Pediatric Thrombotic Disorders
Pediatric Thrombotic Disorders

Edited by

Neil A. Goldenberg, MD, PhD
Associate Professor of Pediatrics, Johns Hopkins University School of Medicine, and Chief Research Officer and Director, Thrombosis Program, All Children’s Hospital, Johns Hopkins Medicine, St Petersburg, FL, USA

Marilyn J. Manco-Johnson, MD
Director of the Hemophilia and Thrombosis Center and Professor of Pediatrics at the University of Colorado, Aurora, CO, USA
# Contents

<table>
<thead>
<tr>
<th>List of contributors</th>
<th>page vi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preface</td>
<td>ix</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>x</td>
</tr>
</tbody>
</table>

## Section 1. Epidemiology, etiology, diagnosis, treatment, outcomes

1. **Extremity and caval deep venous thrombosis**  
   Madhvi Rajpurkar and Shoshana Revel-Vilk  
   page 1

2. **Pulmonary embolism**  
   Suzan Williams and Michael Wang  
   page 16

3. **Cerebral sinovenous thrombosis in children and neonates**  
   Mahendranath Moharir and Gili Kenet  
   page 33

4. **Gastrointestinal and visceral thromboembolism**  
   Courtney A. Lyle and Christoph Male  
   page 47

5. **Renal and adrenal vein thromboses**  
   Robert Francis Sidonio, Jr. and Leonardo R. Brandao  
   page 60

6. **Cancer and thrombosis**  
   Uma Athale  
   page 72

7. **Epidemiology, etiology, and pathophysiology of infection-associated venous thromboembolism in children**  
   Anjali A. Sharathkumar, Neil A. Goldenberg, and Anthony K.C. Chan  
   page 88

## Section 2. Special considerations in pediatric patients

8. **Developmental hemostasis I**  
   Paul Monagle  
   page 107

9. **Developmental hemostasis II**  
   Marilyn J. Manco-Johnson  
   page 119

10. **Pediatric thrombophilia evaluation: Considerations for primary and secondary venous thromboembolism prevention**  
    Ulrike Nowak-Göttl, Gili Kenet, and Neil A. Goldenberg  
    page 133

11. **Role of global assays in thrombosis and thrombophilia**  
    Meera Chitlur and Mindy L. Simpson  
    page 142

12. **Heparin-induced thrombocytopenia and thrombosis syndrome in children**  
    Courtney D. Thornburg  
    page 158

13. **Severe thrombophilias**  
    Cameron C. Trenor III and Marilyn J. Manco-Johnson  
    page 166

14. **Thrombolysis**  
    Donald L. Yee, Catherine M. Amlie-Lefond, and Peter H. Lin  
    page 180

15. **New anticoagulants in children: A review of recent studies and a look to the future**  
    Guy Young and Neil A. Goldenberg  
    page 200

16. **Prevention of VTE in children**  
    Brian R. Branchford and Leslie Raffini  
    page 207

17. **Arterial ischemic stroke in children**  
    Timothy J. Bernard and Ulrike Nowak-Göttl  
    page 219

Index  
page 231

See colour plate section in between pages 182 and 183.
Contributors

Catherine M. Amlie-Lefond, MD
Associate Professor of Neurology and Director, Pediatric Vascular Neurology Program, University of Washington, Seattle Children’s Hospital, Seattle, WA, USA

Uma Athale, MD
Associate Professor of Pediatrics, Division of Hematology/Oncology, McMaster Children’s Hospital, McMaster University, Hamilton, ON, Canada

Timothy J. Bernard, MD
Associate Professor of Pediatrics, Neurology and Child Neurology and Director, Pediatric Stroke Program, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA

Brian R. Branchford, MD
Instructor, Section of Hematology/Oncology/Bone Marrow Transplantation, Department of Pediatrics, University of Colorado–Anschutz Medical Campus & Children’s Hospital Colorado, Aurora, CO, USA

Leonardo R. Brandao, MD, MSc
Assistant Professor of Pediatrics, Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada

Anthony K.C. Chan, MD
Division of Hematology/Oncology, McMaster University Health Sciences Center, Hamilton, ON, Canada

Meera Chitlur, MD
Barnhart-Lusher Hemostasis Research Endowed Chair, Director, Hemophilia Treatment Center and Hemostasis Program, Director, Special Coagulation Laboratory, and Associate Professor of Pediatrics, Wayne State University, Division of Hematology/Oncology, Children’s Hospital of Michigan, Detroit, MI, USA

Neil A. Goldenberg, MD, PhD
Associate Professor of Pediatrics, Departments of Pediatrics and Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; All Children’s Research Institute, All Children’s Hospital, Johns Hopkins Medicine, St Petersburg, FL, USA

Gili Kenet, MD
Director, Thrombosis Unit, National Hemophilia Center, Sheba Medical Center, Tel-Hashomer, Israel

Peter H. Lin, MD
Chief of Vascular Surgery, Baylor College of Medicine, Houston, TX, USA

Courtney A. Lyle, MD, MAS
Department of Pediatrics, Division of Hematology/Oncology, Billings Clinic, Billings, MT, USA

Christoph Male, MD, MSc
Department of Pediatrics, Division of Hematology, Medical University of Vienna, Vienna, Austria

Marilyn J. Manco-Johnson, MD
Director of the Hemophilia and Thrombosis Center Professor of Pediatrics, Section of Hematology/Oncology/Bone Marrow Transplantation, University of Colorado–Anschutz Medical Campus & Children’s Hospital Colorado, Aurora, CO, USA

Mahendranath Moharir MD, MSc, FRACP
Assistant Professor, University of Toronto, and Staff Pediatric Neurologist, Division of Neurology, Department of Pediatrics, The Hospital for Sick Children, Toronto, ON, Canada

Paul Monagle, MD
Department of Paediatrics, University of Melbourne, Department of Haematology, Royal Children’s Hospital, Melbourne, VIC, Australia
List of contributors

Ulrike Nowak-Göttl, MD
Thrombosis and Hemostasis Unit, Department of Clinical Chemistry, University Hospital of Kiel & Lübeck, Germany

Leslie Raffini, MD, MSCE
Associate Professor of Pediatrics, Division of Hematology, Children’s Hospital of Philadelphia, University of Pennsylvania Perlman School of Medicine, Philadelphia, PA, USA

Madhvi Rajpurkar, MD
Assistant Professor of Pediatrics, Chief, Division of Hematology and Thrombosis Service, Children’s Hospital of Michigan and Wayne State University, Detroit, MI, USA

Shoshana Revel-Vilk, MD, MSc
Director, Pediatric Hematology Center, Pediatric Hematology/Oncology Department, Hadassah Medical Center, Jerusalem, Israel

Anjali A. Sharathkumar, MD, MS
Assistant Professor of Pediatrics, Hematology, Oncology and Stem Cell Transplantation, Hemophilia and Thrombosis Program, Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA

Robert Francis Sidonio Jr., MD, MSc
Assistant Professor of Pediatrics, Hemostasis/Thrombosis, Allele Cancer and Blood Disorders Center, Emory University, Atlanta, GA, USA

Mindy L. Simpson, MD
Assistant Professor of Pediatrics, Hematology/Oncology, Rush University Medical Center, Chicago, IL, USA

Courtney D. Thornburg, MD
Department of Pediatrics, University of California San Diego and Rady Children’s Hospital, San Diego, CA, USA

Cameron C. Trenor III, MD
Attending Physician in Pediatric Hematology–Oncology, Boston Children’s Hospital, Dana-Farber Cancer Institute, Co-Director, Cerebrovascular Disorders and Stroke Program, Director of Clinical Research, Vascular Anomalies Center, and Instructor in Pediatrics, Harvard Medical School, Boston, MA, USA

Michael Wang, MD
Associate Professor of Pediatrics, Clinical Director, Hemophilia & Thrombosis Center, University of Colorado–Anschutz Medical Campus and Children’s Hospital Colorado, Aurora, CO, USA

Suzan Williams, MD, MSc
The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Donald L. Yee, MD
Associate Professor of Pediatrics, Baylor College of Medicine, and Attending Physician, Texas Children’s Hospital, Houston, TX, USA

Guy Young, MD
Director, Hemostasis and Thrombosis Center, Children’s Hospital Los Angeles, and Associate Professor of Pediatrics, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA
Over the past few decades, thrombotic disorders have become increasingly recognized as an important problem in pediatrics, affecting neonates through teens and young adults. These thrombotic disorders include both venous and arterial thromboembolism, as well as peripheral vascular, central vascular, cardiac, or cerebrovascular events. Accordingly, their optimal diagnosis and acute and chronic management often requires the ongoing expertise of diverse pediatric specialists, from hematologists to radiologists, emergentologists, intensivists, cardiologists, and neurologists, among others—all of whom can benefit from the collective work of a broad panel of experts brought together to produce this comprehensive text, *Pediatric Thrombotic Disorders*.

The chapters of this book are designed to provide up-to-date coverage of many of the most salient and topical issues in pediatric thrombotic disorders, including: thrombophilia evaluation, thrombolysis, heparin-induced thrombocytopenia/thrombosis, pulmonary embolism, arterial ischemic stroke, and new antithrombotic agents. In addition, this text contains chapters seldom addressed by other books or special issues devoted to thromboembolism or pediatric hematology/oncology, such as: gastrointestinal and visceral thromboses, infection-associated venous thromboembolism, and severe thrombophilias.

One of our greatest rewards is the opportunity to mentor and teach students, residents, fellows, and junior faculty. Accordingly, we and our coauthor colleagues have striven in this book to develop content that is suitable and of interest across a broad range of readers and “learners,” among which last category we include ourselves. We hope you share our perspective that every chapter in this text offers knowledge and perspectives from which each reader—whether coming from a background of pediatric hematology or another discipline, and whether a medical student or a professor emeritus—may benefit…. and we welcome your feedback and ideas for improving upon it in future editions.

We dedicate this book to the pediatric patients with thrombotic disorders for whom we have had the privilege of caring, and who have taught us so much clinically, in research, and in our own lives.

Neil A. Goldenberg, MD, PhD
Marilyn J. Manco-Johnson, MD
Acknowledgments

The editors are sincerely grateful to Nisha Doshi, Jane Seakins, and Beata Mako of Cambridge University Press, as well as to Laurel McDevitt of All Children's Hospital, Johns Hopkins Medicine, for their editorial and production expertise and tireless support throughout the development of this text.