Contents

SECTION 1

FETAL HEMATOLOGY AND ANTENATAL DIAGNOSIS OF HEMATOLOGICAL DISORDERS

Section Editors: **Anupam Sachdeva, Shubha R Phadke**

1. Physiology of Hematopoiesis 3

Vinod Gunasekaran, Anupam Sachdeva

Steps in Fetal Hematopoiesis **3**
Normal Blood Counts in Fetus **4**
Regulation of Hematopoiesis **4**
Stress Erythropoiesis **5**
Erythroid Lineage Differentiation **5**
Differentiation of White Blood Cells **6**
Clinical Significance of Fetal Hematopoiesis **6**

2. Developmental Hemostasis and Physiology of Hemostasis in the Fetus and the Newborn 8

Shrimati Shetty

Primary Hemostasis **9**
Secondary Hemostasis **9**
Neonatal Hemostasis **10**
Role of Micro-RNA in Developmental Hemostasis **11**
Significance of Understanding Fetal and Neonatal Hemostasis **11**

3. Granulocytes: Development and Physiology 13

Tulika Seth

Present Knowledge **13**
Granulopoiesis **13**
Infection and Cytokine **14**
Infection in Neonates: Granulocyte Response **15**
Future Perspectives **17**

4. Developmental Aspects of Platelets 19

Sangeeta Mudaliar

Developmental Aspects of Platelets **19**
Megakaryocytes during Fetal Development **19**
Megakaryocyte Maturation and Development **21**

Platelet Formation **22**
Megakaryocyte Maturation **22**
Endomitosis **22**
Practical Aspects of Megakaryocyte Cell Biology and Clinical Use of Thrombopoietic Agents **24**

5. Fetal Anemia 25
Meenal Agarwal
Definition **25**
Causes of Fetal Anemia **25**
Noninvasive Predictors of Fetal Anemia **26**
Ultrasonography-based Predictors of Fetal Anemia **26**
Plan for Conservative Management or Invasive Sampling **27**
Intrauterine Fetal Transfusion: The Technique **28**

6. Thalassemia in the Fetus: Prenatal Diagnosis 33
Prajnya Ranganath
Preventive Strategies for Beta-thalassemia **33**

7. Genetic Counseling for Hematological Disorders 38
Roshan Colah, Khushnooma Italia
Burden of the Inherited Hematological Disorders **38**
Genetic Testing versus Genetic Screening **38**
Indian Scenario **38**
Genetic Counseling **39**

8. Fetal Hematological Disorders: Future Ahead 43
Shubha R Phadke
Diagnosis of Fetus **43**
Fetal Therapy **44**

SECTION 2
RBC DISORDERS AND ANEMIA IN NEWBORN

Section Editors: **MR Lokeshwar, Ratna Sharma**

9. Developmental Erythropoiesis 49
Nimish Kulkarni, Ratna Sharma
Basics of Erythropoiesis **49**
Globin Loci **49**
Embryonic Development of Erythropoiesis **49**
Erythroid Cell Maturation **52**
Autonomous Silencing **54**
Sequence of Activation of Globin Genes **55**
Future Possibilities **55**

10. Normal Hematological Values and Variation in Newborn Period with Special Reference to Hb and RBC Parameters 58
MR Lokeshwar, Sheikh Minhaj Ahmed, Ratna Sharma
Antenatal Erythropoiesis **58**
Normal Hematological Values and Variation in Newborn Period **59**

11. Effect of Nutritional Deficiency Anemia during Pregnancy on Fetus and Newborn 63
BD Bhatia, Shweta Singh, Nagendra Chaudhary
Epidemiology **63**
Etiology **63**
Physiological Anemia **63**
Maternal Effects of Anemia **64**
Fetal Effects **64**
Treatment of Iron Deficiency Anemia **66**
Folic Acid Deficiency Anemia **67**
Dimorphic Anemia **67**
Future Perspective **68**

12. Anemia of Prematurity 70
Jayashree Mondkar
Etiopathogenesis **70**
Clinical Features **70**
Investigations **70**
Differential Diagnosis **70**
Management **71**
Optimizing Nutritional Support **72**

13. Clinical Aspect of Immune Hemolytic Disease of Newborn 74
ATK Rau, Soundarya M, Aarathi R Rau
Rh Blood Group System and Rh Isoimmunization **74**
Etiopathogenesis **75**
Clinical Features **76**
Diagnosis of Immune Hemolytic Disease in the Newborn **76**
Management of Rh Isoimmunization **77**
ABO Blood Group System and ABO Hemolytic Disease **78**

14. Laboratory Management of ABO and Rh Hemolytic Disease of the Fetus and Newborn 81
Snehalata C Gupte
Pathophysiology of Hemolytic Disease of the Newborn **81**
ABO Hemolytic Disease of the Newborn **81**
Incidence **81**
Diagnosis **81**

Rh Hemolytic Disease of the Fetus and Newborn **82**
Maternal Laboratory Investigations **83**
Spectrophotometric Analysis of Amniotic Fluid **84**
Investigation of Fetus **84**

15. Nonimmune Hemolytic Anemia 87
Anirban Das, Deepak Bansal
Confounding Factors in the Evaluation of Neonatal Hemolysis **88**
Extrinsic Causes of Hemolysis In Neonates **88**
Disorders of the RBC Membrane **91**
Enzyme Deficiencies **94**
Hemoglobinopathies in the Neonate **96**

16. Inherited Bone Marrow Failure Syndromes 102
Tathagata Chatterjee, Ujjwal Dimri, VP Choudhry
Fanconi Anemia **102**
Dyskeratosis Congenita **106**
Severe Congenital Neutropenia **109**
Thrombocytopenia Absent Radii **109**

17. Polycythemia and Hyperviscosity Syndrome in Newborn 111
MR Lokeshwar, Sheikh Minhaj Ahmed, Swati Kanakia
Incidence **111**
Pathophysiology **111**
Etiology **112**
Clinical Features **112**
Investigations **113**
Medical Management of Polycythemia **113**

SECTION 3
COAGULATION DISORDERS IN NEWBORN
Section Editors: **Mamta Vijay Manglani, Jagdish Chandra**

18. Congenital Coagulation Disorders in the Neonate 119
Mamta Vijay Manglani, Pooja Balasubramanian, Nimish Kulkarni, Snehavardhan Pandey
Inheritance Patterns **119**
Clinical Presentation **119**
Laboratory Investigations and Interpretation **120**
Specific Coagulation Factor Deficiencies **122**
Von Willebrand Factor Deficiency **122**
Rare Bleeding Disorders **122**
Hereditary Deficiencies of Multiple Coagulation Factors 124
Defects in the Fibrinolytic Pathway **125**

19. Vitamin K Deficiency Bleeding 127
Jagdish Chandra, Piali Mandal
Epidemiology **127**
Etiology **128**
Pathogenesis **129**
Clinical Features **129**
Diagnosis **130**
Therapy **131**
Risks and Disadvantages of Different Forms of Vitamin K Prophylaxis **132**

20. Disseminated Intravascular Coagulation in the Neonatal Period 135
Anand Prakash, Shashidhar A
Etiology **135**
Pathogenesis/Pathophysiology **136**
Clinical Presentation **136**
Diagnosis **136**
Management **138**
Outcomes/Prognostic Factors **139**

21. Thrombophilia in Newborns 141
Satyendra Katewa
Epidemiology **141**
Etiology **141**
Pathophysiology **144**
Clinical Features **144**
Diagnosis **145**
Management **146**

SECTION 4
PLATELETS, PLATELET DISORDERS AND APPROACH TO BLEEDING IN NEWBORN

Section Editors: **Nitin K Shah, Amita Mahajan**

22. Approach to Neonatal Thrombocytopenia 153
Nitin K Shah
Neonatal Megakaryopoiesis and Thrombopoiesis **153**
Incidence **153**
Causes of Neonatal Thrombocytopenia **154**

23. Neonatal Thrombocytopenia: Syndromic Causes 159
Manas Kalra, Amita Mahajan
Causes of Syndromic Thrombocytopenia in Newborn **159**

24. Qualitative Platelet Disorders 163
Purvi Kadakia Kutty
Pathophysiology **163**
Etiology **163**
Clinical Features of Platelet Functional Defects 163
Hereditary Platelet Dysfunction Disorders **163**
Acquired Platelet Function Defects **166**
Investigations **167**
Recommendations for Specimen Collection and Processing **167**
Challenges in Diagnosing Platelet Function Disorders in Infants **172**
Treatment of Qualitative Platelet Defects **172**

25. Approach to a Bleeding Neonate 174
Gaurav Tripathi, Amita Mahajan
Epidemiology **174**
Pathophysiology **175**
Etiology **175**
Clinical Presentation **176**
Diagnosis of Bleeding in a Neonate **176**
Recent Development in the Diagnostics 177
Management **177**
Prognostic Factors **179**
Prevention **180**

SECTION 5
NEUTROPHIL DISORDERS

Section Editors: **Bharat Agarwal, Tulika Seth**

26. Neutrophilia 183
Bhavna Dhingra, Bharat Choudhary
Neutrophil Counts in Newborn **183**
Mechanism of Neutrophilia in Newborns **183**
Factors Affecting Neutrophil Counts **184**
Disorders with Neutrophilia **185**

27. Important Causes of Neutropenia including Inherited Conditions: Diagnosis and Work-up 188
Nitin Gupta, Rahul Arora
Symptoms of Neutropenia **188**
Neutropenia by Etiology **189**
Neutropenia Associated with Metabolic Diseases **192**

Nutritional Deficiencies **192**
Neutropenia Caused by Extrinsic Factors **192**
Immune Neutropenia **193**
Therapy for Neonatal Neutropenia **195**

28. Neutrophil Function Defects 198
Praveen Narsaria, Sushil K Kabra, Rakesh Lodha
Disorder of Adhesion **198**
Disorders of Chemotaxis **199**
Disorders of Degranulation **199**
Disorders of Microbicidal Metabolism **201**
Approach to the Diagnosis of Neutrophil Function Defects **204**

29. Management of Neutropenia and Infections 206
Sangeeta Mudaliar, Bharat Agarwal
Management of Neutropenia and Infections **206**
Causes of Neutropenia **207**
Cyclic Neutropenia **208**
Clinical Evaluation of Neutropenia in Neonates **209**
Laboratory Evaluation of Neutropenia in Neonates **209**
Clinical Management of a Neonate with Neutropenia **210**
Treatment **210**
How to Use Recombinant G-CSF? **212**
Prevention **212**

SECTION 6
FETAL AND NEONATAL MALIGNANCY

Section Editors: **Girish Chinnaswamy, Arpita Bhattacharya**

30. Cancers in Infants 217
Akanksha Chichra, Purna Kurkure
Special Features **217**
Fetal Origins of Cancer **217**
Epidemiology **217**
Challenges in Management of Infantile Cancers **218**
Pain Assessment and Management **218**
Common Hematolymphoid and Solid Tumors in Infants **218**
Neuroblastoma **219**
Clinical Features **219**
Risk Stratification **220**
Risk Based Treatment **220**
Brain Tumors **220**

Ependymoma **222**
Medulloblastoma **222**
Atypical Teratoid or Rhabdoid Tumor **222**
Retinoblastoma **222**
Screening for Cancers in Infants: is there any Role? **222**
Balancing Cure and Quality of Life **223**

31. Neonatal Leukemia 225
Anirban Das, Akanksha Chichra, Anupama S Borker
Epidemiology **225**
Etiology and Pathogenesis **225**
Clinical Features **226**
Investigations **226**
Differential Diagnoses **226**
Management and Outcomes for Major Subtypes of Neonatal Leukemia **226**

32. Neonatal Liver Tumor 230
Sajid Qureshi
Epidemiology **230**
Benign Neonatal Liver Tumors **230**
Infantile Hepatic Hemangioma **230**
Malignant Neonatal Liver Tumors **232**
Metastatic Liver Lesion **234**
Recent Advances **234**
Indian Data **235**

33. Neuroblastoma 238
Arpita Bhattacharya, Dipshikha Maiti
Epidemiology **238**
Pathogenesis **238**
Ploidy (Tumor Cell DNA Content) **238**
Familial Neuroblastoma and Genetic Susceptibility **239**
Pathology **239**
Clinical Presentation **239**
Prognostic Factors **240**
Diagnosis **241**
Management **241**
Screening **242**

34. Renal Tumors in Neonates 244
Julius Xavier Scott, Latha M Sneha
Overview of the Common Renal Tumors **244**
Mesoblastic Nephroma **245**
Wilms' Tumor **246**

Malignant Rhabdoid Tumor of the Kidney **246**
Clear Cell Sarcoma of the Kidney **246**
Ossifying Renal Tumor of Infancy **247**
Nephroblastomatosis **247**
Miscellaneous Renal Tumors **247**

35. Neonatal Soft Tissue Sarcomas 250
Venkatraman Radhakrishnan
Approach to a Neonate with Soft Tissue Swelling **250**
Common Soft Tissue Neoplasms **251**

36. Fetal and Neonatal Germ Cell Tumors 254
Maya Prasad
Epidemiology **254**
Etiology and Pathogenesis **254**
Clinical Presentation **254**
Histology **256**
Diagnosis and Work-up in Fetal and Neonatal Germ Cell Tumors **257**
Management of Fetal and Neonatal Germ Cell Tumors **258**
Outcomes and Prognostic Factors **260**
Late Effects of Treatment and Follow-up **260**
Future Directions **260**

37. Retinoblastoma and its Prenatal Screening 263
Ashwin Mallipatna, Swathi Shetty, Prathima Radhakrishnan
Inheritance Pattern **263**
Clinical Features **263**

38. Pharmacology of Anticancer Drugs in Neonate 267
Saroj P Panda
Absorption **267**
Distribution **267**
Metabolism **268**
Renal Excretion **268**

39. Challenges in Neonatal Malignancies 270
Nirav Thacker, Shripad D Banavali
Epidemiology **270**
Challenges in Neonatal Malignancies **270**
Which Tumors to Treat? **271**
Challenges in Treatment **272**
Problems Specific to Developing Countries **273**
Lack of Adequate Expertise, Equipment and Infrastructure **273**

SECTION 7

BLOOD TRANSFUSION (COMPONENT THERAPY) AND SUPPORTIVE THERAPY

Section Editors: **Anand Deshpande, Avneet Kaur**

40. Cellular Blood Components in Neonatal Practice 277

Naveen Gupta, Avneet Kaur

Various Components of Blood **277**
Whole Blood Transfusion **277**
Packed Red Blood Transfusions in Neonates **277**
Evidence for Threshold of Transfusion **278**
Indications **279**
Dose and Duration of Therapy **279**
Preparation **279**
Evidence **280**
Types of Platelets Available **281**
Side Effects **281**
Indications of Irradiated Cellular Products **281**
Future Directions **281**

41. Plasma and its Derivatives 283

Vivek Choudhury

Coagulation System in Neonates **283**
Plasma and its Derivatives **284**
Plasma Transfusion Guidelines in Neonates **284**
Adverse Effects with Plasma Transfusion **285**

42. Technical Aspects of Blood and Blood Components Transfusion including Leukodepletion and Irradiation 286

Rajesh B Sawant, Anand Deshpande

Some Technical Aspects about the Administration of Blood and Blood Components **286**
Leukocyte Depletion and Gamma Irradiation of Blood Components **288**
Risk Factors Associated with Occurrence of Transfusion Associated Graft-Versus-Host Disease **289**
Indications for Irradiation of Blood and Blood Components **289**
Blood and Blood Components to be Irradiated **290**
Dosimetry of Blood Irradiator **290**

43. Risk of Transfusion in Fetus and Neonate 294

Sanjeev Chetry, Kumar Ankur, Avijeet Yadav

Intrauterine Transfusion **294**
Evaluation of Fetal Anemia **294**
Management of Fetal Anemia **294**

Risk of Intrauterine Transfusion **295**
Intrauterine Platelet Transfusion **295**
Adverse Effects of Transfusion in Neonates **295**
Transfusion-associated Graft-Versus-Host Disease **296**

44. Hematological Growth Factors as Supportive Therapy 298
Satyen K Hemrajani, Anupam Sachdeva
Granulocyte-colony Stimulating Factor or Granulocyte-macrophage Colony-stimulating Factor **298**
Role of G-CSF and GM-CSF in Neonatal Sepsis **300**
Clinical Trials of G-CSF **300**
Clinical Trial of GM-CSF **302**
G-CSF or GM-CSF: Which One has Better Effect in Neonate? **302**
Role of G-CSF or GM-CSF in Other Neutropenias **302**
Future Proposed Uses of G-CSF or GM-CSF in Neonatal Intensive Care Unit **303**
Side Effects of G-CSF or GM-CSF **303**
Anemia of Prematurity **304**
Complications **306**
Dose **307**
Use in Rhesus Sensitization **307**
Use in Jehovah's Witness **308**
Other Uses: Neuroprotection **308**

SECTION 8
IMMUNOLOGICAL DISORDERS

Section Editors: **Manisha Madkaikar, Nita Radhakrishnan**

45. Introduction to Immunology 317
Amit Rawat, Biman Saikia, Jitendra K Shandilya
The Immune System **317**
Components of the Innate Immune System **318**
Nucleotide Oligomerization Domain Receptors/Nucleotide Oligomerization Domain Leucine-Rich Repeat Containing Receptors **321**
Adaptive Immune System **321**

46. Fetal and Neonatal Immunity 325
Biman Saikia, Parikshaa Gupta
Fetal Immunity **325**
Development of the Immune System **326**
Neonatal Immunity **327**
Adaptive Immune System **330**
Organs of the Immune System **331**

Neonatal Humoral Responses **331**
Neonatal Cell-mediated Responses **331**
Passive Immunity in Neonates **332**
Transplacental Transfer **332**
Colostrum and Breast Milk **332**
Deleterious Effects of Maternal Antibodies **333**

47. Infections in Neonatal Period: Primary Immunodeficiency Perspective 336
Vinod Gunasekaran, Nita Radhakrishnan
Neonatal Sepsis **336**
Epidemiology **336**
Early Onset Neonatal Sepsis **336**
Late Onset Sepsis **336**
Clinical Features **337**
Investigations **337**
Management **337**
Prevention of Late Onset Sepsis **337**
Neonatal Immune System and Predisposition to Infections **337**
Uncommon Infections in Neonate and Role of Primary Immunodeficiency **338**

48. Approach to Newborns with Immunodeficiency 341
Manisha Madkaikar, Mukesh Desai, Jahnavi Aluri
Primary Immunodeficiency Disorders **341**
Advanced Tests for Specific Disorders **344**
Prevention **345**

49. Neutrophil Functions and Disorders of Neutrophils in Newborns 347
Sagar Bhattad, Surjit Singh
Normal Development and Function of Neutrophils **347**
Disorders in Neutrophils **348**

50. Combined T- and B-cell Defects 354
Mamta Vijay Manglani, Omkar Nagesh Khandkar, Savita Khadse
Epidemiology **354**
Etiology and Pathophysiology **354**
Types of Combined T- and B-cells Disorders (Classification) **357**
Other Immunodeficiency Disorders **360**
Clinical Presentation **361**
Diagnosis **362**
Treatment **362**
Prognosis **364**
Neonatal Screening **364**

51. Primary Antibody Deficiencies 366
Deepti Suri, Vignesh P
X-linked Agammaglobulinemia **367**
Clinical Manifestations **368**
Laboratory Diagnosis **369**
Treatment and Prognosis **370**
Autosomal Recessive Hypogammaglobulinemia **371**
Common Variable Immunodeficiency **371**
Clinical Manifestations **371**
Laboratory Diagnosis **372**
Management **372**
Selective Immunoglobulin A Deficiency **372**
Transient Hypogammaglobulinemia of Infancy **373**
Specific Antibody Deficiency **373**

52. Combined Immunodeficiencies with Associated or Syndromic Features 376
Biman Saikia, Parvati Joshi
Congenital Thrombocytopenias **376**
Hyperimmunoglobulin E Syndromes **381**
Defects of Vitamin B_{12} and Folate Metabolism **383**

53. Immune Dysregulation Syndromes 387
Anupa Mishra, Nitin K Shah
Hemophagocytic Lymphohistiocytosis 389
Epidemiology **389**
Pathophysiology **389**
Genetics of Hemophagocytic Lymphohistiocytosis **392**
Clinical Presentation of Hemophagocytic Lymphohistiocytosis **394**
Diagnosis **397**
Treatment of Hemophagocytic Lymphohistiocytosis **400**
Autoimmune Lymphoproliferative Syndrome 404
Pathophysiology **404**
Clinical Presentation **404**
Laboratory Investigations **405**
Diagnosis **405**
Classification **406**
Differential Diagnosis **406**
Principles of Treatment **407**
ITK Deficiency **408**
APECED **409**
IPEX **409**

54. Complement Disorders 415
Ankur Kumar Jindal, Surjit Singh
Epidemiology **417**
Etiology and Pathogenesis **417**
Investigations **420**
Differential Diagnoses **423**
Management **423**

55. Autoinflammatory Syndromes 428
Latika Gupta, Amita Aggarwal
Epidemiology **428**
Pathogenesis **428**
Classic Autoinflammatory Syndromes **429**
Newer Syndromes **430**
Treatment **434**

56. Management of Specific Immunodeficiencies 436
Vinod Gunasekaran, Nita Radhakrishnan, Anupam Sachdeva
Immune System of Human Body **436**
Classification of Primary Immunodeficiency **436**
Importance of Early Diagnosis **436**
Management of Specific Primary Immunodeficiencies **437**
Vaccination in Patients with Primary Immunodeficiencies **439**

57. Neonatal Screening and Prenatal Diagnosis of Primary Immunodeficiency Disorders 441
Manisha Madkaikar, Jahnavi Aluri, Maya Gupta
Why should we Include Primary Immunodeficiency Disorders in NBS? **441**
Need for Newborn Screening for SCID and Other T-cell Immunodeficiencies **441**
TREC Assay and its Utility as a Screening Test for SCID **442**
Recent Advancement **443**
National Status **443**
Prenatal Diagnosis **444**
Advances in Prenatal Diagnosis Techniques **446**

Index *449*