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.