancy screening may be warranted for any issues raised by the patients or primary care physician. As mentioned above, all patients should receive the HPV vaccine beginning at age nine to reduce the risk of HPV-associated malignancies. All FA patients should wear sunscreen to reduce the risk of skin cancer and cutaneous chronic GvHD. Patients with suspicious nevi or other abnormal skin lesions should be examined by a dermatologist.

Patients with biallelic *BRCA2* mutations require at least annual brain MRIs to assess for the development of medulloblastoma. Renal ultrasounds should be performed at least annually in these high-risk individuals to assess for Wilms tumors.[12]

Other medical considerations

The three major ocular complications after transplantation are cataracts, keratoconjunctivitis sicca syndrome (usually associated with GvHD), and ischemic microvascular retinopathy.[1] All patients should be considered for an ophthalmology evaluation one year after HSCT, depending on symptomatology. In addition, patients with signs or symptoms of chronic GvHD should have a Schirmers' test to screen for decreased tear production. Any change in visual acuity should be assessed immediately.

A significant proportion of FA patients have congenital neurosensory auditory deficiencies. All patients should

be considered for audiograms after HSCT as hearing may significantly worsen after exposure to ototoxic medications.

Quality of life

Late effects include the medical needs and the care of the entire person, including neurocognitive deficits, anxiety, depression, social withdrawal, the effects of re-entry into society or school, and insurance problems. These quality of life issues are a vital component in the assessment of long-term health in all FA patients, regardless of age or type of therapy received. In a survey conducted by the University of Minnesota group, parents reported an improved quality of life after transplant as restoration of normal hematopoiesis resulted in fewer physician visits and less worry about risks for bleeding and infections.

Conclusions

Fortunately, advances in the care of FA patients have led to larger numbers of patients who survive for many years post-transplant. The goals are to understand and monitor the late effects that they face as they age, to identify the mediating factors, and to develop strategies to prevent these late effects.

Table 2: Fanconi Anemia Long-term Follow-up Clinical Evaluation							
Return Visit Post-Transplant	**1 year**	**2 year**	**3 year**	**4 year**	**5 year**	**Every year**	**Every 5 years**
History, exam, vital signs	X	X	X	X	X	X	X
Hematology							
CBC with differential	X	X	X	X	X		X
Bone marrow aspirate/biopsy with chimerism, cytogenetics[a]	X	X					
Ferritin plus total body iron assessment[b]	X	R	R	R	R		X
Endocrine							
Oral glucose tolerance test (OGTT)	X	X	X	X	X	X	X
Free T4, TSH	X	X	X	X	X	X	X
LH/FSH (females ≥10 yr, males ≥11 yr)[c]	X	X	X	X	X		C
Ultrasensitive Estradiol (females ≥10 yr)[c]	X	X	X	X	X		C
Testosterone[†] (males ≥11 yr)[c]	X	X	X	X	X		C
IGF-1, IGFBP-3 (<18 yr)	X	X	X	X	X		C
25-OH vitamin D, calcium	X	X	X	X	X	X	X
Bone age (5-18 yr)	X	X	X	X	X	X	
DXA Scan (≥5 yr)[c]	X	R	R	R	R	R	X[d]
Growth and Development							
Height and weight	X	X	X	X	X	X	X
Growth chart (<18 yr)	X	X	X	X	X	X	X
Neuropsychology evaluation[e]	X	C	C	C	C		C
Cardiology							
Lipid profile (fasting)	X				X		X
ECHO	X	R	R	R	X		X
EKG	X	R	R	R	X		

Return Visit Post-Transplant	**1 year**	**2 year**	**3 year**	**4 year**	**5 year**	**Every year**	**Every 5 years**
Pulmonary							
Pulmonary function tests with DLCO (carbon monoxide diffusing capacity)	X	R	R	R	X		C
Hepatic Function							
ALT, AST, bilirubin, Alkaline Phosphatase, Albumin	X	X	X	X	X		
Hep B sAg, Hep B sAb, Hep C Ab	X				C		
Renal							
BUN, Cr, Urinalysis	X	X	X	X	X		X
Immunology							
T-cell subset	X						
Ig G, A, M, E	X	R	R	R	R		R
Immunizations including HPV[f]	X	X					
ENT	X	X	X	X	X	X	
Dental every 6 months	X	X	X	X	X	X	
Gynecology (females ≥13 yr)	X	X	X	X	X	X	
Dermatology	C	C				C	
Audiology	C	C			C		C
Ophthalmology	C	C			C		C
If *BRCA2*, head MRI, renal ultrasound	X	X	X	X	X	X	
Quality of life assessment	X	X			X		X

X = to be done.
C = consider; check with MD.
R = repeat if previously abnormal.
†Repeat annually until full pubertal development achieved.
[a] If mixed chimerism, follow BM ± PB chimerism beyond two years.
[b] See text for details; if high, consider phlebotomy or chelation.
[c] Assess at puberty if not already being performed.
[d] When >18 years of age.
[e] If considered high risk, e.g.,<36 mo. at time of HSCT.
[f] As per individual's transplant center.

References

1. Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. *Biology of Blood and Marrow Transplantation* 2006; **12**: 138-151.

2. Giri N, Batista DL, Alter BP, Stratakis CA. Endocrine abnormalities in patients with Fanconi anemia. *Journal of Clinical Endocrinology and Metabolism* 2007; **92**: 2624-2631.

3. Brennan BM, Shalet SM. Endocrine late effects after bone marrow transplant. *British Journal of Haematology* 2002; **118**: 58-66.

4. Leiper AD. Non-endocrine late complications of bone marrow transplantation in childhood: Part I. *British Journal of Haematology* 2002; **118**: 3-22.

5. Leiper AD. Non-endocrine late complications of bone marrow transplantation in childhood: Part II. *British Journal of Haematology* 2002; **118**: 23-43.

6. Socie G, Salooja N, Cohen A, et al. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood* 2003; **101**: 3373-3385.

7. Baker KS, Ness KK, Steinberger J, et al. Diabetes, hypertension, and cardiovascular events in survivors of hematopoietic cell transplantation: a report from the bone marrow transplantation survivor study. *Blood* 2007; **109**: 1765-1772.

8. Majhail NS, Flowers ME, Ness KK, et al. High prevalence of metabolic syndrome after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplantation* 2008.

9. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi anemia. *Blood* 2003; **101**: 822-826.

10. Rosenberg PS, Huang Y, Alter BP. Individualized risks of first adverse events in patients with Fanconi anemia. *Blood* 2004; **104**(2): 350-355.

11. Rosenberg PS, Socie G, Alter BP, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. *Blood* 2005; **105**: 67-73.

12. Wagner JE, Tolar J, Levran O, et al. Germline mutations in BRCA2: shared genetic susceptibility to breast cancer, early onset leukemia, and Fanconi anemia. *Blood* 2004; **103**: 3226-3229.

13. Guardiola P, Socie G, Li X, et al. Acute graft-versus-host disease in patients with Fanconi anemia or acquired aplastic anemia undergoing bone marrow transplantation from HLA-identical sibling donors: risk factors and influence on outcome. *Blood* 2004; **103**: 73-77.

14. Masserot C, Peffault de Latour R, Rocha V, et al. Head and neck squamous cell carcinoma in 13 patients with Fanconi anemia after hematopoietic stem cell transplantation. *Cancer* 2008; **113**: 3315-3322.

Chapter 12

Novel Treatment Options

Jakub Tolar, MD, PhD

Opportunities and Challenges

Physicians have made remarkable progress in hematopoietic cell transplantation over the last decade, and the care of FA patients in need of transplantation has improved dramatically. A minority of patients, however, cannot be transplanted because of their medical conditions or do poorly during or after transplant. Therefore, we aim to investigate all possibilities that can translate into better care for FA patients.

The prime candidates in this realm are gene therapy, stem cell therapy, and stem cell gene therapy.

Gene Therapy

Gene therapy vectors

Delivering a gene into a cell is not a trivial matter. Investigators in the past have realized this and have used viruses as vectors for this purpose. Viruses have developed their own means of delivering their genes into cells, and researchers have "borrowed" these properties to insert genes of interest into cellular genomes.

The retroviral vector is the traditional vector, although improved lentiviral vectors, with an added advantage of being able to transduce non-dividing cells, have been used recently. Small DNA viruses, called pyroviruses, represented by adenovirus and adeno-associated virus, represent another group of viruses that have been investigated in great detail in preclinical gene therapy testing.

Their main advantage is that they do not integrate into the genomes of cells. Their main disadvantage is that they very easily elicit an immune response in the recipient.[1]

In addition to the viral strategies, non-viral means of gene delivery have been under investigation as well—most prominently "jumping genes," termed transposons (for example, *Sleeping Beauty* transposon).[2]

The genetic manipulation of the cell can occur either outside the patient, called *ex vivo*, or the vector can be injected directly into the patient, termed *in vivo*.

Mechanisms of gene therapy

There are two main mechanisms whereby gene therapy can occur. The first is gene replacement when a gene of interest is inserted at a more or less random spot in the genome of the recipient. This results in predictable complications: e.g., dysregulation of the delivered gene in that new genomic site as well as disruption of the genes that are located in the region of the insertion.[3] The second mechanism of gene therapy is gene correction, which is based upon a capacity of genomes to repair themselves using a process called homologous recombination. As a result of such homologous recombination, the faulty gene is corrected at its original locus. Its regulation remains intact, and no other genomic region is affected by the gene therapy process.[4]

Side effects of gene therapy

The most important side effect of gene therapy is insertional mutagenesis,[3,5-9] a side effect that is unavoidable if a gene replacement approach is used. It is possible, however, to target the gene insertion into a so-called "safe haven" region of the genome, where fewer or no genes of importance are located. The important

consideration in assessing insertional mutagenesis is that the genotoxicity related to it may vary from patient to patient. The latency of the side effect can be quite long, as we have learned from the first several gene therapy trials. The additional side effects relate to the immune reaction to the virus and to inappropriate expression—either related to the site in the genome or the differentiation status of the cell where the gene is expressed.[1] In theory, gene transfer can also result in germ line transmission, but this has not been documented to date.

Stem Cell Therapy

Stem cell therapy vectors

The traditional stem cell therapy vector is a bone marrow cell, which has been experimentally and clinically proven in many thousands of successful bone marrow transplants over the last 50 years.[10] Hematopoietic stem cell transplant remains the prototype of cellular therapy and a testament to the consistently remarkable fact that a stem cell can be transferred from one organism to another (from a donor to a recipient) and that it can reconstitute the full functional lymphohematopoietic system from relatively few cells.

Embryonic stem cells represent an opportunity for understanding more deeply how stem cells work but, due to biological (e.g., generation of teratomata in the recipient) and legal constraints, they do not constitute a useful strategy at present.[11]

Stromal stem cells (e.g., mesenchymal stromal cells) are non-hematopoietic cells of the bone marrow and other organs in the body.[12,13] They are presumed to be located in the wall of the vessels and to exert multiple critical functions, including support of the hematopoietic stem

cell in the bone marrow, and immunomodulation, which has been harnessed clinically in the therapy of graft-versus-host disease.[14,15]

Mechanisms of stem cell therapy

Stem cell replacement is the mechanism of traditional hematopoietic stem cell transplantation in which the entire lymphohematopoietic system of the recipient is replaced with that of the host.

The second mechanism is immunomodulation. An example is the use of mesenchymal stem cells to support engraftment or to treat steroid-resistant graft-versus-host disease.[16]

An additional mechanism is likely to be the role of stem cells, especially mesenchymal stem cells, in tissue repair and healing after injury.[17] This occurs in the setting of bone marrow transplant, due to tissue damage from chemotherapy, and immune reactions such as graft-versus-host disease. Mesenchymal stem cells are known to home to the site of injury. The injury is amplified in the setting of transplantation in Fanconi anemia patients because of their DNA repair defect and, therefore, represents an especially appealing modality applicable to the Fanconi anemia patients in need of transplant.

Side effects of stem cell therapy

The possible side effect of stem cell therapy can be tumorigenesis (i.e., generation of benign and malignant tumors). Most cancers originate from so-called cancer stem cells, which are in many processes and metabolic pathways indistinguishable from a normally functioning stem cell. Therefore, some donor stem cells will likely lead to malignancies in the recipients. We have seen this in multiple examples of donor-derived leukemias

in hematopoietic cell transplantation recipients.[18] We and others have observed this in animal models when mesenchymal stem cells were transplanted from one organism to another and gave rise to cancers.[19] Additional side effects are related to the specific functions of these cells. For example, immunomodulation generated by mesenchymal stem cells will lead to immunosuppression of the recipient, which in turn can translate into a reactivation of latent infections, especially DNA viral infections, or can favor tumor growth and result in a permissive state for leukemia.[20]

Stem Cell Gene Therapy

It seems only logical that the parallel tracks of gene therapy and stem cell therapy should be joined in one concerted effort termed "stem cell gene therapy." The intention is to correct the gene in the stem cells of the recipient *ex vivo* and then return them to the patient.

The specific challenges of Fanconi anemia can be seen as specific opportunities for stem cell gene therapy. For example, as a consequence of DNA repair disease, Fanconi anemia stem cells are more sensitive than their wild-type counterparts.[21-23] The phenotype of Fanconi anemia cells is that of clastogen sensitivity, which can be manipulated to the advantage of the patient by using low-dose chemotherapy as an *in vivo* selection in the patient who has received a mixture of cells that are corrected and cells that are not corrected.

An additional phenotypic feature is the paucity of the stem cells, especially hematopoietic stem cells in the bone marrow of Fanconi anemia patients. There are approximately six-fold fewer $CD34^+$ cells in Fanconi anemia patients when compared with non-Fanconi anemia patients, even before cytopenia occurs. In other

words, there are about ten-fold fewer colony-forming cells generated from the bone marrow source of the FA patient, pointing to the decreased repopulating capacity of these cells.[24-26]

Last, the data from mosaicism observed in about 25% of Fanconi anemia patients point to the possibility of mimicking this naturally occurring "gene therapy" in a clinical setting.[27-32]

Stem cell gene therapy trials in Fanconi anemia

The three Fanconi anemia clinical trials conducted to date have used retroviral means of delivery of Fanconi anemia A or Fanconi anemia C genes. Viral transduction, however, resulted in no or only transient correction of hematopoietic cells, an observation consistent with only short-term functional complementation.[33-40]

A lesson learned from these experiments was that the cells collected from the Fanconi anemia patients are extremely sensitive and extremely few. This led the investigators in a Spanish clinical trial, which is in preparation, to argue that no pre-stimulation of hematopoietic cells with growth factors is needed or wanted in this process, and that only a short exposure to a retrovirus is warranted.[41,42]

Stem cell gene therapy trials for other diseases

The gene therapy trials performed to correct other genetic diseases have resulted in correction of the disease phenotype in many, but also have produced significant side effects.[1] First, the adenoviral-based trials for ornithine transcarbamylase deficiency and Factor XI deficiency have been unsuccessful in correcting the phenotype of the patients, primarily as a consequence of host immune response to the virus, which in one case resulted in the death of the patient.

Second, the retroviral-based gene therapy trials for immunodeficiencies, such as severe combined immune deficiency, adenine deaminase deficiency, and chronic granulomatous disease, have resulted in the correction of the immune deficiency in all but one patient. Unfortunately, four leukemias occurred in the severe combined immunodeficiency trial (with one death), and two clonal myeloproliferations occurred in the chronic granulomatosis disease trial (with one death). It is worth noting that the clonal disorders have occurred in the defective lineage in these patients; that is, in T cells in the severe combined immunodeficiency patients and in myeloid cells in the patients with chronic granulomatous disease. To date, there are no side effects observed in the two patients who were treated for adenine deaminase deficiency.

Third, the latent period after which these side effects occur is much longer than expected. It follows from this that the cancer risk assessment testing systems at the moment are inadequate to assess the changes that can occur years after the gene treatments. In turn, animal tests, typically in the murine models, have to be modified so that the short life span of mice when related to humans is offset by sensitizing the mice to development of tumors in a much shorter period of time and then testing these putative gene therapy agents in these cancer-prone animals. Alternatively, the cellular testing can be performed by sensitizing the cell cultures to unearth the hidden potential of the gene therapy agents for transformation.[1]

The Evolution of Thinking about Fanconi Anemia Stem Cell Gene Therapy

Available gene therapy and stem cell therapy data suggest that there are several specifics that can make stem cell gene therapy in Fanconi anemia more successful.

First, we need to focus on the stem cell exhaustion and stem cell stress which are inherent features of the Fanconi anemia phenotype. In Fanconi anemia, the poor mobilization of the hematopoietic stem cell, impaired clonogenicity, and repopulation are features that cannot be removed from the stem cell gene therapy manipulations. Fanconi anemia genes themselves are anti-apoptotic, so it comes as no surprise that these cells deficient in DNA repair have increased cell cycling and are easily exhausted in numbers and function. It is important to note that this is not an engraftment defect, but a replicative deficiency. In turn, this offers hope for increasing the homing potential of these stem cell grafts in order to achieve more complete and longer-lasting phenotypic correction.[43]

Second, the gene therapy viral infection is associated with cellular proliferation in transduced cells, which only adds to the potential of the few rapidly cycling Fanconi anemia cells to transform into malignancy or, alternatively, by default into apoptosis and graft failure.

Third, cell expansion prior to transduction (which is usually a part of standard gene therapy transfer) is likely a counter-productive measure in Fanconi anemia gene therapy trials. Fanconi anemia cells have been known to be sensitive to reactive oxidative species and pro-inflammatory cytokines, so it seems logical to limit apoptosis by limiting their pre-stimulation by choice of the growth factors and by short time of their *ex vivo* manipulation. On the other hand, we might be able to rely on a competitive advantage of the corrected Fanconi anemia cells, such as has been seen in the immune deficiency gene therapy trials and, perhaps, even enhance this selection by administration of alkylator agents to the patients at a low dose after infusion of gene-corrected autologous stem cells.

Last, the pre-stem cell infusion cytoreduction that has been a component of the only successful and side-effect-free gene trial (for adenine deaminase deficiency) may need to be part of future Fanconi anemia gene therapy trials. Another possibility is to use non-genotoxic conditioning with the inflammatory cytokines (for example, interferon gamma), which has been shown to provide a mild ablation in mice with a genetically engineered deficiency in Fanconi anemia proteins.[44]

The Challenges That Lie Ahead

The ultimate goal of our effort in stem cell gene therapy for Fanconi anemia is to reduce the off-target effects and to fine-tune expression of Fanconi anemia genes. In addition to the means mentioned above, the vector design and treatment of the cells may translate into a large reduction in the off-target side effects. This will likely require weak promoters, strong insulators, and strong polyadenylation sequences to isolate the functions of the inserted genes from the genome and that of the genome from the inserted genes. Micro RNA is a new gene therapy tool and can be of huge importance in accurately targeting of gene expression to the desired cell population and away from the cells that should not be targeted by the gene therapy vector (e.g., antigen presenting cells that can mediate immune response to the vector).[45] As mentioned above, most of the efforts from now on will probably require minimization of oxidative stress on these cells. It is likely that combined modalities will be explored as well. For example, correction of hematopoietic stem cells and mesenchymal stem cells from the same patient, and co-infusion of these cells, may provide a better environment for engraftment of the gene-corrected hematopoietic stem cells.

Summary

Gene therapy, stem cell therapy, and stem cell gene therapy are powerful tools that will improve care for Fanconi anemia patients in the future. We have learned from Fanconi anemia gene therapy trials that they will not be successful unless they are changed. The limitations relate to the sensitivity and paucity of hematopoietic stem cells available for correction.

We should remain optimistic that the collective knowledge and unique enthusiasm of Fanconi anemia researchers and clinicians will provide a winning combination of ideas and well-designed experiments that will translate into improved care for Fanconi anemia transplant patients in the near future.

References

1. Porteus MH, Connelly JP, Pruett SM. A look to future directions in gene therapy research for monogenic diseases. *Public Library of Science Genetics* 2006; **2**: e133.

2. Ivics Z, Kaufman CD, Zayed H, Miskey C, Walisko O, Izsvak Z. The Sleeping Beauty transposable element: evolution, regulation and genetic applications. *Current Issues in Molecular Biology* 2004; **6**: 43-55.

3. Baum C, Dullmann J, Li Z, et al. Side effects of retroviral gene transfer into hematopoietic stem cells. *Blood* 2003; **101**: 2099-2114.

4. Porteus MH, Baltimore D. Chimeric nucleases stimulate gene targeting in human cells. *Science* 2003; **300**: 763.

5. Fischer A, Abina SH, Thrasher A, von Kalle C, Cavazzana-Calvo M. LMO2 and gene therapy for severe combined immunodeficiency. *New England Journal of Medicine* 2004; **350**: 2526-2527; author reply 2526-2527.

6. Hacein-Bey-Abina S, von Kalle C, Schmidt M, et al. A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. *New England Journal of Medicine* 2003; **348**: 255-256.

7. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. *Science* 2003; **302**: 415-419.

8. McCormack MP, Forster A, Drynan L, Pannell R, Rabbitts TH. The LMO2 T-cell oncogene is activated via chromosomal translocations or retroviral insertion during gene therapy but has no mandatory role in normal T-cell development. *Molecular and Cellular Biology* 2003; **23**: 9003-9013.

9. von Kalle C, Fehse B, Layh-Schmitt G, Schmidt M, Kelly P, Baum C. Stem cell clonality and genotoxicity in hematopoietic cells: gene activation side effects should be avoidable. *Seminars in Hematology* 2004; **41**: 303-318.

10. Copelan EA. Hematopoietic stem-cell transplantation. *New England Journal of Medicine* 2006; **354**: 1813-1826.

11. Daley GQ. Missed opportunities in embryonic stem-cell research. *New England Journal of Medicine* 2004; **351**: 627-628.

12. Prockop DJ. "Stemness" does not explain the repair of many tissues by mesenchymal stem/multipotent stromal cells. *Clinical Pharmacology and Therapeutics* 2007; **82**: 241-243.

13. Prockop DJ, Olson SD. Clinical trials with adult stem/progenitor cells for tissue repair: let's not overlook some essential precautions. *Blood* 2007; **109**: 3147-3151.

14. Le Blanc K, Rasmusson I, Sundberg B, et al. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. *The Lancet* 2004; **363**: 1439-1441.

15. Le Blanc K, Ringden O. Immunobiology of human mesenchymal stem cells and future use in hematopoietic stem cell transplantation. *Biology of Blood and Marrow Transplantation* 2005; **11**: 321-334.

16. Le Blanc K, Samuelsson H, Gustafsson B, et al. Transplantation of mesenchymal stem cells to enhance engraftment of hematopoietic stem cells. *Leukemia* 2007; **21**: 1733-1738.

17. Tolar J, Wang X, Braunlin E, et al. The host immune response is essential for the beneficial effect of adult stem cells after myocardial ischemia. *Experimental Hematology* 2007; **35**: 682-690.

18. Brunstein CG, Hirsch BA, Hammerschmidt D, McGlennen RC, Nguyen PL, Verfaillie CM. Leukemia in donor cells after allogeneic hematopoietic stem cell transplant. *Bone Marrow Transplantation* 2002; **29**: 999-1003.

19. Tolar J, Nauta AJ, Osborn MJ, et al. Sarcoma derived from cultured mesenchymal stem cells. *Stem Cells* 2007; **25**: 371-379.

20. Ning H, Yang F, Jiang M, et al. The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study. *Leukemia* 2008; **22**: 593-599.

21. D'Andrea AD, Grompe M. The Fanconi anaemia/BRCA pathway. *Nature Reviews Cancer* 2003; **3**: 23-34.

22. Grompe M, D'Andrea A. Fanconi anemia and DNA repair. *Human Molecular Genetics* 2001; **10**: 2253-2259.

23. D'Andrea AD, Grompe M. Molecular biology of Fanconi anemia: implications for diagnosis and therapy. *Blood* 1997; **90**: 1725-1736.

24. Kelly PF, Radtke S, von Kalle C, et al. Stem cell collection and gene transfer in Fanconi anemia. *Molecular Therapy* 2007; **15:** 211-219.

25. Williams DA, Croop J, Kelly P. Gene therapy in the treatment of Fanconi anemia, a progressive bone marrow failure syndrome. *Current Opinion in Molecular Therapeutics* 2005; **7**: 461-466.

26. Croop JM, Cooper R, Fernandez C, et al. Mobilization and collection of peripheral blood $CD34^+$ cells from patients with Fanconi anemia. *Blood* 2001; **98**: 2917-2921.

27. Alter BP, Joenje H, Oostra AB, Pals G. Fanconi anemia: adult head and neck cancer and hematopoietic mosaicism. *Archives of Otolaryngology - Head and Neck Surgery* 2005; **131**: 635-639.

28. Soulier J, Leblanc T, Larghero J, et al. Detection of somatic mosaicism and classification of Fanconi anemia patients by analysis of the FA/BRCA pathway. *Blood* 2005; **105**: 1329-1336.

29. Gross M, Hanenberg H, Lobitz S, et al. Reverse mosaicism in Fanconi anemia: natural gene therapy via molecular self-correction. *Cytogenetic and Genome Research* 2002; **98**: 126-135.

30. Gregory JJ, Jr., Wagner JE, Verlander PC, et al. Somatic mosaicism in Fanconi anemia: evidence of genotypic reversion in lymphohematopoietic stem cells. *Proceedings of the National Academy of Sciences* 2001; **98**: 2532-2537.

31. Waisfisz Q, Morgan NV, Savino M, et al. Spontaneous functional correction of homozygous Fanconi anaemia alleles reveals novel mechanistic basis for reverse mosaicism. *Nature Genetics* 1999; **22**: 379-383.

32. Lo Ten Foe JR, Kwee ML, Rooimans MA, et al. Somatic mosaicism in Fanconi anemia: molecular basis and clinical significance. *European Journal of Human Genetics*. 1997; **5**: 137-148.

33. Yamada K, Ramezani A, Hawley RG, et al. Phenotype correction of Fanconi anemia group A hematopoietic stem cells using lentiviral vector. *Molecular Therapy* 2003; **8**: 600-610.

34. Yamada K, Olsen JC, Patel M, Rao KW, Walsh CE. Functional correction of Fanconi anemia group C hematopoietic cells by the use of a novel lentiviral vector. *Molecular Therapy* 2001; **3**: 485-490.

35. Liu JM, Kim S, Read EJ, et al. Engraftment of hematopoietic progenitor cells transduced with the Fanconi anemia group C gene (FANCC). *Human Gene Therapy* 1999; **10**: 2337-2346.

36. Fu KL, Thuss PC, Fujino T, Digweed M, Liu JM, Walsh CE. Retroviral gene transfer for the assignment of Fanconi anemia patients to a FA complementation group. *Human Genetics* 1998; **102**: 166-169.

37. Fu KL, Foe JR, Joenje H, Rao KW, Liu JM, Walsh CE. Functional correction of Fanconi anemia group A hematopoietic cells by retroviral gene transfer. *Blood* 1997; **90**: 3296-3303.

38. Liu JM, Young NS, Walsh CE, et al. Retroviral mediated gene transfer of the Fanconi anemia complementation group C gene to hematopoietic progenitors of group C patients. *Human Gene Therapy* 1997; **8**: 1715-1730.

39. Walsh CE, Grompe M, Vanin E, et al. A functionally active retrovirus vector for gene therapy in Fanconi anemia group C. *Blood* 1994; **84**: 453-459.

40. Muller LU, Milsom MD, Kim MO, Schambach A, Schuesler T, Williams DA. Rapid lentiviral transduction preserves the engraftment potential of Fanca(-/-) hematopoietic stem cells. *Molecular Therapy* 2008; **16**: 1154-1160.

41. Antonio Casado J, Callen E, Jacome A, et al. A comprehensive strategy for the subtyping of patients with Fanconi anaemia: conclusions from the Spanish Fanconi Anemia Research Network. *Journal of Medical Genetics* 2007; **44**: 241-249.

42. Jacome A, Navarro S, Casado JA, et al. A simplified approach to improve the efficiency and safety of ex vivo hematopoietic gene therapy in Fanconi anemia patients. *Human Gene Therapy* 2006; **17**: 245-250.

43. Skinner AM, O'Neill SL, Grompe M, Kurre P. CXCR4 induction in hematopoietic progenitor cells from Fanca(-/-), -c(-/-), and -d2(-/-) mice. *Experimental Hematology* 2008; **36**: 273-282.

44. Si Y, Ciccone S, Yang FC, et al. Continuous in vivo infusion of interferon-gamma (IFN-gamma) enhances engraftment of syngeneic wild-type cells in Fanca-/- and Fancg-/- mice. *Blood* 2006; **108**: 4283-4287.

45. Brown BD, Gentner B, Cantore A, et al. Endogenous microRNA can be broadly exploited to regulate transgene expression according to tissue, lineage and differentiation state. *Nature Biotechnology* 2007; **25**: 1457-1467.

Chapter 13

Head and Neck Squamous Cell Carcinoma in Fanconi Anemia Patients

Bhuvanesh Singh, MD, PhD

Introduction

Head and neck cancers are among the most common tumors to develop in patients with Fanconi anemia.[1,2] Although these tumors are histopathologically similar to those in patients without FA, the frequency, distribution, and clinical course are significantly different and must be taken into account when considering cancer management in patients with FA (Table 1). This chapter provides an overview of head and neck squamous cell carcinomas (HNSCC) in the general population in contrast to those occurring in FA patients, with a focus on aspects of prevention, treatment, and surveillance in FA patients.

Head and Neck Cancer in the General Population

Head and neck cancer is a group of diseases linked together by a common histopathology, squamous cell carcinoma (SCC). These diseases can occur anywhere in the mucosal linings of the upper aerodigestive tract, beginning in the oral cavity and nasopharynx, and extending to the oropharynx, larynx or hypopharynx. About 30,000 new patients present annually with head and neck cancer in the United States and about 30% succumb to their disease. Internationally, head and neck

cancer is a significant health concern as one of the five most prevalent malignancies.[3]

Head and neck SCC development has been closely associated with the use of tobacco and alcohol.[4,5] Betel nut chewing, a common practice in Southeast Asia, has also been linked to the pathogenesis of head and neck cancer.[6] More recently, cancer-causing viruses, such as the human papillomavirus (HPV) and Epstein-Barr virus (EBV), have been suggested to play a role in the pathogenesis of these tumors.[7,8] Since a detailed review of head and neck cancer is not feasible in this chapter, we recommend consulting the following reference textbooks: (Shah, Jatin P., and Snehal G. Patel, 2003. *Head & Neck Surgery & Oncology*, 3rd Edition. Edinburgh: Mosby; and Harrison, Louis, et al., 1999. *Head and Neck Cancer: A Multidisciplinary Approach*. Philadelphia: Lippincott Williams & Wilkins Publishers, 1999.)

Head and Neck Cancer in Patients with Fanconi Anemia

Three separate reports have shown a 500- to 700-fold increase in the incidence of head and neck cancer in patients with FA.[1,2,9,10] The cumulative risk for developing head and neck cancer is approximately 14% for patients surviving to the age of forty.[2] This may be an underestimation of risk as the relative risk increases with age, and many FA patients succumb to other diseases before the age of 20. The impact of increased survival resulting from bone marrow transplantation protocols on the incidence of head and neck cancer in FA patients remains to be determined. Moreover, as head and neck cancer may be the presenting manifestation of FA, testing for FA should be considered in younger SCC patients (<40 years of age), especially if

they have atypical findings (e.g., borderline anemia) or an atypical response to cytotoxic treatment.

The presentation, distribution and course of head and neck cancer are also altered in patients with FA. These patients present at a younger age, and there is an increased prevalence of oral cavity tumors. In general, FA patients develop HNSCC at a high rate without associated risk factors. The biological behavior of FA-associated HNSCC is considered aggressive with early lymph node metastases and early soft tissue invasion, which is reflected in their overall worse outcome (Table 1).

Table 1: Summary of the characteristics of HNSCC in the FA population

	FA-associated HNSCC	**Non-FA HNSCC**
Cumulative incidence by age 40 years	14%*	0.038%
Age of presentation (median)	31 years	53 years
Tobacco and alcohol use	16%	>85%
Primary tumor site	Oral cavity: 65% Oropharynx: 10% Hypopharynx: 10% Larynx: 10% Unknown: 5%	Oral cavity: 27% Oropharynx: 24% Hypopharynx: 8% Larynx: 41%
Development of secondary primary tumors	63%	15%
2 year overall survival	49%	70%
Standard treatment	Surgery	Surgery, Radiation, Chemotherapy

* Considered an underestimation of risk as the relative risk increases with age, and many FA patients succumb to other diseases before the age of 20.

Symptoms are variable at presentation, with presence of a lesion being the most common complaint (Table 2). These patients typically present with multifocal changes, including premalignant and invasive lesions. There is a bimodal distribution of stage; about half of the patients present with early and the remainder with advanced stage disease. These tumors are quite aggressive, with two-year survival rates less than 50%. In addition, the majority of patients develop second primary tumors (63%), even after effective treatment of the index cancer. These factors clearly need to be taken into account in any treatment planning for head and neck cancers in patients with FA.

Table 2: Presenting symptoms and frequency in FA patients with HNSCC

Presenting Symptoms	**Frequency**
Oral lesion	37%
Pain	17%
Dysphagia	14%
Odynophagia	14%
Loose dentition	14%
Ulcer	7%
Neck mass	3%
Oral bleeding	3%
Hoarseness	3%

Prevention of Head and Neck Cancer

The precise cause of this increased risk for head and neck cancer in patients with FA remains to be defined, but may be related to increased susceptibility to human papillomavirus (HPV) infection and/or its carcinogenic effects. A study by Kutler et al. showed that 83% of

FA head and neck SCC patients have HPV DNA present, compared to a 20-30% incidence in head and neck cancer patients from the general population.[11] Another study found contradictory results. Thus, this observation requires further study to establish a causal relationship between HPV and squamous cell carcinoma development in FA; however, it potentially provides a mechanism for preventative approaches in this population. A study published in *The New England Journal of Medicine* has suggested that vaccination against HPV type 16, the most common type of HPV in head and neck cancer in the general population and possibly in some FA patients, can effectively prevent tumor development.[12] The role of chemopreventative drugs and vaccinations is under investigation and should only be used as part of an appropriate protocol. This includes vaccination against the human papillomavirus.

At present, the most prudent preventative measures in FA patients include:

1. **Abstinence from tobacco/alcohol exposure:** Tobacco and alcohol exposure, especially in combination, is the most significant factor associated with SCC head and neck cancer development in the non-FA population. Fewer than 20% of FA patients with head and neck cancer report any tobacco/alcohol use, but this is significantly higher than the rate observed in FA patients without head and neck cancer. Accordingly, abstinence from tobacco and alcohol, including exposure to secondhand smoke, should be strictly avoided by FA patients. In addition, mouthwashes containing alcohol should be avoided.

2. **Maintenance of proper oral hygiene:** Although the evidence is not as compelling, several reports suggest that poor oral hygiene and repeated trauma may

promote head and neck cancer development. Accordingly, maintenance of proper oral hygiene and routine dental evaluations are recommended.

3. **The use of oral appliances:** Given the lack of evidence to suggest a causal association with head and neck cancer, the use of oral appliances, including braces, need not be restricted in FA patients.

Surveillance for Head and Neck Cancer

The high incidence of head and neck cancer in patients with FA, combined with the ineffectiveness of available treatment approaches, underscores the need for aggressive surveillance. Surveillance should begin by the age of 10-12 years (based on literature reports of the earliest age at presentation with head and neck cancer) on a semiannual basis by an experienced professional; i.e., an ear, nose and throat specialist, an oral surgeon or other doctor experienced in head and neck cancer detection and treatment (Figure 1).

Since head and neck cancer in patients with FA commonly occurs in the oral cavity, the surveillance approach should focus on this region. However, as part of the routine screening, a flexible fiberoptic examination should be performed which includes evaluation of the nasopharynx, oropharynx, hypopharynx, and larynx. The use of routine esophagoscopy for screening is not mandated, but should be considered in any patient with odynophagia, dysphasia or other localizing symptoms. In these circumstances, evaluation could be performed either with endoscopy or barium swallow, with the specific findings guiding further evaluation and therapy. Focus should be on the cervical esophagus, which represents the region at highest risk for Fanconi-associated squamous cell carcinomas.

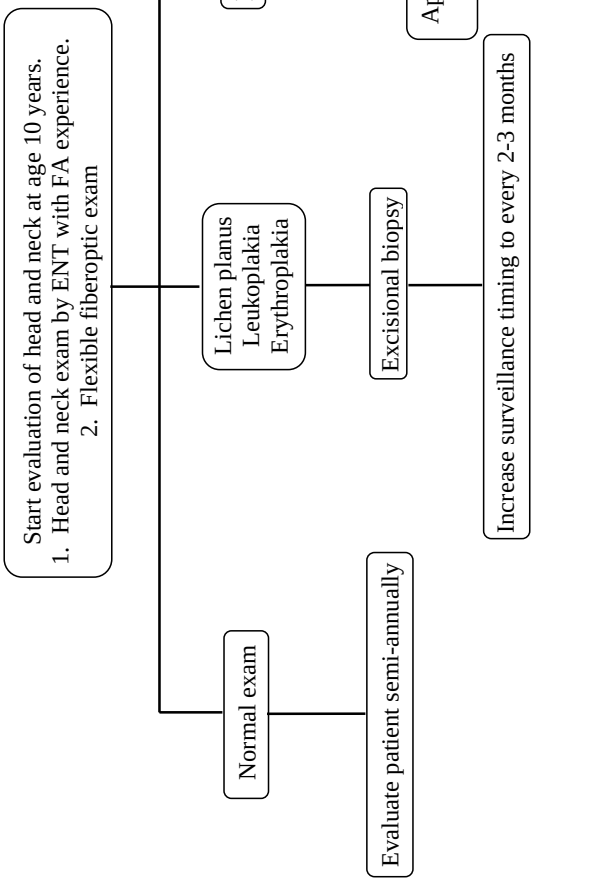

Figure 1: This flow chart describes the appropriate evaluation, surveillance, and diagnosis of head and neck lesions identified in the FA patient. The degree of dysplasia within the lesion should not influence decision-making regarding treatment. For example, even mild dysplastic lesions should be excised when feasible.

The head and neck examination should include not only the identification of malignant lesions, but also pre-malignant pathology. Lichen planus, leukoplakia, and erythroplakia should be specifically identified as part of the screening evaluation. When one of these lesions is identified in the head and neck region, an excisional biopsy should be performed, based on the size of the lesion. If an excisional biopsy cannot be obtained successfully, then a biopsy of the most representative/suspicious regions should be performed. In this patient population, the degree of dysplasia should not influence decision-making regarding treatment, and even mild dysplastic lesions should be excised, when feasible, to prevent the eventual progression to invasive cancer. The use of brush biopsies is not considered appropriate for the management of these patients, as there is a high incidence of false negative results due to non-representative sampling of the tumor.

Once a premalignant or malignant lesion is identified, the surveillance timing should be changed to once every 2-3 months, since this finding heightens the concern for development of subsequent premalignant and even invasive cancerous lesions. In patients who have been successfully treated for head and neck cancer, an annual chest x-ray should be included as part of the screening process.

Treatment of Head and Neck Cancer in Fanconi Anemia Patients

The core armamentarium used to treat patients with head and neck cancer in the general population includes surgery, radiation therapy, and chemotherapy. Many non-FA patients with advanced cancer of the head and neck will require multi-modality therapy to treat their tumors. However, in patients with FA, significant

sequelae can result from the use of radiation therapy and/or chemotherapy. Therefore, the use of these modalities must be individualized and only applied when absolutely required. Conversely, surgical therapy of head and neck cancer in patients with FA is reasonably well-tolerated. There does not seem to be an increased incidence of complications, including wound infections or long term sequela associated with surgical scarring. Accordingly, the consensus opinion is that surgical therapy needs to be entertained as the primary curative modality in all FA patients with head and neck cancer.

Surgery

Surgery in this patient population should follow dicta established for the general population with head and neck cancer, with a few modifications. In general, a wide complete excision of the primary tumor should be performed with adequate margins. The exact type of surgical resection required is dictated by the primary site, size, and the extent of the tumor. In general, oral cavity and pharyngeal tumors should be excised with at least one centimeter margins. The margins for laryngeal tumors need not be as comprehensive, due to the unique anatomy of the larynx.[13] Reconstruction of the primary site defect should follow dicta established for reconstruction in the general population with head and neck cancer, and should not be limited based on the presence of FA. Therefore, the standard application of free flaps for reconstruction should be considered as indicated, without restriction.

The management of clinically detectable cervical lymphadenopathy should follow dicta established for the general population. For lymph nodes greater than 3 cm, multiple lymph nodes on the same side of the neck or contralateral cervical adenopathy, a modified

radical neck dissection should be performed. In cases where a modified neck dissection is not feasible, a radical neck dissection can be considered.

For patients presenting without clinically detectable cervical adenopathy, elective nodal dissection should be considered for those who are at high risk for occult nodal metastasis. These high-risk regions include tumors of the oral cavity, oropharynx, and hypopharynx. For oral cavity tumors, the standard elective neck dissection consists of an ipsilateral supraomohyoid neck dissection extended to include level IV and should be performed in the majority of cases. For midline tumors, due to the high rate of nodal metastases bilaterally, a bilateral elective nodule dissection should be performed in all cases. For pharyngeal tumors, bilateral jugular nodal dissection consisting of levels 2-4 should be performed in all cases. If a suspicious node is identified during the course of an elective neck dissection, it should be sent for frozen section examination and, if metastatic disease is confirmed to be present within the node, a more comprehensive dissection of the cervical lymphatics should be undertaken.

External beam radiation

Adjuvant radiation therapy may be required in FA patients, especially those presenting with advanced disease. For the general population, advanced T-stage and the presence of nodal metastasis are significant indicators for the use of radiation therapy. In patients with FA, these same oncologic indicators exist; however, consideration must be given to minimize the sequelae of radiation therapy treatment. In the study by Kutler et al., four out of six patients who received radiation had significant treatment related sequela, two of whom died as a consequence of the treatment itself.[14] The selection

of patients for radiation should, therefore, be modified in patients with FA.[15] Bulky nodal metastasis and concern about incomplete resection of the disease are the most significant indicators to add radiation in this population. If radiation is to be given, a full course of radiation should be attempted, as it does not appear that tumors derived from patients with FA have the same degree of sensitivity to radiation as do non-tumorous cells from these patients.

Several considerations must be taken into account when treating FA patients with radiation. First, intensity modulated radiation therapy (IMRT) is recommended to decrease the toxic effects on non-cancerous tissues. Second, these patients must be monitored closely, not only for loco-regional problems but also for systemic sequelae such as bone marrow failure. To limit the risk for loco-regional problems, aggressive oral hygiene should be initiated in all patients undergoing radiation treatment, including routine brushing and oral/pharyngeal irrigation with a combination of salt water and baking soda solution. This solution can be made by boiling one quart of water and adding one teaspoon of salt and one teaspoon of baking soda. The irrigation should be performed at least every three to four hours on a daily basis during the waking hours. Third, aggressive observation of these patients for development of fungal infections should be maintained, and systemic antifungals initiated should evidence of infection be present. Delay or termination of therapy should be considered if significant and/or life-threatening side effects are becoming manifest. In addition to acute management, patients should be placed on long-term care specifically with respect to dental management. Use of fluoride treatments should be considered in all

patients. Monitoring of dentition should be maintained, and prevention measures for caries initiated.

Chemotherapy

Similar to the use of radiation therapy, the use of chemotherapy should be used with caution. Typically, chemotherapy protocols for head and neck cancer include a combination of cisplatin and 5-FU. These chemotherapeutic agents can have significant side effects in FA patients. Aggressive monitoring for these side effects, especially bone marrow failure, must be considered routine. In addition, monitoring for cisplatin effects on sensorineural hearing should also be a routine in these patients. If hearing sequelae develop as a consequence of the cisplatin treatment, cisplatin should be changed to carboplatin, which has similar efficacy but lower risk for ototoxicity. Recent studies have shown that, when given with radiation, cetuximab improves locoregional control in non-FA patients with head and neck cancer.[16] More importantly, these patients did not have increases in toxicities associated with radiation. The use of cetuximab in patients with FA and head and neck cancer is attractive, as its activity does not involve DNA damage. Nonetheless, the role for cetuximab in the treatment of FA patients remains investigational and should only be used under the recommendations and care of experienced oncologists.

Conclusions

Patients with FA have an increased risk for developing aggressive head and neck cancer, especially of the oral cavity. Until new therapeutic and preventative measures are available, strict abstinence from tobacco and alcohol, avoidance of second-hand smoke, maintenance of oral hygiene, and aggressive routine screening are the most immediate ways to reduce the development

and morbidity of head and neck cancer in this patient population. Early and frequent head and neck examinations, including careful oral cavity evaluations and flexible fiberoptic laryngoscopy are important surveillance measures. Appropriate surgical resection remains the mainstay of treatment for FA patients, since radiation and chemotherapy are poorly tolerated. If radiation and chemotherapy are required for advanced tumors, they should be used with caution and by physicians who have experience in identifying, preventing, and treating associated complications.

References

1. Alter BP, Greene MH, Velazquez I, Rosenberg PS. Cancer in Fanconi anemia. *Blood* 2003; **101**(5): 2072-2073.

2. Kutler DI, Auerbach AD, Satagopan JH, et al. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. *Archives of Otolaryngology-Head & Neck Surgery* 2003; **192**(1): 106-112.

3. Ries, LAG, Melbert D, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2005, National Cancer Institute, Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008.

4. Maier H, Sennewald E, Heller GFWD, Weidauer H. Chronic alcohol consumption-the key risk factor for pharyngeal cancer. *Archives of Otolaryngology-Head and Neck Surgery* 1994; **110**(2): 168-173.

5. Blot WJ, Mclaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Research* 1988; **48**(11): 3282-3287.

6. Sanghvi LD, Rao DN, Joshi S. Epidemiology of head and neck cancers. *Seminars in Surgical Oncology* 1989; **5**(5): 305-309.

7. Gillison JL, Shah KV. Human papillomavirus-associated head and neck squamous cell carcinoma: mounting evidence for an etiologic role for human papillomavirus in a subset of head and neck cancers. *Current Opinion in Oncology* 2001; **13**(3): 183-188.

8. Hording U, Daugaard S, Bock JE. Human papillomavirus, Epstein-Barr-virus, and cervical-carcinoma in Greenland. *International Journal of Gynecological Cancer* 1992; **2**(6): 314-317.

9. Alter BP. Cancer in Fanconi anemia, 1927-2001. *Cancer* 2003; **97**(2): 425-440.

10. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi anemia. *Blood* 2003; **101**(3); 822-826.

11. Kutler DI, Wreesmann VG, Goberdhan A, et al. Human papillomavirus DNA and p53 polymorphisms in squamous cell carcinomas from Fanconi anemia patients. *Journal of National Cancer Institute*, 2003, **95**(22): 1718-1721.

12. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine* 2002; **347**(21): 1645-1651.

13. Kirchner JA. Spread and barriers to spread of cancer within the larynx. In: Silver CE, ed. *Laryngeal Cancer*. New York, NY: Thieme Medical Publishers; 1991:7.

14. Kutler DI, Singh B, Satagopan J, et al. A 20-year perspective on the International Fanconi Anemia Registry (IFAR). *Blood* 2003; **15**(101(4)): 1249-1256.

15. Alter BP. Radiosensitivity in Fanconi's anemia patients. *Radiotherapy and Oncology* 2002; **62**(3): 345-347.

16. Booner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *New England Journal of Medicine* 2006; **354**(6): 567-578.

Chapter 14

The Adult Fanconi Anemia Patient

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Introduction

Adult FA patients (≥18 years of age) are an increasing proportion of the general FA population. This group consists of individuals diagnosed and treated in childhood and those newly diagnosed as adults. The former group is growing as a result of increased recognition and testing, combined with better transplant results and improved supportive care options. The latter is growing as a result of wider testing of family members and increased testing and diagnosis of adult patients who present with FA medical issues, such as head and neck cancer at younger than expected ages. These two groups have both common and divergent needs and issues. Some adult patients are transplant survivors while others are not transplant candidates or have refused transplant, further highlighting the diverse profile of the adult FA population.

Major health care issues in the adult FA population have been described in general database reports by the International Fanconi Anemia Registry (IFAR) and a North American Survey (NAS) based at NIH.[1-3] Some of these issues are already recognized as unique to the adult FA population. However, to date, the adult population has not been studied as a group in prospective studies.

In this chapter, we will review the specialized needs of the adult FA patient, emphasizing the required multidisciplinary nature of the care team. The current paucity

of data does not permit a comprehensive approach to specific medical concerns, as many issues are just beginning to be recognized and evaluated. However, we have commented where there is sufficient information and have referenced other chapters where appropriate.

General Considerations

Whether addressing patients diagnosed in childhood or newly diagnosed, the initiation of an appropriate management plan for an adult with FA begins with a complete survey of medical issues in a patient age-appropriate manner. Issues will differ by degree of prior evaluation and treatment, current symptom complex, and the evolving clinical database pertinent to this patient group. The provider will need to consider age-specific issues (e.g., hypertension, lipid profile, fertility, sexual functioning) as well as FA-specific issues (e.g., increased cancer risk) and treatment-specific issues (e.g., cataract risk after transplant, transfusional iron overload) and the potential interactions of these three fields. For the adult patient, management of expectations, family dynamics and external drivers, such as workplace and social environment, are likely to be critical components of care. Experience in other disorders highlights that the need for a clear definition of the relative roles and responsibilities of the care team and the patient is particularly relevant for individuals diagnosed in childhood and historically managed in the context of (surrogate) parental decision-making.[4] In contrast, the newly diagnosed adult patient has a far different need for education and for assistance in addressing alterations in workplace, community, and family relationships.

The medical consequences of FA itself in aging patients are poorly described, as are the consequences of the

treatments administered to affected children surviving to adulthood. This knowledge gap affects not only the development of the best medical plan, but also confounds a clear delineation of expectations at any point in the patient's adult experience. Further, the current data shed little light on the efficacy or tolerability of general medical treatments commonly used in adult patients when used in adults with FA. Such information will be a critical part of managing the issues listed below, as well as additional needs and problems to be defined.

Hematologic Issues in the Adult FA Patient

The currently recognized, non-transplanted adult FA population is small. Although a few of these patients have not developed bone marrow failure or hematologic malignancies, and some may not do so in their lifetimes, all require scheduled hematologic evaluations (see Chapter 3). Those adult non-transplanted FA patients with bone marrow failure may require treatment and/or transfusions and will require frequent evaluation for the development of hematologic malignancies. They may also be at risk for iron overload and need chelation or may be chronically chelated and require management of chelation side-effects (see Chapter 3). Importantly, the improving results of transplantation, particularly from unrelated donors, suggest that transplantation will remain an option for many of these patients. The dialogue regarding a possible decision to proceed to transplant should be informed by the most current transplant results in adult patients and requires continuing education and counseling of affected individuals.

Even patients who have undergone transplantation may have hematologic issues. There is a small chance of

hematologic relapse in these patients, for which they require continued hematologic evaluation. Long-term use of medications and chronic graft-versus-host disease may affect hematopoietic functioning. Ongoing evaluation of chimerism may be indicated.

Solid Tumors in the Adult FA Patient

This issue is discussed in depth in Chapters 6 and 13 and is perhaps the most significant health issue recognized to date facing the adult FA patient. In particular, squamous cell cancers of the head and neck, and cervical and vulvar cancers in women, occur at remarkably high rates and at younger than expected ages. An estimated 1/3 of FA patients will develop a solid tumor by the age of 48, most in the 2nd and 3rd decades of life.[3] These cancers may occur even earlier in transplanted patients.[5] Patients must be continually re-educated regarding this complication and be screened by an educated specialist. FA specialists should be consulted when these tumors are diagnosed, because treatment of these cancers may require different treatment modalities than used for the same cancers in non-FA patients. Behaviors increasing risk for these malignancies, such as smoking and alcohol consumption, should be discussed as part of a pre-emptive strategy.

The role of human papillomavirus (HPV) in the genesis of these cancers in FA patients remains a topic of debate, but one that is likely to be settled in the next few years. Consequently, patients should be appropriately counseled in regard to the potential of HPV vaccination to prevent HPV infections (and subsequent cancers) in the cervix and oropharynx. The benefit seems likely to be as great or greater than that of the general population, although the data regarding the ultimate cancer-preventing efficacy of these vaccines

in any population remain to be determined. In addition, the incidence of other tumors, including gastrointestinal and breast cancers in particular, may be excessive. The evolving data will need to be carefully evaluated to develop appropriate monitoring (and treatment) strategies that respect the desire to minimize radiation exposure and treatment-related toxicity.

Gynecologic and Fertility Issues in the Adult FA Patient

Discussions of expectations regarding fertility and life-expectancy are obviously quite different with an adult patient than with a child and his/her parents. Adult FA women experience early menopause, need high-risk management of pregnancies, and have an increased risk of gynecologic malignancies (see Chapter 6). Adult FA men are generally azoospermic and infertile. Advances in assisted reproduction techniques have led to new possibilities for the prevention and treatment of infertility. Early referral to a fertility clinic may be warranted. These issues may be particularly challenging to address with newly diagnosed patients.

Diabetes and Vascular Health

While the data on glucose intolerance are becoming better described in children with FA (see Chapter 7), the natural history in FA adults is unknown. In addition, the effects of oral hypoglycemics developed for the general population will need to be evaluated in this patient subgroup.

The interaction of FA with vascular disease of aging is unknown. Long-term follow up studies of children surviving transplant, as well as other cancer treatments, suggest that vascular and cardiac disease incidence will

be increased. However, the best practice for following and managing patients is unknown and will need to be established by collaboration between various expert providers. Further challenges in these areas will be provided by integrating the side-effects of prior and ongoing therapies with management of these, and other, results of normal aging.

Transition of Care

Transition of care from pediatric to adult medicine is an important issue in young adults with complex and chronic illnesses.[4,6,7] Although the authors are not aware of specific transition programs for young adults with FA, evidence supports the benefits of an anticipated and coordinated transition process.[4,7,8] Effective transition programs have been developed in other chronic illnesses, such as cystic fibrosis, diabetes, juvenile idiopathic arthritis, and sickle cell anemia. European countries with comprehensive state-supported health care systems have often taken the lead in the development of these transition systems.

Transition of health care is important for two main reasons:

1. In most centers, pediatric services define their target population by age, and adults may not be treated by pediatric subspecialists or in pediatric in-patient facilities. This is obviously dependent on the locality and varies widely.
2. Young adult patients must develop independence and undertake personal responsibility for their health care.

Timing of transition is important and must be seen as a process, not an abrupt transfer of services. Data show

that the most successful transitions are initiated at a very early stage with prospective education of the family and patient regarding future transition.[4,8] As this process proceeds and adolescents take on more health care responsibilities, they should be involved in education and decision-making. The timing should be individualized and not dependent on age. In contrast, timing may be very situation-dependent, as it is likely to be inappropriate to transition a patient with quickly progressing disease or at the "end of life."

As more FA patients reach adulthood, the management and development of transition of health care services are becoming increasingly important and must be addressed on a national level. Focus groups and surveys have identified barriers to transition,[4,7,8-11] including:

- Reluctance of patients and their families to leave trusted health care providers and comfortable clinical settings.
- Differences in approaches to the chronically ill by pediatric and adult providers; i.e., family medicine with prospective multidisciplinary support versus expectation of adult independence and self-reliance with more focused requested support.
- Concerns about the experience, knowledge base and quality of care that will be offered by specialists in adult medicine in regard to childhood-onset diseases.
- Physician reluctance to transition.
- Lack of continuing health care coverage for the young adult.
- Lack of adequate education and preparation of patients and families.

The key element to successful transition is continuous preparation of the patient and family and the identification of a willing and appropriate specialist in adult medicine who can be the primary coordinator of health care issues. The new and prior team should work to define necessary subspecialty providers who either have experience in FA or are willing to be educated as to the needs of this patient population. Because of the rarity of FA, the above goals are often not realistic. In this case, it is essential that an FA specialist remain involved in patient care decisions and be available for consultation, especially regarding the screening and treatment of secondary cancers or other newly recognized issues in adult FA patients. FA patients who have been transplanted may have the option at the larger centers to be followed in long-term survivor clinics where many of their health care needs can be coordinated.

Psychosocial Issues in the Adult FA Patient

The primary psychosocial components involved in growth and development from childhood through adolescence into adulthood are significantly complicated by chronic disease. As in all childhood diseases, surrogate decision-making imposes many demands on parents and guardians. There is a potential risk of parental over-protectiveness in the setting of requisite attention to safety, and the age-appropriate pursuit of adolescent independence may be particularly difficult for parents. The inability to participate fully in childhood activities (i.e., school, sports, and leisure) may isolate FA children and delay development of peer relationships. Recent follow-up of adult survivors of childhood acute lymphoblastic leukemia shows more adverse mental health functional impairment and activity limitations compared with their healthy siblings.[12] In addition, rates

of marriage, college graduation, employment and health insurance coverage were all lower compared to their healthy siblings. We expect that FA adults experience these same issues. Studies to date show that these latter issues of adulthood are also inadequately addressed in many pediatric healthcare settings, thus further exacerbating the stress on patients and families.[4,8]

For these reasons, the adult FA patient diagnosed in childhood may need extensive vocational, educational, and psychosocial support and guidance. High-risk behaviors, such as alcohol and drug use, are common in patients with chronic illness, as in the general population, and have been a major problem in FA adults (Gillio personal communication). Medical compliance may also be an issue, particularly during adolescence and during the transition period. For individuals newly diagnosed in adulthood, the ramifications of established relationships (with spouses, partners, employers, etc.) may be extreme. The magnitude of these psychosocial problems has not been assessed in FA adults and should be assessed in contemporary patient cohorts in the future.

Summary

The growing population of adult FA patients presents particular challenges to the community of FA care providers. The knowledge base is as yet insufficient for understanding best practices, and the provider pool within the community of physicians caring for adult patients is not yet well educated as to either the nature of the disorder or the needs of the patients. This places great responsibility on FA specialists in terms of education of patients and other providers, coordination of transitional care, and addressing the research needed to develop information to assure the best outcomes for patients.

References

1. Butturini A, Gale RP, Verlander PC, Adler-Brecher B, Gillio A, Auerbach AD. Hematologic abnormalities in Fanconi anemia: an International Fanconi Anemia Registry study. *Blood* 1994; **84**: 1650-1655.

2. Kutler DI, Singh B, Satagopan J, et al. A 20-year perspective on the International Fanconi Anemia Registry (IFAR). *Blood* 2003; **101**: 1249-1256.

3. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi anemia. *Blood* 2003; **101**: 822-826.

4. McLaughlin SE, Diener-West M, Indurkhya A, Rubin H, Heckmann R, Boyle MP. Improving transition from pediatric to adult cystic fibrosis care: lessons from a national survey of current practices. *Pediatrics* 2008; **121**: e1160-1166.

5. Rosenberg PS, Socie G, Alter BP, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. *Blood* 2005; **105**: 67-73.

6. McDonagh JE, Kelly DA. Transitioning care of the pediatric recipient to adult caregivers. *Pediatric Clinics of North America* 2003; **50**: 1561-1583, xi-xii.

7. Reiss JG, Gibson RW, Walker LR. Health care transition: youth, family, and provider perspectives. *Pediatrics* 2005; **115**: 112-120.

8. Boyle MP, Farukhi Z, Nosky ML. Strategies for improving transition to adult cystic fibrosis care, based on patient and parent views. *Pediatric Pulmonology* 2001; **32**: 428-436.

9. Scal P, Evans T, Blozis S, Okinow N, Blum R. Trends in transition from pediatric to adult health care services for young adults with chronic conditions. *Journal of Adolescent Health* 1999; **24**: 259-264.

10. Flume PA, Anderson DL, Hardy KK, Gray S. Transition programs in cystic fibrosis centers: perceptions of pediatric and adult program directors. *Pediatric Pulmonology* 2001; **31**: 443-450.

11. Flume PA, Taylor LA, Anderson DL, Gray S, Turner D. Transition programs in cystic fibrosis centers: perceptions of team members. *Pediatric Pulmonology* 2004; **37**: 4-7.

12. Mody R, Li S, Dover DC, et al. Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood* 2008; **111**: 5515-5523.

Chapter 15

Genetic Counseling

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Introduction

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.[1] All individuals with FA and their families should receive genetic counseling from a genetic counselor familiar with FA at diagnosis and at various points throughout life. A genetic counseling consultation should include health, family, and pregnancy histories, should clarify the mode of inheritance of FA, and should explain the genetic testing process. Additionally, the consultation should include information about current research opportunities and support groups, future reproductive options and their familial implications.

Family History

The genetic counselor should obtain a detailed family history from the parents of children with FA or from young adults with FA. This history can be helpful in determining the inheritance pattern as well as the genetic basis of the disease. In obtaining the family history, the counselor should pay particular attention to FA-related clinical manifestations and associated cancers, as well as miscarriages and infertility.

Inheritance

Fanconi anemia is predominantly inherited in an autosomal recessive fashion. A small fraction of individuals,

less than 1%, has mutations in the *FANCB* gene which is inherited in an X-linked recessive manner.

Cancer Background

The counselor should obtain a detailed investigation of family cancer history, with a special emphasis on breast, ovarian, and prostate cancer. Each family history should be assessed using risk models to determine if the parents of an FA patient carry a *BRCA2*, *FANCJ* or *FANCN* mutation. Features of hereditary cancer syndromes include multiple close family members with cancer, an autosomal dominant pattern of cancer inheritance, an early age of onset of cancer, bilateral breast cancer, more than one primary tumor, and male breast cancer. Cancer diagnoses should be verified with medical records whenever possible.[2]

Ethnic Background

Identification of an individual's ethnic background is important to determine the potential complementation group and/or specific gene mutations causing FA. Most mutations found in patients with FA have not arisen predominantly in one ethnic population, but in certain ethnic groups common mutations are found at an increased frequency. When an individual is of an ethnic background known to be associated with an FA founder mutation, targeted mutation analysis should be performed for that specific mutation. If a person's ethnic background is not indicative of a specific mutation, the complementation group should be determined before mutation analysis is attempted.

Consanguinity

In non-founder groups, the incidence of FA is rare and the carrier frequency is low. In the general population

of the United States, the chance of being a carrier for any of the FA gene mutations is ~1 in 300. Rare autosomal recessive diseases have an increased frequency of carriers who are consanguineous.

Table 1: Examples of FA Founder Mutations in Ethnic Populations[3-10]

Ethnicity	Gene	Mutation(s)	Carrier Frequency	Reference
Africaans-speaking South African (Transvaal Province)	*FANCA*	Deletion of Exons 12-31 (~60%) Deletion of Exons 11-17 (13%) 3398delA (6%)	~1/80	(Rosendorff et al., 1987) (Tipping et al., 2001)
Ashkenazi Jewish	*FANCC*	c.465+4A>T (IVS4+4A>T)	1/90	(Whitney et al., 1993) and (Verlander et al., 1995)
Black South African (Bantu-speaking populations of sub-Saharan Africa)	*FANCG*	Deletion (c.637_643delTACCGCC)	1/100	(Morgan et al., 2005)
French Acadian	*FANCG*	c.1480+1G>C (IVS11+1G>A)	Unknown	(Auerbach et al., 2003)
Japanese	*FANCG*	c.307+1G>A (IVS3+1>G)	Unknown	(Yagasaki et al., 2003)
Portuguese-Brazilian	*FANCG*	c.1077-2A>G (IVS8-2A>G)	Unknown	(Auerbach et al., 2003)

Genetic Testing

Genetic test results may determine medical management, prognosis, and mode of inheritance, and exclude diseases with similar manifestations. For these reasons, genetic testing should not be delayed and should be completed in a step-wise progression. Typically, experts first perform diagnostic chromosome breakage studies, then complementation group analysis and, finally, mutation analysis of the corresponding FA gene. Alternative

testing strategies include ethnicity-based genetic subtyping and comprehensive mutation screening.[11]

Complementation Group Testing

Complementation group testing is used to classify individuals with FA according to the specific gene defect causing chromosomal instability. Retrovirus-mediated complementation group testing requires cells from patients that can be grown and are sensitive to cross-linking agents.[12] In some cases, multiple blood samples and/or other tissue samples may be needed to complete the testing. For some patients, complementation group testing will not be possible due to these sample limitations. Furthermore, complementation group testing can currently classify patients into 8 of the 13 known complementation groups. Groups that currently can be classified by complementation group testing include (A, B, C, G, E, F, J, and L). Genes not currently identifiable by complementation group testing include D1, D2, I, M, and N. Mutation analysis is necessary to classify individuals into one of these five groups. In approximately 2-3% of the cases, a complementation group will not be identified and a gene mutation will not be found in any of the known 13 genes (personal correspondence with Arleen Auerbach, PhD, The Rockefeller University).

Mutation Analysis

Mutation analysis identifies the specific gene changes that lead to FA. Mutation analysis is used to confirm the initial complementation group result, to perform other genetic tests such as carrier testing, prenatal testing, and preimplantation genetic diagnosis and, in some cases, to direct medical care and/or enroll in specific research studies. As of September 2008, mutation analyses of the *FANCA*, *FANCC*, *FANCD1*, *FANCE*, *FANCF*, and *FANCG* genes were available on a clinical basis in the

United States. Mutation analysis for other genes may be completed on a research basis.

Table 2: Examples of Benefits, Risks, and Limitations of Genetic Testing

Benefits	**Risks**	**Limitations**
Genetic testing results may give important information which would alter medical management (i.e., more frequent bone marrow biopsies).	Genetic testing information is a part of an individual's medical record and may be examined by health and life insurance providers.	Genetic testing results may not give additional information to guide medical management.
Genetic testing results can be used for carrier testing, prenatal testing, and preimplantation genetic diagnosis.	Genetic testing could show unknown family relationships (e.g., non-paternity).	Genetic testing results may be inconclusive or mutations may not be identified.
Genetic testing information can be helpful to family members (i.e., identify who may or may not be at increased risk of having a child with FA or developing cancer).	Family members may not want to know information obtained through genetic testing. Genetic information could alter family dynamics.	
Genetic testing results may relieve anxiety.	Genetic testing results may create anxiety, distress, and feelings of guilt.	
Genetic testing results may be used for inclusion in certain research projects or clinical trials.		

The decision to proceed with mutation analysis should be at the discretion of the parents of a child with FA or the adult patient with FA. Genetic testing can have many benefits, risks, and limitations and is a personal decision. For individuals with FA, the implications for the family can be even greater than in other genetic disorders due to the fact that carriers of mutations in certain FA genes have an increased risk of cancer.

Parents should be well informed of the possibility that their child's genetic testing results may affect their own health. A detailed conversation and informed consent of the patient and/or legal guardian must be completed prior to undertaking mutation analysis.

Genotype-Phenotype Correlations

In most cases it is not possible to predict the clinical course of this genetically and clinically heterogeneous disease. Lack of genotype-phenotype correlation is evidenced by siblings with the exact same gene mutations with radically different phenotypic manifestations. Medical management for most individuals with FA will be selected according to the presenting problems but, for complementation groups FA-D1 and FA-N, genotype is essential for proper cancer surveillance and medical management. For other groups, such as FA-A, FA-C, and FA-G, genotype information may be helpful for prognostic purposes.

FANCD1

Patients with FA in the FA-D1 complementation group have biallelic mutations in the *BRCA2* gene[13] and have markedly increased spontaneous chromosomal aberration rates.[14] These individuals commonly develop solid tumors such as medulloblastoma, astrocytoma, and Wilms tumor, which are rarely seen in individuals in other FA complementation groups. Leukemia is seen at a much earlier age than is expected for individuals of other FA subtypes. If *BRCA2*-related family history or clinical manifestations are suspected or if a patient is known to be in the D1 complementation group, additional tests such as a brain MRI and kidney ultrasound should be completed immediately to rule out any evidence of tumors. *BRCA2* testing should be considered in all patients with FA who have an unknown

complementation group and/or who develop leukemia at or before the age of five.[15]

FANCN

FANCN/PALB2 (partner and localizer of *BRCA2*) is another gene associated with a more severe clinical presentation. Individuals in the FA-N complementation group have a similar clinical presentation as FA-D1 individuals with development of early onset solid tumors and leukemia.[16] Similar cancer surveillance recommendations as listed for patients with biallelic *FANCD1* mutations should be followed for individuals in the FA-N complementation group.

FANCA/FANCC/FANCG

An attempt to decipher distinct clinical manifestations between complementation groups and specific gene mutations was conducted by the European FA Research Group[17] and the International Fanconi Anemia Registry (IFAR).[18] The results of these studies showed several associations. Individuals with *FANCA* homozygous null mutations producing no protein had an earlier age of anemia and higher incidence of leukemia than those with an altered protein. In the European FA Research Group, it was reported that individuals in the FA-G complementation group had more severe cytopenia and a higher incidence of leukemia, but this was not found in the IFAR data set. Kutler et al. noted that individuals in complementation group C had an earlier age of onset of bone marrow failure when compared to complementation group A and G.[18] Furthermore, it has been noted that *FANCC IVS4* and exon 14 mutations had an earlier age of hematological abnormalities and poorer survival compared to individuals who had exon 1 mutations.[18,19] Since this publication, a study of Japanese patients with FA did not show an association with *FANCC* IVS4+4A>T mutation and a severe phenotype.[20]

Hematologists may consider more frequent monitoring or early intervention for individuals with a specific mutation or a higher-risk group.

Cancer Risks for Fanconi Anemia Carriers

The current data collected through the International Fanconi Anemia Registry show that most carriers are not at increased risk of cancer, but several specific genes and particular mutations do confer cancer risks.[21] Three FA genes, *FANCD1*, *FANCN* and *FANCJ*, have been identified as identical to the breast cancer genes *BRCA2*, *PALB2* and *BRIP1* respectively. Case control studies have proven that *FANCJ* and *FANCN* are low-risk breast cancer susceptibility alleles,[22,23] whereas *FANCD1* is a higher-risk breast cancer susceptibility gene.

FANCD1/BRCA2 Carriers

Female and male family members of individuals with biallelic mutations in the *BRCA2* gene are at significantly increased risk of developing certain cancers. Most families with FA who have mutations in the *BRCA2* gene will present with the typical pattern of hereditary breast and ovarian cancer. However, in some families it has also been noted that a number of *BRCA2* alleles associated with a diagnosis of FA may not confer the same cancer risks seen in typical *BRCA2* families.[24] Female *BRCA2* carriers have a risk of breast cancer ranging from 40% at the age of 80 to a lifetime risk of ~80%. Ovarian cancer risks range from 10-20% at the age of 70. The risk of male breast cancer for *BRCA2* carriers is ~7%.[25] Prostate cancer risk is ~20% before the age of 80.[26] The estimated lifetime risk of pancreatic cancer in *BRCA2* carriers may be as high as 5%.[26] Melanoma may also be increased in *BRCA2* carriers. Due to the increase in these specific cancers,

recommendations for proper screening and surgical options have been created by the National Comprehensive Cancer Network as described below.[27] Individuals may wish to participate in research to help increase detection of cancers which currently do not have surveillance recommendations.

Table 3: BRCA2-related Cancer Screening Recommendations

Female Screening	**Recommendation**
Breast	
Self Exam	Monthly, beginning at the age of 18 years of age
Clinical Breast Exam	Semi-annually, beginning at 25 years of age
Mammogram	Annually, beginning at 25 years of age or based on age of diagnosis
Breast MRI	Annually, beginning at 25 years of age or based on age of earliest onset in family
Ovarian	
Pelvic Exam	Every 6-12 months, beginning at age 25 years
Concurrent transvaginal ultrasound and CA-125 blood test	Every 6 months, starting at 35 years or 5-10 years earlier than earliest age of onset of ovarian cancer in the family
Prevention	**Specifics**
Breast	
Chemoprevention	Consider on a case-by-case basis
Prophylactic Surgery	Discussion of degree of protection, reconstructive options, and risk
Ovarian	
Prophylactic Surgery	Recommended between the ages of 35-40 years or when childbearing is complete. Discussion should include reproductive plans, menopausal symptoms, and degree of protection for breast and ovarian cancer.
Male Screening	**Recommendation**
Prostate	
Prostate specific antigen (PSA)	Annually, beginning at 40 years of age
Digital Rectal Exam	Annually, beginning at 40 years of age
Breast	
Self Exam	No standard screening recommendations have been created. Self exam may be advised.
Clinical Breast Exam	Seek medical advice for any breast mass, pain or change
Mammogram	Not typically advised in the absence of other risk factors such as gynecomastia

In addition to screening for cancer, ways to attempt to reduce the risks of cancer include chemoprevention and surgery. Chemoprevention for breast cancer is most commonly achieved using the drug tamoxifen. The use of tamoxifen for five years has been shown to reduce the incidence of breast cancer by 43% in women who have an increased risk.[28] The surgical interventions of salpingo-oophorectomy and mastectomy provide the greatest reduction in cancer incidence.[29] A physician or genetic counselor should discuss the risks and benefits of chemoprevention and surgery with possible *BRCA2* carriers.

FANCN Carriers

Although FA-N and FA-D1 patients present with a similar phenotype, carriers of *FANCN* mutations may have a lower risk of cancer than *BRCA2* carriers. Monoallelic truncating mutations in *FANCN* (*PALB2*) are associated with an approximately two-fold increased risk of breast cancer.[23] Erkko et al. analyzed cumulative breast cancer risk for the Finnish founder mutation c.1592delT and found a 40% cumulative risk at the age of 70.[30] Female *FANCN* carriers are encouraged to discuss this increased risk with their health care providers and design a breast cancer screening plan which may entail more frequent clinical breast exams, mammograms or breast MRI examinations. No specific recommendations have been published for screening of *FANCN* carriers.

FANCJ Carriers

Carrier risk in *FANCJ* (*BRIP1*) individuals was first investigated in a group of patients with hereditary breast cancer who did not have mutations in the *BRCA1* or *BRCA2* genes. Investigators determined that truncating *FANCJ* mutations confer a relative risk of 2.0.[22] However, some missense variants confer a risk for

breast cancer while others do not. Carriers of mutations known to confer an increased risk of breast cancer should be aware of this increased risk and consider screening similar to *FANCN* carriers.

FANCC Carriers

Mutations in the *FANCC* gene may confer an increased risk of breast cancer. Berwick et al. showed that grandmothers who carried a *FANCC* mutation were 2.5 times more likely to develop breast cancer than noncarriers.[21] The molecular basis of this increased risk is not well understood and, thus, this finding must be further investigated. Carriers should be informed of this potential increased risk and be encouraged to discuss this finding with their health care providers.

Reproductive Issues

Reproductive counseling is part of the genetic counseling process. Individuals with FA may seek reproductive counseling for assistance with infertility and/or information of risks for their own children. Parents of individuals with FA should be aware of the chances of their children having FA to permit informed decision-making about future pregnancies. Reproductive choices include natural pregnancy, adoption, birth control, prenatal testing, and various reproductive technologies such as preimplantation genetic diagnosis (PGD).

Preimplantation Genetic Diagnosis

Preimplantation genetic diagnosis is genetic testing used in combination with *in vitro* fertilization to allow parents the opportunity to choose embryos that do not have Fanconi anemia and/or are HLA matches for siblings. Selected embryos are transferred into the mother's uterus with the hope that the couple will have a pregnancy with the specific genetic make-up that they

choose. PGD reduces the likelihood that a family will have a child with Fanconi anemia and can increase the chances of an HLA-match, but it does not guarantee that the child will not have FA and/or be a match. There is always a chance that an error leading to misdiagnosis could occur in the testing or embryological process. Thus, it is recommended that prenatal testing in the form of chorionic villus sampling or amniocentesis be completed to validate the PGD results.

Individuals considering PGD should consider the following factors. The theoretical chances of an individual having a matched sibling with FA includes a 3 in 4 chance that the embryo will not have FA and a 1 in 4 chance that an embryo will be HLA identical; thus, the odds are 3 in 16 or 18.75% for each embryo to be non-affected and an HLA-match. In actuality, many couples will need multiple rounds of IVF and PGD to obtain a clinical pregnancy resulting in a live born baby. Each IVF and PGD center will have specific statistics on its experience, and couples considering this procedure should obtain that data. The major steps in the process from PGD to transplant are as follows:

- Consult with a transplantation physician and genetic counselor;
- Obtain complementation group and mutation analysis results;
- Obtain HLA typing of individual with FA as well as the mother and father;
- Consult with PGD center staff and affiliated IVF center staff;
- Complete PGD work-up, fertility work-up, and required medical procedures;

- Complete PGD and choose suitable embryos for implantation and, if applicable, embryo preservation;
- Obtain a pregnancy test and genetic testing with CVS/amniocentesis to confirm PGD results;
- Arrange umbilical cord collection and harvest;
- Obtain confirmatory testing of umbilical cord blood/newborn baby;
- Proceed to transplantation of HLA-matched umbilical cord for sibling.

PGD remains a controversial procedure. It can be a very stressful experience physically, emotionally, and financially for couples who undergo the procedure. PGD can require many doctor appointments, medical treatments, tough decisions, ethical/religious questions, and the addition of a new member to a family. It may be helpful for families to discuss PGD with other families who have gone through the process for a realistic description of their experiences.

References

1. National Society of Genetic Counselors. Genetic counseling as a profession. Available at: http://www.nsgc.org/about/definition.cfm. Accessed 9/8/2008.

2. Berliner JL, Fay AM. Practice issues subcommittee of the National Society of Genetic Counselors' Familial Cancer Risk Counseling Special Interest Group. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: Recommendations of the National Society of Genetic Counselors. *Journal of Genetic Counseling* 2007; **16**: 241-260.

3. Auerbach AD, Greenbaum J, Pujara K, et al. Spectrum of sequence variation in the *FANCG* gene: an International Fanconi Anemia Registry (IFAR) Study. *Human Mutation* 2003; **21**: 158-168.

4. Morgan NV, Essop F, Demuth I, et al. A common Fanconi anemia mutation in black populations of Sub-Saharan Africa. *Blood* 2005; **105**: 3542-3544.

5. Rosendorff J, Bernstein R, Macdougall L, Jenkins T. Fanconi anemia: another disease of unusually high prevalence in the Afrikaans population of South Africa. *American Journal of Medical Genetics* 1987; **27**: 793-797.

6. Tipping AJ, Pearson T, Morgan NV, et al. Molecular and genealogical evidence for a founder effect in Fanconi anemia families of the Afrikaner population of South Africa. *The Proceeding of the National Academy of Sciences USA* 2001; **98**: 5734-5739.

7. Verlander PC, Kaporis A, Liu Q, Zhang Q, Seligsohn U, Auerbach AD. Carrier frequency of the IVS4 + 4 A→T mutation of the Fanconi anemia gene FAC in the Ashkenazi Jewish population. *Blood* 1995; **86**: 4034-4038.

8. Whitney MA, Jakobs P, Kaback M, Moses RE, Grompe M. The Ashkenazi Jewish Fanconi anemia mutation: incidence among patients and carrier frequency in the at-risk population. *Human Mutation* 1994; **3**: 339-341.

9. Whitney MA, Saito H, Jakobs PM, Gibson RA, Moses RE, Grompe M. A common mutation in the FACC gene causes Fanconi anaemia in Ashkenazi Jews. *Nature Genetics* 1993; **4**: 202-205.

10. Yagasaki H, Oda T, Adachi D, et al. Two common founder mutations of the Fanconi anemia group G gene *FANCG/XRCC9* in the Japanese population. *Human Mutation* 2003; **21**: 555.

11. Ameziane N, Errami A, Leveille F, et al. Genetic subtyping of Fanconi anemia by comprehensive mutation screening. *Human Mutation* 2008; **29**: 159-166.

12. Chandra S, Levran O, Jurickova I, et al. A rapid method for retrovirus-mediated identification of complementation groups in Fanconi anemia patients. *Molecular Therapy* 2005; **12**: 976-984.

13. Howlett NG, Taniguchi T, Olson S, et al. Biallelic inactivation of *BRCA2* in Fanconi anemia. *Science* 2002; **297**: 606-609.

14. Hirsch B, Shimamura A, Moreau L, et al. Association of biallelic *BRCA2/FANCD1* mutations with spontaneous chromosomal instability and solid tumors of childhood. *Blood* 2004; **103**: 2554-2559.

15. Wagner JE, Tolar J, Levran O, et al. Germline mutations in *BRCA2*: Shared genetic susceptibility to breast cancer, early onset leukemia, and Fanconi anemia. *Blood* 2004; **103**: 3226-3229.

16. Reid S, Schindler D, Hanenberg H, et al. Biallelic mutations in *PALB2* cause Fanconi anemia subtype FA-N and predispose to childhood cancer. *Nature Genetics* 2007; **39**: 162-164.

17. Faivre L, Guardiola P, Lewis C, et al. Association of complementation group and mutation type with clinical outcome in Fanconi anemia. European Fanconi Anemia Research Group. *Blood* 2000; **96**: 4064-4070.

18. Kutler DI, Singh B, Satagopan J, et al. A 20-year perspective on the International Fanconi Anemia Registry (IFAR). *Blood* 2003; **101**: 1249-1256.

19. Gillio AP, Verlander PC, Batish SD, Giampietro PF, Auerbach AD. Phenotypic consequences of mutations in the Fanconi anemia FAC gene: an International Fanconi Anemia Registry Study. *Blood* 1997; **90**: 105-110.

20. Futaki M, Yamashita T, Yagasaki H, et al. The IVS4 + 4 A to T mutation of the Fanconi anemia gene *FANCC* is not associated with a severe phenotype in Japanese patients. *Blood* 2000; **95**: 1493-1498.

21. Berwick M, Satagopan JM, Ben-Porat L, et al. Genetic heterogeneity among Fanconi anemia heterozygotes and risk of cancer. *Cancer Research* 2007; **67:** 9591-9596.

22. Seal S, Thompson D, Renwick A, et al. Truncating mutations in the Fanconi anemia J gene *BRIP1* are low-penetrance breast cancer susceptibility alleles. *Nature Genetics* 2006; **38**: 1239-1241.

23. Rahman N, Seal S, Thompson D, et al. *PALB2*, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nature Genetics* 2007; **39**: 165-167.

24. Alter BP, Rosenberg PS, Brody LC. Clinical and molecular features associated with biallelic mutations in *FANCD1/BRCA2*. *Journal of Medical Genetics* 2007; **44**: 1-9.

25. Offit K. BRCA mutation frequency and penetrance: new data, old debate. *Journal of the National Cancer Institute* 2006; **98**: 1675-1677.

26. Cancer risks in *BRCA2* mutation carriers. The breast cancer linkage consortium. *Journal of the National Cancer Institute* 1999; **91**: 1310-1316.

27. Daly M. NCCN clinical practice guidelines in oncology. Genetic/familial high risk assessment of breast and ovarian cancer. Available at: http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf. Accessed 9/22/08.

28. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *Journal of the National Cancer Institute* 2005; **97**: 1652-1662.

29. Robson M, Offit K. Clinical practice. Management of an inherited predisposition to breast cancer. *New England Journal of Medicine* 2007; **357**: 154-162.

30. Erkko H, Dowty JG, Nikkila J, et al. Penetrance analysis of the *PALB2* c.1592delT founder mutation. *Clinical Cancer Research* 2008; **14**: 4667-4671.

Chapter 16

Psychosocial Issues

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Introduction

Upon learning the diagnosis of Fanconi anemia, the family must make important decisions that require a sophisticated understanding of a complex illness with many treatment options. While any serious illness in childhood can isolate a family, isolation is more likely with an unusual condition such as FA. There is often no inherent societal support for rare, unfamiliar diseases. The disease path for families affected by FA is interwoven with grief, loss, and uncertainty at every juncture. The diagnosis of FA imposes a change on the family system. The challenge is for parents to balance their ensuing sense of loss and grief, while orchestrating their child's medical care, maintaining hope, and sustaining a semblance of normal family life. FA is an illness with a course that is ever changing, allowing for much potential for optimism after the impact of the shock of the initial diagnosis.

The Course of the Illness

FA presents different issues for families depending on the developmental stage of the child and the course of the disease for the individual child. Initially, before FA has been clearly diagnosed, families will be hopeful that the diagnosis will be incorrect. Without indisputable confirmation, there is always the hope that their child will not be severely affected.

The time of diagnosis itself is an emotional crisis; it takes time before parents can move from shock and disbelief to a more proactive mode of coping. The number of children with FA in the family, the number of unaffected siblings, and the ages of the children will affect the emotional profile and needs of a family at a given time. All families worry that they will not be able to learn enough about the disease to make good decisions for their children.

Depending on the age of the parents at the time of the diagnosis, the implications for the family are great. Will they have the physical or the emotional energy, the time, the desire or the financial resources to have more children? Will they arrange for prenatal diagnosis or histocompatibility (HLA) typing for subsequent pregnancies?

At any age, parents of children with FA often find themselves in the position of having to make difficult decisions, whether about medications or other treatment options. They may need help thinking through their choices and the implications of those choices. They need information that they can understand to make the best choice given the present state of knowledge.

Children with FA can be stable or asymptomatic for long periods of time. Emotionally calmer times may alternate with more volatile ones. As described in *The Damocles Syndrome*,[1] parents are constantly waiting for the next bad thing to happen. Helping families adjust to living each day to the fullest and to focus on activities apart from the illness are crucial components in day-to-day coping. The moments that are not driven by medical crises are times for families to learn and stay abreast of salient treatment options and to prepare themselves for the future. Living with uncertainty, and preparing

for a future with potentially complex medical situations, while helping a child embrace life and establish dreams, visions, and plans for the future, place the parent of a child with FA on a unique and challenging journey.

Should a child's condition deteriorate and alternate treatment options be considered, the family may be thrown into emotional crisis again and feel hopeless and immobilized. Being prepared to take appropriate action, feeling informed, and feeling supported, all help family members to move forward with the necessary tasks during these periods.

With some of the very difficult choices that parents will have to make for and with their children, there is no turning back. Therefore, each major decision requires that families and older patients know all they can prior to making the decision, with an opportunity to integrate the information and reflect upon and accept the choices they have made. In certain cases, families will be making decisions about experimental procedures and protocols which have been utilized with very few patients. Families experience a vulnerability and a unique anxiety when they know they are traveling on a road that few have traveled before.

Parents' Journeys

Parents may cope separately and very differently with FA. One parent may need to learn everything there is to learn to plan strategically for the future, whereas the other may choose to stay focused in the moment. One parent may need to talk and to cry, whereas the other may not. Differences in coping styles as they relate to gender and culture should be recognized so each can be supported for his or her strengths, insight, and ability during the course of the illness.

If a marital relationship was previously stressed, difficulties in the relationship will often be exacerbated by the illness. On the other hand, some couples have felt that the strain and the magnitude of the issues they face have made them stronger together.

Depression and anxiety are two uncomfortable emotions characteristics that may accompany this disease. Many parents feel anxious or depressed from the onset, unsure of what to anticipate. The ability to contain the anxiety or depression, to make decisions, to enjoy life, and to continue to function are skills to be mastered.

Staying informed of current research and the ever-growing knowledge base about FA and potential treatments can help parents feel calmer, focused, and grounded. Talking to other parents, understanding their decision-making processes, and getting support help parents to maintain the balance they need. Counseling, information, and support from the Fanconi Anemia Research Fund, its e-groups, and communication with professionals play effective roles in helping with the ongoing adaptation of children with FA and their families. These support groups offer parents the opportunity to be parents: to be able to compare their child to other children, to seek companionship of another parent in a similar situation, to brainstorm, to share information, and to join the fight against Fanconi anemia and become empowered in the face of the illness.

Families may be viewed incorrectly as aggressive when they advocate in the interests of their children. There may be moments when families and individual physicians do not agree on treatment options and alternatives (e.g., hematopoietic stem cell transplantation). The involved professionals must work to make the best decisions with, and not for, families. This strategy will

help minimize potential later regrets for families and professional staff.

Relationships with their physicians are of tremendous value and significance to families affected by FA. The quality of these relationships often influences the family's entire experience of the disease. Helping navigate the course of the illness, and thinking through decisions can help those facing such rare illnesses feel much less isolated.

Families truly manage to become experts about FA. They must integrate tremendous amounts of information, while attending to their child's medical needs, and managing all the other activities of the family. It is not surprising that, when parents of children with FA are asked about what they've learned about themselves or their children since the diagnosis, they overwhelmingly suggest that they have learned how strong and capable they and their children are. Parents describe having a greater appreciation for the things they do with their children, learning how to experience each day to its fullest.

With ongoing innovations in technology and the refinement of preimplantation genetic diagnosis (PGD), some families are trying this option to facilitate having a child who could be a matched donor for a stem cell transplant for their child with FA. This process can be financially, emotionally, and physically draining and in some cases, all-consuming. Unsuccessful PGD attempts will serve to delay having more children and can create other conflicts for the family. This phase can be an emotional one in the life of an FA family, as treatment options as well as additional children stand in the balance. Successful PGD attempts, joyous in nature, can set the course of a family towards having a baby and planning a stem cell

transplant, creating an unusual dichotomy: anticipating the transplant and anticipating the birth of a child in the same instance. Families can benefit from talking with others who have been in this situation to help mitigate the intense emotions that can occur during this time. Parents who are of an advanced age and unable to utilize PGD as an option may experience remorse that this technology was not perfected earlier in the course of their child's illness.

Children with FA

How parents accept and face the illness will influence how children with FA grow and adapt. If parents create an environment that allows for questions, discussions, and an expression of feelings, children will feel free to ask their parents about their illness and treatment options and become active participants in the disease management.

Children often know much more about what is happening than adults might believe. In addition to what they have been told, they pick up information from ambient conversation, have independent interactions with professionals, and surmise things from the emotional climate around them. They will ask questions when they want to know, and will often shy away from questions to which they do not want the answers. Children are good regulators of their own knowledge base, providing cues to the adults around them at all junctures.

Visible characteristics of the disease, such as the frequent short stature or missing thumbs of a patient, serve as a constant reminder to the outside world that the child with FA is different. At all ages, physical and other differences may set children with FA apart from their peers and can be factors which cause children

to feel isolated, lonely or depressed, affecting their self-esteem and ability to focus on age-appropriate achievements. Counseling can be a great benefit during these times. Children need to be able to confide in their parents and others when they feel limited physically or socially by Fanconi anemia.

A major concern of parents is what and how to tell children about FA. At each stage of development, children need age-appropriate explanations of their diagnosis and treatment. These explanations should grow in sophistication as the child grows. Information offered regularly to children will enhance their ability to understand their disease and establish trusting relationships. As they get older and medical problems emerge, groundwork set in earlier years will encourage patients to rely on health care providers.

School may present unique issues for children with FA. Some may have cognitive impairments that will require special attention. Others may have no known problems but, because of illness-related absence, may need extra assistance. School is the place where children may begin to feel as though they are unlike other children, if they are frequently absent because of doctor's visits, if they are sick and unable to attend, if they are unable to participate in activities or if they are perceived as different from their peers. They may need support to learn how to adapt, respond, and connect to their peers. Clearly assessing the child's educational and social needs, the educational program, and what works in a family will open discussion of these issues and allow for the best academic and social plan.

School-age children develop increasingly strong relationships with their peers as they begin to differentiate themselves from their families. Physical limitations

necessitating dependency may influence the child's social activities. Each child and family must find a balance in social and family relationships, which allows for a blend of independence and dependence, nurturing and differentiation.

Children with FA, facing multiple hospitalizations and medical treatments, are exposed to difficult experiences, including the deaths of other children or siblings. They may, therefore, come to understand and deal with issues with which adults may not feel comfortable. Although parents work to "normalize" their children's lives, patients' experiences are unique and force them to deal with issues associated with death at an "age-inappropriate" time, certainly at younger ages than other children. Thus, they may seem more mature than their chronological ages and often are more sophisticated than their peers in matters of illness and death. They may also appreciate life, and the meaning of life, more than the adults they encounter.

For adolescents, challenging the rules is age-appropriate and functional at times for emotional growth. It allows them to assert themselves as individuals and to begin to learn to take responsibility for their actions. However, for adolescents with FA this can be a time of rebelling against the "rules" of the disease. Young adults report stopping their medications, sun bathing, drinking alcohol, smoking, etc. Compliance with medication regimens may be of concern and should be given particular attention at this stage, as should the risk-taking behaviors associated with greater chances of malignancy.

As children get older, they need to be involved in assenting, consenting, and participating in actual decisions about their medical care. As their children become more active decision-makers, parents may feel some

relief that they are now making decisions with, rather than for, their children. Yet as children approach young adulthood, parents have expressed anxiety about how their children will learn to make complicated, sophisticated decisions for themselves. For some young adults, the decisions will continue to be made in partnership with their parents. Others will want full responsibility, and parents will need to trust their grown children's choices. This time of growth for the person with Fanconi anemia also becomes a time of growth for parents. There can be occasional dissonance between parents and children. In some cases, cognitive factors may limit the child's ability to make decisions.

Living with FA is a long and arduous journey for many children, yet they respond as children and often have more energy than adults would in similar circumstances. Children of all ages need to be allowed to continue to grow, regardless of the status of their medical conditions. Maximizing the capacity of the child with FA inherently helps all family members to acknowledge and delight in the child's gains, as opposed to focusing only on losses. Achievements, great or small, cultivate growth and satisfaction for both children and parents. Children need to be prepared to be successful and motivated in life, and not exclusively focused on Fanconi anemia. FA is a component of the life of the person who is diagnosed, but it is not what defines him or her.

Siblings

Siblings present their own unique concerns, some visible and some invisible. They may feel guilty that the disorder happened to their sibling and not to them or may feel that they are less important because they are not getting as much attention. Siblings care about and

worry about each other a great deal. For many, their universe is defined by their role as either an older or younger brother or sister. Siblings of children with life-threatening or fatal illnesses often have as much of an emotional response to the illness as the affected children.

Open communication, the opportunity for expression, and the ability to process the experience help siblings to find their place in the world. It is important for families to address their unaffected children's feelings and questions, while involving them in the activities of the child(ren) with FA whenever possible. Siblings need their own time with parents, medical knowledge appropriate to their age, and to truly be and feel that they are an integral part of the family. Anxiety, jealousy, and guilt are among the emotions experienced by siblings.

The already complex relationships of siblings are further complicated when there is more than one child with FA in the family. Siblings often use each other as reference points, in life and beyond. These relationships have a very powerful presence that may not always be visible in a family. It is important that affected and non-affected siblings have the opportunity to talk with each other and with their parents. These can be among the strongest relationships in life and need to be cultivated and nurtured during this journey.

Young Adults and Adults with FA

Becoming a young adult leads to a more comprehensive understanding of the illness, perhaps responding emotionally to Fanconi anemia in a new way, and addressing salient issues that may have been dormant at other developmental stages. Young adults who face the most severe manifestations of the illness may, of necessity,

remain more physically and emotionally dependent on family members. On the other hand, their family connections may reach deeper levels than those of their healthy peers. At each stage, issues of dependence and independence may need negotiation.

Advice to parents from a group meeting of young adults included:

- Don't worry about what is going to happen. It is going to happen anyway, so don't waste time.
- Don't feel guilty or responsible for the disease.
- Don't be overprotective.
- Don't forget the siblings.

Finding their own voices, taking responsibility for managing their own illness, becoming the primary decision-maker, using their parents as partners or consultants, and truly becoming independent are appropriate and very significant steps for young adults with FA. It is important to help such individuals gain their independence while helping them understand that they can still rely on their families for support and assistance. The partnership with parents should be well established long before this age. Family members need to work together to understand the best decision-making practices in their families. Fanconi anemia affects the whole family, not just when a child is initially diagnosed, but throughout the course of the illness. It affects the current generation and future generations. Some of the magnitude of the diagnosis is not apparent to the child until he or she reaches adolescence and young adult years.

Normal developmental challenges do not evade young adults with FA, yet age-appropriate experiences may have greater intensity and significance. Relationships,

peer pressure, experimentation with drugs and alcohol, and sexual relationships all pose emotional and physical challenges. Because of the inherent increased risks of cancers from some of these behaviors, young adults with FA (once informed) are torn between the desire to take care of themselves and their desire to fit in with peers. Ambivalence and anxiety can plague the young adult with FA, who needs to take care of himself or herself and constantly be on top of the unique challenges of living with the illness, while struggling to be like everyone else. It is difficult to understand how the multitude of illness-related factors affects the day-to-day emotional well-being and sense of self for persons with FA. Beyond the personal components of dealing with the disease, FA patients may feel accountable towards their peers with FA, parents, doctors, and the professionals with whom they have developed connections. This network may encourage young adults to do the "right thing." Always present are the feelings of isolation and distance adults with FA may feel from those who do not have to face living with a life-threatening illness.

Deciding when to tell potential partners about FA—the short version, and then the long version—becomes part of the dating process for the person with FA. The issues of whom to tell, when to tell, and what to tell seem to be related to whom to trust and an ongoing evaluation of who needs to know what and why. These issues can frame early stages of relationships with roommates and romantic partners.

As relationships flourish, there is a natural inclination to think towards the future. This reflective process can be different for persons with FA who may simultaneously be trying to figure out their future goals in the context

of what they know about their medical condition. All of this may influence how they make choices of friends, relationships, careers, marriage, and parenthood.

Partners of young adults with FA often need help understanding the disease and its implications for their relationship, as well as the roles of other family members. Partners also need an outlet for information, expression, and help at times when their partner is not doing well or has to make major life decisions. Many understand the disease intellectually, but it is not until their partner's condition worsens that they begin to understand what some of their own concerns may be. Negotiating their roles as partners and with parents who have nurtured their children for decades can be quite challenging. Information, support, and counseling are important for this population.

For the adult with FA, having grown up with uncertainty of the future, establishing and mastering life goals, forging lifelong commitments, dealing with the issues of partnership, sexuality, marriage, children, ongoing cancer risks, financial and insurance concerns, and myriads of other problems all present unique challenges for this population.

These adult FA patients serve as an inspiration to all, yet should be recognized for their own needs, aspirations, and struggles. Increasing numbers of children are becoming young adults and adults with Fanconi anemia. In the same way that the needs of the children and then teens became a priority as treatment evolved, now the needs of these adults, physically and emotionally, become the priority. The medical course of Fanconi anemia is evolving, allowing for the emotional and physical sequelae to be better understood. Emotional connections for this group can be found in young adults

and adults with other rare illnesses who have survived to adulthood.

The Death of a Child

If a patient nears death, the patient and the family need emotional support, clear thinking, concrete assistance, and tremendous understanding. By this point, the family has lived through many struggles with the illness and therefore may continue fighting longer than others might expect. Fighting, trying the next thing, and looking towards experimental options are the armor that families use to cope. For some, it may make sense to continue in that vein as long as possible. No one else should determine when a specific family should lose hope. Providing information and opportunities for discussion, helping families make decisions, supporting their choices, comforting, remembering, and remaining available are significantly helpful to families at this stage.

Support after the death of a child is necessary, but difficult to find. Rarely do bereaved parents feel that their loss is understood and therefore their ability to accept support, except from people in similar situations, may be limited. It is difficult to understand what they may be going through. Parental grief does not go away; it changes over time. Variables that have been shown to complicate mourning for families include: a markedly dependent relationship with the deceased; prior unresolved losses and stresses; a perceived sense of lack of support; death after an overly-lengthy illness; and the mourner's perception of preventability.[2] Families who lose a child to Fanconi anemia exhibit many of these factors. After having fought so hard, there can be a sense of guilt at not having been able to prevent the child's death.

Relationships with families should not end abruptly during the bereavement period, because it is a most difficult phase for them. Assisting families to understand many of the more intense feelings (anger, regret, loneliness, depression) as part of the natural process at this time is helpful. Ongoing communication to reflect on the child's life, referrals for counseling and support groups, and caring about the family's struggle are important. The death of one's child or one's sibling, regardless of the age of the child (young adults, older adults) is devastating, and can have lifelong implications for the family. The complication of having a genetic illness, an illness that a family will have to deal with for generations to come, adds to the complexity of coping after a child dies. FA will always be an issue for an affected family.

Recommendations for the Physician

- Provide the opportunity for an initial psychosocial assessment of the child and family at the time of diagnosis.
- Provide the family access to appropriate counseling and other resources throughout the life of the person with Fanconi anemia.
- Provide developmentally appropriate communication for patients to enhance their understanding of and comfort with FA. Encourage dialogue among children with FA or other bone marrow failure diseases or other life-threatening illnesses.
- Encourage involvement with activities through the FA Research Fund to help families develop and maintain a current knowledge base, to gain support, and to afford families an active role in supporting research seeking to help their children.

- Encourage families to create a working partnership between the physician and the family, allowing for mutual respect for what each has to offer to the situation.

Enable patients, as they mature, to become responsible and proactive with regard to their medical care (recommended by a focus group of parents).

References

1. Koocher GP, O'Malley JE. *The Damocles Syndrome: Psychosocial Consequences of Surviving Childhood Cancer*. New York, NY: McGraw-Hill; 1981.

2. Rando TA. The increasing prevalence of complicated mourning: the onslaught is just the beginning. *Omega* 1992-93; **26:** 43–45.

Chapter 17

A Mother's Perspective: The Grieving Process and the Physician's Role

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The Grieving Process

The realization that one's child, children or spouse suffers from a life-threatening illness triggers a grieving process. This process can begin at the moment of a child's birth, when parents realize that physical anomalies could well signify a serious underlying problem. Or grieving can begin later, when baffling physical symptoms finally lead to the diagnosis of Fanconi anemia.

The knowledge that one's precious child or beloved spouse suffers from a condition which usually leads to premature death represents a terrible loss. The grief one experiences often proceeds in predictable stages, as one struggles to cope with this devastating reality. Since this illness often progresses slowly and patients sometimes live for years or decades after diagnosis, the family suffers from chronic grief. With every acute crisis of this illness, loved ones experience again the most painful phases of the grieving process.

Experts who study stages of grieving often refer to four phases, which usually proceed in order, but can co-exist in the same time frame. It is also possible to survive one phase only to find oneself experiencing feelings or behaviors characteristic of an earlier phase. Any one individual may experience this process very differently.

Stages of the Grieving Process

Shock or denial

The first stage of grieving is usually described as shock or denial. This phase is characterized by numbness and an inability to accept the diagnosis. Some individuals appear calm and can appear to be functioning normally. They carry on with their daily routine, perform regular tasks, ask appropriate questions, but in fact are functioning on "automatic pilot." Often they cannot hear, remember or process information accurately. This phase can last from hours to months and is often intermingled with the second stage of grief.

Protest

Shock and denial give way to or alternate with protest. This phase is characterized by a roller-coaster of emotionality. Emotions commonly experienced are crippling sadness, anger, guilt, anxiety, despair, terror, and feeling out of control. Sudden outbursts of tearfulness or expressions of rage are common. With any loss one frequently experiences some level of guilt. When parents have unknowingly passed lethal genes on to their children, feelings of guilt can be quite intense, however irrational. The protest phase usually lasts for months. And even much later, whenever a patient's stability gives way to periods of precarious health, the intense emotionality of this period may return.

Disorganization

The third phase of the grieving process is often referred to as a period of disorganization. Gradually the intense emotionality described above slows down. The emotions of the second phase continue, but the waves of sadness, anger, anxiety, and other disabling emotions are less intense. This period is characterized by feelings of low self-esteem, dread about the future, and physi-

cal and emotional fatigue. Most parents feel that part of their role is to protect their children from dangerous, unhappy experiences. They often feel quite helpless when confronted with the knowledge that they are unable to protect precious children from a life-threatening condition. Feelings of isolation and loneliness are common, as one realizes that others usually deal with problems of a much smaller magnitude. Many parents experience chronic depression at this stage.

Parents who live for years or decades with a life-threatening, chronic illness can get "stuck" in different phases of the grieving process. Many can manage to lead productive lives, but, with new symptoms and the onset of dreaded or unexpected medical problems, they must deal, again, with the most painful phases of grief.

Reorganization

For those who have experienced the finality of a loss (for example, the death of a loved one), earlier phases of grieving are experienced once again and a final phase of grieving occurs, which is often called reorganization or reintegration. Some eventually come to peace with the loss and learn to live with grief. Many gradually find increased energy to attach to other people, work and new pursuits. The pain of the loss may continue for many years, sometimes forever, but many are able to get on with their lives. For others, tragically, this is not possible. Self-destructive behavior, such as alcoholism or suicide, may result.

Other complications of the grieving process

Some behavioral and emotional characteristics of the grieving process are outlined above. In addition, a grieving parent or spouse can experience cognitive and physical changes. One can suffer forgetfulness, short-term memory loss, slowed thinking, confusion, short

attention span, and difficulty in making decisions or problem-solving. Common physical symptoms include insomnia, headaches, respiratory problems, higher blood pressure, gastro-intestinal problems, and weight gain or loss. Those experiencing chronic grief are themselves at higher risk for serious health problems.

Spouses often react in different ways to the illness of their child. Some cry frequently and need to express their emotions constantly. Others compartmentalize their grief, not showing their distress outwardly most of the time. Some are uncomfortable expressing their feelings and believe they must project "strength" to their family and friends. Differences in coping often lead to marital stress, as spouses can feel misunderstood, unappreciated and resentful of one another. Each may feel that the other spouse is unable or unwilling to provide sufficient emotional support. The grieving process can even threaten a previously strong marriage. Marriage counseling may be crucial to help couples learn to be more tolerant, understanding and supportive of one another throughout this extremely painful time.

Several factors influence one's ability to cope with a long-term, chronic illness. Past experiences with loss may make this process even more difficult. A support network (family, friends, co-workers, and therapists) can help enormously. Many family members affirm that their religious beliefs have been crucial to their emotional survival.

The Physician's Role: What Helps and What Hurts

How physicians can help

A patient's physician is not expected to "treat" the emotional distress of the grieving parents or spouse,

although it may be appropriate for the physician to refer the parents or spouse to a support group (e.g., The Fanconi Anemia Research Fund), grief counselor or other appropriate professional. The power of the patient's physician to affect the emotional state of the caregivers is nonetheless enormous. The physician can play a crucial role in helping the family move from the depths of despair, anger and self-blame into understanding the disease, making and participating in a treatment plan, and maintaining hope.

Physician Characteristics Which Help

Almost all pediatricians or family doctors and many hematologists have had no prior experience in treating FA patients. The treating physician needs to be willing to learn, eager to explore current literature and seek out information from experts, and able to invest the time to learn new therapeutic approaches. It is also helpful if he or she is a caring, warm individual, concerned about the welfare of this patient and the stress the family is experiencing.

Treating physicians must be good at both explaining and listening. They must communicate in a language the family will understand. Physicians need to listen to fears and concerns, and answer questions in understandable terms. It is all right for doctors to admit they don't know all the answers, but they will try to find out.

Maintaining hope

The treating physician must be honest, straightforward, and frank in discussing the diagnosis of Fanconi anemia. The family needs to know that this is a very serious, life-threatening disorder. False reassurances are not helpful. At the same time, doctors should encourage families to be hopeful. The literature on Fanconi anemia

and the dire statistics presented reflect past treatment approaches. Statistics do not include the possibility that bone marrow transplant outcomes will continue to improve, that new methods of gene therapy could change life expectancies, and that future discoveries could improve overall survival rates. Families need to know that scientific discovery concerning this rare disorder has progressed at a very rapid pace over the past few years and that many laboratories are actively pursuing new, hopeful approaches. When appropriate, they need to know that new discoveries could greatly improve the prognosis for their child or spouse.

Depressed parents (and FA parents have reason to be depressed) must work harder than most to be great parents. They can unwittingly create an atmosphere of sadness and worry which permeates every day. As a result, the time a patient has may not be quality time at all. By emphasizing progress and helping to instill hope, physicians can greatly assist in improving the patient's quality of life.

Entering into a partnership with families

Family members should be encouraged to educate themselves about this disorder and to play an active role in the treatment plan. Becoming a part of the decision-making process enables many to cope with the anxiety, depression, and loss of control they are experiencing. The relationship between physician and family should be one of mutual respect, shared information, and joint decision-making. Caretakers know the patient well, are aware of subtle or abrupt changes in the patient's condition, and can be an invaluable source of information.

Family members may need permission to voice their concerns or disagreements. Some are intimidated by medical authority, or fear appearing foolish by asking

inappropriate questions. But parents or spouses must live with the results of any medical intervention, so they must understand and agree with decisions. Often, decisions are not clear-cut. Outcomes are unknown and risks are enormous. Parents must believe that the most appropriate decisions were made, given what was known at the time. When parents are ill-informed and have never voiced their questions or concerns, they may forever feel guilty if the outcome is not good.

Being responsive to patient needs

A doctor's responsiveness and empathy with the patient helps foster a good relationship with other family members. When the physician is warm, caring and concerned about the patient, parents feel positively towards that provider. Whether the patient's immediate concerns are about pain, nausea, fear, or side effects of treatment, these concerns need to be addressed in a caring manner. Parents are terrified that their child will experience unmanageable pain. It is this writer's belief that a great deal of pain can be eliminated when pain management is a priority. Bone marrow aspirations and biopsies can be performed under very short-term, total anesthesia, leaving the patient with a painless experience. Bone marrow transplant centers have done this routinely for years. But outpatient clinics, aware of the importance of this issue, may be able to offer the same service. Even though total anesthesia is more costly, and the assistance of an anesthesiologist is mandatory, the children who must experience these procedures on a regular basis should not have to endure unnecessary pain. On very rare occasions, a patient's clinical status makes total anesthesia unusually risky. However, in many cases in which patients are not provided with total anesthesia, it is because it is not suggested or offered.

Communicating diagnostic results in a timely way
Much of the distress family members experience occurs while waiting for the results of tests. From a simple CBC to a full-body CAT scan or MRI, parents or spouses wait with excruciating anxiety for results which may tell them if their loved one is doomed to die soon or has dodged a terrible diagnosis. For many, the waiting process is more painful than dealing with the results. Once you know the extent of the problem, you can begin to deal with it. The treating physician should make sure that family members get crucial information as soon as possible. If the news is catastrophic, it is important that the patient's primary doctor deliver the bad news if at all feasible.

Encourage normalcy while remaining alert to unusual symptoms
When appropriate and within prudent medical guidelines, physicians should encourage patients to live as normally as possible. Sometimes it is necessary to curtail physical activity, but simple measures such as a protective helmet might make normal activities possible. Consideration should always be given to maximizing the quality of a patient's life.

On the other hand, physicians need to be alert to a wide variety of symptoms which seem unusual, and should be more aggressive in pursuing a diagnosis. For example, physicians should inform patients and their families of changes which might suggest a malignancy, and work together to monitor a patient's clinical status.

Being "there" for a family when patient's condition worsens
When a patient's condition worsens suddenly or when he or she approaches death, a physician should not suddenly withdraw from the family. Many families

believe this occurs regularly, and suspect that doctors need to protect themselves from the family's emotional response and their own feelings of grief. But families desperately need support at this time, and are deeply appreciative when physicians are able to empathize with them during the hardest times.

Attitudes and Behaviors Which Do Not Help

Family members are well aware of physicians' behaviors which have not been helpful to them. The doctor who knows little or nothing about Fanconi anemia and has no time to become informed is not helpful. Doctors who appear cold, distant, and unsympathetic do not gain the family's confidence. Physicians who speak in complicated medical terms, have little time to answer questions, are rushed or impatient, deal with families in a condescending way, or do not consider the family's input are not appreciated.

Many parents tell stories of doctors who informed them that their child would probably die within a specific period of time or before reaching a certain age. These comments have devastated parents and have frequently proven to be untrue. Too much is unknown about how any one individual will progress. The positive impact of future therapies is obviously unknown and cannot be addressed in the medical literature available today.

Doctors who are noticeably missing when bad diagnostic news is delivered or who never come to see a dying patient bring additional pain to a grieving family.

The physician with endless time to research an orphan disease and provide ideal patient care may be difficult to find in these times of work overload, HMOs, and pressures from other patients equally in need of quality care. But having dealt with this illness for over twenty

years, this writer has experienced enormous variance from one physician to another in terms of ability to work with families burdened with a life-threatening, chronic illness. Families should try to locate physicians who can best meet the patient's physical and emotional needs. Physicians should become more aware of and responsive to the needs of this unique group of families.

Appendix

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Glossary

Ablation: To remove or destroy, especially by cutting or abrading diseased tissue.[1]

Absolute neutrophil count (ANC): This number is important in determining the body's capacity to fight a bacterial infection. To determine the ANC, multiply the percentage of neutrophils (found in the "differential" section of the CBC) by the total number of white blood cells. Include both mature neutrophils (usually designated as "segs") and more immature forms (often called "bands").[2]

Acute lymphocytic leukemia (ALL): An aggressive (fast-growing) type of leukemia (blood cancer) in which too many lymphoblasts (immature white blood cells) are found in the blood and bone marrow. Common symptoms are weakness and fatigue, easy bruising and petechiae, and sometimes frequent infections.[4] ALL is uncommon in FA patients.

Acute myeloid leukemia (AML): A quickly progressing disease which frequently develops in FA patients, in which too many immature white blood cells (not lymphocytes) are found in the blood and bone marrow. The cells that dominate the bone marrow of patients with AML are known as "blasts." Anemia, low platelet counts, and variable white blood cell counts characterize this disease. Common symptoms are weakness and fatigue, easy bruising and petechiae, and sometimes frequent infections. Also called acute myeloblastic leukemia, acute myelogenous leukemia, acute nonlymphocytic leukemia, AML, and ANLL.[2,4]

Adenocarcinoma: Cancer that begins in cells that line certain internal organs, such as the liver, stomach, and lungs, and that have gland-like (secretory) properties.[4,5]

Adenoma: An ordinarily benign neoplasm of epithelial tissue, such as in the liver, in which the tumor cells form glands or gland-like structures in the stroma.[6]

Adenopathy: Any enlargement involving lymph nodes.

Adrenal insufficiency: An endocrine or hormonal disorder characterized by weight loss, muscle weakness, fatigue, low blood pressure, and sometimes darkening of the skin in both exposed and nonexposed parts of the body. Occurs when the adrenal glands do not produce enough of the hormone cortisol and, in some cases, the hormone aldosterone.[7] Adrenal insufficiency also occurs if there is ACTH deficiency. In FA patients, this is most often an acquired abnormality due to prolonged use of steroids necessitating slow withdrawal. The disease is also called Addison's Disease or hypocortisolism.

Adrenocorticotropic hormone (ACTH): An ACTH test measures the adrenocorticotropic hormone, a hormone released from the anterior pituitary gland in the brain. ACTH levels in the blood are measured to help detect, diagnose, and monitor conditions associated with excessive or deficient cortisol in the body.[3]

Alanine aminotransferase (ALT): An enzyme found mostly in the liver; smaller amounts of it are also in the kidneys, heart, and muscles. A blood test can be done to measure the level of ALT.[5] When the liver is damaged, such as by some drugs or viruses, ALT is released into the blood stream, usually before more obvious symptoms of liver damage occur, such as jaundice (yellowing of the eyes and skin).[3]

Alkaline phosphatase (Alk Phos or ALP): A protein found in all body tissues. Tissues with particularly high amounts of ALP include the liver, bile ducts, and bone. A blood test can be done to measure the level of ALP.[5]

Amniocentesis: A prenatal test usually performed in the 15th to 17th week of pregnancy. A needle is inserted through the abdomen or through the cervix into the uterus, and amniotic fluid is extracted. Cells are studied for the detection of chromosome abnormalities, either abnormal numbers of chromosomes (as in Down syndrome, in which there are three chromosome 21s) or hypersensitivity to DEB (as in patients with FA). These fetal cells can also be tested for HLA matching.[3]

Anastamosis: The surgical union of parts and especially hollow tubular parts, such as the anastomosis of the ureter and colon.[1]

Androgens: Artificial male hormones that may stimulate production of one or more types of blood cells for extended periods of time in FA patients.[2] Androgens are also normally made in boys during puberty and in adult men.

Anemia: Decrease in the oxygen-carrying capacity of the blood; indicated by a low red blood cell count, low hemoglobin, low hematocrit.[2]

Angiography: The radiographic visualization of the blood vessels after injection of a radiopaque substance (anything that does not let x-rays or other types of radiation penetrate).[1]

Antibody: A complex molecule produced by certain blood cells in response to stimulation by an antigen. Antibodies bind to antigens, thus marking them for removal or destruction. The marked antigens are then destroyed by other blood cells.[2]

Antigens: Proteins present on the surface of all cells, bacteria, and viruses. Bodies are accustomed to their own antigens and usually don't attack them, but the body considers foreign antigens (such as bacteria, viruses, or grains of pollen) dangerous and will attack them. Bone marrow transplant specialists look for "matching" HLA antigens on the white cells. These antigens can help predict the likely success of a marrow transplant.[2]

Anti-thymocyte globulin (ATG): A purified gamma immunoglobulin (IgG) with immunosuppressive activity which specifically recognizes and destroys T lymphocytes. Administering antithymocyte globulin with chemotherapy prior to stem cell transplantation may reduce the risk of graft-versus-host disease.[8]

Aperistalsis: Absence of peristalsis, which is successive waves of involuntary contraction passing along the walls of the esophagus or intestine and forcing the contents onward.[6] Common but transient complication during BMT or after surgery.

Apheresis: Withdrawal of blood from a donor's body, removal of one or more components (such as plasma, blood platelets, or white blood cells) from the blood, and transfusion of the remaining blood back into the donor; also called pheresis.[1]

Aplasia: Lack of development of an organ or tissue, or of the cellular products from an organ or tissue. In the case of FA, this term refers to lack of adequate blood cell production from the bone marrow. Also refers to the lack of thumb and radius in some FA patients.[2]

Aplastic anemia: Failure of the bone marrow (aplasia) to produce one or more of the three blood cell types (red blood cells, white blood cells, or platelets). Anemia

typically refers to decreased hemoglobin in red blood cells but, when used in this context, refers to any new blood cells. Bone marrow biopsy results reveal a lower number of blood cells than normal.[9]

Aspartate aminotransferase (AST): An enzyme found in liver cells. Testing for AST is usually done to detect liver damage. AST levels are also often compared with levels of other liver enzymes, ALP, and ALT, to determine which form of liver disease is present.[3] A blood test can be done to measure the level of AST.[5]

Atresia: Absence or closure of a natural passage of the body, such as of the small intestine or absence or disappearance of an anatomical part (such as an ovarian follicle) by degeneration.[1]

Audiogram: A graphic representation of the relation of sound or acoustic frequency and the minimum sound intensity for a hearing test to determine hearing loss.[1]

Autoimmune hemolytic anemia: A drop in the number of red blood cells due to increased destruction by the body's defense (immune) system.[5]

Autologous stem cells: Bone marrow stem cells derived from the patient.

Autosomal recessive: One of several ways that a trait, disorder or disease can be inherited. An autosomal recessive disorder means that two copies of an abnormal gene must be present in order for the disease or trait to appear. Genes are found in pairs, one from the mother and one from the father. Recessive inheritance means both genes in a pair must be defective to cause disease. People with only one gene that is not working in the pair do not have the disease but are carriers. They can pass the non-working gene to their children.[5]

Avascular necrosis (AVN): Avascular necrosis occurs when part of the bone does not get blood and dies. If this condition is not treated, bone damage gets worse. Eventually, the healthy part of the bone may collapse.[5]

Azospermia: Lack of sperm.[1]

B cells: Type of lymphocytes responsible for antibody production.

Baseline test: Test which measures an organ's normal level of functioning. Used to determine if any changes in organ function occur following treatment.[2]

Basophil: Type of white blood cell; a type of granulocyte, involved in allergic reactions.[2]

Bicornuate uterus: Commonly referred to as a heart-shaped uterus, is a type of a uterine malformation where two horns form at the upper part of the uterus.[1] This is one example of a congenital uterine malformation. These malformations do not cause infertility. The extent and location of the malformation can affect the likeliness of a pregnancy reaching full-term. Sometimes called hemi-uterus.

Bifid: Separated or cleft into two parts. In FA patients, most commonly refers to a thumb abnormality.

Biliary: Of, relating to, or conveying bile.[1]

Biliary ducts: Ducts by which bile passes from the liver or gallbladder to the duodenum.[1]

Bilirubin: A product that results from the breakdown of hemoglobin. Total and direct bilirubin are usually measured to screen for or to monitor liver or gallbladder problems.[5]

Blast cell: An immature cell. Too many blast cells in the bone marrow or blood may indicate the onset of leukemia.[2]

Blind loop syndrome: Occurs when part of the intestine becomes blocked, so that digested food slows or stops moving through the intestines. This causes bacteria to overgrow in the intestines and causes problems in absorbing nutrients.[5]

Blood urea nitrogen (BUN): Urea nitrogen is what forms when protein breaks down. A test can be done to measure the amount of urea nitrogen in the blood.[5]

Bone marrow: Soft tissue within the bones where blood cells are manufactured.[2]

Bone marrow aspiration: Test in which a sample of bone marrow cells is removed with a sturdy needle and examined under a microscope. Aspirates are used to examine more specifically the types of cells in the bone marrow, and the chromosomal pattern.[2]

Bone marrow biopsy: Procedure in which a special type of needle is inserted into the bone, and a piece of bone (a plug) with marrow is removed. This test is very helpful in assessing the architecture and arrangement of cells within the bone marrow. Commonly used to test for cellularity of the bone marrow.

Bone mineral density (BMD) test: Used to assess for osteopenia or osteoporosis.[5]

Brainstem-evoked auditory response (BAER): A test to measure the brain wave activity that occurs in response to clicks or certain tones. The test is done to help diagnose nervous system problems and hearing losses (especially in low birth weight newborns), and to assess neurological functions.[5]

Bullae: Bullae are blisters wider than 1 centimeter. Bullae that are filled with clear fluid may occur on the skin.[5]

***Café au lait* spot:** A birthmark that is light tan, the color of coffee with milk.[5]

Cardiomyopathy: A weakening of the heart muscle or a change in heart muscle structure, often associated with inadequate heart pumping or other heart function problems.[5]

Carpectomy: Removal of a carpal bone(s).

Carpus: The group of bones supporting the wrist.[1]

Central line: See **Hyperalimentation**.

Chelation: The use of a chelator (an organic chemical that bonds with and removes free metal ions) to bind with a metal (such as iron) in the body. Chelation may inactivate and/or facilitate excretion of a toxic metal. In FA patients, most often refers to a method for getting rid of excess iron.

Cholestasis: Any condition in which the flow of bile from the liver is blocked. Blood tests may show higher than normal levels of bilirubin and alkaline phosphatase. Imaging tests are used to diagnose this condition.[5]

Chorionic villus sampling (CVS): An early prenatal diagnostic test. In the first trimester of pregnancy, an instrument is inserted vaginally or through the abdomen into the uterus under ultrasound guidance to identify the placenta and the fetus. Villus cells, which later form part of the placenta, are removed. These cells are then studied for chromosome abnormalities, either for abnormal numbers of chromosomes (as in Down syndrome, where there are three chromosome 21s) or

hypersensitivity to DEB (as in patients with FA). These cells may also be tested for HLA matching.

Chromosomes: Structures in the cell nucleus which contain the genes responsible for heredity. Normal human cells contain twenty-three pairs of chromosomes. One of each pair is inherited separately from a person's father and mother.[2]

Cirrhosis: Scarring of the liver and poor liver function as a result of chronic liver disease.[5]

Clastogen: An agent that causes breaks in chromosomes.[6]

Colony stimulating factors (also known as hematopoietic growth factors or cytokines): Substances produced naturally by the body (and also synthetically) which stimulate the production of certain blood cells. Examples are G-CSF (Neupogen), GM-CSF, various "interleukins," stem cell factor (or steel factor), erythropoietin (EPO, Epogen), etc.[2]

Colposcopy: An examination by means of a colposcope, a magnifying instrument designed to facilitate visual inspection of the vagina and cervix. The instrument usually contains a green filter which enables the clinician to see abnormal vessels related to any lesions.

Comparative genomic hybridization (CGH): A fluorescent molecular cytogenetic technique that identifies DNA gains, losses, and amplifications, mapping these variations to normal chromosomes. It is a powerful tool for screening chromosomal copy number changes in tumor genomes and has the advantage of analyzing entire genomes within a single experiment.[10]

Complementation groups: When a mutant (or defective) cell is able to restore normal function to (or complement) another defective cell, the mutations in those cells are said to be in different complementation groups. That means the mutations are in different genes. If a mutant or defective cell is not able to restore normal function to another defective cell, the mutations are said to be in the same complementation group (in other words, in the same gene).[2]

Complete blood count (CBC): Gives the number, and/or percentage, and/or characteristics of certain blood cells, primarily white cells, red cells, and platelets.

Computed tomography (CT, aka CT scan): An imaging method that uses x-rays to create cross-sectional pictures of the body.[5]

Consanguinity: Relationship by blood via descent from the same ancestor, and not by marriage or affinity.

Cortisol level: A blood test that measures the amount of cortisol, a steroid hormone produced by the adrenal cortex in response to a hormone called ACTH (produced by the pituitary gland). Cortisol levels are often measured to evaluate how well the pituitary and adrenal glands are working.[5]

Creatinine: The creatinine blood test is usually ordered along with a BUN (blood urea nitrogen) test to assess or monitor kidney function.

Cryptorchidism: The condition that occurs when one or both testicles fail to descend into the scrotum before birth.[5]

Culture: A specimen of blood, urine, sputum or stool which is taken and grown in the laboratory. This culture

is then tested to determine whether infection is present and which antibiotic to use.[2]

Cytokines: See **Colony stimulating factors**.[2]

Cytomegalovirus (CMV): A condition caused by a member of the herpesvirus family which can cause disease in different parts of the body in people with weakened immune systems, such as during a bone marrow transplant.[5]

Cytopenia: A deficiency of cellular elements of the blood, especially deficiency of one or more specific elements (as granulocytes in granulocytopenia).[1]

Dermatofibroma: A benign, chiefly fibroblastic, nodule of the skin, found especially on the extremities of adults.[1]

Desquamation: Shedding of the outer layers of the skin; peeling off in the form of scales.[1]

Diepoxybutane (DEB): A chemical agent that damages DNA in cell culture and is used in a diagnostic test for FA, either before or after birth.[2]

Differential: Percent of different types of white blood cells in the blood.[2]

DNA: This abbreviation stands for deoxyribonucleic acid. DNA is the component of the chromosomes that carries the genetic code.[2]

DNA repair: A collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome. The DNA repair ability of a cell is vital to the integrity of its genome and thus to its normal functioning and that of the organism.[11] This is abnormal in patients with FA.

Dorsal: Being or located near, on, or toward the back or posterior part of the human body.[1]

Dual energy absorptiometry (DXA or DXA-scan): The primary test used to identify osteoporosis and low bone mass. It uses a low energy x-ray to evaluate bone density in the hip and/or spine and sometimes the wrist.

Dyslipidemia: A disorder characterized by high blood cholesterol and triglycerides in the blood. A lipid disorder increases the risk for atherosclerosis and heart disease.[5]

Dysphagia: Difficulty swallowing.[5]

Dysplasia: A deleterious change in the microscopic appearance of cells. Can suggest early stages of progression to cancer.

Ectopic: Occurring in an abnormal position, such as a pregnancy occurring in a Fallopian tube instead of in the uterus.[1]

Encopresis: The voluntary or involuntary passage of stools in a child over age four, which causes the soiling of clothes.[5]

Endoscope: A medical device consisting of a camera mounted on a flexible tube. Small instruments can be used to take samples of suspicious tissues through the endoscope. In gastrointestinal (digestive tract) endoscopy, this device is inserted through the mouth or anus.[5]

Enteral alimentation: Tube feeding whereby liquid food is given through a tube into the stomach or small bowel.[12]

Eosinophil (EOS): A type of white blood cell; a type of granulocyte.[2]

Epicanthal folds: Skin of the upper eyelid, from the nose to the inner side of the eyebrow, that covers the inner corner (canthus) of the eye. The presence of an epicanthal fold is normal in people of Asiatic descent. However, it may also be due to certain medical conditions.[5]

Epiphysis: The growth area near the end of long bones. A part or process of a bone that ossifies separately and, at the end of childhood growth, becomes fused to the main part of the bone, especially an end of a long bone. This signals the end of linear growth.

Epithelium: Cells that line hollow organs and glands and those that make up the outer surface of the body to protect or enclose organs. Most produce mucus or other secretions. Certain types of epithelial cells have tiny hairs called cilia, which help remove foreign substances, for example, from the respiratory tract. Epithelial cells are arranged in single or multiple layers, depending on the organ and location.[5]

Epstein-Barr virus (EBV): A herpesvirus that causes infectious mononucleosis and is associated with Burkitt's lymphoma and nasopharyngeal carcinoma.[1] Reactivation of the virus after organ or bone marrow transplant can result in post-transplant lympho-proliferative disease (PTLD) or lymphoma.

Erythroblast: An immature red blood cell.[2]

Erythrocyte: Red blood cell; red blood cells go through various stages, starting out as erythroblasts, changing to reticulocytes, and finally becoming erythrocytes.[2]

Erythrocyte sedimentation rate: Used to detect and monitor the activity of inflammation as an aid in the diagnosis and activity of the underlying cause.[3]

Erythroderma: Generalized skin redness.[5]

Erythroplasia (Erythroplakia): A reddened patch with a velvety surface on the oral or genital mucosa that is considered to be a precancerous lesion.[1]

Erythropoietin (EPO): A colony-stimulating factor which influences red cell production in some conditions.[2]

Esophageal atresia (EA): A disorder of the digestive system in which the esophagus does not develop properly. There are several types. In most cases, the upper esophagus ends and does not connect with the lower esophagus and stomach. The top end of the lower esophagus connects to the windpipe. This connection is called a tracheoesophageal fistula (TEF). Other types of esophageal atresia involve narrowing of the esophagus, and may also be associated with other birth defects.[5]

Esophagoscopy: Examination of the esophagus by means of an esophagoscope, a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.[8]

Extramedullary leukemia: The occurrence of myelogenous leukemia outside the bone marrow, such as in the spinal fluid, testes or ovaries, or skin.[13]

Ferritin: The form in which iron is stored in the body.

5'-nucleotidase (5'-NT): 5'-nucleotidase is a protein produced by the liver; the test measures the amount of this protein in the blood.[5]

Fluorescent *in situ* hybridization (FISH): A research method to visualize and map the genetic material in an individual's cells, including specific genes or portions of genes. This is important for understanding a variety of chromosomal abnormalities and other genetic mutations. Unlike most other techniques used to study chromosomes, FISH does not have to be performed on cells that are actively dividing.[14] This makes it a very sensitive procedure for detecting chromosomal abnormalities.

Folate deficiency (aka folic acid): A type of B vitamin. Folic acid is found naturally in dark-green leafy vegetables, citrus fruits, beans, and whole grains. Not getting enough folate results in a form of megaloblastic anemia.[5]

Follicle stimulating hormone (FSH): A hormone from the anterior lobe of the pituitary gland that stimulates the growth of the ovum-containing follicles in the ovary in women and that activates sperm-forming cells in men. At menopause in women, the level stays persistently high.

Forced Expiratory Volume (FEV1): The volume of air that can be forced out in one second after taking a deep breath, an important measure of pulmonary function.[15]

Founder effect: The effect on the resulting gene pool that occurs when a new isolated population is founded by a small number of individuals possessing limited genetic variation relative to the larger population from which they have migrated.[16] If one or more members of the founder group were carriers of an FA gene mutation, the descendants would be more likely to contain carriers of that mutated gene.

Fructosamine: A protein that attaches to glucose in the bloodstream. If a patient's fructosamine is elevated, then the patient's average glucose level over the previous 2 to 3 weeks has also been elevated.[17]

Gamma-glutamyl transpeptidase (GGT): A test to measure the amount of the enzyme GGT in the blood to detect diseases of the liver, bile ducts, and kidney. It is also used to differentiate liver or bile duct disorders from bone disease. High concentrations of GGT are found in the liver, bile ducts, and the kidney. GGT is measured in combination with other tests. In particular, the enzyme ALP is increased in liver and bile duct disease as well as in bone disease. GGT is elevated in liver and bile duct disease, but not in bone disease. So, a patient with an elevated ALP and a normal GGT probably has bone disease, not liver or bile duct disease.[5]

Gastritis: Gastritis is an inflammation of the lining of the stomach.[5] It may be accompanied by pain and bleeding.

Gastroesophageal reflux (GER): A condition in which food or liquid travels backwards from the stomach to the esophagus.[5]

Gastroesophageal reflux disease (GERD): Heartburn and other disease occurring as a result of irritation of the esophagus.

Gastroparesis: Delayed gastric emptying; a condition in which the stomach's ability to empty its contents is impaired, unrelated to obstruction.[5]

Gastrostomy: The surgical formation of an opening through the abdominal wall into the stomach, often used to provide nutrition.[1]

Giardia: A microscopic organism, Giardia lamblia, that causes Giardiasis, an infection of the small intestine.[5]

Gingival atrophy: Recession of the gums around the teeth.

Glomerular filtration rate (GFR): A test used to check how well the kidneys are working. Specifically, it estimates how much blood passes through the tiny filters in the kidneys, called glomeruli, each minute. The GFR test measures how well kidneys are filtering a waste called creatinine, which is produced by the muscles. When the kidneys aren't working as well as they should, creatinine builds up in the blood.[5]

Glycosylated hemoglobin (HbA1c): The test represents average blood sugar over the life span of the red cell by measuring glycated hemoglobin in the blood. Glycated hemoglobin is a substance in red blood cells formed when blood sugar (glucose) attaches to hemoglobin. It can measure blood sugar control over several months and can give a good estimate of how well a patient has managed diabetes over the last 2 or 3 months.[5]

GM-CSF: Drug that stimulates the marrow to make more white blood cells. See **Colony-stimulating factors**.

Gonadotropin releasing hormone (GnRH): Normally, the hypothalamus in the brain releases GnRH, which stimulates the pituitary gland to release other hormones, including FSH and LH. These hormones then stimulate the female ovaries and male testes to secrete hormones that are responsible for normal sexual development in puberty and are important to the process of ovulation in females. A disruption in this chain of events causes a

deficiency of the sex hormones (estrogen and testosterone) and halts normal sexual maturation.[5]

Graft-versus-host disease (GvHD): A complication of bone marrow transplantation which occurs when donor T-cells attack the patient's cells. GvHD is more likely to occur when there is HLA mismatching. GvHD is classified in stages from Grade I (minor) to Grade IV (extremely serious).[2]

Granulocyte: Type of white blood cell. It is also called neutrophil or polymorphonuclear leukocyte (poly), which is the infection-fighting cell.

Gynecomastia: The development of large breasts in males. Gynecomastia during puberty is not uncommon and usually goes away over a period of months.[5]

H2-antagonists: Medicines that help decrease stomach acid.[5]

Hematocrit: Ratio of red blood cells to plasma in the blood; portion of the blood's total volume that is made up of red blood cells.[2]

Hematopoiesis: The formation and development of blood cells.[2]

Hematopoietic growth factors: See **Colony stimulating factors**.

Hemochromatosis (aka iron overload): Occurs when too much iron builds up in the liver. This leads to liver enlargement. In Fanconi anemia, this is usually caused from ineffective blood production, abnormal iron absorption, or receiving a large number of blood transfusions, which boost iron levels.

Hemodynamic: Relating to or functioning in the mechanics of blood circulation.[1]

Hemoglobin: The oxygen-carrying pigment of the red blood cells; combines with oxygen from the lungs and carries it to the body's cells.[2]

Hemoglobinopathy: A blood disorder (such as sickle-cell anemia) caused by a genetically determined change in the molecular structure of hemoglobin.[1]

Hepatic sinusoids: A minute endothelium-lined space or passage for blood in the tissues of the liver.[1]

Hepatitis: Inflammation of the liver.[5]

Hepatocellular carcinoma: Cancer of the liver.[5]

Hepatomegaly: Enlarged liver.[5]

Herpes simplex (HSV): An infection that mainly affects the mouth or genital area. There are two strains of HSV: **Type 1 (HSV-1)** is usually associated with infections of the lips, mouth, and face. It is transmitted by contact with infected saliva. By adulthood, up to 90% of people will have antibodies to HSV-1. **Type 2 (HSV-2)** is sexually transmitted. Symptoms include genital ulcers or sores. However, some people have HSV-2 but do not show symptoms. Up to 30% of U.S. adults have antibodies against HSV-2. Cross-infection of type 1 and 2 viruses may occur from oral-genital contact.[5] Tested prior to transplant because it can reactivate during periods of immune suppression.

Heterozygotes: Everyone has two copies of nearly all of his genes. Heterozygous means that one of the copies of a gene is slightly different from the other copy of the gene. One gene may have an FA mutation and the other may not (i.e., a carrier is heterozygous). An individual with FA may be heterozygous if he has two different mutations in his FA genes.

Homozygous: Both copies of a gene are exactly the same. An individual with FA is homozygous if he has the same gene mutation in both copies of his FA genes.

Human leukocyte antigen (HLA) tissue typing: The tissue-typing test done on white cells to determine if a bone marrow donor and recipient are compatible.[2]

Human papillomavirus (HPV): There are more than 100 different types of HPV. Some types are associated with benign, common or flat warts on the skin. Some HPV types are spread primarily through sexual contact and can cause genital warts or cancer of the oropharynx, cervix, vulva, vagina, anus, and (rarely) penis.

Hydronephrosis: Bilateral hydronephrosis is the enlargement (distention) of the pelvis and urine collecting structures of both kidneys which occurs when urine is unable to drain from the kidney down the ureters into the bladder. It is not itself a disease, but rather a physical result of whatever disease is keeping urine from draining out of the kidneys, ureters, and bladder. Unilateral hydronephrosis is swelling of one kidney due to a backup of urine.[5]

Hydroureter: Abnormal distension of the ureter with urine or watery fluid, due to obstruction.[1]

Hyperalimentation: The administration of nutrients by intravenous feeding, especially to patients who cannot ingest food through the alimentary tract. Total parenteral nutrition (TPN) is a method of feeding that bypasses the gastrointestinal tract. Fluids are given into a vein to provide most of the necessary nutrients the body needs. An IV line is often placed into a vein in the hand, foot, or scalp. The belly button also has a large vein (umbilical vein) that may be used. Sometimes a longer IV, called a central line or peripherally-inserted

central catheter (PICC) line, is used to provide long-term IV fluids or feedings. This type of IV can deliver nutrients of higher concentration to larger veins located centrally in the body.[1,5]

Hyperbilirubinemia: The presence of an excess of bilirubin in the blood.[1]

Hyperglycemia: Abnormally high blood sugar.[5]

Hyperlipidemia: High blood cholesterol and/or triglycerides.[5]

Hyperpigmentation: Excess pigmentation in a body part or tissue (such as the skin).[1]

Hyperplasia: Hyperplasia is a thickening of normal tissue. Specifically, it is the increased cell production in a normal tissue or an organ. Hyperplasia may be a sign of precancerous changes.[5]

Hypogonadism: Occurs when the gonads produce little or no hormones. In men, the gonads are the testes; in women, they are the ovaries. In girls, hypogonadism during childhood will result in lack of menstruation and breast development and short height. If hypogonadism occurs after puberty in females, symptoms include loss of menstruation, low libido, hot flashes, and loss of body hair. In boys, hypogonadism in childhood results in lack of muscle and beard development and growth problems. In men the usual complaints are sexual dysfunction, decreased beard and body hair, breast enlargement, and muscle loss.[5]

Hypoparathyroidism: A condition in which the body produces too little parathyroid hormone. Calcium and phosphorus form the mineral component of bones. Parathyroid hormone (PTH) regulates the amount of calcium and phosphorus in bone and blood. PTH is

made by four small parathyroid glands located in the neck behind the thyroid gland. Hypoparathyroidism occurs when there is too little PTH. Blood calcium levels fall, and phosphorus levels rise.[5]

Hypopharynx: The lower part of the pharynx and the part of the throat that connects to the esophagus.

Hypopigmentation: Diminished pigmentation in a body part or tissue (such as the skin).[1]

Hypoplastic: A condition of arrested development in which an organ or part remains below the normal size or in an immature state.[1]

Hypospadias: A relatively common congenital defect in which the opening of the urethra is on the underside, rather than at the end, of the penis. Infants with hypospadias should not be circumcised; the foreskin should be preserved for use in later surgical repair.[5]

Hypothalamus: An area of the brain that produces chemical messages that control body temperature, hunger, moods, release of hormones from many glands, especially the pituitary gland. These messages also influence sex drive, sleep, and thirst.[5]

Hypothyroidism: A condition in which the thyroid gland fails to produce enough thyroid hormone.[5]

Ileus: Obstruction of the bowel; the condition is commonly marked by a painful distended abdomen, vomiting of dark or fecal matter, toxemia, and dehydration that results when the intestinal contents back up because peristalsis fails, although the lumen (the inside space of a tubular structure, in this case the bowel) is not occluded.[1,11]

IM: Refers to giving an injection intramuscularly.

Immune response: The body's defense against disease and foreign substances, including transplanted bone marrow; substances may be recognized as "foreign" and then killed by other cells.[2]

Immunoglobulin: A protein produced by plasma cells and lymphocytes and characteristic of these types of cells. Immunoglobulins play an essential role in the body's immune system. They attach to foreign substances, such as bacteria, and assist in destroying them. Immunoglobulin is abbreviated Ig. The classes of immunoglobulins are termed Immunoglobulin A (IgA), Immunoglobulin D (IgD), Immunoglobulin E (IgE), Immunoglobulin G (IgG), and Immunoglobulin M (IgM).[15]

Immunosuppression: Suppression (as by drugs) of natural immune responses necessary to fight disease or a harmful substance.[1,5]

Imperforate anus: A congenital defect in which the opening to the anus is missing or blocked. It may occur in several forms. The rectum may end in a blind pouch that does not connect with the colon. Or, it may have openings to the urethra, bladder, base of penis or scrotum in boys, or vagina in girls. In girls, it is associated with malformations of the uterus and vagina which can affect sexual function and fertility. A condition of stenosis (narrowing) of the anus or absence of the anus may be present.[5]

Insulin-like growth factor 1 (IGF-1): The hormone produced by the liver, bones, and other tissues in response to growth hormone, with production declining after puberty.

Intravenous (IV): Injection directly into the vein.[2]

***In vitro* fertilization (IVF):** Fertilization of an egg in a laboratory dish or test tube via a mixture of sperm with eggs. The eggs are surgically removed from an ovary, mixed with the sperm, and then one or more of the resulting fertilized eggs are implanted into a female's uterus.[1]

Jejunum: The section of the small intestine that comprises the first two-fifths beyond the duodenum and that is larger, thicker-walled, more vascular and with more circular folds and fewer Peyer's patches than the ileum.[1]

Karnofsky Performance Status (KPS): A standard way of measuring the ability of cancer or bone marrow transplant patients to perform ordinary tasks. The Karnofsky Performance Status scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial.[4]

Keratoconjunctivitis sicca syndrome: Dry eye syndrome in which the tear glands produce fewer tears than normal.[5]

Klippel-Feil Syndrome: A rare disorder characterized by the congenital fusion of any 2 of the 7 cervical (neck) vertebrae. The most common signs of the disorder are short neck, low hairline at the back of the head, and restricted mobility of the upper spine.[18]

Lagophthalmos: Pathological incomplete closure of the eyelids; inability to close the eyelids fully.[1]

Lansky status: A performance test to quantify cancer or bone marrow transplant patients' general wellbeing to determine whether they can receive chemotherapy,

whether dose adjustment is necessary, and as a measure for the required intensity of palliative care. It is also used in cancer randomized controlled trials as a measure of quality of life. Children, who might have more trouble expressing their experienced quality of life, are evaluated according to the Lansky status criteria, using a somewhat more observational scoring system, such as "fully active, normal" to "doesn't play, does not get out of bed" to "unresponsive."[19]

Larynx: The upper part of the respiratory passage that is bounded above by the glottis, is continuous below with the trachea, has a complex cartilaginous or bony skeleton capable of limited motion through the action of associated muscles, and has a set of elastic vocal cords that play a major role in sound production and speech; also called "voice box."[1]

Leukemia: Leukemia is a group of bone marrow diseases involving an uncontrolled increase in white blood cells (leukocytes). The leukemia most commonly acquired by FA patients is acute myelogenous leukemia.[5]

Leukocytes: White blood cells.[2]

Leukopenia: Low white cell count.[2]

Leukoplakia: A condition commonly considered precancerous in which thickened white patches of epithelium occur on the mucous membranes especially of the mouth, vulva, and renal pelvis.[1]

Lichen planus: A condition of the genitals, skin or mouth that results in an itchy, swollen rash on the genitals (typically on the vulva); tender, painful, bluish-white lesions in the mouth; and/or shiny, scaly, flat-topped, purplish-pink bumps on the skin.

Luteinizing hormone (LH): A glycoprotein hormone that in the female stimulates ovulation and, together with follicle-stimulating hormone, secretion of estrogen from developing ovarian follicles. In the male stimulates the development of interstitial tissue in the testis and the secretion of testosterone.[1]

Lymphadenopathy: Abnormal enlargement of the lymph nodes.[1]

Lymphocyte: Type of white blood cell that fights infection by producing antibodies and other protective substances; occurs in two forms: B cells that recognize specific antigens and produce antibodies against them, and T-cells that recognize specific antigens, release factors that attract other T-cells, natural killer cells and macrophages to remove foreign cells and microbial pathogens. Lymphocytes are produced in the lymph system, not in the bone marrow.[2]

Lymphoid: Referring to lymphocytes, a type of white blood cell. Also refers to tissue in which lymphocytes develop.[4]

Lymphoma: Cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One is Hodgkin lymphoma, which is marked by the presence of a type of cell called the Reed-Sternberg cell. The other category is non-Hodgkin lymphomas, which includes a large, diverse group of cancers of immune system cells; some of these cancers have a slow-growing course and some have a fast-growing course. They behave and respond to treatment differently. Both Hodgkin and non-Hodgkin lymphomas can occur in children and adults, and prognosis and treatment depend on the stage and the type of cancer.[4]

Macrocyte: An abnormally large erythrocyte (red blood cell).[2]

Macrophage: A type of white blood cell that assists in the body's fight against bacteria and infection by engulfing and destroying invading organisms.[2]

Matched platelet transfusions: Transfusions from a donor who has been HLA-matched to a particular patient.[2]

Medulloblastoma: A malignant brain tumor that begins in the lower part of the brain and that can spread to the spine or to other parts of the body.[4]

Megakaryocyte: Large cell in the bone marrow from which pieces break off to form platelets.[2]

Menopause: The transition period in a woman's life when her ovaries stop producing eggs, her body produces less estrogen and progesterone, and menstruation becomes less frequent, eventually stopping altogether.[5]

Mesenchymal stromal cells (MSC): Multipotent stem cells that can differentiate into a variety of cell types, such as bone cells, fat cells, and cartilage cells. MSC are typically isolated from bone marrow.

Metacarpus: The part of the hand (metacarpal) or foot (metatarsal) between the carpus and the phalanges that contains five elongated bones when all the digits are present.

Microcephaly: A condition of abnormal smallness of the head.[1]

Micrognathia: Abnormal smallness of one or both jaws.[1]

Micropenis: Smallness of the penis, especially to an abnormal degree.[1]

Microphthalmia: Abnormal smallness of the eye, usually occurring as a congenital anomaly.[1]

Mitomycin C (MMC): A chemical which, in sufficient doses, causes destruction and rearrangement of the chromosomes in cells. Because Fanconi anemia cells are unusually sensitive to MMC, it is used to diagnose this condition.[2]

Motile or motility: Exhibiting or capable of movement.[1]

Murine model: A model of disease for use in research, using mice as the model animal for preclinical experimentation.[1]

Mutation: A mutation is a change in the DNA of a gene that causes the gene either not to make any protein or to change the protein so that it does not work correctly. DNA is made up of the chemical letters A, C, T, and G. A mutation can be the addition, deletion, or simply a change in the chemical letters of DNA that makes up the gene.

Myelodysplasia (MDS or myelodysplastic syndrome): Abnormal production, maturation, and appearance of blood cells; often leading to deficiency of red cells, white cells and platelets; sometimes leading to bone marrow failure or leukemia.[2]

Myelosuppressive: Suppression of the bone marrow's production of blood cells and platelets.[1]

Myocardium: The middle muscular layer of the heart wall.[1]

Myofasciitis: Inflammation of a muscle and its fascia.[20]

Nasogastric tube: A tube inserted through the nasal passages into the stomach, often used to provide nutrition.

Nasojejunal tube: A soft feeding tube inserted through the nasal passages into the small bowel. It is placed by using an x-ray monitor to guide the tube.

Nasopharynx: The upper part of the pharynx continuous with the nasal passages.[1]

Neck dissection: Surgery to remove lymph nodes and other tissues in the neck.[8]

Neoplasia: Abnormal cell growth resulting in formation of either benign, precancerous or cancerous tumors.

Neuroblastoma: Cancer that arises in immature nerve cells and affects mostly infants and children.[4]

Neutropenia: Low neutrophil (poly) count.[2]

Neutrophil: Type of white blood cell; also called a poly; granulocyte; the body's primary defense against harmful bacteria.[2]

Nevi: A congenital or acquired usually highly pigmented area on the skin that is either flat or raised, such as a mole.[1]

Non-alcoholic steato hepatitis (NASH): A common, often silent, liver disease. It resembles alcoholic liver disease, but occurs in people who drink little or no alcohol. The major feature is fat in the liver, along with inflammation and damage. NASH can be severe and can lead to cirrhosis, in which the liver is permanently damaged, scarred, and no longer able to work properly.[7]

Odynophagia: Pain produced by swallowing.[1]

Oral glucose tolerance test (OGTT): An OGTT is a series of blood glucose tests. Blood samples for fasting glucose and insulin are collected; then the patient drinks a standard amount of a glucose solution to challenge his

or her system. This is followed by one or more additional glucose and insulin tests performed at specific intervals to track glucose and insulin levels over time. The OGTT may be ordered to help diagnose diabetes and as a follow-up test to an elevated blood glucose.[3]

Oropharynx: The part of the pharynx that is below the soft palate and above the epiglottis and is continuous with the mouth.[1]

Osteosarcoma: A malignant tumor derived from bone or containing bone tissue; also called osteogenic sarcoma.[1]

Osteotomy: A surgical operation in which a bone is divided or a piece of bone is excised (as to correct a deformity).[1]

Otoacoustic emission test (OAE): A test that can show whether parts of the ear respond properly to sound. During this test, a sponge earphone is placed into the ear canal. The ear is stimulated with sound, and the echo is measured. The echo is found in everyone who hears normally. If there is no echo, it could indicate a hearing loss.[21]

Ototoxic: Having an adverse effect on organs or nerves involved in hearing or balance.[5]

Oxidative stress: Physiological stress on the body that is caused by the cumulative damage done by free radicals inadequately neutralized by antioxidants and that is held to be associated with aging and several congenital conditions, such as Fanconi anemia.[1]

Pancytopenia: Abnormally low number of red and white cells and platelets.[2]

Panorex: A dental x-ray taken outside of the mouth that shows all of the teeth on one view, in a panoramic fashion.[22]

Parenteral infusion: Situated or occurring outside the intestine, such as parenteral drug administration by intravenous, intramuscular, or subcutaneous injection; especially introduced otherwise than by way of the intestines.[1]

Peliosis hepatis: An abnormal condition characterized by the occurrence of numerous small blood-filled cystic lesions throughout the liver.[1]

Peptic: Refers to pepsin, a stomach enzyme that breaks down proteins. A peptic ulcer is erosion in the lining of the stomach or duodenum (the first part of the small intestine). If a peptic ulcer is located in the stomach, it is called a gastric ulcer.[5]

Peripheral blood: The blood in the bloodstream.[2]

Peripherally inserted central catheter (PICC line): A line inserted into a major vein to allow for administration of IV fluids or hyperalimentation.

Peritonitis: An inflammation (irritation) of the peritoneum, the tissue that lines the wall of the abdomen and covers the abdominal organs.[5]

Petechiae: Tiny red dots on the skin due to bleeding under the skin caused by low platelet count.[2]

Phagocytosis: Cell-eating. The engulfment and destruction of dangerous microorganisms or cells by certain white blood cells, including neutrophils (see **Absolute neutrophil count**).[2]

Phalanx: Any of the digital bones of the hand or foot distal to the metacarpals or metatarsals. Humans have

three digital bones in each finger and toe with the exception of the thumb and big toe, which have only two each.[1]

Phlebotomy: The letting of blood for transfusion, apheresis, diagnostic testing, or experimental procedures. In the past, phlebotomy was widely used to treat many types of disease but is now limited to the treatment of only a few specific conditions (such as hemochromatosis).[1]

Photophobia: Eye discomfort in bright light. Severe photophobia may be associated with eye problems and cause severe eye pain, even in relatively low light.[5]

Pituitary: A small gland joined to the hypothalamus (part of the brain). The pituitary produces many of the hormones that indirectly or directly affect basic bodily functions and include substances exerting a controlling and regulating influence on other endocrine organs, controlling growth and development, the body's response to stress, or modifying the contraction of smooth muscle, renal function, and reproduction.[1,5]

Plasma: A colorless fluid which contains water and other components in which red cells, white cells, and platelets are suspended.[2]

Platelets: Blood cell fragments containing clotting factors which prevent bleeding and bruising.[2]

Pneumocystis: A genus of microorganisms of uncertain affiliation that are usually considered protozoans or sometimes fungi and that include one (*P. carinii*) causing pneumonia, especially in immunocompromised individuals. This organism is common in the environment and does not cause illness in healthy people.[1] Transplant patients are typically given antibiotics to prevent pneumocystis.

Polypharmacy: The practice of administering many different medicines, especially concurrently for the treatment of the same disease.[1]

Portal hypertension: Hypertension in the hepatic portal system caused by venous obstruction or occlusion that produces splenomegaly (abnormal enlargement of the spleen) and ascites (abnormal accumulation of serous fluid in the abdominal cavity) in its later stages.[1]

Post-prandial: Occurring after a meal.[1]

Prenatal diagnosis: Many diseases that involve a single gene defect can now be diagnosed very early in pregnancy. Prenatal diagnosis looks at fetal cells in the mother's blood, amniotic fluid, or chorionic villi. This may detect problems while the baby is still growing or after birth. In late pregnancy, tests may examine blood from the umbilical cord.[5]

Proband: An individual being studied (as in a genetic investigation). Often the proband is the first affected family member who seeks medical attention.[1]

Puberty: The time during which sexual and physical characteristics mature due to hormonal changes. The exact age a child enters puberty depends on many factors, such as a person's genes, nutrition, and gender. During puberty, various endocrine glands produce hormones that cause body changes and the development of secondary sex characteristics. In girls, the ovaries begin to increase production of estrogen and other female hormones. In boys, the testicles increase production of testosterone. Breast development is the main sign that a girl is entering puberty. The first menstrual period (menarche) usually follows within about two years. The first sign of puberty in boys is enlargement of both testicles.[5]

Radial ray deficiency: The underdevelopment or total loss of the radius bone in the forearm. This condition often affects the development of the thumb. Some children with FA are born with no thumbs or thumbs not normally developed.[5]

Radius: The bone on the thumb side of the forearm.[1]

Reactive airway disease: The terms "reactive airway disease" and "asthma" are often used interchangeably; however, they're not necessarily the same thing. Reactive airway disease is a general term that doesn't indicate a specific diagnosis. It may be used to describe a history of coughing, wheezing or shortness of breath of unknown cause. These signs and symptoms may or may not be caused by asthma.[9]

Recessive: A mutation is said to be recessive if an individual must inherit two copies of the mutant gene, one from each parent, to show the mutant trait. Individuals with one mutant and one normal gene appear normal. They are called "carriers."[2]

Red blood cell (erythrocyte): Oxygen-carrying cell in the blood which contains the pigment hemoglobin; produced in the bone marrow.[2]

Refractory: Resistant to treatment or cure.[1]

Reticulocyte: An immature red blood cell.[2]

Retinoblastoma: A cancer of the retina that generally affects children under the age of 6. It is most commonly diagnosed in children aged 1-2 years.[5]

Schirmers' test: This test determines whether the eye produces enough tears to keep it moist.[5]

Scleroderma: A widespread connective tissue disease that involves changes in the skin, blood vessels,

muscles, and internal organs. Causes a build-up of collagen in the skin and other organs, which leads to the symptoms associated with the disease.[5]

Sertoli cell mass: Any of the elongated striated cells in the testis to which the spermatids become attached and from which they apparently derive nourishment.[1]

Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT): Enzymes that are normally present in liver and heart cells. SGOT and SGPT are released into blood when the liver or heart is damaged. The blood SGOT and SGPT levels are thus elevated with liver damage (such as from viral hepatitis) or with an insult to the heart (such as a heart attack). Some medications can also raise SGOT and SGPT levels. SGOT is also called *aspartate aminotransferase* (AST). SGPT is also called *alanine aminotransferase* (ALT).[15]

SGA: Acronym for birth weight that was low or small for gestational age.

Sicca syndrome: A chronic inflammatory autoimmune disease that is characterized by dryness of mucous membranes, especially of the eyes and mouth, and by infiltration of the affected tissues by lymphocytes. Also called Sjögren's disease.[1]

Siderosis: The deposition of iron in tissue.[6]

Situs inversus: A congenital abnormality characterized by lateral transposition of the viscera (as of the heart or the liver).[1]

Spectral karyotyping (SKY): A molecular cytogenetic technique that permits the simultaneous visualization of all human (or mouse) chromosomes in different colors, considerably facilitating karyotype analysis.[10]

Spina bifida: A birth defect in which the backbone and spinal canal do not close before birth. Spina bifida includes any birth defect involving insufficient closure of the spine.[5]

Sprengel: A condition in which the shoulder blade on one or both sides is underdeveloped and abnormally high.[1]

SQ infusions: Acronym for subcutaneous infusions.

Stenosis: A narrowing or constriction of the diameter of a bodily passage or orifice.[1]

Stroma: The supporting tissue of the bone marrow. This tissue provides the growth environment for blood cells.[2]

Surveillance, Epidemiology and End Results Program (SEER): A premier source for cancer statistics in the United States; sponsored by the National Cancer Institute, NIH. SEER collects information on incidence, survival, and prevalence from specific geographic areas representing 26 percent of the country's population and compiles reports on all of these, plus cancer mortality for the entire U.S.[8]

Syndactyly: A union of two or more fingers or toes that occurs in humans, often as a hereditary disorder marked by the joining or webbing of two or more fingers or toes.[1]

T-cells: Lymphocytes responsible for "cell-mediated" immune reactions; critical for immune resistance to viruses, fungi, parasites and certain bacteria; important cells in transplant (graft rejection and GvHD) reactions.[2]

T-score: A T-score compares your bone density to the optimal peak bone density for your gender. It is reported as number of standard deviations below the average. A T-score above minus-1 is considered normal. A T-score of minus-1 to minus-2.5 is considered osteopenia, and a risk for developing osteoporosis. A T-score below minus-2.5 is diagnostic of osteoporosis.[23]

Teratoma: A neoplasm composed of multiple tissues, such as skin, hair, and muscle, including tissues not normally found in the organ in which it arises, caused by the development of independent stem cells. Also called teratoblastoma or teratoid tumor.[6]

Thalassemia: Inherited disorders characterized by abnormal production of hemoglobin. They result in low hemoglobin production, and excessive destruction of red blood cells.[5]

Thenar eminence: The muscles at the base of the thumb.

Thenar muscles: Any of the muscles that comprise the intrinsic musculature of the thumb within the thenar eminence and include the abductor pollicis brevis, adductor pollicis, flexor pollicis brevis, and opponens pollicis.

Thrombocyte (platelet): Cell fragment which releases clotting factors in the blood.[2]

Thrombocytopenia: Low platelet count.[2]

Thromboembolism: The blocking of a blood vessel by a particle that has broken away from a blood clot at its site of formation.[1]

Thymocytes: T-cells.[2]

Thyroid: A gland located in the front of the neck below the larynx, or voice box, and comprises two lobes, one on either side of the windpipe. The thyroid is one of a group of glands that is part of the endocrine system. The endocrine glands produce, store, and release hormones into the bloodstream that travel through the body and direct the activity of the body's cells. Thyroid hormones regulate metabolism, which is the way the body uses energy, and affect nearly every organ in the body. The thyroid gland makes two thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4). Thyroid hormones affect metabolism, brain development, breathing, heart and nervous system functions, body temperature, muscle strength, skin dryness, menstrual cycles, weight, and cholesterol levels. Thyroid hormone production is regulated by **thyroid-stimulating hormone (TSH)**, which is made by the pituitary gland. Located in the brain, the pituitary gland is the "master gland" of the endocrine system. The thyroid gland's production of **thyroid hormones (T_3 and T_4)** is triggered by thyroid-stimulating hormone (TSH), which is made by the pituitary gland.[5]

Thyrotropin: Another term for thyroid-stimulating hormone (TSH).

Thyroxine-binding globulin (TBG): Serum TBG level is a blood test to measure the level of the protein, thyroxine-binding globulin, that moves thyroid hormone throughout the body.[5]

Total body irradiation (TBI): Radiation therapy to the entire body, usually followed by umbilical cord blood, bone marrow or peripheral stem cell transplantation.

Total parenteral nutrition: See **Hyperalimentation**.

Tracheoesophageal fistula (TEF): See **Esophageal atresia**.[5]

Tracheomalacia: Congenital tracheomalacia is a weakness and floppiness of the walls of the windpipe (trachea). Because the windpipe is the main airway, breathing difficulties begin soon after birth.[5]

Transvaginal ultrasound: A method to look at a woman's reproductive organs, including the uterus, ovaries, cervix, and vagina. Transvaginal means across or through the vagina.[5]

25-OH vitamin D: This test is the most accurate measure of the amount of vitamin D in the body.[5]

Umbilical cord blood: Blood left in the placenta and cord after a baby is born. Blood contains hematopoietic stem cells.

Unicornuate uterus: One half of a uterus that forms with a cervix and is usually connected to the vagina. This uterus will function normally, although the woman is at risk for premature delivery of a fetus and for breech presentation which may necessitate a cesarean section. Sometimes called hemi-uterus.[24]

White blood cells: Blood cells which fight infection.[2]

Wilms tumor: A cancerous tumor of the kidney that occurs in children.[5]

Z-score: A Z-score is used to compare a patient's results to results in healthy persons of the same age, weight, ethnicity, and gender. This is useful to determine if there is something unusual contributing to the patient's bone loss.[23]

References

1. Medline Plus Medical Dictionary, National Library of Medicine, National Institutes of Health (NIH): www.nlm.nih.gov.

2. *Fanconi Anemia: A Handbook for Families and Their Physicians*, Third Edition, 2000.

3. Lab Tests Online: labtestsonline.org.

4. Dictionary of Cancer Terms, National Cancer Institute, NIH: www.cancer.gov.

5. Medline Plus Medical Encyclopedia, National Library of Medicine, NIH: www.nlm.nih.gov.

6. *PDR Medical Dictionary*. Baltimore, MD: Williams and Wilkins; 1995.

7. National Institute of Diabetes and Digestive and Kidney Diseases, NIH: www.niddk.nih.gov.

8. National Cancer Institute, NIH: www.nci.org.

9. Mayo Clinic: www.mayoclinic.com.

10. National Center for Biotechnology Information, National Library of Medicine, NIH: www.ncbi.nlm.nih.gov.

11. Wikipedia: www.wikipedia.com.

12. American Society for Parenteral and Enteral Nutrition: www.nutritioncare.org.

13. Medscape: www.medscape.com.

14. National Human Genome Research Institute, NIH: www.genome.gov.

15. Medicine Net: www.medicinenet.com.

16. Merriam-Webster Online Dictionary: www.merriam-webster.com.

17. Islets of Hope: www.isletsofhope.com.

18. National Institute of Neurological Disorders and Stroke, NIH: www.ninds.nih.gov.

19. Nation Master: www.nationmaster.com.

20. Medical Dictionary, The Free Dictionary: www.medical-dictionary.thefreedictionary.com.

21. National Institute on Deafness and Other Communication Disorders, NIH: www.nidcd.nih.gov.

22. Dental Glossary: www.dentalglossary.net.

23. About.Com.Orthopedics: www.orthopedics.about.com.

24. Children's Hospital Boston: www.childrenshospital.org.

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