Chronic graft versus host disease (GVHD) is the most common complication of allogeneic bone marrow transplantation. Because of the protracted clinical course of chronic GVHD, transplant centers and hematology/oncology offices are inadequately equipped to manage these immuno-incompetent patients with a multisystem disorder. Practitioners need to be able to recognize and effectively manage chronic GVHD as a late effect of more than half of allogeneic transplantations. The text is oriented for the clinician, with chapters covering staging, organ site and system-specific manifestations, treatment options, and supportive care. Drs. Georgia B. Vogelsang and Steven Z. Pavletic have been pioneers in the recognition of the multiorgan complexity of this disease and have gathered the input of a variety of subspecialist physicians for this book. This book fills the gap in practical literature on chronic GVHD, providing a comprehensive, up-to-date, and clinically relevant resource for anyone who deals with cancer patients posttransplant.

Georgia B. Vogelsang, MD, is Professor of Oncology at the Johns Hopkins University School of Medicine, Baltimore, Maryland.

Steven Z. Pavletic, MD, is the head of the Graft versus Host and Autoimmunity Unit in the Experimental Transplantation and Immunology Branch of the National Cancer Institute, Bethesda, Maryland.
Chronic Graft versus Host Disease: Interdisciplinary Management

Edited by

Georgia B. Vogelsang
Johns Hopkins University School of Medicine, Baltimore, Maryland

Steven Z. Pavletic
National Cancer Institute, Bethesda, Maryland
# Contents

List of Contributors .......................... ix
Preface ........................................... xiii

## Part I: General Principles

1. Historical Aspects of Chronic Graft versus Host Disease  
   Alois Gratwohl ............................... 3

2. The Pathophysiology of Acute Graft versus Host Disease  
   Carrie Kitko and James L. M. Ferrara ........ 8

3. Pathophysiology of Chronic Graft versus Host Disease  
   Kirk R. Schultz .............................. 17

4. Animal Models of Chronic Graft versus Host Disease  
   Yu-Waye Chu, Ronald Gress, and Warren D. Shlomchik . 31

5. Incidence and Trends  
   Sally Arai, Mukta Arora, and Douglas J. Rizzo ..... 46

6. Clinical Manifestations and Natural History  
   Mary Evelyn D. Flowers and Georgia B. Vogelsang . 56

7. Risk Factors and Predictive Models for Chronic Graft versus Host Disease  
   Gorgun Akpek and Stephanie J. Lee ............. 70

8. Biomarkers in Chronic Graft versus Host Disease  
   Ernst Holler and Anne Dickinson ............... 79

## Part II: Clinical Management

9. Diagnosis and Staging  
   Madan Jagasia, Howard M. Shulman, Alexandra H. Filipovich,  
   and Steven Z. Pavletic ....................... 87

10. Chronic Graft versus Host Disease Pharmacology  
    Thomas Hughes and Timothy R. McGuire ....... 101

11. Prevention of Chronic Graft versus Host Disease  
    Andrea Bacigalupo and Nelson J. Chao ........ 117

12. Front Line Treatment of Chronic Graft versus Host Disease  
    Paul J. Martin and Andrew L. Gilman .......... 124

13. Salvage Therapy in Chronic Graft versus Host Disease  
    Hildegard T. Greinix and Joseph H. Antin .... 134

14. Evaluating Therapeutic Response in Chronic Graft versus Host Disease  
    David A. Jacobsohn, Sandra A. Mitchell, and Steven Z. Pavletic . 146
CONTENTS

15. General Principles of Ancillary and Supportive Care
   Paul A. Carpenter and Daniel R. Couriel

Part III: Organ Site or System-Specific Manifestations

16. Cutaneous Manifestations of Chronic Graft versus Host Disease
   Edward W. Cowen and Sharon R. Hymes

17. Oral Chronic Graft versus Host Disease
   Nathaniel S. Treister, Mark M. Schubert, and Jane M. Fall-Dickson

18. Chronic Ocular Graft versus Host Disease
   Stella K. Kim, Janine A. Smith, and James P. Dunn, Jr.

19. Gynecological Manifestations of Chronic Graft versus Host Disease
   Maria L. Turner and Pamela Stratton

20. Gastrointestinal and Hepatic Manifestations of Chronic Graft versus Host Disease
   Miwa Sakai and George B. McDonald

21. Chronic Graft versus Host Disease and the Lung
   Javier Bolaños-Meade and Jason W. Chien

22. Hematologic Complications of Chronic Graft versus Host Disease
   Corey Cutler

23. Neurological Manifestations of Chronic Graft versus Host Disease
   Harry Openshaw

24. Rehabilitation Evaluation and Treatment of Patients with Chronic Graft versus Host Disease
   Li Li, Leighton Chan, and Lynn H. Gerber

25. Infections
   Juan Gea-Banacloche and Michael Boeckh

26. Endocrine and Metabolic Effects of Chronic Graft versus Host Disease
   Paul A. Carpenter and Jean E. Sanders

27. Other Manifestations of Chronic Graft versus Host Disease
   Kristin Baird and Andrew L. Gilman

28. Psychosocial Issues in Chronic Graft versus Host Disease
   Loretta A. Williams and Karen L. Syrjala

29. Secondary Malignancies and Other Late Effects
   Gérard Socié and H. Joachim Deeg

30. Health-Related Quality of Life (HRQOL) in Chronic Graft versus Host Disease
   Sandra A. Mitchell and Bryce B. Reeve

Part IV: Special Considerations in Chronic GVHD

31. Design of Clinical Trials Testing Treatment for Chronic Graft versus Host Disease
   Paul J. Martin, Donna Przepiorka, and Stephanie J. Lee

32. Spectrum of Chronic Graft versus Host Disease in Unique Clinical Situations: The Role of Stem-Cell Source Including Cord Blood Stem Cells, Reduced-Intensity Conditioning, and Donor Leukocyte Infusions
   Mohamad Mohty, Juliet N. Barker, and Claudio Anasetti
33. Pediatric Chronic Graft versus Host Disease
   Kristin Baird, Alan S. Wayne, and David A. Jacobsohn
   369

34. Principles of Interdisciplinary Practice in the Care
    of Patients with Chronic Graft versus Host Disease
    Viki Anders, Carina Moravec, and Sandra A. Mitchell
    386

35. Patient Advocacy, Education and Psychosocial Support
    Kathleen M. Castro, Susan Stewart, Myra J. Jacobs, and Paula Kim
    396

36. Future Directions
    Stephanie J. Lee
    406

Index

409
CONTRIBUTORS

Görgün Akpek, MD, MHS Blood and Marrow Transplantation Program, Greenebaum Cancer Center, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland

Claudio Anasetti, MD H. Lee Moffitt Comprehensive Cancer Center, Tampa, Florida

Viki Anders, RN, MSN, CRNP Graft-Versus-Host Disease Clinic, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland

Joseph H. Antin, MD Department of Medicine, Dana-Farber Cancer Institute, Harvard Medical School, Cambridge, Massachusetts

Sally Arai, MD Department of Medicine, Division of Blood and Marrow Transplantation, Stanford Cancer Center, Stanford, California

Mukta Arora, MD Department of Medicine, Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, Minnesota

Andrea Bacigalupo, MD European Group for Bone Marrow Transplantation, Department of Hematology, Ospedale San Martino, Genova, Italy

Kristin Baird, MD Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Juliet N. Barker, MD Memorial Sloan-Kettering Cancer Center, New York, New York

Michael Boeckh, MD Fred Hutchinson Cancer Research Center, Department of Medicine, University of Washington, Seattle, Washington

Javier Bolaños-Meade, MD Department of Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Division of Hematologic Malignancies, Baltimore, Maryland

Paul A. Carpenter, MD Fred Hutchinson Cancer Research Center, Seattle, Washington

Kathleen M. Castro, RN, MS, ACCN Clinical Center, National Institutes of Health, Bethesda, Maryland

Leighton Chan, MD Rehabilitation Medicine Department, Warren G Magnuson Clinical Research Center, National Institutes of Health, Bethesda, Maryland

Nelson J. Chao, MD, MBA Departments of Medicine and Immunology, Duke University, Durham, North Carolina

Jason W. Chien, MD, MS Division of Pulmonary and Critical Care, University of Washington, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington

Yu-Waye Chu, MD National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Daniel R. Couriel, MD Stem Cell Transplantation and Cellular Therapy, M.D. Anderson Cancer Center, The University of Texas, Houston, Texas

Edward W. Cowen, MD, MHSc Dermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Corey Cutler, MD, MPH, FRCPc Department of Medicine, Harvard Medical School, Dana-Farber Cancer Institute, Boston, Massachusetts
LIST OF CONTRIBUTORS

H. Joachim Deeg, MD Fred Hutchinson Cancer Research Center, Department of Medicine, University of Washington, Seattle, Washington

Anne Dickinson, MD NorthEast England StemCell Institute, Marrow Transplant Biology, University of Newcastle Medical School, Newcastle upon Tyne, United Kingdom

James P. Dunn, Jr., MD Division of Ocular Immunology, The Wilmer Ophthalmological Institute, Baltimore, Maryland

Jane M. Fall-Dickson, PhD, RN Symptom Management Branch, National Institute of Nursing Research, National Institutes of Health, Bethesda, Maryland

James L. M. Ferrara, MD Departments of Pediatrics and Internal Medicine, Blood and Marrow Transplant Program, University of Michigan, Ann Arbor, Michigan

Alexandra H. Filipovich, MD Department of Pediatrics, Division of Hematology/Oncology, Immunodeficiency and Histiocytosis Program, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Mary Evelyn D. Flowers, MD Clinical Research Division, Fred Hutchinson Cancer Research Center, Department of Medicine, University of Washington, Seattle, Washington

Juan Gea-Banacloche, MD Experimental Transplantation and Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Lynn H. Gerber, MD Center for the Study of Chronic Illness and Disability, College of Health and Human Services, George Mason University, Fairfax, Virginia

Andrew L. Gilman, MD Department of Pediatrics, Pediatric Blood and Marrow Transplantation, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Alois Gratwohl, MD Hematology Department, University Hospital, Basel, Switzerland

Hildegard T. Greinix, MD Medical University of Vienna, Vienna, Austria

Ronald Gress, MD National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Ernst Holler, MD Department of Hematology/Oncology, University of Regensburg, Regensburg, Germany

Thomas Hughes, MD National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Sharon R. Hymes, MD Department of Dermatology, M.D. Anderson Cancer Center, The University of Texas Medical School, Houston, Texas

Myra J. Jacobs, MA National Bone Marrow Transplant Link, Southfield, Michigan

David A. Jacobsohn, MD Department of Pediatrics, Northwestern University School of Medicine, Stem Cell Transplant Program, Children's Memorial Hospital, Chicago, Illinois

Madan Jagasia, MBBS, MS Department of Medicine, Division of Hematology-Oncology, Vanderbilt Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, Tennessee

Paula Kim Translating Research across Communities, California

Stella K. Kim, MD Departments of Ophthalmology and Radiation Oncology, M.D. Anderson Cancer Center, The University of Texas, Houston, Texas

Carrie Kitko, MD Departments of Pediatrics and Internal Medicine, Blood and Marrow Transplant Program, University of Michigan, Ann Arbor, Michigan

Stephanie J. Lee, MD Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington

Li Li, MD Rehabilitation Medicine Department, Warren G Magnuson Clinical Research Center, National Institutes of Health, Bethesda, Maryland

Paul J. Martin, MD Division of Clinical Research, Fred Hutchinson Cancer Research Center, Departments of Medicine and Pediatrics, University of Washington, Seattle, Washington

George B. McDonald, MD Gastroenterology/Hepatology Section, Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle, Washington

Timothy R. McGuire, PharmD, FCCP Department of Pharmacy Practice, College of Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska

Sandra A. Mitchell, CRNP, MSN, AOCN Clinical Center, National Institutes of Health, Bethesda, Maryland, National Cancer Institute, Bethesda, Maryland, Cancer Research, University of Utah College of Nursing, Salt Lake City, Utah

Mohamad Mohty, MD Hematology Department, CHU Hotel-Dieu, University of Nantes, Nantes, France

Carina Moravec, ARNP, MA Fred Hutchinson Cancer Research Center, Seattle, Washington
Harry Openshaw, MD Department of Neurology, City of Hope National Medical Center, Duarte, California

Steven Z. Pavletic, MD Graft-versus-Host and Auto-Immunity Unit, National Cancer Institute, Center for Cancer Research, Bethesda, Maryland

Donna Przepiorka, MD Center for Biologics, Evaluation Research, U.S. Food and Drug Administration, Rockville, Maryland

Bryce B. Reeve, PhD National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Douglas J. Rizzo, MD, MS Department of Medicine, Division of Neoplastic Diseases and Related Disorders, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin

Miwa Sakai, MD Gastroenterology/Hepatology Section, Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle, Washington

Jean E. Sanders, MD Pediatric Clinical Hematopoietic Cell Transplantation, Fred Hutchinson Cancer Research Center, Seattle, Washington

Mark M. Schubert, DDS, MSD Department of Oral Medicine, University of Washington, Oral Medicine, Seattle Cancer Care Alliance, Seattle, Washington

Kirk R. Schultz, MD Division of Oncology/BMT Faculty of Medicine – Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada

Warren D. Shlomchik, MD Department of Immunology, Yale School of Medicine, New Haven, Connecticut

Howard M. Shulman, MD Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Department of Pathology, University of Washington, Seattle, Washington

Janine A. Smith, MD Division of Epidemiology and Clinical Research, National Eye Institute, National Institutes of Health, Bethesda, Maryland

Gérard Socié, MD, PhD Department of Transplantation and Hematology, University Paris VII: Hospital Saint Louis, Paris, France

Susan Stewart BMT InfoNet, Highland Park, Illinois

Pamela Stratton, MD Reproductive Biology and Medicine Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

Karen L. Syrjala, MD Clinical Research Division, Fred Hutchinson Cancer Research Center, University of Washington, Department of Medicine, Seattle, Washington

Nathaniel S. Treister, DMD, DMSc Harvard School of Oral Medicine, Cambridge, Massachusetts, Division of Oral Medicine and Dentistry, Brigham & Women’s Hospital, Boston, Massachusetts

Maria L. Turner, MD Dermatology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Georgia B. Vogelsang, MD Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Alan S. Wayne, MD Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Loretta A. Williams, PhD, MSN, RN Department of Symptom Research, M.D. Anderson Cancer Center, The University of Texas, Houston, Texas
Bone marrow transplantation has changed remarkably from its earliest days. Patients were transplanted with bone marrow as a last resort for refractory leukemia or aplastic anemia. The transplant procedure required prolonged hospital stays – often months – with significant uncontrolled toxicities from the pre-parative regimen, limited antimicrobial success, and even more limited ability to prevent or treat acute graft versus host disease (GVHD). The lucky survivors now marvel at how different the experience is for patients receiving allografts as outpatients.

Unfortunately, the same level of improvement has not been seen in chronic GVHD. The reasons for this lack of success are varied – including the latency of chronic GVHD, lack of accepted readily reproducible animal models, and complex underlying immuno-pathology. It is no wonder that patients with this affliction felt like abandoned stepchildren.

Over the last 5 years, there has been both a resurgence of interest and progress in chronic GVHD. To a significant degree, the NIH-sponsored Consensus Conference on Chronic GVHD is responsible for this change. This conference suggested working definitions, standardized staging and response criteria, recommended supportive care measures, and suggested areas for future study. Although the indolent nature of the disease means that clinical progress is going to be time consuming, there has been remarkable progress since the initial NIH-sponsored meeting. One of the main lessons learned is that it is imperative to have transplant centers cooperate in studying this disorder. The success of NIH-sponsored multicentered trials, cooperative group–sponsored clinical studies, Clinical Trials Network proposals, and cooperation of European transplant groups all suggest that a new era has begun in which more patients will be intensely studied.

Our hope with this book is to provide a solid reference for this effort. By collecting in one book the state of the art, our hope is that it will provide a reference that will be valuable in many settings, including transplant clinics, oncology/hematology clinics, specialty clinics, and basic research laboratories. It is only by gathering all these diverse groups together that we are going to be able to understand the basic immunologic processes responsible for the disorder and to provide treatment to relieve the discomfort caused to the patients suffering with this disorder.

We wish to thank all those who have made this book possible. The book grew out of the NIH-sponsored Consensus Conference on Chronic GVHD – all participants in that meeting contributed to this book, whether or not they actually penned a chapter. Their thoughts and their efforts played a major part in the final Consensus Conference recommendations. Obviously, we are indebted to all of the contributors. Most of the chapters are group efforts and reflect the cooperative spirit that has made such a profound difference in the hope for the future for this disorder. Finally, we are indebted to our patients, who have waited many years for a book concerned with and dedicated to the burden they live with every day.