

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 multi-disciplinary 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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