Introduction

Fanconi Anemia: Guidelines for Diagnosis and Management, Fourth Edition, is the result of a Consensus Conference held by the Fanconi Anemia Research Fund in Herndon, Va., April 5-6, 2013. It replaces earlier editions published in 1999, 2003, and 2008. These guidelines are published for physicians who provide care for FA patients, and for patients and families who wish to secure optimal treatment by improving their understanding of all facets of Fanconi anemia, medical consultation, and appropriate referral.

These guidelines begin with detailed information on diagnosis and evaluation of FA. Subsequent chapters examine more specific health issues faced by persons with FA, followed by two chapters on psychosocial considerations that bear upon the well-being of the person with FA and his or her extended family. The guidelines conclude with a comprehensive checklist and diagnostic criteria for physicians and medical specialists.

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. Every effort has been made to give fair voice to discordant medical opinions when evidence is lacking and controversy exists. All chapters have been peer-reviewed and describe best practices as of the date of publication. To avoid being excessively prescriptive, the title of this book was changed in our last edition from "Standards" to "Guidelines." From the discussions at this and earlier Consensus Conferences, 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 significantly advanced since the last publication in 2008:

- At least 16 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 and it is anticipated that this information will become increasing relevant to patient care.

- Phenotypic and genotypic predictors of the natural history and outcome of the disease are beginning to emerge. As the costs of full genomic analyses continue to fall, we may expect the development of even more specific and powerful methods of diagnosis and, hopefully, therapy.
- 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 (carriers) is being evaluated.
- A growing cohort of post-transplant adult FA survivors presents new medical surveillance and treatment issues that include the unknown issues of aging with underlying FA, the pitfalls of pharmaceuticals commonly used in adult medicine in persons with FA, and the common presentation of anticipated post-transplant complications with the unknowns of alternative presentations and treatment tolerance in individuals with FA.
- With increased longevity for patients with FA the management of transfusion-acquired iron overload requires serious consideration.
- A series of major scientific publications on the role of aldehydes in FA has markedly changed the focus of research inquiry and therapeutic strategy in very recent years. These discoveries bear not only on the on-going debate as to whether DNA damage is the primary biological mechanism underlying FA disease pathology, but suggest that attention be turned to understanding the relevance of limiting exposure of persons with FA to exogenous and endogenous aldehydes, including alcohol. Finally, this rapidly developing research has inspired development of new small molecule therapies and other forms of intervention that might lessen damage to FA stem cells, suppress malignant transformation, or both.
- The availability of pre-implantation genetic diagnosis (PGD) for FA and for HLA determination provides a potential parental choice for securing a 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

As was true of earlier occasions, 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); selection of appropriate persons for FA gene therapy trials; and genetic counseling to the family.
- Expertise in FA treatment is highly specialized and to date is heavily concentrated in a few, critically important centers. Many persons with FA 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 multi-disciplinary 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.
- The transition from pediatric to adult care, and from parent monitoring to self-care, presents particularly important challenges which require thoughtful management.

FA must be considered a multi-system disease.

- The name of the disorder, Fanconi anemia, may disserve both doctors and patients because the hematologic manifestations of FA are not the sole (or often even the most important) problem for persons with FA.
- The FA phenotype is quite variable and leads to misdiagnosis and failure of diagnosis. Monitoring must be multi-disciplinary and include hearing evaluation, assessment of endocrine system and GI tract issues, and long-term cancer surveillance.
- For the majority of persons with FA, 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 person's lifetime, even post-transplant.
- The intrinsic genetic instability of FA cells means that exposure to ionizing radiation, environmental carcinogens, and chemotherapeutic agents likely poses special risks to persons with FA. Consequently, diagnostic x-ray exposure and some otherwise routine medical tests or agents may need to be limited, or used with great caution. Thus, lifestyle choices such as tobacco and alcohol use may well have serious adverse consequences, even beyond those encountered in the general population.

FA is a psychosocially demanding disorder.

- The pressures on patients, parents, and siblings over an extended time can be overwhelming, particularly where there are multiple affected family members.
- Persons with FA, their 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.
- FA adults experience quite distinct issues, and their psychosocial concerns are emerging as a distinct field of inquiry.

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 both 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 with their providers in discussing what alternative practices they are using. 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 who have this serious and life-threatening disorder. We welcome comments that may inform future improvements in care and treatment.

On behalf of the Fanconi Anemia Research Fund, we extend profound thanks to the many authors and editors who contributed to this work. Our special gratitude goes to those persons with FA, and their families. The toll of this affliction inspires our efforts, and their fervent hope for a cure motivates the urgency of our collective work. Finally, the remarkable progress in understanding FA biology buoys our optimism for ever-improving clinical outcomes.

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