
Preface

Fanconi anemia (FA) is a rare disease caused by pathogenic variants in at least 23 genes that cause faulty DNA repair in every cell of the body. Fanconi anemia is a multi-system disease and the clinical manifestations are highly variable; therefore, the complexities that arise require a comprehensive and interdisciplinary approach to clinical care. In 1999, The Fanconi Anemia Research Fund published the first edition of a clinical care reference guide for people affected by the disease and their families. The clinical reference guide was developed by FA expert physicians with the intent to provide information for care providers with limited knowledge of this rare disease. Since the first edition was published in 1999, three subsequent editions were published by the Fanconi Anemia Research Fund in 2003, 2008, and 2014.

The fifth edition, which is titled *Fanconi Anemia Clinical Care Guidelines*, is a revision of the fourth edition published in 2014. The contributing authors are physicians or clinical care providers with expertise in treating patients with FA. The fifth edition provides evidence-based recommendations from published peer-reviewed medical literature and is geared toward clinical providers as the primary intended audience. Where possible, the chapters have been peer-reviewed and effort was made to provide a balanced view on discordant medical opinions.

The fifth edition starts with a brief summary of the molecular mechanisms of the FA DNA repair pathway (Chapter 1). Over the past few decades, researchers have charted the complexities of the FA DNA repair pathway with the hope that unlocking mechanisms that drive faulty DNA repair in FA cells would enable development of new treatments for the disease. Although research on the FA pathway has expanded knowledge of the coordinated events that lead to FA cell fragility, more work is needed to develop a comprehensive understanding of how targeting the pathway can be exploited as a way to treat the clinical manifestations of FA.

Beyond an overview of the FA pathway, the fifth edition covers the diagnostic testing process for FA (Chapter 2). The chromosome breakage test remains the gold standard diagnostic test for FA; however, molecular diagnostics, such as whole genome or exome sequencing, are quickly becoming important components of the diagnostic cascade. The

inheritance patterns of FA, genetic testing for family members, and updated information regarding cancer risk for carriers of FA variants is also discussed in Chapter 2.

Monitoring the onset of bone marrow failure (BMF) in persons with FA and treatment recommendations for when it occurs are outlined in Chapter 3. To date, hematopoietic cell transplant (HCT) is the only curative treatment option for BMF for persons with FA. The fifth edition provides an overview of recent advancements in HCT published in peer-reviewed clinical research studies. Advancements in HCT protocols and long-term care continue to improve survival rates of persons with FA following HCT. Despite these advancements, the high risk of developing squamous cell carcinoma (SCC) in individuals who have undergone an HCT is a major concern. The development of HCT-related graft-versus-host disease is correlated with increased risk; however, it is unclear whether additional factors associated with the HCT process also confer an increased risk. It is thought that the use of genotoxic chemotherapy and radiotherapy regimens may contribute to increased risk, but more studies are needed to delineate the specifics of each contributing factor. The Fanconi Anemia Research Fund is currently supporting ongoing pre-clinical research focused on using antibody depletion of stem cells as a way to reduce toxic conditioning regimens. Results from these studies may provide a new way to perform HCT that decreases SCC risk. Gene therapy trials are also underway as a curative approach for BMF in patients with FA; however, it is too early to know whether these trials will be successful.

The risk of developing head and neck squamous cell carcinoma (HNSCC) and SCC in anogenital regions is extremely high for persons with FA. There is also an increased risk of developing non-HNSCC solid tumors in other areas of the body (Chapter 4). The risk of solid tumors is age-dependent and associated with undergoing HCT, but risk is also high in patients who have never undergone HCT. Most non-HNSCC and HNSCC tumors develop in patients with FA at a substantially younger age than in the general population (20-50 years vs. 60-70 years). Chapters 5 and 7 cover updated recommendations for early surveillance, prevention, and treatment of HNSCC and anogenital SCC in patients with FA, respectively.

New in the fifth edition is the recommendation to perform comprehensive oral examination combined with brush biopsy of suspicious HNSCC lesions (Chapter 5), to determine whether the presence of pre-cancerous or cancerous lesions warrant further analysis by incisional biopsy. Individuals with FA often have multiple lesions in their oral cavities and use of brush biopsies as an early surveillance tool reduces trauma and leads to early diagnosis of cancer when successful surgical removal is possible. Surgical removal of tumors, both HNSCC and anogenital SCC, remains the best option for curative treatment for persons with FA, although radiation therapy has proved efficacious in some cases. More research is needed to understand the natural history of FA SCC tumors to develop chemopreventive or non-genotoxic treatment modalities. Identifying methods to prevent and treat FA SCC tumors will be a high priority for the Fanconi Anemia Research Fund in the coming years.

Fanconi anemia is a multi-system disease and hematologic manifestations and cancer are not the sole problems for patients with FA. Comprehensive care for FA patients requires an interdisciplinary team that focuses on all body systems simultaneously. The fifth edition covers recommendations for optimal oral health care (Chapter 6), gynecologic care and infertility (Chapter 7), dermatologic issues (Chapter 8), and gastrointestinal and endocrine issues (Chapters 9 and 10, respectively). Expert opinion on how to manage auditory problems (Chapter 11) and skeletal anomalies (Chapter 12) is also covered.

The final chapter (Chapter 13) provides a brief overview of the care recommendations mentioned throughout other chapters. The chapter also provides currently available care recommendations for adults who have FA. Persons with FA are surviving longer due to advancements in HCT and diagnosis of the disease in adults is occurring more often. Filling the gaps that exist around transitioning from pediatric to adult care and specific recommendations for the myriad of issues adults with FA face will be a focus for the Fanconi Anemia Research Fund in the coming years.

Starting in 2021, the *Fanconi Anemia Clinical Care Guidelines*, and all subsequent revisions, will be available on the Fanconi Anemia Research Fund website in an interactive format. The virtual resource guide will enable rapid incorporation of peer-reviewed updates for clinical care recommendations. The FA field changes rapidly and providing timely access to up-to-date recommendations is imperative. Printed editions of content from the website will be made available every five years.

On behalf of the Fanconi Anemia Research Fund, we extend a profound thank you to the many authors who contributed to the *Fanconi Anemia Clinical Care Guidelines* fifth edition. We also extend a heartfelt appreciation for individuals with FA and their families without whom this publication would not have been possible. It is our hope that this resource guide will serve as a valuable resource for physicians who treat patients with FA and ultimately, that it will extend lives and improve the quality of life of those affected by the disease.

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