

AVERY'S DISEASES *of the* NEWBORN

CHRISTINE A. GLEASON | SANDRA E. JUUL



TENTH EDITION

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Avery's Diseases of the Newborn

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Tenth Edition

Christine A. Gleason, MD

Professor of Pediatrics
Division of Neonatology
Department of Pediatrics
University of Washington
Seattle Children's Hospital
Seattle, Washington

Sandra E. Juul, MD, PhD

W. Alan Hodson Endowed Chair in Pediatrics
Professor of Pediatrics
Chief, Division of Neonatology
Department of Pediatrics
University of Washington
Seattle Children's Hospital
Seattle, Washington

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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*To the babies—our patients—who humble and inspire us.
To their families, who encourage us to keep moving our field forward.
To neonatal caregivers everywhere, with gratitude for all you do.*

Contributors

Steven H. Abman, MD

Professor
Department of Pediatrics
University of Colorado Health Sciences Center
Director
Pediatric Heart Lung Center
The Children's Hospital
Aurora, Colorado

Karel Allegaert, MD, PhD

Professor
Department of Woman and Child
KU Leuven
Leuven, Belgium
Consultant
Department of Surgery and Intensive Care
Erasmus MC-Sophia Children's Hospital
Rotterdam, The Netherlands

Bhawna Arya, MD

Assistant Professor
Department of Pediatrics and Pediatric Cardiology
University of Washington
Seattle Children's Hospital
Seattle, Washington

David Askenazi, MD, MSPH

Associate Professor
Department of Pediatrics
University of Alabama at Birmingham
Birmingham, Alabama

Timur Azhibekov, MD

Assistant Professor of Clinical Pediatrics
Fetal and Neonatal Institute
Division of Neonatology
Children's Hospital of Los Angeles
Department of Pediatrics
Keck School of Medicine
University of Southern California, Los Angeles
Los Angeles, California

Stephen A. Back, MD, PhD

Professor of Pediatrics and Neurology
Oregon Health and Science University
Clyde and Elda Munson Professor of Pediatric Research
Director
Neuroscience Section
Papé Family Pediatric Research Institute
Portland, Oregon

H. Scott Baldwin, MD

Professor of Pediatrics and Cell and Developmental Biology
Vanderbilt University Medical Center
Chief
Division of Pediatric Cardiology
Co-Director
Pediatric Heart Institute
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee

Roberta A. Ballard, MD

Professor
Department of Pediatrics and Neonatology
University of California, San Francisco, School of Medicine
San Francisco, California

Eduardo Bancalari, MD

Professor of Pediatrics
Director
Division of Neonatology
University of Miami Miller School of Medicine
Chief
Newborn Service
Jackson Memorial Hospital
Miami, Florida

Carlton M. Bates, MD

Professor of Pediatrics
Vice Chair for Basic Research
Department of Pediatrics
University of Pittsburgh School of Medicine
Chief of Pediatric Nephrology
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, Pennsylvania

Maneesh Batra, MD, MPH

Associate Professor
Department of Pediatrics
University of Washington School of Medicine
Seattle, Washington

Cheryl B. Bayart, MD, MPH

Department of Pediatric Dermatology
University of Washington
Seattle Children's Hospital
Seattle, Washington

Gary A. Bellus, MD, PhD

Associate Professor
 Department of Pediatrics and Dermatology
 University of Colorado School of Medicine
 Aurora, Colorado
 Director
 Clinical Genetics and Genomic Medicine
 Geisinger Health System
 Danville, Pennsylvania

Thomas J. Benedetti, MD, MHA

Professor
 Department of Obstetrics and Gynecology
 University of Washington School of Medicine
 Seattle, Washington

John T. Benjamin, MD, MPH

Assistant Professor of Pediatrics
 Department of Pediatrics
 Division of Neonatology
 Vanderbilt University Medical Center
 Nashville, Tennessee

James T. Bennett, MD, PhD

Assistant Professor of Pediatrics
 Division of Genetic Medicine
 Center for Developmental Biology and Regenerative
 Medicine
 Assistant Director
 Molecular Diagnostic Laboratories
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Gerard T. Berry, MD

Harvey Levy Chair in Metabolism
 Director
 Metabolism Program
 Division of Genetics and Genomics
 Boston Children's Hospital
 Professor of Pediatrics
 Harvard Medical School
 Boston, Massachusetts

Gil Binenbaum, MD, MSCE

Attending Surgeon
 Department of Ophthalmology
 The Children's Hospital of Philadelphia
 Associate Professor of Ophthalmology
 Department of Ophthalmology
 Perelman School of Medicine at the University of
 Pennsylvania
 Philadelphia, Pennsylvania

Markus D. Boos, MD, PhD

Assistant Professor
 Department of Pediatrics
 Division of Dermatology
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Maryse Bouchard, MD, MSc

Associate Professor
 Orthopaedic Surgery
 University of Washington
 Pediatric Orthopedic Surgeon
 Department of Orthopedics and Sports Medicine
 Seattle Children's Hospital
 Seattle, Washington

Heather A. Brandling-Bennett, MD

Associate Professor
 Department of Pediatrics
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Darcy E. Broughton, MD

Clinical Fellow
 Department of Obstetrics and Gynecology
 Division of Reproductive Endocrinology and Infertility
 Washington University in St. Louis
 St. Louis, Missouri

Zane Brown, MD

Professor
 Division of Perinatology
 Department of Obstetrics and Gynecology
 Division of Women's Health
 University of Washington
 Seattle, Washington

Katherine H. Campbell, MD, MPH

Assistant Professor
 Department of Obstetrics, Gynecology, and Reproductive
 Sciences
 Yale University School of Medicine
 New Haven, Connecticut

Suzan L. Carmichael, PhD, MS

Professor
 Department of Pediatrics
 Stanford University
 Stanford, California

Brian S. Carter, MD

Professor of Pediatrics
 Division of Neonatology
 University of Missouri-Kansas City School of Medicine
 Bioethicist
 Bioethics Center
 Children's Mercy Hospital
 Kansas City, Missouri

Stephen Cederbaum, MD

Research Professor
 Department of Psychiatry, Pediatrics, and Human Genetics
 University of California, Los Angeles
 Los Angeles, California

Shilpi Chabra, MD

Associate Professor
Department of Pediatrics
University of Washington and
Seattle Children's Hospital
Seattle, Washington

Justine Chang, MD

Assistant Professor
Department of Obstetrics and Gynecology
University of Washington
Seattle, Washington

Edith Y. Cheng, MD, MS

Professor
Chief of Service
Obstetrics
Division Chief
Maternal Fetal Medicine
Department of Maternal Fetal Medicine and Medical Genetics
University of Washington
Seattle, Washington

Karen M. Chisholm, MD, PhD

Anatomic Pathologist
Department of Laboratories
Seattle Children's Hospital
Clinical Assistant Professor
Department of Laboratory Medicine
University of Washington
Seattle, Washington

Robert D. Christensen, MD

Robert L. Jung Presidential Chair
Professor and Division Chief
Division of Neonatology
Professor
Division of Hematology/Oncology
University of Utah School of Medicine
Director of Research
Department of Women and Newborns
Intermountain Healthcare
Salt Lake City, Utah

Terrence Chun, MD

Associate Professor of Pediatrics
Department of Pediatrics
University of Washington
Seattle, Washington

Nelson Claire, MSc, PhD

Research Associate Professor
Director
Neonatal Pulmonary Research Laboratory
Department of Pediatrics
Division of Neonatology
University of Miami Miller School of Medicine
Miami, Florida

Ronald I. Clyman, MD

Professor of Pediatrics and Senior Staff
Cardiovascular Research Institute
University of California, San Francisco
San Francisco, California

Tarah T. Colaizy, MD, MPH

Associate Professor of Pediatrics
Stead Department of Pediatrics
University of Iowa
Iowa City, Iowa

DonnaMaria E. Cortezzo, MD

Assistant Professor
Pediatrics and Anesthesiology
Division of Neonatology and Pulmonary Biology
Division of Pediatric Palliative Care
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

C. Michael Cotten, MD, NHS

Professor of Pediatrics
Department of Pediatrics and Neonatology
Duke University School of Medicine
Durham, North Carolina

Michael L. Cunningham, MD, PhD

Professor and Chief
Division of Craniofacial Medicine
Department of Pediatrics
University of Washington
Medical Director
Craniofacial Center
Seattle Children's Hospital
Seattle, Washington

Alejandra G. de Alba Campomanes, MD, MPH

Associate Professor of Clinical Ophthalmology and Pediatrics
Department of Ophthalmology
University of California, San Francisco
San Francisco, California

Ellen Dees, MD

Assistant Professor of Pediatrics
Pediatric Cardiology Training Program
Vanderbilt Children's Hospital
Nashville, Tennessee

Sara B. DeMauro, MD, MSCE

Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Program Director
Neonatal Follow-Up and Attending Neonatologist
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Scott C. Denne, MD

Professor of Pediatrics
Department of Pediatrics
Indiana University
Indianapolis, Indiana

Emöke Deschmann, MD, MMSc

Faculty/Attending Neonatologist
 Department of Women's and Children's Health
 Division of Neonatology
 Karolinska Institute
 Department of Neonatology
 Karolinska University Hospital
 Stockholm, Sweden

Carolina Cecilia DiBlasi, MD

Clinical Assistant Professor
 Division of Endocrinology and Diabetes
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Robert M. DiBlasi, RRT-NPS, FAARC

Respiratory Research Coordinator
 Center for Developmental Therapeutics
 Seattle Children's Research Institute
 Seattle, Washington

Reed A. Dimmitt, MD, MSPH

Associate Professor of Pediatrics and Surgery
 Director
 Division of Neonatology and Pediatric Gastroenterology and
 Nutrition
 University of Alabama at Birmingham
 Birmingham, Alabama

Sara A. DiVall, MD

Assistant Professor
 Department of Pediatrics and Endocrinology
 University of Washington
 Seattle, Washington

Orchid Djahangirian, BSc, MD, FRCSC

Fellow
 Department of Pediatric Urology
 University of California, Irvine
 Irvine, California

Dan Doherty, MD, PhD

Professor
 Department of Pediatrics
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Eric C. Eichenwald, MD

Professor of Pediatrics
 Department of Pediatrics
 Perelman School of Medicine at the University of Pennsylvania
 Chief
 Division of Neonatology
 Children's Hospital of Philadelphia
 Philadelphia, Pennsylvania

Rachel Engen, MD

Ann and Robert H. Lurie Children's Hospital of Chicago
 Chicago, Illinois

Cyril Engmann, MBBS, FAAP

Attending Neonatologist and Professor
 Department of Pediatrics and Global Health
 University of Washington Schools of Medicine and Public
 Health
 Global Program Leader and Director
 Maternal, Newborn, Childhealth, and Nutrition
 PATH
 Seattle, Washington

Jacquelyn R. Evans, MD

Associate Division Chief of Neonatology
 Department of Pediatrics
 Children's Hospital of Philadelphia and
 Perelman School of Medicine at the University of Pennsylvania
 Chair
 The Children's Hospital Neonatal Consortium
 Philadelphia, Pennsylvania

Kelly N. Evans, MD

Assistant Professor
 Department of Pediatrics
 University of Washington
 Craniofacial Center
 Seattle Children's Hospital
 Seattle, Washington

Diana L. Farmer, MD, FACS, FRCS

Professor and Chair
 Surgeon-in-Chief
 Department of Surgery
 University of California, Davis
 Sacramento, California

Patricia Y. Fehner, MD

Medical Director
 DSD Program
 Seattle Children's Hospital
 Professor
 Department of Pediatric Endocrinology
 University of Washington School of Medicine
 Seattle, Washington

Patricia Ferrieri, MD

Chairman's Fund Endowed Professor in Laboratory Medicine
 and Pathology
 Professor
 Department of Pediatrics
 Division of Infectious Diseases
 University of Minnesota Medical School
 Director
 Infectious Diseases Diagnostic Laboratory
 University of Minnesota Medical Center
 Minneapolis, Minnesota

Neil N. Finer, MD

Division of Neonatal-Perinatal Medicine
 Department of Pediatrics
 University of California, San Diego
 San Diego, California

Rachel A. Fleishman, MD

Penn Medical Clinician
University of Pennsylvania School of Medicine
Attending Neonatologist
CHOP Newborn Care Network
Children's Hospital of Pennsylvania
Philadelphia, Pennsylvania

Bobbi Fleiss, PhD

Division of Imaging Sciences and Biomedical Engineering
King's College London
London, Great Britain

Joseph T. Flynn, MD, MS

Dr. Robert O. Hickman Endowed Chair in Pediatric Nephrology
Professor of Pediatrics
University of Washington
Chief
Division of Nephrology
Seattle Children's Hospital
Seattle, Washington

Katherine T. Flynn-O'Brien, MD, MPH

Resident Physician
Department of Surgery
University of Washington
Seattle, Washington

Mark R. Frey, PhD

Associate Professor
Department of Pediatrics, and Biochemistry and Molecular
Medicine
The Saban Research Institute of Children's Hospital
University of Southern California, Los Angeles
Los Angeles, California

Lydia Furman, MD

Professor of Pediatrics
Rainbow Babies and Children's Hospital
Co-Chair
UHCMC Institutional Review Board
Case Western Reserve University School of Medicine
Cleveland, Ohio

Renata C. Gallagher, MD, PhD

Professor of Clinical Pediatrics
Department of Pediatrics
University of California, San Francisco
San Francisco, California

Estelle B. Gauda, MD

Professor of Pediatrics
Department of Pediatrics
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Christine A. Gleason

Professor of Pediatrics
Division of Neonatology
Department of Pediatrics
University of Washington
Seattle Children's Hospital
Seattle, Washington

Michael J. Goldberg, MD

Clinical Professor
Department of Orthopaedics and Sports Medicine
University of Washington
Seattle Children's Hospital
Seattle, Washington

Adam B. Goldin, MD, MPH

Associate Professor
Department of Pediatric General and Thoracic Surgery
University of Washington
Seattle Children's Hospital
Seattle, Washington

Sidney M. Gospe, Jr., MD, PhD

Herman and Faye Sarkowsky Endowed Chair of Child
Neurology
Professor
Department of Neurology and Pediatrics
University of Washington
Head
Division of Neurology
Seattle Children's Hospital
Seattle, Washington

Pierre Gressens, MD, PhD

Research Officer and Director
Robert-Debre Hospital
Paris, France

Deepti Gupta, MD

Assistant Professor
Department of Pediatrics
Division of Dermatology
University of Washington
Seattle Children's Hospital
Seattle, Washington

Susan H. Guttentag, MD

Julia Carell Stadler Professor of Pediatrics
Department of Pediatrics
Division of Neonatology
Monroe Carell, Jr., Children's Hospital at Vanderbilt
Nashville, Tennessee

Chad R. Haldeman-Englert, MD

Clinical Geneticist
Fullerton Genetics Center
Asheville, North Carolina

Thomas N. Hansen, MD

Senior Investigator
Center for Developmental Therapeutics
Seattle Children's Research Institute
Seattle, Washington

Anne V. Hing, MD

Professor
Department of Pediatrics
University of Washington
Seattle, Washington

Sangeeta Hingorani, MD, MPH

Associate Professor
 Department of Pediatrics
 University of Washington
 Seattle Children's Hospital
 Assistant Member
 Clinical Research Division
 Fred Hutchinson Cancer Research Center
 Seattle, Washington

Susan R. Hintz, MD, MS

Robert L. Hess Family Professor
 Professor of Pediatrics, and Obstetrics and Gynecology
 Associate Chief for Prenatal Services
 Division of Neonatal and Developmental Medicine
 Stanford University School of Medicine
 Medical Director
 Fetal and Pregnancy Health Program
 Lucile Packard Children's Hospital
 Palo Alto, California

Shinjiro Hirose, MD

Associate Professor and Division Chief
 Pediatric General, Thoracic, and Fetal Surgery
 Department of Surgery
 University of California, Davis
 Sacramento, California

W. Alan Hodson, MMSc, MD

Professor Emeritus
 Department of Pediatrics
 University of Washington
 Seattle, Washington

Kara K. Hoppe, DO

Department of Obstetrics and Gynecology
 Maternal Fetal Medicine
 University of Wisconsin-Madison
 Madison, Wisconsin

Margaret K. Hostetter, MD

BK Rachford Professor and Chair
 Department of Pediatrics
 Cincinnati Children's Hospital Medical Center
 Cincinnati, Ohio

Benjamin Huang, MD

Clinical Instructor
 Department of Pediatrics
 University of California, San Francisco
 San Francisco, California

Sarah Bauer Huang, MD, PhD

Child Neurology Resident
 Department of Neurology
 University of Washington
 Seattle, Washington

Terrie E. Inder, MBChB, MD

Cristian Ionita
 Department of Neurology
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Cristian Inoita, MD

Clinical Associate Professor
 Department of Pediatrics
 Yale University School of Medicine
 New Haven, Connecticut

J. Craig Jackson, MD, MHA

Professor
 Department of Pediatrics
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Deepak Jain, MD

Assistant Professor of Pediatrics
 Department of Pediatrics
 Division of Neonatology
 University of Miami Miller School of Medicine
 Jackson Memorial Hospital
 Miami, Florida

Lucky Jain, MD, MBA

Richard W. Blumberg Professor and Chairman
 Department of Pediatrics
 Emory University School of Medicine
 Chief Academic Officer
 Children's Healthcare of Atlanta
 Atlanta, Georgia

Patrick J. Javid, MD

Associate Professor of Surgery
 Department of Surgery
 University of Washington
 Pediatric Surgeon
 Seattle Children's Hospital
 Seattle, Washington

Cassandra D. Josephson, MD

Associate Professor
 Pathology and Pediatrics
 Director Clinical Research
 Department of Pathology
 Center for Transfusion and Cellular Therapies
 Director
 Transfusion Medicine Fellowship Program
 Department of Pathology
 Center for Transfusion and Cellular Therapies
 Emory University School of Medicine
 Medical Director
 Pathology Department
 Blood and Tissue Services
 Children's Healthcare of Atlanta
 Atlanta, Georgia

Emily S. Jungheim, MD, MSCI

Assistant Professor
Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology and Infertility
Washington University in St. Louis
St. Louis, Missouri

Sandra E. Juul, MD, PhD

W. Alan Hodson Endowed Chair in Pediatrics
Professor of Pediatrics
Chief
Division of Neonatology
Department of Pediatrics
University of Washington
Seattle Children's Hospital
Seattle, Washington

Anup Katheria, MD, FAACP

Assistant Professor of Pediatrics
Department of Pediatrics
Loma Linda University
Loma Linda, California
Director
Neonatal Research Institute
Sharp Mary Birch Hospital for Women and Newborns
San Diego, California

Benjamin A. Keller, BS, MD

Chief Surgical Resident
Department of Surgery
University of California, Davis
Sacramento, California

Roberta L. Keller, MD

Professor of Clinical Pediatrics
Vice Chair
Clinical Translational Research
Director of Neonatal Research
Director
Neonatal ECMO Program
Director of Neonatal Services
Fetal Treatment Center
UCSF Benioff Children's Hospital
University of California, San Francisco
San Francisco, California

Thomas F. Kelly, MD

Clinical Professor and Chief
Division of Perinatal Medicine
Department of Reproductive Medicine
University of California, San Diego
School of Medicine
La Jolla, California
Director of Maternity Services
University of California, San Diego Medical Center
San Diego, California

Kate Khorsand, MD

Department of Pediatrics
Division of Dermatology
Seattle Children's Hospital
Seattle, Washington

Grace Kim, MD, MS

Assistant Professor
Department of Endocrinology
Seattle Children's Hospital
Seattle, Washington

John P. Kinsella, MD

Professor
Department of Pediatrics
University of Colorado School of Medicine
Children's Hospital Colorado
Aurora, Colorado

Ildiko H. Koves, MD, FRACP

Associate Professor
Department of Endocrinology and Diabetes
Seattle Children's Hospital
Seattle, Washington

Christina Lam, MD

Assistant Professor
Biochemical Genetics
Department of Pediatrics
Division of Genetic Medicine
University of Washington
Seattle Children's Hospital
Seattle, Washington
Guest Researcher
NIH, NHGRI
Bethesda, Maryland

Erin R. Lane, MD

Fellow
Pediatric Gastroenterology
University of Washington
Seattle, Washington

John D. Lantos, MD

Professor
Department of Pediatrics
University of Missouri–Kansas City
Kansas City, Missouri

Daniel J. Ledbetter, MD

Professor
Department of Surgery
University of Washington
Attending Surgeon
Department of Pediatric General and Thoracic Surgery
Seattle Children's Hospital
Seattle, Washington

Ben Lee, MD, MPH, MSCR

Associate Professor of Clinical Pediatrics
Weill Cornell Medicine-Qatar
Medical Director of Operations
Division of Neonatal and Perinatal Medicine
Sidra Medical and Research Center
Doha, Qatar

Harvey L. Levy, MD

Senior Physician in Medicine/Genetics
 Division of Genetics and Genomics
 Boston Children's Hospital
 Professor of Pediatrics
 Harvard Medical School
 Boston, Massachusetts

Ofer Levy, MD, PhD

Principal Investigator
 Precision Vaccines Program
 Division of Infectious Diseases
 Boston Children's Hospital
 Associate Professor
 Department of Human Biology and Translational Medicine
 Harvard Medical School
 Boston, Massachusetts

Mark B. Lewin, MD

Professor and Division Chief
 Department of Pediatric Cardiology
 University of Washington School of Medicine
 Seattle, Washington

David B. Lewis, MD

Professor of Pediatrics
 Chief
 Division of Immunology and Allergy
 Department of Pediatrics
 Stanford University School of Medicine
 Stanford, California
 Attending Physician
 Lucile Salter Packard Children's Hospital
 Palo Alto, California

P. Ling Lin, MD, MSc

Associate Professor
 Director
 Pediatric Infectious Diseases Fellowship Program
 Department of Pediatrics
 Division of Infectious Diseases
 Children's Hospital of Pittsburgh of UPMC
 University of Pittsburgh School of Medicine
 Pittsburgh, Pennsylvania

Tiffany Fangtse Lin, MD

Pediatric Hematology Oncology Adjunct Instructor
 Department of Pediatrics
 University of California, San Francisco
 San Francisco, California

Scott A. Lorch, MD, MSCE

Associate Professor
 Department of Pediatrics
 Perelman School of Medicine of the University of Pennsylvania
 Harriet and Ronald Lassin Endowed Chair in Pediatric Neonatology
 Director
 Neonatal-Perinatal Medicine Fellowship
 Division of Neonatology
 Director
 Center for Perinatal and Pediatric Health Disparities Research
 The Children's Hospital of Philadelphia
 Philadelphia, Pennsylvania

Akhil Maheshwari, MD

Professor of Pediatrics and Molecular Medicine
 Pamela and Leslie Muma Endowed Chair in Neonatology
 Chief
 Division of Neonatology
 Assistant Dean
 Graduate Medical Education
 Department of Pediatrics
 University of South Florida
 Tampa, Florida

Emin Maltepe, MD, PhD

Associate Professor
 Department of Pediatrics, Biomedical Sciences, and
 Developmental and Stem Cell Biology
 Division of Neonatology
 University of California, San Francisco
 San Francisco, California

Ketzela J. Marsh, MS, MD

Fellow in Pediatric and Adult Infectious Diseases
 University of Minnesota Medical School and Masonic
 Children's Hospital
 Minneapolis, Minnesota

Richard J. Martin, MBBS

Professor
 Department of Pediatrics, Reproductive Biology, and Physiology
 and Biophysics
 Case Western Reserve University School of Medicine
 Drusinsky/Fanaroff Professor
 Department of Pediatrics
 Rainbow Babies and Children's Hospital
 Cleveland, Ohio

Dennis E. Mayock, BS, MD

Professor
 Department of Pediatrics
 University of Washington
 Seattle, Washington

Ryan Michael McAdams, MD

Associate Professor
 Department of Pediatrics
 University of Wisconsin School of Medicine and Public Health
 Madison, Wisconsin

Irene McAleer, MD, JD, MBA

Health Sciences Clinical Professor of Urology
 Departments of Urology and Pediatric Urology
 University of California, Irvine
 Irvine, California

Steven J. McElroy, MD

Associate Professor
 Interim Division Director
 Departments of Pediatrics, and Microbiology and
 Immunology
 University of Iowa
 Iowa City, Iowa

Kera M. McNelis, MD

Fellow
Department of Neonatology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Patrick McQuillen, MD

Professor of Pediatrics & Neurology
Department of Pediatrics
University of California, San Francisco
San Francisco, California

William L. Meadow, MD, PhD

Professor
Department of Pediatrics
University of Chicago
Chicago, Illinois

Paul A. Merguerian, MD, MS

Professor
Department of Urology
University of Washington
Chief
Division of Urology
Seattle Children's Hospital
Seattle, Washington

Lina Merjaneh, MD

Assistant Professor
Department of Pediatrics and Endocrinology
University of Washington
Seattle, Washington

J. Lawrence Merritt, II, MD

Associate Professor
Department of Pediatrics
University of Washington
Seattle, Washington

Valerie Mezger, PhD

CNRS
Epigenetics and Cell Fate
Univ Paris Diderot, Sorbonne Paris Cité
Département Hospitalo-Universitaire PROTECT
Paris, France

Marian G. Michaels, MD, MPH

Professor of Pediatrics and Surgery
Division of Pediatric Infectious Diseases
Children's Hospital of Pittsburgh of UPMC
Professor of Pediatrics and Surgery
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Steven P. Miller, MDCM, MAAS

Division Head
Department of Pediatrics
Division of Neurology
The Hospital for Sick Children
Professor of Pediatrics
Department of Pediatrics
University of Toronto
Senior Scientist
Neuroscience and Mental Health
Sick Kids Research Institute
Chair in Pediatric Neuroscience
Bloorview Children's Hospital
Toronto, Ontario, Canada

Sowmya S. Mohan, MD

Assistant Professor
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
Emory University
Atlanta, Georgia

Thomas J. Mollen, MD

Clinical Associate
Department of Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

Thomas R. Moore, MD

Professor of Maternal and Fetal Medicine
CEO
Faculty Practice
Dean for Clinical Affairs
University of California, San Diego
San Diego, California

Jeffrey C. Murray, MD

Professor
Department of Pediatrics
The University of Iowa
Iowa City, Iowa

Karen F. Murray, MD

Chief
Division of Gastroenterology and Hepatology
Department of Pediatrics
Seattle Children's Hospital
Seattle, Washington

Debika Nandi-Munshi, MD

Assistant Clinical Professor
Department of Pediatric Endocrinology and Diabetes
Seattle Children's Hospital
University of Washington
Seattle, Washington

Niranjana Natarajan, MD

Assistant Professor
Department of Neurology
Division of Child Neurology
University of Washington
Seattle, Washington

Jeffrey J. Neil, MD, PhD

Professor of Neurology
Department of Neurology
Boston Children's Hospital
Boston, Massachusetts

Kathryn D. Ness, MD, MSCI

Clinical Associate Professor
Department of Pediatrics
Seattle Children's Hospital
Seattle, Washington

Josef Neu, MD

Professor
Department of Pediatrics
University of Florida
Gainesville, Florida

Angel Siu-Ying Nip, MBChB

Fellow
Department of Endocrinology
Seattle Children's Hospital
Seattle, Washington

Shahab Noori, MD

Associate Professor of Pediatrics
Fetal and Neonatal Institute
Division of Neonatology
Children's Hospital Los Angeles
Department of Pediatrics
Keck School of Medicine
University of Southern California
Los Angeles, California

Lila O'Mahony, MD

Clinical Assistant Professor
Department of Pediatric Emergency Medicine
University of Washington
Seattle Children's Hospital
Seattle, Washington

Jonathan P. Palma, MD, MS

Clinical Assistant Professor
Department of Pediatrics
Stanford University School of Medicine
Medical Director of Clinical Informatics
Stanford Children's Health Clinical Informatics Fellowship
Program Director
Stanford Medicine
Palo Alto, California

Nigel Paneth, MD, MPH

University Distinguished Professor
Department of Epidemiology and Biostatistics and Pediatrics
and Human Development
Michigan State University
East Lansing, Michigan

Thomas A. Parker, MD

Professor
Department of Pediatrics
University of Colorado School of Medicine
Children's Hospital of Colorado
Aurora, Colorado

Ravi Mangal Patel, MD

Associate Professor
Department of Pediatrics
Emory University School of Medicine
Children's Healthcare of Atlanta
Atlanta, Georgia

Anna A. Penn, MD, PhD

Associate Professor
Department of Pediatrics
George Washington University School of Medicine
Attending Physician
Director of Translational Research for Hospital-Based Services
Co-Director of Cerebral Palsy Prevention Program
Fetal and Transitional Medicine, Neonatology
Children's National Medical Center
Investigator
Children's Research Institute Center for Neuroscience
Children's National Medical Center
Washington, DC

Christian M. Pettker, MD

Associate Professor
Department of Obstetrics, Gynecology, and Reproductive
Sciences
Yale University School of Medicine
New Haven, Connecticut

Shabnam Peyvandi, MD

Assistant Professor of Pediatrics
Department of Pediatric Cardiology
University of California, San Francisco
Benioff Children's Hospital
San Francisco, California

Cate Pihoker, MD

Professor of Pediatrics
Department of Endocrinology and Diabetes
University of Washington
Seattle Children's Hospital
Seattle, Washington

Erin Plosa, MD

Assistant Professor of Pediatrics
Department of Pediatrics
Vanderbilt University
Nashville, Tennessee

Brenda B. Poindexter, MD, MS

Associate Professor of Pediatrics
Section of Neonatal-Perinatal Medicine
Indiana University School of Medicine
Indianapolis, Indiana

Michael A. Posencheg, MD

Medical Director
Intensive Care Nursery
Neonatology and Newborn Services
Hospital of the University of Pennsylvania
Associate Professor of Clinical Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

Benjamin E. Reinking, BA, MD

Clinical Professor of Pediatrics
Stead Family
Department of Pediatrics
University of Iowa Carver College of Medicine
Iowa City, Iowa

Samuel Rice-Townsend, MD

Attending Surgeon
Department of Surgery
Boston Children's Hospital
Assistant Professor
Harvard Medical School
Boston, Massachusetts

Morgan K. Richards, MD, MPH

Resident
Department of Surgery
University of Washington
Seattle, Washington

C. Peter Richardson, PhD

Associate Research Professor
Department of Pediatrics
University of Washington
Department of Pulmonary and Newborn Care
Seattle Children's Hospital
Principal Investigator
Center for Developmental Therapy
Seattle Children's Research Institute
Seattle, Washington

Kelsey Richardson, MD

Pediatric Nephrology Fellow
Department of Nephrology
Seattle Children's Hospital
Seattle, Washington

Kevin M. Riggle, MD

Resident
Department of Surgery
University of Washington
Seattle, Washington

Elizabeth Robbins, MD

Clinical Professor
Department of Pediatrics
University of California, San Francisco
San Francisco, California

Mark D. Rollins, MD, PhD

Professor
Director
Obstetric and Fetal Anesthesia
Department of Anesthesia and Perioperative Care
Department of Surgery
Department of Obstetrics, Gynecology, and Reproductive
Sciences
University of California, San Francisco
San Francisco, California

Mark A. Rosen, MD

Professor Emeritus
Department of Anesthesia and Perioperative Care
Department of Obstetrics, Gynecology, and Reproductive
Sciences
University of California, San Francisco
San Francisco, California

Courtney K. Rowe, MD

Pediatric Urology Fellow
University of Washington
Seattle, Washington

Inderneel Sahai, MD

Chief Medical Officer
New England Newborn Screening Program
University of Massachusetts
Worcester, Massachusetts

Sulagna C. Saitta, MD, PhD

Director
Clinical Genetics
Center for Personalized Medicine
Department of Pathology
Children's Hospital Los Angeles
Associate Professor of Clinical Pathology
Department of Pathology
Keck School of Medicine of USC
Los Angeles, California

Parisa Salehi, MD

Assistant Professor of Pediatrics
Division of Endocrinology
University of Washington
Seattle Children's Hospital
Seattle, Washington

Pablo Sanchez, MD

Professor of Pediatrics
Nationwide Children's Hospital
The Ohio State University College of Medicine
Divisions of Neonatal-Perinatal Medicine and Pediatric
Infectious Diseases
Director
Clinical and Translational Research (Neonatology)
Center for Perinatal Research
The Research Institute at Nationwide Children's Hospital
Columbus, Ohio

Matthew A. Saxonhouse, MD

Associate Professor
 Division of Neonatology
 Department of Pediatrics
 Levine Children's Hospital at Carolinas Medical Center
 University of North Carolina Charlotte Campus
 Charlotte, North Carolina

Richard J. Schanler, MD, FAAP

Associate Chairman
 Director
 Neonatal Services
 Cohen Children's Medical Center
 Northwell Health
 Professor
 Department of Pediatrics
 Hofstra Northwell School of Medicine
 New Hyde Park, New York

Mark R. Schleiss, MD

American Legion and Auxiliary Heart Research Foundation
 Endowed Chair
 Department of Pediatrics
 Professor and Director
 Division of Pediatric Infectious Diseases and Immunology
 Co-Director
 Center for Infectious Diseases and Microbiology
 Translational Research
 University of Minnesota Medical School
 Minneapolis, Minnesota

Thomas Scholz, MD

Professor of Pediatrics
 Stead Family Department of Pediatrics
 University of Iowa College of Medicine
 Iowa City, Iowa

Andrew L. Schwaderer, MD

Pediatric Nephrologist
 Nationwide Children's Hospital
 Columbus, Ohio

David Selewski, MD, MS

Assistant Professor
 Department of Pediatrics
 University of Michigan
 Ann Arbor, Michigan

Zachary M. Sellers, MD, PhD

Fellow
 Pediatric Gastroenterology, Hepatology, and Nutrition
 LeRoy Matthews Physician-Scientist
 Cystic Fibrosis Foundation
 Lucile Packard Children's Hospital
 Stanford University School of Medicine
 Stanford, California

Istvan Seri, MD, PhD, HonD

Professor
 Semmelweis University
 Faculty of Medicine
 First Department of Pediatrics
 Budapest, Hungary
 Keck School of Medicine
 University of Southern California
 Children's Hospital Los Angeles
 Los Angeles, California

Margarett Shnorhavorian, MD, MPH, FAAP, FACS

Surgical Director
 DSD Program
 Director
 Research Division of Urology
 Seattle Children's Hospital
 Assistant Professor of Urology
 University of Washington
 Seattle, Washington

Eric Sibley, MD, PhD

Associate Professor of Pediatrics
 Assistant Dean for Academic Advising
 Associate Chair for Academic Affairs
 Department of Pediatrics
 Stanford University School of Medicine
 Stanford, California
 Member
 The Child Health Research Institute

Robert Sidbury, MD, MPH

Professor
 Department of Pediatrics
 Chief
 Division of Dermatology
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Rebecca Simmons, MD

Hallam Hurt Professor of Pediatrics
 Department of Pediatrics
 Children's Hospital of Philadelphia
 Philadelphia, Pennsylvania

Caitlin Smith, MD

Fellow
 Department of Pediatric Surgery
 Seattle Children's Hospital
 Seattle, Washington

Martha C. Sola-Visner, MD

Assistant Professor of Pediatrics
 Department of Medicine
 Division of Newborn Medicine
 Children's Hospital Boston and Harvard Medical School
 Boston, Massachusetts

Lakshmi Srinivasan, MBBS

Clinical Associate
Department of Pediatrics
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Robin H. Steinhorn, MD

Senior Vice President
Children's National Health System
Professor of Pediatrics
George Washington University
Washington, DC

David K. Stevenson, MD

Harold K. Faber Professor of Pediatrics
Division of Neonatal and Developmental Medicine
Stanford University
Stanford, California

Helen Stolp, BSc(Hons), PhD

Perinatal Imaging and Health
King's College London
London, Great Britain

Craig Taplin, MBBS, FRACP

Associate Professor of Pediatrics
Division of Endocrinology and Diabetes
University of Washington
Seattle Children's Hospital
Seattle, Washington

Peter Tarczy-Hornoch, MD

Chair and Professor
Biomedical Informatics and Medical Education
Professor
Department of Pediatrics
Adjunct Professor
Computer Science and Engineering
University of Washington
Seattle, Washington

James A. Taylor, MD

Child Health Institute
University of Washington
Seattle, Washington

Janet A. Thomas, MD

Associate Professor
Department of Pediatrics
University of Colorado School of Medicine
Children's Hospital Colorado
Aurora, Colorado

Tracy Thompson, MPH

Program Director
Department of Epidemiology and Biostatistics
College of Human Medicine
Michigan State University
East Lansing, Michigan

George E. Tiller, MD, PhD

Regional Chief
Department of Genetics
Southern California Permanente Medical Group
Co-Chair
Interregional Genetics Workgroup
Los Angeles, California

Benjamin A. Torres, MD

Associate Professor
Department of Pediatrics
Division of Neonatology
University of South Florida
Medical Director
Jennifer Leigh Muma NICU
Tampa General Hospital
Tampa, Florida

Christopher Michael Traudt, MD

Assistant Professor
Department of Pediatrics
University of Washington
Seattle, Washington

John N. van den Anker, MD, PhD

Chief
Clinical Pharmacology
Department of Pediatrics
Children's National Health System
Washington, DC
Chair
Paediatric Pharmacology and Pharmacometrics
Department of Pediatrics
University Children's Hospital Basel
Basel, Switzerland
Adjunct Faculty
Intensive Care
Department of Pediatric Surgery
Erasmus Medical Center-Sophia Children's Hospital
Rotterdam, The Netherlands

Margaret M. Vernon, MD

Assistant Professor
Department of Pediatrics
Division of Cardiology
University of Washington
Seattle Children's Hospital
Seattle, Washington

Betty Vohr, MD

Director of Neonatal Follow-Up
Department of Neonatology
Women and Infants Hospital
Professor of Pediatrics
Department of Pediatrics
Alpert Medical School of Brown University
Providence, Rhode Island

Valencia P. Walker, MD

Associate Clinical Professor
 Department of Pediatrics
 Co-Chairperson
 Pediatric Faculty Committee on Diversity
 Division of Neonatology
 David Geffen School of Medicine at UCLA
 Los Angeles, California

Linda D. Wallen, MD

Clinical Professor of Pediatrics
 Associate Division Head for Clinical Operations
 Division of Neonatology
 Department of Pediatrics
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Matthew B. Wallenstein, MD

Obstetrics and Gynecology
 Stanford, California

Peter (Zhan Tao) Wang, BSc, MD, FRCSC

Assistant Professor
 Schulich School of Medicine and Dentistry
 Western University
 London, Ontario, Canada

Bradley A. Warady, MD

Professor of Pediatrics
 Department of Pediatrics
 University of Missouri-Kansas City School of Medicine
 Senior Associate Chairman
 Chief
 Section of Nephrology
 Director
 Dialysis and Transplantation
 Department of Pediatrics
 Children's Mercy Hospitals and Clinics
 Kansas City, Missouri

Robert M. Ward, MD

Professor Emeritus
 Department of Pediatrics
 University of Utah
 Salt Lake City, Utah

Jon F. Watchko, BS, MD

Professor of Pediatrics, Obstetrics, Gynecology, and
 Reproductive Sciences
 Division of Newborn Medicine
 University of Pittsburgh School of Medicine
 Pittsburgh, Pennsylvania

Elias Wehbi, BSc, MSc, MD, FRCSC

Assistant Professor
 Department of Urology
 Division of Pediatric Urology
 University of California, Irvine
 Orange, California

Joern-Hendrik Weitkamp, MD

Associate Professor of Pediatrics
 Department of Pediatrics
 Vanderbilt University Medical Center
 Nashville, Tennessee

David Werny, MD, MPH

Assistant Professor of Pediatrics
 Division of Endocrinology and Diabetes
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Klane K. White, MD, MSc

Associate Professor
 Orthopaedic Surgery
 University of Washington
 Pediatric Orthopedic Surgeon
 Department of Orthopedic Surgery and Sports Medicine
 Seattle Children's Hospital
 Seattle, Washington

Laurel Willig, MD, MS

Assistant Professor
 Department of Pediatrics
 Children's Mercy Hospital
 Kansas City, Missouri

David Woodrum, BA, MD

Emeritus Professor
 Department of Pediatrics
 University of Washington
 Seattle, Washington

George A. Woodward, MD, MBA

Professor
 Department of Pediatrics
 Seattle Children's Hospital
 Seattle, Washington

Clyde J. Wright, MD

Assistant Professor
 Section of Neonatology
 Department of Pediatrics
 University of Colorado School of Medicine
 Aurora, Colorado

Jeffrey A. Wright, MD

Associate Professor
 Department of General Pediatrics
 University of Washington
 Seattle, Washington

Karyn Yonekawa, MD

Associate Clinical Professor
 University of Washington
 Seattle Children's Hospital
 Seattle, Washington

Elaine H. Zackai, MD

Division of Genetics
 Department of Pediatrics
 The Children's Hospital of Pennsylvania
 Philadelphia, Pennsylvania

Preface

“The neonatal period ... represents the last frontier of medicine, territory which has just begun to be cleared of its forests and underbrush in preparation for its eagerly anticipated crops of saved lives.” Introduction to the first edition of Schaffer’s Diseases of the Newborn

History

The first edition of *Diseases of the Newborn* was published in 1960 by Dr. Alexander J. Schaffer, a well-known Baltimore pediatrician who coined the term *neonatology* to describe this emerging pediatric subspecialty that concentrated on “the art and science of diagnosis and treatment of disorders of the newborn infant.” Schaffer’s first edition was used mainly for diagnosis, but also included descriptions of new neonatal care practices (i.e., the use of antibiotics, temperature regulation, and attention to feeding techniques)—practices that had led to a remarkable decrease in the infant mortality rate in the United States, from 47 deaths per 1000 live births in 1940 to 26 per 1000 in 1960. But a pivotal year for the fledgling subspecialty of neonatology came 3 years later in 1963, with the birth of President John F. Kennedy’s son, Patrick Bouvier Kennedy, at 35 weeks’ gestation (i.e., late preterm). His death at 3 days of age, from complications of hyaline membrane disease, accelerated the development of infant ventilators that, coupled with micro-blood gas analysis and expertise in the use of umbilical artery catheterization, led to the development of intensive care for newborns in the 1960s on both sides of the Atlantic. Advances in neonatal surgery and cardiology, along with further technological innovations, stimulated the development of neonatal intensive care units and regionalization of care for sick newborn infants over the next several decades. These developments were accompanied by an explosion of neonatal research activity that led to improved understanding of the pathophysiology and genetic basis of diseases of the newborn, which in turn has led to spectacular advances in neonatal diagnosis and therapeutics—particularly in the care of preterm infants. Combined, these efforts led to continued improvements in the infant mortality rate in the United States, from 26 deaths per 1000 live births in 1960 to 5.8 deaths per 1000 live births in 2014. Current research efforts are focused on decreasing the striking regional, ethnic, and global disparities in infant mortality rates, improving neonatal outcomes, advancing neonatal therapeutics, preventing newborn diseases, and finally—teaming with our obstetrical colleagues—preventing prematurity. We neonatologists would like to begin downsizing, instead of continually expanding, our neonatal intensive care units!

Dr. Mary Ellen Avery joined Dr. Schaffer for the third edition of *Diseases of the Newborn* in 1971. For the fourth edition in 1977, Drs. Avery and Schaffer recognized that their book now needed multiple contributors with subspecialty expertise and they became co-editors, rather than sole co-authors, of the book. In the preface

to that fourth edition, Dr. Schaffer wrote, “We have also seen the application of some fundamental advances in molecular biology to the management of our fetal and newborn patients”—referring to the new knowledge of hemoglobinopathies. Dr. Schaffer died in 1981 and Dr. H. William Taeusch joined Dr. Avery as co-editor for the fifth edition in 1984. Dr. Roberta Ballard joined Drs. Taeusch and Avery for the sixth edition in 1991, with the addition of Dr. Christine Gleason for the eighth edition in 2004. Drs. Avery, Taeusch, and Ballard retired from editing the book in 2009, and became “editors emeriti.” Dr. Sherin Devaskar joined Dr. Gleason as co-editor for the ninth edition, bringing a wonderfully fresh perspective, as well as new contributors to the book. For this, the tenth edition, Dr. Sandra “Sunny” Juul teamed with Dr. Gleason as co-editor—the first time that co-editors have been faculty at the same institution since the fifth edition was published in 1984.

What’s New and Improved About This Edition?

We are thrilled that the book is now in full color—no need to flip back and forth from the chapter text to the color plates at the front of the book! Also new to this edition are several Key Points that contributors have added to the beginning of each chapter, providing readers with a quick summary of the most important content. The Expert Consult eBook version includes new features, such as ultrasound videos, and has been enhanced to make content more easily searchable, shareable (via a new Social Media feature), portable, and perpetual.

The book continues to be thoroughly (and sometimes painfully) revised and updated by some of the best clinicians and investigators in their field—several of whom are new contributors to this edition. Some chapters required more extensive revision than others, particularly those that deal with areas in which we have benefitted from new knowledge and/or its application to new diagnostic and therapeutic practices. This is particularly true in areas such as neurology, hematology, global health and neonatal screening, and genomics. Several new chapters have been added that reflect the continued growth and development of our subspecialty. These include chapters on brain injury (both preterm and term), palliative care, gastroesophageal reflux, platelet disorders, transfusion therapy, neonatal hypertension, and the ear/hearing disorders.

With the incredible breadth and depth of information immediately available to neonatal caregivers and educators on multiple online sites, what’s the value of a printed textbook? We, the co-editors of this tenth edition, believe that textbooks such as *Diseases of the Newborn* and all forms of integrative scholarship, will always be needed—by clinicians striving to provide state-of-the-art neonatal care, by educators striving to train the next generation of caregivers, and by investigators striving to advance neonatal research and

scholarship. A textbook's content is only as good as its contributors and this textbook, like the previous editions, has awesome contributors. They were chosen for their expertise and ability to integrate their knowledge into a comprehensive, readable, and useful chapter. They did this despite the demands of their day jobs in the hopes that their syntheses could, as Ethel Dunham wrote in the foreword to the first edition, "spread more widely what is already known ... and make it possible to apply these facts."

Although the online versions of this and other textbooks enjoy increasingly popular use, in 2017—a full 57 years after the publication of the first edition of this book—we still find copies of this and other textbooks important to our subspecialty lying dog-eared, coffee-stained, annotated, and broken-spined in places where neonatal caregivers congregate. These places, these congregations of neonatal caregivers, are now present in nearly every country around the world. The tentacles of neonatal practice and education are spreading—ever deeper, ever wider—to improve the outcome of pregnancy worldwide. Textbooks connect us to the past, bring us up to date with the present, and prepare and excite us for the future. We will always need them, in one form or another, at our sites of practice. To that end, we have challenged ourselves to meet, and hopefully exceed, that need—for our field, for our colleagues, and for the babies.

Acknowledgments and Gratitude

We wish to thank key staff at Elsevier—Dee Simpson, senior developmental editor, Kate Dimock, our original publishing director, Sarah Barth, our new senior content strategist, and Sharon Corell, senior project manager. Each demonstrated patience, guidance, and persistence; without them, we would still be hard at work, trying to make this book a reality! We also wish to thank our staff and colleagues at our academic institution, the University of Washington, especially our Department Chair, F. Bruder Stapleton, whose leadership and unwavering support have meant a great deal to us both. We are indebted to our contributors, who actually *wrote* the book and did so willingly, enthusiastically, and (for the most part) in a timely fashion—despite myriad other responsibilities in their lives. Finally, we are deeply grateful for the support of our families throughout the long, and often challenging, editorial process.

Christine Gleason and Sandra Juul

Video Contents

Part XV: Hematologic System and Disorders of Bilirubin Metabolism

79 Neonatal Bleeding and Thrombotic Disorders

- 79-1 A Model of Hemostasis Combining the Vascular,
Platelet, and Plasma Phases
- 79-2 Fibrinolysis
- 79-3 Hemostatic Processes

1

Neonatal and Perinatal Epidemiology

NIGEL PANETH AND TRACY THOMPSON

KEY POINTS

- Population-level study of pregnancy and infancy has been an important component of the success of newborn care.
- Disease, mortality, and later outcomes patterns are complex. Some factors (i.e., preterm birth and birthweight) are stable, while others (i.e., cesarean section and twinning rates) can undergo rapid change.
- The success of newborn intensive care is well established and has substantially lowered mortality rates in a short period of time primarily because of the evidence-based nature of neonatal practice.
- Survivors of neonatal intensive care face educational and rehabilitative needs. Recent interventions have reduced the burden of brain damage.
- Sudden infant death syndrome (SIDS), through careful epidemiologic study and active discouragement of prone sleeping, has been reduced by 70% in the United States.
- Observational research and randomized trials have led to increased folate intake and a substantial reduction in neural tube birth defects.

The period surrounding the time of birth, the *perinatal* period, is a critical episode in human development, rivaling only the period surrounding conception in its significance. This time period is when the infant makes the critical transition from its dependence upon maternal and placental support (oxidative, nutritional, and endocrinologic) and establishes independent life. That this transition is not always successful is signaled by a mortality risk in the neonatal period that is not exceeded until age 75–84 and risks for damage to organ systems, most notably the brain, that can be lifelong (Murphy et al., 2013). The developing human organism often does not manifest the immediate effects of even profound insults. Years must pass before the damage to higher cortical functions of insults and injuries occurring during the perinatal period can be reliably detected. Epidemiologic approaches to the perinatal period must therefore be bidirectional: looking backwards from birth to examine the underlying causes of adverse health conditions that arise or complicate the perinatal period and looking forward to later life to see how these conditions shape disorders of health in childhood and adulthood.

Health Disorders of Pregnancy and the Perinatal Period

Key Population Mortality Rates

Maternal and child health in the population has traditionally been assessed by monitoring the two key rates of maternal mortality and infant mortality (IM). Maternal mortality is defined by the World Health Organization (WHO) as the death of a woman during pregnancy or within 42 days of pregnancy, denominated either to live births or to all births (this must be specified) in the population being studied (WHO, 2010). Because pregnancy can contribute to deaths beyond 42 days, some have argued for examining all deaths within a year of a pregnancy but later deaths are not included in standard tabulations of maternal mortality (Hoyert, 2007). When the cause of death is attributed to a pregnancy-related condition, it is described as *direct*. When pregnancy has aggravated an underlying health disorder present before pregnancy, the death is termed an *indirect* maternal death. The WHO recommends that both direct and total (direct plus indirect) maternal mortality rates be provided.

Deaths unrelated to pregnancy, but taking place in women within 42 days of pregnancy, are termed *incidental* maternal deaths and are not included in maternal mortality (Khalat, 2006). But even incidental deaths may bear a relation to pregnancy; homicide and suicide, for example, are more common during pregnancy and shortly thereafter and might not be entirely incidental to it (Shadigian and Bauer, 2005; Samandari et al., 2010).

In most geographic entities, IM is defined as all deaths occurring from birth to 365 days of age in a calendar year divided by all live births in the same year. This approach makes for imprecision, as some deaths in the examined year occurred in the previous year's birth cohort, and some births in the examined year will die as infants in the following year. In recent years, birth–death linkage has permitted vital registration areas in the United States to provide IM rates that avoid this imprecision. The standard IM rate reported by the National Center for Health Statistics (NCHS) links *deaths* for the index year to all births, including those taking place the *previous* year. This form of IM is termed *period* IM. An alternative procedure is to take births for the index year and link them to

infant deaths, including those taking place the *following* year. This is referred to as *birth cohort* IM and is not used for regular annual comparisons because it cannot be completed in as timely a fashion as period IM (Mathews, 2015).

Infant deaths are often divided into deaths in the first 28 days of life (*neonatal* deaths) and deaths later in the first year (*postneonatal* deaths). Neonatal deaths, which are largely related to preterm birth and birth defects, tend to reflect the circumstances of pregnancy whereas postneonatal deaths, when high, are nearly all from infection, often in the setting of poor nutrition. Thus in underdeveloped countries, postneonatal deaths dominate; in industrialized countries, the reverse is true. In the United States, neonatal deaths have been more frequent than postneonatal deaths since 1921. In recent years, the ratio of neonatal to postneonatal deaths in the United States has consistently been about 2:1.

Perinatal mortality is a term used for a rate that combines stillbirths and neonatal deaths in some fashion (Box 1.1) Stillbirth reporting prior to 28 weeks, even in the United States, where such stillbirths are required to be reported in every state, is probably incomplete. Nonetheless, stillbirths continue to be reported at a level not much lower than that of neonatal deaths, and our understanding of the causes of stillbirth remains very uncertain (Paneth, 2012; Lawn et al., 2016).

Sources of Information on Mortality–Vital Data

All US mortality data depend upon the collection of information about all births and deaths. Routinely collected vital data are the

• BOX 1.1 Glossary of Terms

Preterm birth – less than 37 weeks' gestation

- **Very preterm** – less than 32 weeks' gestation
- **Extremely preterm** – less than 28 weeks' gestation

Low birth weight – infant weighs less than 2500 g (5 lb 8 oz) at birth regardless of gestational age

- **Moderately low birth weight** – an infant weighing at least 1500 g but less than 2500 g at birth regardless of gestational age
- **Very low birth weight** – an infant weighing less than 1000 g (2 lb 3 oz) at birth regardless of gestational age

Maternal mortality ratio – death of a woman during pregnancy or within 42 days of pregnancy compared with either live births or with all births in the population

- **Direct maternal mortality** – a maternal death attributed to a pregnancy-related cause
- **Incidental maternal mortality** – a maternal death occurring during the defined time period for maternal mortality but unrelated to pregnancy
- **Indirect maternal mortality** – a maternal death caused by the pregnancy aggravating an underlying health disorder present before pregnancy

Infant mortality rate – all deaths occurring from birth to 365 days of age in a calendar year divided by all live births in the same year

Birth cohort infant mortality – births for the index year are linked to infant deaths including those taking place the following year

Neonatal mortality – infant deaths within the first 28 days of life

Perinatal mortality rate – number of stillbirths that occur after 22 weeks' gestation and deaths in the first week of life per 1000 total births

Period infant mortality – all infant deaths in a calendar year linked to births, including births that took place in the previous year

Postneonatal mortality – infant deaths after the first 28 days of life but before the 366th day of life

nation's key resource for monitoring progress in caring for mothers and children. Annual counts of births and deaths collected by the 52 vital registration areas of the United States (50 states, District of Columbia, and New York City) are assembled into national data sets by the NCHS. Unlike data collected in hospitals or clinics, or even from nationally representative surveys, birth and death certificates are required by law to be completed for each birth and death. Birth and death registration have been virtually 100% complete for all parts of the United States since the 1950s. The universality of this process renders many findings from vital data analyses stable and generalizable, although formatting changes in 2003, affecting both the death and birth certificates, have created some difficulties in interpretation.

For example, since 2003 the US Standard certificate of death, which is recommended for adoption by US vital registration areas, has included a special requirement for identifying whether the decedent, if female, was pregnant or had been pregnant in the previous 42 days. This simple check box on the death certificate has been shown to increase the number of deaths recognized as maternal in states that have followed the 2003 model and incorporated questions about pregnancy in their death certificates (Mac et al., 2011).

Fig. 1.1 illustrates the most recent (2003) nationally recommended standard for birth certificate data collection, which had been adopted for use by 33 states by 2010 (Curtin et al., 2013). The remaining states use birth certificates formatted according to the 1989 standard. While, as we discuss below, some items are collected differently on the two certificate templates, unlike maternal mortality, these changes do not affect the number of reported deaths.

The limitations of vital data are well known. Causes of death are subject to certifier variability and perhaps more importantly to professional trends in diagnostic categorization. The accuracy of recording of conditions and measures on birth certificates is often uncertain and variable from state to state and from hospital to hospital. Yet the frequencies of births and deaths in sub-groups defined objectively and recorded consistently, such as birthweight and mode of delivery, are likely to be valid.

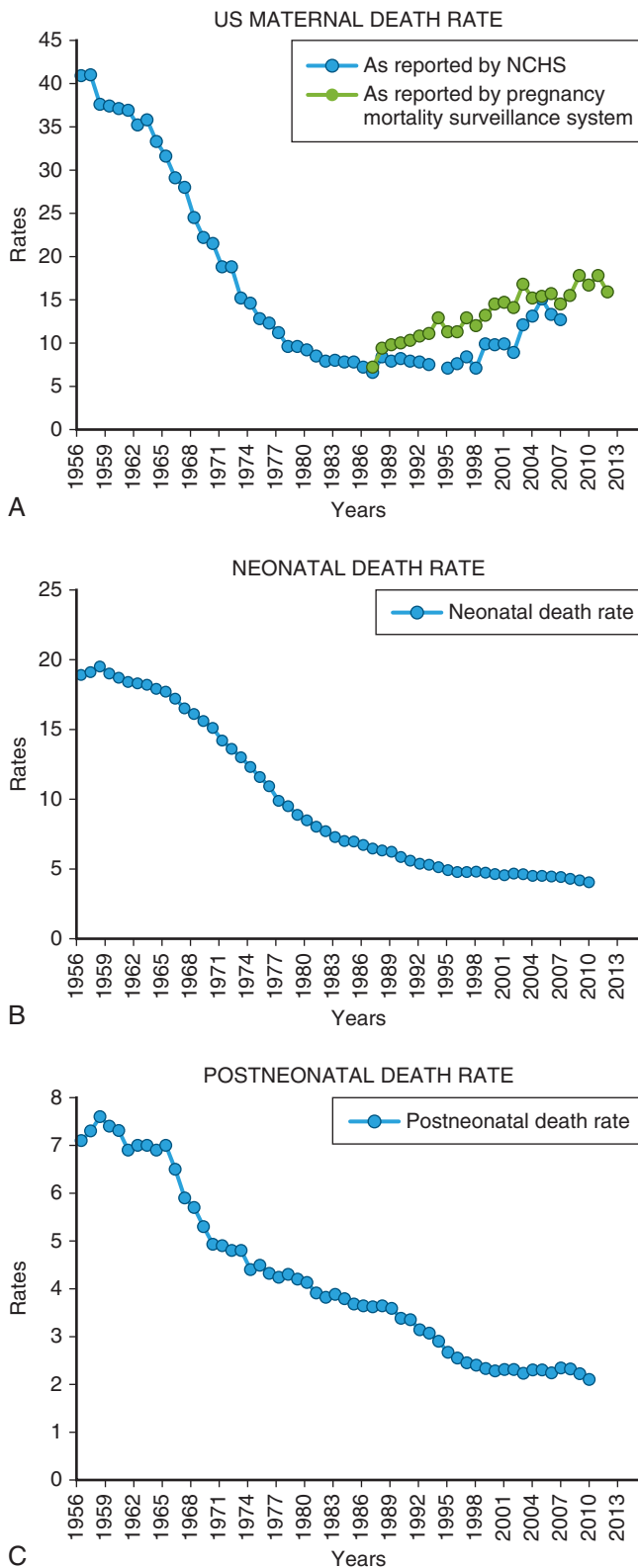
Time Trends in Mortality Rates of the Perinatal Period in the United States

Maternal mortality and IM declined steadily through the 20th century. By 2000, neonatal mortality was 10% of its 1915 value, postneonatal mortality less than 7%, and maternal mortality less than 2%. The contribution to these changes of a variety of complex social factors, including improvements in income, housing, birth spacing, and nutrition, has been widely documented, as has the role of ecologic-level public health interventions that have produced cleaner food and water (Division of Reproductive Health, 1999). Public health action at the individual level, including targeted maternal and infant nutrition programs and immunization programs, has made a lesser but still notable contribution. Medical care per se was, until recently, less critically involved, with the exception of the decline in maternal mortality, which was very sensitive to the developments in blood banking and antibiotics that began in the 1930s. To this day hemorrhage and infection account for a large fraction of the world's maternal deaths (Khan et al., 2006).

A notable feature of the past half-century or so is the sharp decline in all three mortality rates beginning in the 1960s following a period of stagnation in the 1950s (Fig. 1.2) The decline began with maternal mortality, followed by postneonatal, and then

MOTHER	29a. DATE OF FIRST PRENATAL CARE VISIT ____/____/____ M M D D YYYYY No Prenatal Care		29b. DATE OF LAST PRENATAL CARE VISIT ____/____/____ M M D D YYYYY		30. TOTAL NUMBER OF PRENATAL VISITS FOR THIS PREGNANCY _____ (If none, enter A0*)			
	31. MOTHER'S HEIGHT _____ (feet/inches)		32. MOTHER'S PREPREGNANCY WEIGHT _____ (pounds)		33. MOTHER'S WEIGHT AT DELIVERY _____ (pounds)			
	35. NUMBER OF PREVIOUS LIVE BIRTHS (Do not include this child)		36. NUMBER OF OTHER PREGNANCY OUTCOMES (spontaneous or induced losses or ectopic pregnancies)		37. CIGARETTE SMOKING BEFORE AND DURING PREGNANCY For each time period, enter either the number of cigarettes or the number of packs of cigarettes smoked. IF NONE, ENTER A0*.			
	35a. Now Living Number _____ None		35b. Now Dead Number _____ None		36a. Other Outcomes Number _____ None			
35c. DATE OF LAST LIVE BIRTH ____/____/____ MM YYYYY		36b. DATE OF LAST OTHER PREGNANCY OUTCOME ____/____/____ MM YYYYY		39. DATE LAST NORMAL MENSES BEGAN ____/____/____ M M D D YYYYY				
38. PRINCIPAL SOURCE OF PAYMENT FOR THIS DELIVERY Private Insurance _____ Medicaid _____ Self-pay _____ Other (Specify) _____		40. MOTHER'S MEDICAL RECORD NUMBER						
MEDICAL AND HEALTH INFORMATION	41. RISK FACTORS IN THIS PREGNANCY (Check all that apply) Diabetes Prepregnancy (Diagnosis prior to this pregnancy) Gestational (Diagnosis in this pregnancy) Hypertension Prepregnancy (Chronic) Gestational (PIH, preeclampsia) Eclampsia Previous preterm birth Other previous poor pregnancy outcome (Includes perinatal death, small-for-gestational age/intrauterine growth restricted birth) Pregnancy resulted from infertility treatment-If yes, check all that apply: Fertility-enhancing drugs, Artificial insemination or Intrauterine insemination Assisted reproductive technology (e.g., in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT)) Mother had a previous cesarean delivery If yes, how many _____ None of the above		43. OBSTETRIC PROCEDURES (Check all that apply) Cervical cerclage Tocolysis External cephalic version: Successful Failed None of the above		46. METHOD OF DELIVERY A. Was delivery with forceps attempted but unsuccessful? Yes No B. Was delivery with vacuum extraction attempted but unsuccessful? Yes No C. Fetal presentation at birth Cephalic Breech Other D. Final route and method of delivery (Check one) Vaginal/Spontaneous Vaginal/Forceps Vaginal/Vacuum Cesarean If cesarean, was a trial of labor attempted? Yes No			
	42. INFECTIONS PRESENT AND/OR TREATED DURING THIS PREGNANCY (Check all that apply) Gonorrhea Syphilis Chlamydia Hepatitis B Hepatitis C None of the above		44. ONSET OF LABOR (Check all that apply) Premature Rupture of the Membranes (prolonged, ≥12 hrs.) Precipitous Labor (<3 hrs.) Prolonged Labor (≥20 hrs.) None of the above		47. MATERNAL MORBIDITY (Check all that apply) (Complications associated with labor and delivery) Maternal transfusion Third or fourth degree perineal laceration Ruptured uterus Unplanned hysterectomy Admission to intensive care unit Unplanned operating room procedure following delivery None of the above			
			45. CHARACTERISTICS OF LABOR AND DELIVERY (Check all that apply) Induction of labor Augmentation of labor Non-vertex presentation Steroids (glucocorticoids) for fetal lung maturation received by the mother prior to delivery Antibiotics received by the mother during labor Clinical chorioamnionitis diagnosed during labor or maternal temperature ≥38°C (100.4°F) Moderate/heavy meconium staining of the amniotic fluid Fetal intolerance of labor such that one or more of the following actions was taken: in-utero resuscitative measures, further fetal assessment, or operative delivery Epidural or spinal anesthesia during labor None of the above					
	NEWBORN INFORMATION							
NEWBORN	48. NEWBORN MEDICAL RECORD NUMBER		54. ABNORMAL CONDITIONS OF THE NEWBORN (Check all that apply) Assisted ventilation required immediately following delivery Assisted ventilation required for more than six hours NICU admission Newborn given surfactant replacement therapy Antibiotics received by the newborn for suspected neonatal sepsis Seizure or serious neurologic dysfunction Significant birth injury (skeletal fracture(s), peripheral nerve injury, and/or soft tissue/solid organ hemorrhage which requires intervention)		55. CONGENITAL ANOMALIES OF THE NEWBORN (Check all that apply) Anencephaly Meningocele/Spina bifida Cyanotic congenital heart disease Congenital diaphragmatic hernia Omphalocele Gastroschisis Limb reduction defect (excluding congenital amputation and dwarfing syndromes) Cleft Lip with or without Cleft Palate Cleft Palate alone Down Syndrome Karyotype confirmed Karyotype pending Suspected chromosomal disorder Karyotype confirmed Karyotype pending Hypospadias None of the anomalies listed above			
	49. BIRTHWEIGHT (grams preferred, specify unit) ____ grams ____ lb/oz		9 None of the above					
	50. OBSTETRIC ESTIMATE OF GESTATION: ____ (completed weeks)							
	51. APGAR SCORE: Score at 5 minutes: _____ If 5 minute score is less than 6, Score at 10 minutes: _____							
	52. PLURALITY - Single, Twin, Triplet, etc. (Specify) _____							
	53. IF NOT SINGLE BIRTH - Born First, Second, Third, etc. (Specify) _____							
56. WAS INFANT TRANSFERRED WITHIN 24 HOURS OF DELIVERY? 9 Yes 9 No IF YES, NAME OF FACILITY INFANT TRANSFERRED TO: _____		57. IS INFANT LIVING AT TIME OF REPORT? Yes No Infant transferred, status unknown		58. IS THE INFANT BEING BREASTFED AT DISCHARGE? Yes No				

• Fig. 1.1 United States National Standard Birth Certificate 2003 Revision.



• **Fig. 1.2** Maternal, Neonatal, and Postneonatal Mortality Rates 1956–2013. (A) United States maternal death rate. (B) Neonatal death rate. (C) Postneonatal death rate. *NCHS*, National Center for Health Statistics; *US*, United States. (From the pregnancy surveillance system <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html> and Martin JA, Hamilton BE, Ventura SJ, et al. Births: Final data for 2010. National vital statistics reports; vol 61 no 1. Hyattsville, MD: National Center for Health Statistics. 2012.)

neonatal. The contribution of medical care of the neonate was most clearly seen in national statistics in the 1970s, a decade that witnessed a larger decline in neonatal mortality than in any previous decade of the century. All of the change in neonatal mortality between 1950 and 1975 was in mortality for a given birthweight; no improvement was seen in the birthweight distribution (Lee et al., 1980). This finding suggested that the effectiveness of newborn intensive care has had a striking impact on mortality in very small babies. Prior to the development of newborn intensive care, survival at birthweights less than 1000 g was very rare. In 2013, the US survival rate to 1 year for infants with a birthweight between 501 and 999 g was 75%, and the number of survivors at age 1 was over 16,000.

In retrospect, three factors seem to have played critical roles in the rapid development of the newborn intensive care programs that largely accounted for the rapid decline in birthweight-specific neonatal mortality that characterized national trends in the last third of the 20th century. The first was the willingness of medicine to provide more than nursing care to marginal populations such as the premature infant. While the death of the mildly premature son of President Kennedy in 1963 provided a stimulus to the development of newborn intensive care, it should be noted that the decline in IM that began in the 1970s was paralleled by a similar decline in mortality for the extremely old (Rosenwaik et al., 1980). This was, perhaps, an indicator that the availability of federal funding through Medicare and Medicaid enabled previously underserved populations at the extremes of age to receive greater medical attention than they had before. The Medicaid program, adopted in 1965, may have made it feasible for the first time to pay for the intensive care of premature newborns, among whom the medically indigent are over-represented. While financial support for newborn intensive care may have been a necessary ingredient in its development, finances would have not been sufficient to improve neonatal mortality had not new medical technologies, especially those supporting ventilation of the immature newborn lung, been developed at about the same time (Gregory et al., 1975).

Advances in newborn care have ameliorated the impact of premature birth and birth defects on mortality. Unfortunately, the underlying disorders that drive perinatal mortality and the long-term developmental disorders that are sometimes their sequelae have shown no tendency to abate. With the very important exception of neural tube defects, whose prevalence has declined with folate fortification of flour in the United States and programs to encourage intake of folate in women of child-bearing age (Mathews et al., 2002), the major causes of death (preterm birth and birth defects) have not declined, nor has cerebral palsy, the major neurodevelopmental disorder that can be of perinatal origin (Paneth et al., 2006). Progress has come from improved medical care of the high-risk pregnancy and the sick infant, rather than through understanding and prevention of the disorders themselves.

The pace of decline in infant, neonatal, and postneonatal mortality in the United States began to slow in 1995 and changed little in the following decade. A modest decline was seen, however, between 2005 and 2010 (Table 1.1). Data from the Vermont Oxford Neonatal Network encompassing more than a quarter of a million newborns from hundreds of largely North American neonatal units showed a decline in mortality of 12.2% for infants of 501–1500 g for 1990–1999 (Horbar et al., 2002) and a further 13.3% decline for 2000–2009 (Horbar et al., 2012). These declines are more modest than in the early days of newborn intensive care. From 1960–1985, a greater than 50% decline in mortality for

TABLE 1.1 United States Perinatal Mortality, Morbidity, Interventions, and Pregnancy Health Conditions and Behaviors, 1990–2005

	1995	2000	2005	2010	Net Change 1995–2010 (%)
Deaths^a					
Maternal mortality ratio	12.9	13.2	15.2	17.8	+ 38.0
Infant mortality rate	7.6	6.9	6.9	6.1	– 19.7
Neonatal mortality rate	4.9	4.6	4.5	4.0	– 18.4
Postneonatal mortality rate	2.6	2.3	2.3	2.1	– 19.2
Fetal mortality ratio ^b	6.9	6.6	6.2	6.0	– 13.0
Morbidity					
Preterm birth (<37 weeks, %)	11.0	11.6	12.7	12.0	+ 9.0
Very preterm birth (<32 weeks, %)	1.9	1.9	2.0	2.0	+ 5.2
Extremely preterm birth (<28 weeks, %)	0.70	0.72	0.76	0.74	+ 5.7
Moderately low birth weight (%)	6.6	7.1	7.3	6.7	+ 1.5
Low birth weight (%)	7.3	7.6	8.2	8.2	+ 12.3
Very low birth weight (%)	1.4	1.4	1.5	1.5	+ 1.5
Pregnancy-associated hypertension (%)	3.3	3.9	4.0	—	
Diabetes in pregnancy (%)	2.4	2.9	3.8	5.1	+ 212
Interventions					
Cesarean section (%)	20.8	22.9	30.3	32.8	+ 57.7
Induction of labor (%)	15.8	19.9	22.3	23.4	+ 48.1
Health Behaviors					
Smoking (%)	^c 13.7	12.2	^d 10.7	—	
Alcohol intake (%)	^e 1.5	0.9	^f 0.7	—	
Inadequate weight gain (<16 lb) at 40 weeks (%)	9.3	11.6	11.4	—	
Weight gain of >40 lb (%)	17.5	19.2	20.6	20.8	+ 18.9
Late or no prenatal care (%)	4.2	3.9	3.5	—	
Unmarried (%)	32.1	33.2	36.9	40.8	+ 27.1
Multiple births (%)	26.1	—	33.8	34.5	+ 32.2
Fertility rate (women 15–44, %)	64.6	65.3	66.7	64.1	– 0.77

^aMortality rates denominators to 1000 live births, except for maternal mortality, denominators to 100,000 live births.
^bFetal deaths with stated or presumed period of gestation of 20 weeks or more.
^c1995 smoking data include 46 states, New York City, and District of Columbia.
^d2005 smoking data based on 36 states using only yes/no (pre-2003 revision).
^e1995 alcohol intake has no data from California or South Dakota.
^f2005 alcohol use data that includes 36 states, New York City, and District of Columbia.

infants of 501–1500 g was recorded in national data (Buehler et al., 1987; Prager, 1994), even though much of the first decade of that interval preceded the use of newborn intensive care technology in all but a few pioneering centers. The pace of advances in newborn medicine and the expansion of newborn intensive care to populations previously underserved, factors that have exerted a constant downward pressure on IM since the 1960s, have lessened in the past two decades or so.

Reported maternal mortality has actually climbed substantially in recent years, but this is almost certainly the effect of the improved reporting described above. The Centers for Disease Control (CDC) has a special unit dedicated to the problem of maternal mortality, the Pregnancy Mortality Surveillance System (CDC, 2017). Established in 1987, its counts of maternal deaths, based on more in-depth exploration than is possible from a vital registration system alone, have provided consistently higher estimates of maternal

mortality than data reported by the NCHS, as shown in Fig. 1.2. Recognizing this, and the variation in reporting resulting from the variable use by states of the 2003 recommendation for identifying recent pregnancies on death certificates, the NCHS stopped reporting maternal mortality in 2008 (Minino et al., 2011). All recent maternal mortality data in the US are produced by the Pregnancy Mortality Surveillance System.

The risk of preterm birth (<37 weeks' gestation) increased steadily in the first years of the present century, peaked in 2007, and has declined by 8% since (Hamilton et al., 2015). The increase was largely in moderately preterm babies and likely reflected an increased willingness on the part of obstetricians to deliver fetuses earlier in gestation who were not doing well in utero, as well as the increased prevalence of twins and triplets, who are generally born preterm, resulting from in vitro fertilization. The newer data suggest a reversal of these earlier practices.

The recording of diabetes in pregnancy more than doubled from 1995 to 2010, but the NCHS has suggested that some of this might reflect more complete reporting on the 2003 birth certificate revision (Martin et al., 2010b). The differences in the two forms of birth certificate in circulation, and the uneven implementation of the newer version in vital registration areas, led NCHS, in 2008 (Martin et al., 2010a), to omit regular reporting of smoking, alcohol intake, weight gain, late prenatal care, and pregnancy-associated hypertension, among other variables, from its regular tabulations in annual natality reports, and these are not provided for 2010 in Table 1.1.

The cesarean section rate continues its long-term increase, from 5% in 1970 to 23% in 1990, peaking at nearly 33% in 2010, with a faint decline since (Hamilton et al., 2015). The reasons for this increase are multifactorial and include pressures from patients, physicians, and the medical malpractice system. The steady reduction in smoking in pregnancy is likely to be real, whereas trends in the self-reporting of alcohol use in pregnancy may be influenced by societal norms and expectations. Fewer women seem to have late or no prenatal care in recent years, but perhaps surprisingly, more women are found to have inadequate pregnancy weight gain at term. A very slight uptick in the fertility rate follows a long-term (since about 1960) decline in fertility in the United States. More than 4 in 10 mothers in the United States are now unmarried when they give birth.

International Comparisons

The US lag in IM, in comparison to other developed nations, is well known; the United States ranked 26th in IM among the Organization for Economic Co-operation and Development countries in 2010 (MacDorman et al., 2014). This surprising phenomenon, in light of more favorable socioeconomic and medical care circumstances in the United States than in many nations with lower IM, cannot be attributed to inferior neonatal care. Mortality rates for low birth weight infants are generally lower in the United States than in European and Asian nations, though mortality at term may be slightly higher. The key difference, however, is that the United States suffers from a striking excess of premature births. While the US African-American (AA) population is especially vulnerable to prematurity, and especially severe prematurity, prematurity rates are also considerably higher in white Americans than in most European populations. It is likely that the recording of marginally viable small infants as live births rather than stillbirths is more pronounced in the United States than in Europe (Kramer et al., 2002). While this practice does make a

contribution to our higher prematurity and IM rates, it cannot fully explain them.

Premature birth, fetal growth retardation, and IM are tightly linked, in every setting in which they have been studied, to most measures of social class, especially to maternal education. However, uncovering precisely what it is about lower social class that drives these important biologic differences has been elusive. Factors such as smoking have at times been implicated but can only explain a small fraction of the social class effect. It is unlikely that this situation will change until a better understanding of the complex social, environmental, and biologic roots of preterm birth are achieved.

Health Disparities in the Perinatal Period

In 2010, 54.1% of all US births were to non-Hispanic white mothers; 23.6% were to Hispanic mothers; 14.7% were to AA mothers; and the remainder were to mothers of other ethnic groups (Table 1.2). Health disparities are especially prominent in the perinatal period, with AA infant IM stubbornly remaining about double that of white IM in the United States, even as rates decline in both populations. Preterm birth is the central contributor to this racial disparity in IM, and the more severe the degree of prematurity, the higher the excess risk for AA infants. The risk of birth before 37 weeks of gestation was 1.5 times higher in AA mothers than among non-Hispanic whites in 2010, but the risk of birth before 32 weeks was twice as high. Reduction in IM disparities in the United States thus requires better understanding of the etiology and mechanisms of preterm birth. Birth defect mortality shows a less pronounced gradient by ethnic group and does not contribute in a major way to overall IM disparities (Yang et al., 2006).

The *Hispanic paradox* is a term often used to describe the observation that IM is the same or lower in US citizens classified as Hispanic than in non-Hispanic whites, in spite of the generally lower income and education levels of US Hispanics (Hessol and Fuentes-Afflick, 2005). The IM experience of Hispanics in the United States reflects the principle that premature birth and low birth weight are key determinants of IM, as these parameters are also favorable in Hispanics. Smoking is much less common among Hispanics in the United States, but this factor alone does not fully explain the paradox.

Major Causes of Death

Cause-of-death analysis, a staple of epidemiologic investigation, has limitations when applied to the perinatal period. Birth defect mortality is probably reasonably accurate, but causes of deaths among prematures are divided among categories such as respiratory distress syndrome, immaturity, and a variety of complications of prematurity. Choice of which particular epiphenomenon of preterm birth should be chosen to be listed as the primary cause of death is to some extent arbitrary. Some maternal complications, such as preeclampsia, are also occasionally listed as causes of newborn death, and birth defects and preterm birth often overlap. However categorized, prematurity per se accounts for at least a third of infant deaths (Callaghan et al., 2006).

In the period before prenatal ultrasound permitted reasonably accurate gestational age estimation, a high fraction of neonatal deaths were attributed to low birth weight, but most of these deaths occurred in premature infants, because premature birth is much more important as a cause of death than is fetal growth restriction. Extreme prematurity makes a contribution to IM well

TABLE 1.2 Ethnic Disparities in Key Perinatal Outcomes and Exposures in 2010

	Non-Hispanic White	African-American	RR Compared With Whites	Hispanic	RR Compared With Whites
Births (percent of all births, %)	54.1	14.7	—	23.6	—
Deaths^a					
Maternal mortality ratio	11.8	41.1	2.5	—	—
Infant mortality rate	5.2	11.5	2.2	5.3	1.0
Neonatal mortality rate	3.4	7.5	2.21	3.6	1.1
Postneonatal mortality rate	1.8	4.0	2.2	1.7	0.94
Fetal mortality ratio	4.8	10.8	2.3	5.2	1.1
Morbidity					
Preterm birth (%)	11.1	16.9	1.5	11.8	1.1
Early preterm birth (%)	3.0	6.0	2.0	3.3	1.1
Late preterm birth (%)	8.0	10.9	1.36	8.5	1.1
Low birth weight (%)	7.1	13.2	1.9	7.0	0.98
Very low birth weight (%)	1.2	2.9	2.4	1.4	1.2
Diabetes in pregnancy (%)	4.8	4.5	0.94	5.2	1.1
Interventions					
Cesarean section (%)	32.3	35.3	1.1	31.8	0.98
Induction of labor (%)	24.2	21.7	0.90	17.8	0.74
Health Behaviors					
Inadequate weight gain (<16 lb) at 40 weeks (%) ^b	7.6	13.3	1.75	9.5	1.25
More than 40 lb weight gain at 40 weeks (%)	21.3	20.5	0.96	16.5	0.77
Unmarried (%)	35.9	72.1	2.0	53.4	1.5
Fertility rate (women 15–44, %)	64.4	66.3	1.03	80.2	1.25
Multiple births (per 100,000)	181.7	133.7	0.74	98.7	0.54

^aMortality rates denominators to 1000 live births, except for maternal mortality, denominators to 100,000 live births.
^bExcludes California, which does not record weight gain.
Sources: NCHS Natality Reports 2010 and Pregnancy Mortality Surveillance System <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html>. RR, Relative risk.

beyond its frequency in the population. The 1.9% of births born prior to 32 weeks in 2010 contributed 53% of all infant deaths.

After premature birth, the next most important group of causes of death is congenital anomalies. With the signal exception of the folate–neural tube association, we have no clearly effective primary prevention program for any birth defect. Pregnancy screening and termination of very severe defects are, however, an option for many mothers and there is evidence that this practice does contribute to a reduced prevalence of chromosomal anomalies at birth (Loane et al., 2013).

The major postneonatal cause of death since about the 1970s in the United States is the sudden infant death syndrome (SIDS). This cause of death has declined substantially in the United States in parallel with successful public health efforts to discourage prone sleeping in infancy (Mitchell, 2009).

Major Morbidities Related to the Perinatal Period

The principal complications of preterm birth involve five organs – lung, heart, gut, eye, and brain. Management of respiratory distress syndrome and its short-term and longer-term complications is the centerpiece of neonatal medicine. Surgical or medical management of symptomatic patent ductus arteriosus is the major cardiac challenge for the premature, and we have yet to understand the quite striking variations, by time and place, of necrotizing enterocolitis, a disorder that in its most extreme forms can cause death or substantial loss of bowel function. Retinopathy of prematurity (ROP) is closely related to arterial oxygen levels, and the epidemic levels of this disorder encountered in the 1950s, when oxygen was freely administered without monitoring, was a major setback for

neonatal medicine (Silverman, 1980). However, even with much more careful management of oxygen, ROP continues to occur.

The largest unsolved problem in neonatal medicine remains the high frequency of brain damage in premature survivors. The extraordinary decline in mortality rates has not been paralleled by similar declines in rates of neurodevelopmental disabilities in survivors. Indeed, the key epidemiologic feature of cerebral palsy rates in population registries toward the end of the 20th century was a modest overall increase in the prevalence of that disorder attributable entirely to the increasing number of survivors of very low birth weight. There are suggestions that this rise has leveled off since the 1990s (Smithers-Sheedy et al., 2016).

Factors Affecting Perinatal Health

Health States in Pregnancy

The major causes of neonatal morbidity (prematurity and birth defects) generally occur in pregnancies free of antecedent complications. Having a previous birth with an anomaly or a previous preterm birth both raise the maternal risk for recurrence of the condition. Indeed, for preterm birth, no other known risk factor carries as much risk as having previously delivered preterm.

More than a quarter of preterm birth is iatrogenic, the result of induced labor in pregnancies in which the fetus is severely compromised (Morken et al., 2008). Generally the reason is preeclampsia with attendant impairments in uterine blood flow and poor fetal growth, but poor uterine blood flow and impaired fetal growth can also occur independently of diagnosed preeclampsia. The other major complication of pregnancy is diabetes, most often gestational but at times preexisting. Insulin resistance in the mother promotes the movement of nutrients toward the fetus, and typically the infant of the diabetic mother is large for gestational age. Severe diabetes, however, can be accompanied by fetal growth retardation.

Health Behaviors

The most carefully studied and well-established health behavior affecting newborns is maternal cigarette smoking, which more than doubles the prevalence of babies with intrauterine growth retardation and increases the risk of premature birth by 20%–50% (Dietz et al., 2010). Infants growth retarded from smoking paradoxically survive slightly better than do infants of the same weight whose mothers did not smoke, but the net effect of smoking, which also shortens gestation slightly, is to increase perinatal mortality. The risk of SIDS is also increased in the babies of smoking mothers (Mitchell and Milerad, 2006). Although the subject is much debated, it has not been conclusively shown that prenatal smoking has independent long-term effects on child cognitive capacity (Breslau et al., 2005).

Mothers who drink alcohol heavily in pregnancy are at risk of having infants with the cluster of defects known as the fetal alcohol syndrome (Jones et al., 2013). Cocaine use in pregnancy is a severe growth retardant (Janisse et al., 2014) and may affect neonatal behavior, but the long-term effects of this exposure on infant cognition and behavior are not as great as initially feared (Bandstra et al., 2010).

Perinatal Medical Care

In light of the potent effects of medical care on the neonate, it has been important to develop systems of care that ensure, or at

least facilitate, provision of care to neonates in need. This concept was first promoted by the March of Dimes Foundation, which in its committee report of 1976 recommended that all hospitals caring for babies be classified as either Level 1 (care for healthy and mildly ill newborns), Level 2 (care for most sick born-in newborns but not accepting transfers), and Level 3 (regional centers caring for complex surgical disease and receiving transfers) (Health, 1976). This concept of a regional approach to neonatal care, with different hospitals playing distinct roles in providing care, was endorsed by organizations such as the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and by many state health departments. While it is important to transfer sick babies to Level 3 centers when needed, it is preferable, if at all possible, to transfer mothers at risk of delivering prematurely or of having a sick neonate, because transport of the fetus in utero is far superior to any form of postnatal transport. Birth at a Level 3 center has consistently been shown to produce lower mortality rates in low birth weight infants than birth in other levels of care (Lasswell et al., 2010).

Epidemiologic Study Designs in the Perinatal Period

Epidemiologic studies have contributed substantially to better understanding of patterns of risk and prognosis in the perinatal period, to tracking patterns of mortality and morbidity, to assessment of regional medical care, and to assisting physicians and other providers to evaluate the efficacy of treatments. The use of vital data to provide a picture of the overall health of mothers and infants and to monitor important time trends has already been mentioned, but cohort studies and randomized controlled trials have been essential to advances in neonatology.

Cohort Studies in Pregnancy/Birth

Studies that follow populations of infants over time, beginning at birth or even before birth, continuing to hospital discharge, to early childhood, or even into adult life, are the leading sources of information about perinatal risk factors for disease and adverse outcomes. As with all observational studies, cohort studies produce associations of exposures and outcomes whose strength and consistency must be carefully judged in the light of other biologic evidence and with attention to confounding and bias. Collaborations across centers in assembling such data are very valuable. One such notable collaboration is the Vermont–Oxford Network, which provides continuous information on the frequency of conditions observed and diagnoses made in hundreds of US overseas hospitals, with a particular emphasis on using these data for improving care (Horbar et al., 2010). The National Institute of Child Health and Human Development (NICHD)-supported neonatal network has not only been a rich source of randomized trials but also has produced observations about prognosis based on very large samples of low birth weight babies (Stoll et al., 2015). The above collaborations focus mainly on the period until hospital discharge.

Multicenter cohort studies focusing on diagnosis and follow-up of brain injury in prematures, such as the Developmental Epidemiology Network Study (DEN) (Kuban et al., 1999), Neonatal Brain Hemorrhage Study (NBH) (Pinto-Martin et al., 1992), and Extremely Low Gestational Age Newborn Study (ELGAN) (O'Shea et al., 2009), have contributed much to our understanding of the

prognostic value of brain injury imaged by ultrasound in the neonatal period because they include follow-up to age 2 or later. Of particular value have been regional or population-wide studies of low birth weight infants with follow-up to at least school age, among which are included the NBH study from the United States and also important studies from Germany (Breeman et al., 2015; Bruin et al., 2015), Great Britain (Petrou et al., 2013), and Canada (Van Lieshout et al., 2015).

Newborn intensive care has been in place long enough that the first reports of adult outcomes in very small infants are now emerging (Saigal and Doyle, 2008). These studies paint a picture that is perhaps less dire than many had anticipated.

From 1959 to 1966, the National Collaborative Perinatal Project assembled data on approximately 50,000 pregnancies in 12 major medical centers and followed them to age 7 (Niswander, 1972). This highly productive exercise, one of whose major contributions was to show that birth asphyxia is a rare cause of cerebral palsy, has now been followed by the development of even larger pregnancy cohort studies. These studies, all of which archive biologic material such as blood and/or urine in pregnancy, should, in principle, permit us to learn a great deal about the unrecognized pregnancy factors that lead to adverse perinatal and child health outcomes. For reasons not entirely clear, a sample size of 100,000 has been universally adopted in studies in Norway (Magnus et al., 2006), Denmark (Olsen et al., 2001), and most recently Japan (Nitta, 2016). Efforts to mount a similar study in the United States were, unfortunately, not successful (Duncan et al., 2015).

Randomized Controlled Trials

Few areas of medicine have adopted the randomized trial as wholeheartedly as newborn medicine. The number of trials mounted has been large and their influence on practice strong. A notable influence on this field has been the National Perinatal Epidemiology Unit (NPEU) at Oxford University, established in 1978, which prioritized randomized trials among their several investigations of perinatal care practices and other circumstances affecting maternal and newborn outcomes. The NICHD neonatal research network was established in 1986, principally to support trials in *newborns*. Hundreds of trials have been mounted by just these two

organizations alone, but many other centers have contributed to the trial literature.

Trials in *pregnancy or in labor* have also been supported by the NPEU and by a network of obstetric centers supported by NICHD, the maternal-fetal network. These trials have often had important implications for newborns as well as for mothers; most notably, the one trial that has thus far successfully reduced the risk of preterm birth is the administration of 17 alpha-hydroxyprogesterone caproate in mid-gestation to high-risk women (Meis et al., 2003). Vaginal progesterone may also be effective (O'Brien and Lewis, 2016).

Most newborn trials have focused on outcomes evident in the newborn period, such as mortality, chronic lung disease, brain damage visualized on ultrasound, duration of mechanical ventilation, and/or hospital stay. Recently, however, trials extending into infancy or even to early childhood that incorporate measures of cognition or neurologic function have been a welcome addition to the trial arena. In the past few years we have learned from such trials that moderate hypothermia can reduce mortality and disability in asphyxiated term infants (Shankaran et al., 2005), caffeine treatment for apnea may reduce cerebral palsy (Schmidt et al., 2007), and magnesium sulfate administered in labor may reduce the risk of cerebral palsy (Rouse et al., 2008).

Trials in which both mortality and later outcome are combined raise complex methodologic issues. Imbalance in the frequency of the two outcomes being combined can result in random variation in the commoner outcome overwhelming a significant finding in the other. Providing the same weight in a trial to a disability and to a death raises ethical questions. Precisely how best to conduct such dual or multi-outcome trials is the subject of discussion and debate in the neonatal and epidemiologic communities.

As trials multiply, not all of them sufficiently powered, the methodology for summarizing them and drawing effective conclusions has become increasingly important to neonatologists. The terms *systematic review* and *metaanalysis* have firmly entered the research lexicon, especially the randomized trial literature. The Cochrane collaboration is an international organization that uses an army of volunteers to systematically review trial results in all fields of medicine. The collaboration, established in 1993, began in the field of perinatal medical trials. Systematic reviews of neonatal trials reviewed by the Cochrane Collaboration are hosted on the website of NICHD <https://www.nichd.nih.gov/cochrane>.

Summary and Conclusions

The patterns of disease, mortality, and later outcome in the perinatal period are complex. Some factors, such as the long-term trends in preterm birth and birthweight, are reasonably stable, while others, such as the rates of cesarean section and twinning, can undergo rapid change. The success of newborn intensive care is well established. No other organized medical care program, targeted at a broad patient population, has had such remarkable success in lowering mortality rates in such a short period of time. Much of that success is owed to the evidence-based nature of neonatal practice.

Nonetheless, this success has opened the door to new problems as survivors of intensive care face the challenges of the information age. Resource allocations similar to those that permitted the development of newborn intensive care are now needed to address the educational and rehabilitative needs of survivors. A hopeful sign is the success of some recently studied interventions in reducing the burden of brain damage.

On the nontechnologic front, targeted epidemiologic efforts to address perinatal disorders have yielded progress as well. Careful study of the circumstances surrounding infant sleep patterns led to active discouragement of prone sleeping, which has produced a halving of mortality from SIDS. Observational research, followed by two important randomized trials in Europe, led to interventions that increased folate intake in women of child-bearing age and a substantial reduction in the birth prevalence of neural tube defects.

The population-level study of health events occurring in pregnancy and infancy, their antecedents, and long-term consequences have been an important component of the success of newborn care. Careful self-evaluation through monitoring of vital data and of collaborative clinical data, rigorous assessment of new treatments through randomized trials, and alertness to opportunities to implement prevention activities following discovery of important risk factors should continue to guide care of the newborn.

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2

Biomedical Informatics in Neonatology

JONATHAN P. PALMA AND PETER TARCZY-HORNOCH

KEY POINTS

- Although health care remains a quintessentially human endeavor, computers are playing a growing role in information management, particularly in neonatology.
- *Biomedical informatics* can be defined as “the interdisciplinary field that studies and pursues the effective uses of biomedical data, information, and knowledge for scientific inquiry, problem solving, and decision making, driven by efforts to improve human health” (Shortliffe and Blois, 2014).
- The trend in electronic health record (EHR) adoption is moving away from niche systems specific to neonatology and toward enterprise-wide systems, highlighting the importance of neonatologist involvement in the selection, implementation, and optimization of EHRs, which are not configured out of the box for the care of critically ill neonates.
- In evaluating therapeutic recommendations, at least 50% of studied treatments are of uncertain benefit. This gap is an opportunity for both evidence-based medicine (clinical trials) and exploration of “practice-based evidence” generated from EHRs.

Background

At a fundamental level, the practice of neonatology can be considered an information management problem. The care provider is combining patient-specific information (history, physical examination findings, and results of physiologic monitoring, laboratory tests, radiologic evaluation) with generalized information (medical knowledge, practice guidelines, clinical trials, personal experience) to make medical decisions (diagnostic, therapeutic, and management). The Internet has made possible a revolution in the sharing and disseminating of knowledge in all fields, including medicine, with continued growth and maturation of online clinical information resources and tools.

Although medicine remains a quintessentially human endeavor, computers play a vital role in information management, particularly in neonatology. Patient-specific and generalized information (medical knowledge) are increasingly available in electronic form. In the United States, a majority of hospitals have implemented electronic health record (EHR; also known as an *electronic medical record*) systems to manage patient-specific information, with levels of EHR adoption ranging from nursing documentation on electronic flow sheets (93.7%) to entirely paperless hospitals (at least 4.2%) (Healthcare Information and Management Systems Society, 2016) (Table 2.1). The American Recovery and Reinvestment Act of

2009 (ARRA; i.e., the federal economic stimulus plan) included the Health Information Technology for Economic and Clinical Health (HITECH) act, a provision for the investment of \$19 billion in health information technology to motivate physicians to adopt EHRs and \$1.1 billion to research the effectiveness of certain healthcare treatments. These ARRA provisions were predicated on the belief that quality, safety, and efficiency of clinical care can be improved through electronic medical records and evidence-based practice, a notion emphasized in the Institute of Medicine (IOM) reports *To Err is Human* (2000), which suggested that up to 98,000 patients die annually as a result of preventable medical errors, and *Crossing the Quality Chasm* (IOM, 2001), which identified health information technology as one approach to mitigating these errors.

To encourage substantive EHR implementation, the Centers for Medicare and Medicaid Services (CMS) established **Meaningful Use** objectives necessary to qualify for federal incentive payments. In 2011, Stage 1 of Meaningful Use encouraged the implementation of basic EHR systems; in 2014, Stage 2 was designed to promote more advanced EHR functionality; in 2018, Stage 3 objectives, which focus on improving quality, safety, and efficiency to achieve improved health outcomes, will be required in order to avoid penalties (<https://www.healthit.gov/providers-professionals/how-attain-meaningful-use>). Due to challenges in meeting objectives without undue burden on providers, the requirements for each stage continue to evolve. Recently, CMS leadership suggested major changes to Stage 3, adding flexibility and shifting the focus from use of technology to achievement of health outcomes.

Parallel with and related to the adoption of information technology is the growth of societal pressures to improve the quality of medical care while controlling costs. These pressures are beginning to affect the way in which medicine and neonatology are practiced. In turn, it is becoming important for neonatologists to understand basic principles related to biomedical and health informatics, databases, electronic medical record systems, and evaluation of therapeutic recommendations.

This expansion of information technology in clinical practice and the concurrent growth of medical knowledge hold great promise but have potential pitfalls. One pitfall that must not be underestimated, and which is as great a danger today as when Blois (1984) first cautioned against it, is the unquestioning adoption of information technology:

And, since the thing that computers do is frequently done by them more rapidly than it is by brains, there has been an irresistible urge

TABLE 2.1 Healthcare Information and Management Systems Society EMR Adoption Model

UNITED STATES EMR ADOPTION MODEL SM		
Stage	Cumulative Capabilities	2015 Final %
Stage 7	Complete EMR; CCD transactions to share data; data warehousing; data continuity with ED, ambulatory, OP	4.2
Stage 6	Physician documentation (structured templates), full CDSS (variance & compliance), full R-PACS	27.1
Stage 5	Closed loop medication administration	35.9
Stage 4	CPOE, clinical decision support (clinical protocols)	10.1
Stage 3	Nursing/clinical documentation (flow sheets), CDSS (error checking), PACS available outside radiology	16.4
Stage 2	CDR, controlled medical vocabulary, CDS, may have document imaging; HIE capable	2.6
Stage 1	Ancillaries – lab, rad, pharmacy – all installed	1.7
Stage 0	All three ancillaries not installed	2.1
n = 5460		

CCD, continuity of care document; CDR, clinical data repository; CDS, clinical decision support; CDSS, clinical decision support systems; CPOE, computerized provider order entry; ED, emergency department; EMR, electronic medical record; HIE, health information exchange; OP, outpatient; PACS, picture archive and communication systems; R-PACS, Radiology picture archive and communication systems.
Data from HIMSS Analytics™ Database © 2016.

to apply computers to medicine, but considerably less of an urge to attempt to understand where and how they can best be used.

Adoption and meaningful use of EHRs is not simply a technology challenge: it is a people and process challenge as well. The recently established Clinical Informatics medical subspecialty aims to train physicians in the skills required to address each of these challenges.

Another present and real challenge is information overload, both in terms of the exponentially increasing corpus of medical knowledge and the large amounts of data available within EHRs. As early as 1995, [Bero and Rennie](#) observed:

Although well over 1 million clinical trials have been conducted, hundreds of thousands remain unpublished or are hard to find and may be in various languages. In the unlikely event that the physician finds all the relevant trials of a treatment, these are rarely

accompanied by any comprehensive systematic review attempting to assess and make sense of the evidence.

The potential of just-in-time information at the point of care is thus particularly appealing, especially considering that the growth in published literature continues at an accelerating rate, with a flood of new knowledge coming from the latest research in genomics, proteomics, metabolomics, and systems biology. In addition, the adoption of EHRs has resulted in the collection of large amounts of clinical data as a byproduct of routine care. A vision to address this was articulated by one of the editors of the *British Medical Journal*: “New information tools are needed: they are likely to be electronic, portable, fast, easy to use, connected to both a large valid database of medical knowledge, and the patient record” ([Smith, 1996](#)). More recently, the IOM published *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America* (2012), which calls for transformation of the healthcare system into one that learns from each patient treated and makes the information produced from prior patient encounters (along with evidence from the literature) available at the point of care.

Although progress in healthcare information technology tools is being made, there is significant opportunity to develop, implement, and optimize electronic tools for neonatal care.

Biomedical and Health Informatics

In the 1970s, clinicians with expertise in computers became intrigued by the potential of these tools to improve the practice of medicine, and thus the field of medical informatics was born ([McDonald, 1976](#)). The importance of this field in addressing the issues of information management in health care is growing rapidly, as evidenced by the activities of the American Medical Informatics Association ([AMIA; www.amia.org](#)), including the establishment of Clinical Informatics as a subspecialty by the American Board of Medical Specialties (ABMS) in 2011. *Biomedical informatics* can be defined as “the interdisciplinary field that studies and pursues the effective uses of biomedical data, information, and knowledge for scientific inquiry, problem solving, and decision making, driven by efforts to improve human health” ([Shortliffe and Blois, 2014](#)). A more extensive definition can be found at the AMIA website under About AMIA, including professional and training opportunities. The University of Washington (Seattle, Washington, USA) website (<http://bime.uw.edu/>) contains a review of the discipline (found under History, About Us, Vision). The field includes both applied and basic research, with the focus of this chapter being on the applied aspects. Examples of basic research are artificial intelligence in medicine, genome data analysis, and data mining (analyzing data to identify patterns and establish relationships). As our knowledge of the genetic mechanisms of disease expands and more data about patients and outcomes are available electronically, the role of informatics in medicine will expand, particularly in the field of neonatology.

The applied focus of the field in the 1960s and 1970s was data oriented, focusing on signal processing and statistical data analysis. In neonatology, the earliest applications of computers were for physiologic data monitoring in the neonatal intensive care unit (NICU). As the field matured in the 1980s, applied work focused on systems to manage patient information and medical knowledge on a limited basis. Examples include laboratory systems, radiology systems, centralized transcription systems, and, probably the best-known medical knowledge management system, the database of published medical articles maintained by the [National Library of Medicine](#) known first as MEDLARS, then as MEDLINE, and

currently as PubMed (www.ncbi.nlm.nih.gov/pubmed). In addition, neonatologists began to develop tools to aid in the management of patients in the NICU, such as computer-assisted algorithms to help manage ventilators, although the algorithms have not been successfully deployed on a large scale in the clinical setting.

As computers and networking became mainstream in the workplace and home in the 1990s, informatics researchers began to develop integrated and networked systems (Fuller, 1992, 1997). With the explosion of information from the Human Genome Project, the intersection between bioinformatics and medical informatics began to blur, leading to the adoption of the term *biomedical informatics*. The 1990s saw the development of a number of important systems. In terms of patient-specific information retrieval, these systems included integrated electronic medical record systems that in their full implementation can encompass—in a single software application—interfaces to physiologic monitors; electronic flow sheets; access to laboratory and radiology data; tools for electronic documentation (charting), electronic order entry, and integrated billing; and modules to help reduce medical errors. The Internet has permitted ready access and sharing of this information within healthcare organizations and limited secured remote access to this information from home. In terms of patient-population information retrieval, a number of tools were developed to help clinicians and researchers examine aggregate data in these electronic medical records to document outcomes and help to improve quality of care.

The Internet, particularly the World Wide Web, transformed access to medical knowledge (Fuller et al., 1999). Health sciences libraries are increasingly digital, rather than paper repositories. Journals are available online; some are offered exclusively online. Knowledge is available at the point of care in ways that were not previously possible (Tarczy-Hornoch et al., 1997). In 2004, in recognition of the unfulfilled potential of healthcare information technology, the Office of the National Coordinator for Health Information Technology (ONC) was established (<https://www.healthit.gov/>) to achieve the following vision:

Health information technology (HIT) allows comprehensive management of medical information and its secure exchange between health care consumers and providers. Broad use of HIT has the potential to improve health care quality, prevent medical errors, increase the efficiency of care provision, and reduce unnecessary health care costs, increase administrative efficiencies, decrease paperwork, expand access to affordable care, and improve population health.

Throughout the first decade of the 21st century, the focus shifted from demonstrating the promise of electronic medical record and information systems toward implementing them more broadly to realize their benefit (e.g., the ARRA legislation). The pursuit of evidence-based practice can benefit from informatics as an approach to support evaluation of therapeutic recommendations and their implementation (see later discussion) and was part of the ARRA and other approaches to healthcare reform being proposed in 2009. The enormous amount of data being generated through routine use of electronic medical records has the potential to serve as “practice-based evidence,” adding to the medical knowledge base when high quality evidence either doesn’t exist or isn’t applicable to the patient population of interest.

The establishment of Clinical Informatics as a subspecialty in 2011 is further evidence of the evolution of informatics as a medical discipline (Frequently Asked Questions website (<https://>

www.amia.org/clinical-informatics-board-review-course/faq). The core content of the subspecialty was defined by AMIA in 2008, and in 2009 the American Board of Preventive Medicine agreed to sponsor the application to the ABMS for Clinical Informatics as a new subspecialty. The ABMS ultimately approved the proposal in 2011, and the first board examination was offered in 2013. In order to sit for the subspecialty boards, candidates must be certified in another ABMS clinical specialty, hold a valid medical license, and (through 2017) qualify either via a practice pathway (at least 25% of a full-time equivalent for 3 years) or the fellowship training pathway. In 2014, the Accreditation Council for Graduate Medical Education (ACGME) released the Program Requirements for Graduate Medical Education in Clinical Informatics, and beginning in 2018, completion of an ACGME-accredited fellowship training program will be required for subspecialty board eligibility (<https://www.amia.org/programs/academic-forum/clinical-informatics-fellowships>).

The practice of neonatal intensive care can clearly benefit from the support of information technology tools; as such, neonatologists have long been involved in informatics. In 1988, as one of the earlier specialties to develop a national database of clinical care, neonatologists established and expanded the Vermont Oxford Network (VON) (www.vtoxford.org) to improve the quality and safety of medical care for newborn infants and their families. As part of their activities, the VON established and maintained a nationwide database about the care and outcome of high-risk newborn infants. Duncan (2015) maintains a continually updated bibliographic database on the history of computer applications in neonatology.

Databases

In broad terms, a database is an organized, structured collection of data designed for a particular purpose. Thus a stack of 3×5 cards with patient information is a database, as is the increasingly rare paper prenatal record. Most frequently, the term *database* is used to refer to a structured electronic collection of information, such as a database of clinical trial data for a group of patients in a study. Databases come in a variety of fundamental types, such as single-table, relational, and object-oriented.

A simple database can be built using a single table by means of a spreadsheet program such as Microsoft Excel or a database program such as Microsoft Access (Microsoft, Redmond, Washington, USA). The advantage of such a database is that it is easy to build and maintain. For an outcomes database in a neonatology unit, each row can represent a patient and each column represents information about the patients (e.g., name, medical record number, gestational age, birth date, length of stay, patent ductus arteriosus [yes/no], necrotizing enterocolitis [NEC; yes/no]). The major limitation of such a database is that a column must be added to store the information each time the researcher wants to track another outcome (e.g., maple syrup urine disease [MSUD]). This limitation can result in tables with dozens to hundreds of columns, which can become difficult to maintain. The challenges can be illustrated with a few examples. One type of challenge results from adding a new column (e.g., MSUD); one must either review all records (rows) already in the spreadsheet for the presence or absence of MSUD or flag all existing records (rows) in the spreadsheet as *unknown* for MSUD status. Another set of challenges results from the logistics of managing an extremely wide spreadsheet – imagine not adding the 10th column but the 1000th column.

The majority of databases and electronic medical records in neonatology are built using relational database software. To build a simple outcomes relational database that permits easy adding of

Tables in the database:

DEMOGRAPHIC DATA	DIAGNOSES	DIAGNOSIS DICTIONARY
Name Hospital_Number Gestational_Age Birthdate Admit_Date Discharge_Date	Hospital_Number Diagnosis_Code Value	Diagnosis_Code Description

Example entries in the tables:

DEMOGRAPHIC DATA						
Name	Hospital_Number	Gestational_Age	Birthdate	Admit_Date	Discharge_Date	
John Smith	00-00-01	27	1/1/2003	1/1/2003	3/21/2003	
Jane Doe	00-00-02	24	1/2/2003	1/3/2003	4/15/2003	

DIAGNOSES		
Hospital_Number	Diagnosis_Code	Value
00-00-01	1	1
00-00-01	2	1
00-00-02	1	2
00-00-02	10234	

DIAGNOSIS DICTIONARY	
Diagnosis_Code	Description
1	PDA (1 = small, 2 = large)
2	NEC (1 = medical, 2 = surgical)
....	
10234	Maple Syrup Urine Disease

• **Fig. 2.1** Example of a Relational Database. *PDA*, patent ductus arteriosus; *NEC*, necrotizing enterocolitis.

new outcome measures, one could use a three-table database design (Fig. 2.1). The DEMOGRAPHIC DATA table contains demographic information for each patient (e.g., Name, Hospital Number [medical record number], Gestational Age). The DIAGNOSIS DICTIONARY table assigns a code number to each diagnosis or outcome being tracked (e.g., patent ductus arteriosus [PDA] = 1; NEC = 2; MSUD = 10234) and defines additional diagnosis descriptors. The DIAGNOSES table links patients (using Hospital Number [i.e., medical record number]) to their diagnoses and assigns a Value to the Diagnosis Code as a descriptor. Adding a new diagnosis to track simply requires adding an entry to the DIAGNOSIS DICTIONARY table. To add a diagnosis to a patient, one would add an entry to the DIAGNOSES table. For example, Girl Smith (medical record number 00-00-01) has a diagnosis of NEC. To add the diagnosis, add to the DIAGNOSES table an entry of “00-00-01” in the Hospital Number column, “2” (the code for NEC) in the Diagnosis Code column, and “2” in the Value column (corresponding to a Description for surgical in the DIAGNOSIS DICTIONARY). Although relational databases are harder to build, they provide greater flexibility for expansion and maintenance and thus are the preferred implementation for clinical databases. They address the challenges in a simple spreadsheet by tracking dates that new diagnostic codes were added and with user interfaces that allow one to easily view only diagnoses present for a given patient rather than all potential diagnoses.

The distinction between a NICU quality assessment–quality improvement (i.e., outcomes) database and an electronic medical record is largely a matter of degree. Some characteristics typical of a neonatal outcomes database are data collection and data entry after the fact, limited amount of data collected (a small subset of

the information needed for daily care), lack of narrative text, lack of interfaces to laboratory and other information systems, and the episodic (e.g., quarterly) use of the system for report generation. Some characteristics typical of an electronic medical record are real-time (many times daily) data entry, a large amount of data collected (approximating all the information needed for daily care in a fully electronic care environment), narrative text (e.g., progress notes, radiology reports, pathology reports), interfaces to laboratory and other information systems, and, most important, the use of the system for daily patient care, including features such as results review, messaging or alerting for critical results, decision support systems (drug dosage calculators, drug–drug interaction alerts, among others), and computerized electronic order entry.

In the past, the majority of neonatal databases and first-generation NICU electronic medical record systems were developed locally by and for neonatologists. A review describing these efforts is available online at www.neonatology.org/technology/computers.html (Duncan, 2015). Unfortunately the majority of these systems were never published or publicly documented, and thus a number of important and useful innovations have been lost or must be repeatedly rediscovered. Anyone considering building their own neonatology database would be well advised to review the existing literature and existing commercial products before embarking on this path. That said, there is room for improvement of the existing products, and neonatologists continue to develop their own databases today. With the trend toward enterprise-wide, interoperable EHRs, it is likely that the market will continue to transition from external niche applications toward a smaller number of major EHR vendors whose applications include integrated neonatology specific tools.

The largest neonatal outcomes database is the centralized database maintained by the VON with the mission of improving the quality and safety of medical care for infants and their families. One of the key activities of the network is their outcomes database, which involves more than 900 participating intensive care nurseries both in the United States and internationally collecting data on over 60,000 very low birth weight infants each year. Other activities of the network are clinical trials, follow-up of extremely low birth weight infants, and NICU quality and safety studies. Although the initial focus of VON was very low birth weight infants (401–1500 g), a newer “Expanded Database” also includes data on infants in neonatal intensive care units weighing more than 1500 g. Currently the network collects data on the majority of very low birth weight infants born in the United States. The databases focus on tracking outcomes. With the passage of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and federal regulations governing the confidentiality of electronic patient data, some of the anonymous demographic data that were collected by the network in the past have decreased, due to concern that in combination with the identity of the referring center, these data could be used to uniquely identify patients.

Participants in the network submit data and in return receive outcome data for their own institution and comparative data from other nurseries nationwide, including custom reports, comparison groups, and quality management reports. Members also have the ability to participate in collaborative research projects and collaborative multicenter quality-improvement activities. All data except their own are anonymous for all participants. The network does have access to both the individual and aggregate data. The network database is maintained centrally, and data quality monitoring and data entry are centralized. Initially the process involved paper submission of data by participating nurseries. Now, most commercial and custom NICU databases and electronic medical record systems can be used to export much of the information required by the VON, but identification of some clinical details still relies on chart review. Members have the option to submit data electronically in two ways: either directly using the custom eNICQ software developed by VON or by transmitting spreadsheet files to VON for entry into the database.

Certainly, other neonatology outcomes databases exist for purposes ranging from quality improvement to clinical research. Examples include the [Children’s Hospitals Neonatal Database](http://thechn.org/CHND-resources.php) (<http://thechn.org/CHND-resources.php>) for improving quaternary neonatology care and the [National Institute of Child Health and Human Development \(NICHD\) Neonatal Research Network Generic Database](https://neonatal.rti.org/about/gdb_background.cfm) (https://neonatal.rti.org/about/gdb_background.cfm), which in addition to the clinical trials conducted by the Neonatal Network has been enrolling infants at Network sites in an observational study since 1987.

Electronic Health Record

The EHR, also known as an *electronic medical record*, is much more complex than an outcomes database, because the system is intended to be used continually in real time to replace electronically some, if not all, of the record keeping, laboratory result review, and order writing that occur in a NICU (or more generically in any inpatient or outpatient clinical setting). The complexity of this task becomes evident if one imagines that, for a paperless medical record environment, every paper form in a nursery would need to be replaced with an electronic equivalent. Even more challenging is the

conversion of each paper-based workflow element and process into an electronic one.

Most US healthcare organizations have adopted EHR functionality because of a combination of forces, such as the desire to reduce error and to control the spiraling costs of health care. These reasons were addressed at great length in two reports from the IOM ([Institute of Medicine Committee on Improving the Patient Record, 1997](#); [Kohn et al., 2000](#)). Benefits are typically achieved when information is available electronically (e.g., results of laboratory tests, radiology procedures, transcription) and input into the system (e.g., problem lists, allergies) and when both sets of information are combined and checked against electronic orders. The adoption of computerized provider order entry (CPOE) has been shown to reduce errors and affect care provider behavior ([Radley et al., 2013](#)). Combining just electronic laboratory results (e.g., creatinine level) and electronic order entry (e.g., a drug order), for example, enables one to verify that drug dosages have been correctly adjusted for renal failure. This approach is more straightforward in adults, but in neonates, whose renal function is more difficult to assess and for whom drug dosage norms depend on gestational age and post-delivery age, the system must be able to capture additional information (e.g., urine output, gestational age) and requires more sophisticated logic. Nearly two decades following the aforementioned Institute of Medicine reports, and supported by stimulus funding through the ARRA HITECH act, nearly 75% of US hospitals have implemented CPOE ([Healthcare Information and Management Systems Society, 2016](#); [Adler-Milstein, 2015](#)).

Results of review systems include basic demographic data, such as name, age, and address from the hospital registration system. These systems require a moderate amount of work to tie them to the various laboratory, radiology, and other systems and to train users. The benefits are hard to quantify, but users typically prefer them to the paper alternative because of the more efficient access to information. The challenge in moving beyond the results review level to the integrated system level is that some degree of electronic documentation and CPOE are essentially prerequisites but are challenging to implement in terms of both human and financial costs. Implementation of integrated systems requires significant work, including infrastructure demands like the presence of computers at each bedside and network availability, as well as significant effort to educate and train users. The benefits accrue mainly to the organization, in the form of reduced costs of filing, printing, and maintaining paper records and, if providers enter notes electronically instead of dictating them, significant savings in transcription costs. Unfortunately, much of the burden of integrated systems is passed on to end users, who often find that it takes much longer to do their daily work with electronic documentation. Without implementation of CPOE and associated clinical decision support (CDS) systems, the users and patients do not realize major day-to-day benefits.

The benefits of EHR adoption start to accrue more clearly at the next level of electronic order entry. The complexity of implementing and deploying an electronic order entry system cannot be overstated. Interfaces need to be built with all the systems that are part of results review in addition to other systems. Furthermore, a huge database of possible orders must be created. Finally, and most important, training end users presents a significant challenge, because writing orders electronically is more complex and time consuming than writing them by hand. The change in management issues becomes apparent when one considers that typically these systems take the unit assistant out of the loop; therefore much of the oversight that can occur at the unit assistant level does not,

or the burden of oversight is borne by the person entering the orders. Further complicating matters, despite the mitigation of issues like illegibility and order of magnitude math errors, CPOE systems introduce new types of errors, such as juxtaposition errors (e.g., clicking on the wrong patient or selecting the wrong order in a list) (Ash, 2007; Longhurst et al., 2013).

After overcoming the barriers to electronic order entry, organizations can start to benefit from integrated systems. For this reason, the trend today is not a stepwise move from results review to documentation of integrated systems. Instead, organizations are moving from results review directly to integrated systems. Interestingly, the technical complexities and the training and usage complexities of integrated systems are not much higher than those for order entry. Integrated systems add tools to make life easier for care providers using all the data in the system. As an analogy, an integrated EHR system is like an office software suite that encompasses a word processor, a spreadsheet, a slide presentation tool, a graphic drawing tool, and a database, all of which can communicate with one another, making it easy to put a picture from the drawing tool or a graph from a spreadsheet into a slide show.

Integrated systems include (1) checking orders for errors, (2) alerts and reminders triggered by orders or by problems on the problem list or other data in the system, (3) care plans tied to patient-specific information, (4) charting modules customized to the problem list, (5) charting and progress notes that automatically import information (e.g., from laboratory tests, flow sheets) and that help generate orders for the day as the documentation occurs, (6) modules to facilitate hyperalimentation ordering, and (7) modules to assist in management (Palma et al., 2011b, 2011c; Palma and Arain, 2016). For example, a system could be configured such that reminders for screening studies (e.g., for retinopathy of prematurity, intraventricular hemorrhage, and brainstem auditory evoked response) are triggered by gestational age, a problem list, and previous results of screening studies. Similarly, admitting a neonate at a particular gestational age with a particular set of problems could trigger pathways, orders, and reminders specific to that clinical scenario. An important caveat is that all such systems are only as good as the data and rules put into them. The issues raised in the section on evaluation of therapeutic recommendations are important to consider in the context of electronic order entry and integrated systems. Additionally, enterprise-wide (non-niche) EHRs are not sufficiently configured out of the box for optimal care of critically ill and premature neonates.

The EHR market is continually evolving; this is true of products designed specifically for the NICU and more generic products designed to be used throughout a hospital or healthcare system. The ONC was established, in part, to affect the EHR marketplace by creating standards and certification bodies. In particular, the ONC created the Certification Commission for Healthcare Information Technology (CCHIT) and the Health Information Technology Standards Panel to begin to bring more standardization to the marketplace. The CCHIT examined criteria for certifying systems, including functionality, security, and interoperability. Facilitated by ARRA HITECH incentives, integrated systems are becoming more broadly implemented. However, the needs of different healthcare systems and the clinical services within a single health system vary significantly; in general, existing products are not configured to meet all these needs out of the box. Furthermore, the trend among healthcare organizations, EHR developers, and vendors is to move away from niche systems tailored to particular subsets of care providers, such as neonatology, and toward a focus

on systems that are generically useful. There are two important drivers behind this trend.

The first and most important reason for adopting a single integrated system is that the benefits of an EHR system begin to accrue only when an entire organization uses the same one. Consider the following scenario: a woman receives prenatal care in the clinic of an institution and is then admitted to the emergency department in preterm labor. Her infant is delivered in the labor and delivery department, hospitalized in the NICU, and discharged to an affiliated pediatric follow-up clinic. In the era of paper medical records, paper is used to convey information from one site to the other. In an integrated EHR system, all the information for both mother and infant is in one place for all providers to see. Interoperability is important as well if the care described crosses organizational boundaries, such as an outpatient-focused health maintenance organization contracting inpatient obstetric care to one hospital system and neonatal or pediatric care to a children's hospital in a different healthcare system. If a single unified institution were to adopt niche software tailored to the needs of each site, a provider caring for the infant might need to access an emergency department system, an obstetric system, a NICU system, and an outpatient pediatric system to gather all the pertinent information. Each system would require the user to learn a separate piece of software. Learning a site-specific piece of software is a considerably greater burden on care providers than learning to use a site-specific paper form. If care crosses organizations with electronic systems that are not interoperable, then care transitions most often remain on paper.

The second factor driving adoption of integrated systems is economies of scale. The ideal EHR system contains electronic interfaces that automatically import the system data from laboratory, pharmacy, radiology, transcription, integrated electronic orders, error checking, and electronic documentation by care providers. Given that development of these interfaces, training, and maintenance cost more than the purchase of the software itself, it is far more cost-effective to install one system with one set of interfaces and one set of training and maintenance issues than to replicate the process multiple times.

The neonatal intensive care environment poses some unique challenges for EHRs. As a result, it is important to ensure that when healthcare systems are making decisions about the purchase of an EHR, neonatologists and other neonatal healthcare providers are involved in the process. An excellent source of historical information about NICU medical record systems and databases is an article by Stavis (1999). More recently, Palma et al. reviewed several aspects of EHRs related to neonatology, including computerized provider order entry (Palma et al., 2011a), handoffs (Palma et al., 2011c), and clinical data entry and display (Palma et al., 2012b). Neonatal care providers who are helping to select an EHR system should acquire the necessary background knowledge through reading some basic introductory texts on medical informatics, focusing on EHRs. It is then critical that they survey other organizations similar to their own to understand the benefits and drawbacks of various EHR systems for neonatal care. For example, the needs of a level III academic nursery that performs extracorporeal membrane oxygenation are different from those of a community level II hospital that does not perform mechanical ventilation. Systems that work well in teaching hospitals with layers of trainees may not work well in private practice settings and vice versa. Importantly, when using a medical informatics framework, neonatal care providers should develop a list of prioritized criteria specific to their institution and evaluate available products in the marketplace using this list, while also considering whether the system meets CCHIT standards as described earlier.

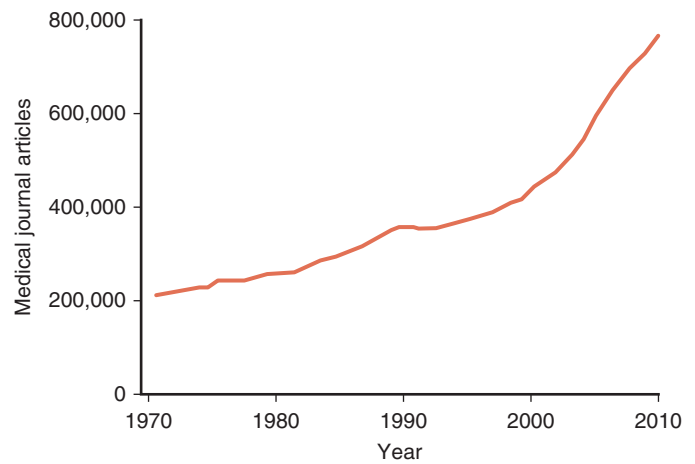
All end users' needs must also be considered. If residents, nurse practitioners, nutritionists, pharmacists, and respiratory therapists are expected to use the system, their input must be solicited. Ensuring broad-based input is especially relevant as the EHR system is likely to require significant data entry by healthcare providers (e.g., electronic nursing and respiratory therapist [RT] documentation, note writing, medication administration records, order entry). Involvement of all stakeholders is an important component of change management; in addition, following implementation, their input is critical for optimizing the system for care in the NICU. Unfortunately there is little literature on this issue, because institutions rarely publicize and publish their failures in this arena, although the situation is beginning to change. A review of some of these challenges and a theoretical framework for looking at them is provided by Pratt et al. (2004), and an evidence-based approach to mitigating unintended consequences of EHR implementation is discussed by Longhurst et al. (2013).

The final step in evaluating and testing a potential system is to develop a series of scenarios and to have potential users test the scenarios. Evaluating usage scenarios prior to vendor selection typically involves visits to sites that have installed the EHR system under consideration. An example scenario might be for a nurse, a respiratory therapist, a resident, and an attending physician to try to electronically replicate, on a given system under consideration, the bedside charting, progress note charting, and order writing for a critically ill patient who undergoes extracorporeal membrane oxygenation from hospital admission through decannulation. Developing and testing such scenarios are the best way to ensure that aspects of charting, note writing, and documentation unique to the NICU are supported by the system.

Evaluating Therapeutic Recommendations

Once all the data about a patient, whether in electronic or paper form, are in hand, the clinician is faced with the challenge of medical decision making and applying all that he or she knows to the problem. It is vital that clinicians understand what is known and what is still uncertain in terms of the validity of therapeutic recommendations. The evaluation of new recommendations arising from a variety of sources, including journal articles (Fig. 2.2), metaanalyses, and systematic reviews, is a critical skill that all neonatologists must master. Broadly speaking, this approach has been termed *evidence-based medicine*. Although a full discussion is beyond the scope of this chapter, there are two outstanding sources of information on the subject, one by Guyatt and Rennie (2015) and the other by Straus et al. (2010). A useful discussion of clinical practice guidelines as they relate to neonatology is provided by Polin and Lorenz (2015). An important caveat is that evidence-based medicine is not a panacea. It is not helpful when the primary literature does not address a particular clinical situation, such as one that is rare or complex. This approach also does not necessarily address broader concerns, such as clinical importance or cost-effectiveness, although it sometimes does. There are potential challenges when combining evidence-based medicine with the emerging humanistic approach to health care, which can heavily weight patient preferences potentially over the evidence base.

In the early days of medicine, the standard practice was observation of individual patients and subjective description of aggregate experiences from similar patients. As the science of medicine evolved, formal scientific methods were applied to help to assess possible therapeutic and management interventions. Important tools in this effort are epidemiology, statistics, and clinical trial design. Currently medicine in general and neonatology in particular are

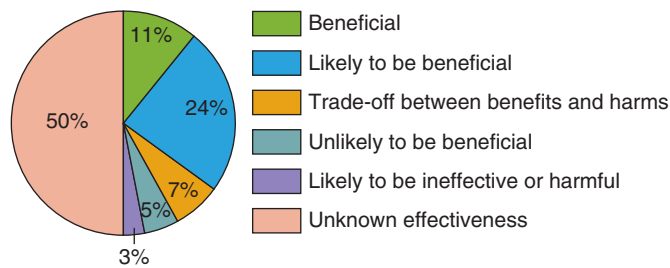


• **Fig. 2.2** Yearly Citation Totals From 2015 MEDLINE/PubMed From 1970 to 2016. (Redrawn from https://www.nlm.nih.gov/bsd/licensee/2017_stats/2017_Totals.html.)

faced with an interesting paradox. For some areas, there is a wealth of information in the form of randomized controlled clinical trials, whereas for others, there is scant information to guide clinical practice. A wealth of well-designed clinical trials on the use of surfactant have been published, for example, but there are essentially no trials addressing the management of chylothorax. The lack of studies of (and therefore evidence for) treatments in neonatology has led to newborns being described as “therapeutic orphans” (Stiers and Ward, 2014).

One might assume that the practice of medicine reflects the available evidence, but this is not the case. McDonald (1996) summarized the problem as follows: “Although we assume that medical decisions are driven by established scientific fact, even a cursory review of practice patterns shows that they are not.” A study of 3000 treatments (as reported in randomized controlled trials) in the *British Medical Journal's* Clinical Evidence database (<http://clinicalevidence.bmj.com>) shows that, as of 2016, 50% of treatments are of unknown effectiveness, 11% are clearly beneficial, 24% are likely to be beneficial, 7% are a tradeoff between beneficial and harmful, 5% are unlikely to be beneficial, and 3% are likely to be ineffective or harmful (Fig. 2.3). As a result, neonatologists have a responsibility to identify what knowledge is available in the literature and elsewhere and to critically evaluate this information before applying it to practice. Furthermore, because this information is constantly evolving, practitioners must continually revisit the underlying literature as it expands (e.g., the recommendations regarding the use of steroids for chronic lung disease).

For the 50% of treatments with known (whether beneficial or harmful) effectiveness, the evidence-based practice of medicine is an approach that addresses these issues. It is helpful to consider the process as involving two steps: first, a critical review of the primary literature and second, the synthesis of information in the primary literature to determine the implications on one's practice. Most neonatologists have significant experience with critical review of the literature through journal clubs and other similar forums. The approach involves systematically reviewing each section of an article (i.e., background, methods, results, discussion) and asking critical questions for each section (e.g., for the Methods section: Is the statistical methodology valid? Were power calculations made? Was a hypothesis clearly stated? Do the methods address the hypothesis? Do the methods address alternative hypotheses? Do the methods address confounding variables?). The formal evaluation of each section must then be synthesized into conclusions. A helpful



Effectiveness of 3000 treatments as reported in randomized controlled trials selected by Clinical Evidence. This does not indicate how often treatments are used in healthcare settings or their effectiveness in individual patients.

• **Fig. 2.3** Effectiveness of 3000 Treatments Reported in Randomized Controlled Trials. (Redrawn from <http://clinicalevidence.bmj.com/x/set/static/cms/efficacy-categorisations.html>.)

question to ask is, “Does this paper change my clinical practice, and if so, then how?” Additional resources for systematic review of the primary literature are listed in the Suggested Readings. It is important to note that guidelines for systematic review of a single article differ according to whether it describes a preventive or therapeutic trial (e.g., use of nitric oxide for chronic lung disease), evaluation of a diagnostic study (e.g., use of C-reactive protein level for prediction of infection), or prognosis (e.g., prediction of outcome from a Score for Neonatal Acute Physiology score).

The second, and arguably more important, step is to determine not the effect of one article on one’s practice but the overall effect of the body of relevant literature on one’s practice. For example, if the preponderance of the literature favors one therapeutic recommendation, then a single article opposing the recommendation must be weighed against the other articles that favor it. This task is complex, and the most complete and formal statistical approach to combining the results of multiple studies (i.e., metaanalysis) requires significant investment of time and effort. Part of the evidence-based practice of medicine approach therefore involves the collaborative development of evidence-based systematic reviews and metaanalyses by communities of care providers. Within the field of neonatology, Sinclair et al. (1992) laid the seminal groundwork for this approach; their textbook *Effective Care of the Newborn Infant* remains an important milestone, but it illustrates the problem of information currency. Because the book was published in 1992, none of the clinical trials in neonatology in the last decade and a half are included. The Internet has permitted creation and continual maintenance of up-to-date information by a distributed group of collaborators, lending itself well to the maintenance of a database of evidence-based medicine reviews of the literature. This international effort is the Cochrane Collaboration, which began in 1993 with the *Cochrane Neonatal Review*. A limitation of the Cochrane approach is illustrated by the relatively restricted scope of topics covered at the NICHD website (<https://www.nichd.nih.gov/cochrane/Pages/default.aspx>). The existence of a review requires adequate literature on a topic and a dedicated and committed clinician to create and update the review.

It is important to distinguish between these formal approaches to reviewing the literature (i.e., systematic literature reviews and metaanalyses) that have specific methodologies and more ad hoc reviews of the literature. Evidence-based medicine aggregate resources such as the Cochrane Collaboration take a more systematic approach, but review articles published in the literature vary in their approach. Metaanalyses are easy to distinguish, but systematic reviews versus

ad hoc reviews are harder to distinguish. Systematic reviews focus on quality primary literature (e.g., controlled studies rather than case series or case reports) and must include a Methods section for the review article that (1) explicitly specifies how articles were identified for possible inclusion and (2) the criteria used to assess the validity of each study and to determine whether to include or exclude primary literature articles in the systematic review. Systematic reviews also tend to present the literature in aggregate tabular form, even when metaanalyses of statistics of all the articles cannot be done. One commonly used source of overview information in neonatology—the *Clinics in Perinatology* series—is a mix of opinion (written in the style of a book chapter), ad hoc literature review, systematic literature review, and metaanalysis. Clinical practice guidelines (e.g., screening recommendations for group B streptococcal infection), although based on a primary literature review, are typically neither metaanalyses nor systematic reviews of the literature. Whereas formal methods are used to derive conclusions with metaanalyses and systematic reviews, frequently guidelines are developed instead by consensus among committee members; this is true of both national and local practice guidelines. General textbooks of neonatology are typically based on ad hoc literature reviews that include both primary literature and systematic literature reviews. When reading overviews of the aggregate state of current knowledge on a given topic in neonatology, it is important to keep these distinctions in mind.

Anyone interested in developing evidence-based reviews on a particular topic should review the textbooks on evidence-based practice referenced at the end of this chapter. Initially, it is a good idea to collaborate with someone with experience in systematic review and metaanalysis. The process consists of the following steps: (1) identifying the relevant clinical question (e.g., management of bronchopulmonary dysplasia); (2) narrowing the question to a focus that enables one to determine whether a given article in the primary literature answers it (e.g., does prophylactic high-frequency ventilation have positive or negative effects on acute and chronic morbidity – pulmonary and otherwise?); (3) extensively searching the primary literature (frequently in collaboration with a librarian with expertise searching the biomedical literature) and retrieving the articles; (4) critically, formally, and systematically reviewing each article for inclusion, validity, utility, and applicability; and (5) formally summarizing the results of the preceding process, including conclusions valid throughout the body of included primary literature.

Online Resources

A number of online resources are valuable for neonatologists. For accessing the primary literature, the most valuable resource is the National Library of Medicine’s database of the published medical literature accessible (PubMed; www.ncbi.nlm.nih.gov/pubmed) along with many other databases accessible from the Health Information Website (www.nlm.nih.gov/hinfo.html). The PubMed system is continually being enhanced; therefore it is useful to review the help documentation online and regularly check the New/Noteworthy section to see what has changed. One of the most powerful yet underused tools is the Similar Articles tool that is available as a link below each article listed on PubMed and is visible as a list adjacent to an article or abstract as it is being viewed (Liu and Altman, 1998). The PubMed system applies a powerful statistical algorithm to each word in the title, each author, each major and minor keyword (Medical Subject Heading terms), and each word in the abstract in order to find similar articles in the database. In general,

this system outperforms novice-to-advanced healthcare providers performing a complex search and approaches the accuracy of an experienced medical librarian. Another powerful search tool within PubMed is the Clinical Query (www.ncbi.nlm.nih.gov/pubmed/clinical). This tool facilitates searches for papers by clinical study category (e.g., etiology, diagnosis, therapy, prognosis), focuses on systematic reviews, and performs Medical Genetics searches – the last of which is particularly useful in the context of neonatology. All the major pediatric journals are available online either through a package at local hospital libraries or by subscription, instead of or in addition to a print subscription. The best free online source of information on evidence-based practice is the *Cochrane Neonatal Review*. Subscriptions to the full Cochrane database can be purchased online as well.

Given the growing role of genetics in health care, and the particular importance of genetic diseases in infants, two notable genetics databases are available free of charge online (in addition to the Medical Genetics search within PubMed Clinical Queries). The first is *Online Mendelian Inheritance in Man* (www.ncbi.nlm.nih.gov/omim). This database, which is a catalog of human genes and genetic disorders, is an online version of the textbook by the same name. It is a diachronic collection of information on genetic disorders, meaning that each disease entry chronologically cites and summarizes key papers in the field. The second is *GeneTests* (www.genetests.org), a directory of genetic testing (what testing is available on a clinical and research basis, where, and how one sends a specimen) and a user's manual (how to apply genetic testing). The user's manual section consists of entries for a growing number of diseases or clinical phenotypes of particular importance. Entries are written by experts, peer reviewed both internally and externally, subjected to a formal process similar to a systematic review, and updated regularly online. As of the spring of 2016, the GeneTests database includes GeneReviews (user's manual entries) for 658 diseases, and the directory includes 1067 genetics clinics, 680 laboratories, and information on 79,004 tests for 4548 diseases covering 5385 genes.

An excellent site that maintains links to the majority of locally developed, neonatology-specific content around the country is maintained by *Duncan (2015)*. In addition to a database of links to clinical resources around the country, the site also has a job listing and a database of the literature on computer applications in medicine.

The clinician must realize that, unlike journals, textbooks, and guidelines, material on the World Wide Web (whether accessed from Duncan's site or using a search engine) is not necessarily subject to any editorial or other oversight; therefore as stated by *Silberg et al., as early as 1997*, “caveat lector” (reader beware). A number of articles and online resources address criteria for assessing the validity and reliability of material on a website (*Health on the Net Foundation*, www.hon.ch; *American Public Health Association*, 2001). With caution in mind, a search of the World Wide Web using a sophisticated search engine (e.g., Google, Google Scholar) can yield valuable information, though search results typically include a lower proportion of quality resources compared with curated resources.

Future Directions

Computers and biomedical informatics continue to play an increasing role in neonatology – for information management and because EHRs are fundamental to the provision of clinical care (*Palma, 2012a*). While significant levels of EHR adoption have been achieved in the United States, the benefits of digitizing the medial record

are not yet fully realized, and both providers and patients are keenly aware of the challenges and shortcomings of many current computer-based workflows (*Toll, 2012; Wachter, 2015*).

One significant and largely unrealized opportunity of EHR adoption is the generation of new knowledge from the vast amounts of clinical data collected electronically (*McGregor, 2013*). As stated previously, the *British Medical Journal's* Clinical Evidence database suggests that 50% of treatments (likely an even greater proportion in neonatology) are of unknown effectiveness. These “gaps in the evidence—where there are no good (randomized controlled trials [RCTs]) or no RCTs that look at groups of people or at important patient outcomes” (*BMJ Clinical Evidence*)—represent areas of opportunity. It is not possible for all of these gaps to be filled by RCTs, a study design that may not be feasible for the treatment or population of interest. On the other hand, with the increasing adoption of EHRs, a wealth of clinical data is being collected as a byproduct of routine care (so-called *practice-based evidence*).

The 2012 IOM report *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America (2012)* calls for and outlines an approach to transformation of the healthcare system into one that learns from practice-based evidence, generating knowledge from earlier patient encounters and making it available (along with evidence from the literature) at the point-of-care. Steps toward the concept of a continuously learning healthcare system are being made, with some examples of practice-based evidence being used for improvement in neonatal care (*Spitzer et al., 2010; Gale and Morris, 2016; Palma and Arain, 2016*). Capitalizing upon clinical data generated in EHRs for the purposes of discovery and improved care will increasingly become a focus of biomedical informatics in neonatology.

Suggested Readings

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3

Ethics, Data, and Policy in Newborn Intensive Care

WILLIAM L. MEADOW AND JOHN D. LANTOS

Philosophy

Ethics in the neonatal intensive care unit (NICU), as in all clinical contexts, starts with the traditional triangular framework of principles. We consider autonomy (do what the patient, or in this case the parent, thinks is right), paternalism (do what the doctor thinks is right), and the complementary concepts of beneficence and nonmaleficence (do the right thing). These principles, independent of context or data, are timeless. Many applications of these traditional ethical principles occur daily in the NICU (e.g., avoid futility, do not torture, and intervene when the data provide compelling evidence to do so).

The problem with timeless principles is that we all have to act in real time and, sometimes, in real time, the timeless principles conflict with one another and we have to decide quickly which compromises or combinations are best. What exactly is the right thing? What facts should be brought to bear in the decision? What weight should be given to each fact? And whose opinion should count in the end? Unfortunately, much of NICU care falls between the relatively straightforward decisions to not resuscitate babies born at 21 weeks, providing obligatory support to babies born at 28 weeks, or not performing cardiopulmonary resuscitation on infants with lethal anomalies. Faced with a difficult case, it is rare that simply applying principles will help to devise a solution. Difficult cases are usually ones in which the principles themselves are in conflict, or their application to the case is ambiguous.

The traditional ethical solution to medical dilemmas is to ground concerns in context, take data into account, and be sympathetic to patient preferences when the balance of benefits and burdens is not clear.

In the NICU, health professionals are constantly and anxiously aware that the burdens of treatment are real, immediate, long term, and significant, whereas the benefits of NICU interventions are distant, statistical, and unpredictable. Babies must undergo months of painful procedures such as intubation, ventilation, and intravenous catheterization. Often, they are left with lifelong sequelae. How should we decide whether we did the right thing in order to help decide whether, in similar circumstances, we should again do the same thing?

NICU success is often viewed as “all or none.” In most of the NICU follow-up literature a Bayley Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI) greater than 70 is classified as *normal*, whereas an MDI or PDI less than 70 is

classified as an *adverse outcome*. We strongly disagree with this dichotomization. There is no single measure of success or failure. Each baby is different, each family is different, and each life course is different.

In order to make good decisions, we need good data.

Getting Good Data

What kind of information would parents, physicians, or judges want to know about the babies in the NICU in order to decide when treatment ought to be obligatory and when it ought to be optional?

The essential truth at the intersection of NICU epidemiology and ethics is that survival depends sharply on gestational age (GA), within relatively precise boundaries. In the United States, as in virtually all the industrialized world, infants born after 25 weeks' gestation have survival rates that are high enough that treatment is generally considered obligatory. For these infants, the ethical principle of best interests requires their resuscitation, in the same way that sick children born at term deserve resuscitation.

Conversely, for infants born before 22 weeks' gestation, survival is essentially zero. Consequently, these infants and their parents deserve our compassion but not our interventions, on the ethical grounds of strict futility.

In between, spanning roughly one gestational month, from 22–25 weeks, we will require not only data but also interpretation. Tyson et al. (2008), using the vast database of the National Institute of Child Health and Human Development network, attempted to go “beyond gestational age” and quantify additional risk factors for both mortality and neurologic morbidity in infants born on the cusp of viability. Their analysis revealed that singleton status, appropriate in utero growth, antenatal steroids, and female gender all improve the likelihood of survival and intact neurologic outcome, independent of GA. By considering these other factors, all of which are available at the time of birth, doctors are able to more accurately estimate the chances that a baby will survive or that survivors will have neurodevelopmental impairment.

However, two problems remain. First, for many infants the predictive value of the Tyson algorithm is still not very good – that is, many of the lower-risk patients will still die, and many of the higher-risk patients will survive. Second, the Tyson algorithm, like GA, ignores a potentially important feature of NICU care – time. The algorithm uses only data that are available at the time of birth.

It does not account for prognostic features that might become available as the infant's course unfolds in the NICU. This is an important limitation that has ethical implications.

There are distinct advantages to making decisions over the first few days of the NICU stay, rather than in the delivery room at the time of birth. The first is emotional. Parents often appreciate the opportunity to get to know their baby as an individual, as opposed to making decisions based only on the anonymous population-based prognostications that are available at the time of birth. Second, there is valuable information to learn while the baby is in the NICU. Two time-sensitive prognostic features have been evaluated in the context of infants born at the border of viability – serial illness severity algorithms (Score for Neonatal Acute Physiology [SNAP]) and intuitions that the patient would “die before NICU discharge” (Meadow et al., 2008). Unfortunately, although SNAPs on the first day of life have good prognostic power for death or survival, their power diminishes over time. Intriguingly, serial intuitions that an individual baby will die before discharge – offered by medical caretakers for patients who require mechanical ventilation and for whom there is an ethical alternative to continued ventilation, namely extubation and palliative care – are remarkably accurate in predicting a combined outcome of either death or survival with neurologic impairment (MDI or PDI <70). Babies with abnormal results from a cranial ultrasound examination whose doctors agree with one another that the babies are likely to die have a less than 5% chance of surviving with both MDI and PDI greater than 70 at 2 years, independent of their GA. The predictive power of these data, acquired over time during an individual infant's NICU course, though not perfect, is greater than any algorithm available at the time of birth.

What do prospective parents or medical caretakers consider when they are asked to decide whether or not to resuscitate their micro-preemie? They may not want the precise prognostic estimates that we try to offer. For many parents, the death of their baby in the NICU is not necessarily the worst outcome. Instead, it may be worse to not even try to save the baby. That decision may leave parents with a life of self-doubt about whether, had they only tried, their baby might have survived. For such parents, trying and failing might be preferable to not trying at all.

If trying and failing is seen as a positive process, then the preferable choice might best be made not by looking at the percentage of intact survivors among all births (the current practice in many studies, including the model, noted above, developed by Tyson et al.) but instead as a function of only those infants who survive to discharge.

Numerous studies analyzing various populations in several countries have converged on the same surprising observation: the incidence of neurologic morbidity in NICU survivors is not very different when comparing infants at 23, 24, 25, and 26–27 weeks' gestation. The essential epidemiologic difference for infants born in this gestational range appears to be whether the baby will survive at all. Once the baby leaves the NICU, the risk of severe morbidity is largely the same; this is true in single-center and multicenter studies, in the United Kingdom, Canada, Europe, and the United States (Tyson et al., 2008; Johnson et al., 2009). Paradoxically, if avoiding survival with permanent crippling neurologic injury is the driving force behind resuscitation decisions, it appears that we should not be worrying about 23- and 24-weekers; rather we should not be resuscitating 26- or 27-weekers. Many more of these more mature babies will survive. Thus even if the rate of disability among survivors is lower, the absolute number of survivors with disability will likely be higher.

A fascinating insight has been offered by Janvier et al. (2008), who have done extensive surveys comparing responses to requests for resuscitation of sick micro-preemies with resuscitation of comparably sick patients at other ages (from term infants to 80 year olds). Consistently, it appears that micro-preemies are devalued – that is, for comparable likelihood of survival and comparable likelihood of neurologic morbidity in survivors, more people would let a micro-preemie die first or at least offer to resuscitate them last. There is no theory to account for these findings.

Finally, there is epidemiologic difficulty in assigning value to morbidity in surviving infants in the NICU. Verrips et al. (2008) have attempted to assess the effects of permanent residual disability for NICU survivors and their immediate families; they have demonstrated consistently that children with disabilities and their parents place a much higher value on their lives, and the quality of those lives, than do either physicians or NICU nurses. The vast majority of infants who survive the NICU, even those with significant permanent neurologic compromise, have “lives worth living,” as judged by the people most affected by those lives.

GA-specific mortality seems to preclude resuscitation for infants born before 22 weeks' gestation and require resuscitation for infants born after 27 weeks' gestation. In between, the outcomes are murky, prognostic indices are imperfect, and sociologic analyses of human behaviors (of parents and physicians) appear inadequate to develop any uniform approach that is satisfactory.

Public Policy: the Baby Doe Case

In the 1980s, the federal government attempted to change the rules for neonatal decisions about babies with congenital anomalies.

In 1982, a baby with Down syndrome and esophageal atresia was born in Bloomington, Indiana (USA). Baby Doe's parents refused to consent to surgery and chose palliative care instead. The court sided with the parents. The doctor and hospital appealed. The Indiana Supreme Court refused to hear the appeal, and the baby died after 8 days (Lantos, 1987).

This led to a national controversy that eventually resulted in amendments to the federal Child Abuse and Treatment Act (Annas, 1986; Kopelman, 1988). While this law has limited authority in regulating clinical decisions, it symbolically endorses the idea that life-sustaining treatment should not be withheld only on the basis of anticipated disability.

There is still controversy when treatments enable survival but have a high likelihood, or certainty, that survival will be accompanied by severe neurologic impairment. As a result, two questions must be asked: How severe will the neurologic impairment be? What is the likelihood that the child will have the most severe possible impairment?

The shift in moral standards regarding babies with Down syndrome was not related to technology but rather sociology. The capacity to repair Arnold–Chiari malformation and duodenal atresia existed long before it was applied to children with myelomeningocele and Down syndrome. What has changed the mood of the country is a growing recognition that disability is as much a social construct as a medical construct, although it is always both and not one or the other.

Malpractice Cases Against Neonatologists

There are also malpractice cases against neonatologists that have shaped the decision-making climate in the NICU. In one, Miller

versus Hospital Corporation of America Inc. (2003) the doctors were sued for resuscitating a tiny preemie over the objections of the parents. The case focused on events that had occurred in 1990, when Mrs. Miller came to a Hospital Corporation of America hospital in Texas in labor at 23 weeks' gestation. The fetus was estimated to weigh 500–600 g. No baby born that size had ever survived at that hospital. Mrs. Miller, her husband, and the attending physicians agreed that the baby was preivable and that no intervention was indicated. The baby was born, but a different physician performed resuscitation, and the infant survived with brain damage. As a result, the Millers sued the hospital for a breach of informed consent and were awarded \$50 million by a trial jury. The case wound its way to the Texas Supreme Court, which dismissed the verdict and articulated an “emergency exception” for physicians – that is, if a Texas physician finds himself or herself in the emergency position of needing to resuscitate a patient to prevent immediate death, the physician can try to perform resuscitation without being obligated to obtain consent from anyone. Whether it would be acceptable for a physician not to perform resuscitation in an emergency was left unarticulated by the Texas court.

In Wisconsin, the case of *Montalvo versus Borkovec (2002)* took the legal obligations of neonatologists and parents to a different place. The case derived from the resuscitation of a male infant born between 23 and 24 weeks' gestation, weighing 679 g. The parents claimed a violation of informed consent, arguing that the decision to use “extraordinary measures” should have been relegated to the parents. The Wisconsin Appellate Court disagreed, holding that “in the absence of a persistent vegetative state, the right of a parent to withhold life-sustaining treatment from a child does not exist.” Because virtually no infant is born in a persistent vegetative state, this decision would apparently eliminate the ethical possibility in Wisconsin of a “gray zone” of parental discretion. No other jurisdiction in the United States has adopted this position. The Wisconsin Appellate Court, like the Texas Supreme Court, was silent on whether physicians have discretion not to resuscitate. However, in Texas and Wisconsin, physicians are apparently not liable if they choose to do so.

A number of other state courts have addressed issues of treatment or nontreatment. In general, the courts are permissive of physicians who resuscitate infants. If courts are asked to sanction decisions to allow infants to die, most will do so only if there is consensus among physicians and parents and occasionally ethics committees. Courts are not eager to punish physicians who treat infants over parental objections or to empower physicians to stop treatment when parents want it to continue.

Future Directions

A number of recent developments may change the way we think about ethical issues in the newborn period. These include the rise of fetal medicine and expanded genomic screening of newborns.

Fetal Medicine Centers

Many children's hospitals are now developing fetal medicine centers. The goal of these centers is to identify fetuses at risk – particularly those with congenital anomalies – and to care for those fetuses and their mothers in centers where there is expertise in fetal diagnosis, therapy, and neonatal care. The hope is that such centers will allow more timely, and therefore more effective, intervention for babies with congenital heart disease, congenital diaphragmatic hernia, or other anomalies.

The medical effectiveness of these fetal medicine centers will depend on two distinct developments. First, on a population basis, these centers will only be as effective as fetal screening and diagnosis. The existence of these centers will almost certainly create an expectation and a demand for better fetal screening. Such screening is likely to include both better imaging and better screening tests that can be performed on maternal blood; both will lead to earlier diagnosis of fetal anomalies. These diagnoses will create more complex dilemmas for perinatologists and parents who will need to decide, in any particular case, whether to terminate the pregnancy, offer fetal therapy, or offer either palliative care or interventions after birth. Ironically, better fetal diagnosis may increase the likelihood of pregnancy termination, even when postnatal treatment is possible, such as in hypoplastic left heart syndrome.

Second, the effectiveness of fetal centers will depend on the effectiveness of fetal interventions. To date, fetal interventions have only been effective in a relatively few conditions. Vascular ablation for twin-to-twin transfusion syndromes clearly improves outcomes in these conditions. In utero surgery for myelomeningocele also leads to better outcomes for babies born with this condition. The vast majority of prenatally diagnosed conditions cannot be treated in utero. The real hope of fetal medicine centers today is that they will improve outcomes by allowing better planning for perinatal interventions. In some cases, that may lead to changing the timing or mode of delivery. In other cases, it may mean that a team of pediatric subspecialists will be prepared and immediately available to treat the baby in the minutes after birth. These sorts of efforts may improve outcomes.

Expanded Newborn Screening

In recent years, the number of diseases and conditions that can be diagnosed through newborn screening has expanded dramatically. Such screening is under the purview of states, rather than the federal government, and there is wide variation in the number of tests that are performed. In 1995 the average number of tests per state was five (range: zero to eight disorders). Between 1995 and 2005 most states added tests so that the average number of screening tests done by 2005 was 24 ([Tarini et al., 2006](#)). Today, there is a panel of 29 tests that has been recommended by the Department of Health and Human Services and has been adopted in all states ([Kemper et al., 2014](#)).

The expansion of newborn screening raises three problems. First, even the most accurate test has false positives. For rare conditions, the percentage of positive tests that are false positives is increased. Thus the more rare conditions that are added to a newborn screening panel, the more false positives there will be. False positives are associated with considerable parental anxiety and can lead to potentially dangerous and unnecessary diagnostic procedures or treatments. Second, expanded newborn screening costs money. Most of the cost is not for testing itself. Instead, it is for the follow-up counseling and testing after positive tests. Such follow-up is essential or the screening programs will not work. The [Centers for Disease Control and Prevention \(2008\)](#) has recently expressed concern about these costs. Finally, there is the potential for discrimination against patients for whom documented heterozygous carrier status conveys no recognized medical infirmity, but social or psychological stigma may be real. There is little funding available to assist or counsel these patients.

Recently, some centers have started to offer whole-genome sequencing (WGS) for newborns. Such testing raises all the issues

noted above for newborn screening. However, like newborn screening, it also offers the tantalizing prospect of better diagnosis leading to better treatment for some newborns whose conditions have been difficult to diagnose using more conventional methods. WGS is much more difficult to interpret than traditional newborn screening because every baby – and every adult – has many genetic variations of unknown significance.

Variants can only be interpreted after a good clinical history, family history, and physical examination have been performed. Data from these preliminary steps allow physicians to assess whether there are similar or related phenotypes in other family members; if so, the inheritance pattern can then be evaluated and assessed. Physical examination findings allow physicians to begin a search for potentially relevant genes. Mode of inheritance and a comprehensive phenotype can then be used to classify the patient's genomic variants. WGS may lead to the discovery of a known pathogenic variant, a novel pathogenic variant that is likely to be disease-causing, or a variant of unknown clinical significance in a gene known to cause human disease.

Clinical validity is a complicated and challenging aspect of WGS. Evidence is required to prove that a specific rare variant in a particular gene, detected by WGS, is indeed pathogenic and responsible for a particular clinical phenotype (Thiffault and Lantos, 2016).

Should Policy Dictate Resuscitation Practices?

Many professional societies in many countries have policies about resuscitation for babies born at the borderline of viability. Guillén et al. (2015) showed that among guidelines in 31 countries, 21 (68%) supported comfort care at 22 weeks' gestation and 20 (65%) supported active care at 25 weeks' gestation. Between 23 and 24 weeks' gestation, there was even greater variation.

These policies have practical effects. They lead to very different survival rates for seemingly similar babies in different countries. For example, in the Netherlands and Switzerland, survival at 25 weeks' gestation is as good as in the United States. Over 75% of infants born at 25 weeks' gestation will survive to discharge (Stoll et al., 2015). Before 25 weeks, however, outcomes in different countries vary widely. In the Netherlands and Switzerland, virtually no infant born at 24 weeks' gestation survives because there are policies not to provide intubation, resuscitation, or neonatal intensive care to such babies. (This has started to change at some centers in these countries – see, e.g., Morgillo et al., 2014.) By contrast, survival rates in the United States are 62% at 24 weeks' gestation and

37% at 23 weeks' gestation. Japan reports survival rates of 30% for babies born at 22 weeks' gestation and 70% for babies born at 23 weeks' gestation (Kusuda et al., 2006).

More interestingly, the policies shape the outcomes statistics that then become the evidence upon which future policies are based. It makes sense to not resuscitate babies if they have a 100% mortality rate. But, if they only have 100% mortality rate because they are not resuscitated, then the policies become a self-fulfilling prophecy.

Such policies may reflect a resources allocation decision. In the Netherlands, there is a limited budget and a communitarian ethic. There is a certain rationale behind spending money on all pregnant women, instead of 1% of micro-preemies. The United States appears ambivalent – we value individuals over community, are fascinated with high technology, and claim to prize our children. On the other hand, we will not spend money to prevent unwanted teen pregnancy, expand maternity leave, or provide visiting nurses for new mothers.

Finally, the concept of generational conflict must be considered. Many doctors appear to be quite comfortable calling delivery-room resuscitation of 24-weekers “optional,” based on GA alone (Janvier and Lantos, 2016). Given what we know about the factors other than GA that influence outcomes, this seems to be a curiously oversimplified approach to clinical decisions. It is not an approach that is used in other areas of medicine. For example, professional societies do not recommend the allocation of intensive care unit resources based on age alone. Such a practice might be called “discriminatory ageism.” However, with regard to premature babies, it ought, perhaps, to be considered equally discriminatory and labeled as “gestational ageism” (Wilkinson, 2012). Some suggest that the reason to limit such treatment is because it is too expensive, but studies show that it is remarkably cost-effective compared with the use of intensive care resources for elderly patients with respiratory failure (Lantos and Meadow, 2011). The relative cost-effectiveness of NICUs compared with medical intensive care units (MICUs) is based on the natural history of illnesses that lead to intensive care unit admissions. Most babies who are admitted to the NICU either die relatively quickly or survive. Thus most of the resources in NICUs are expended on patients who survive to leave the hospital. For adults, the opposite is true. With each passing day in the intensive care unit, the chances that an elderly patient will survive to leave the hospital go down. Thus a much higher percentage of the resources expended in adult intensive care units are used by patients who will not leave the hospital alive.

Summary

Ethical philosophy is a place to start, not a place to finish. Data are relatively easy to acquire and agree on. Policy is intriguingly insensitive to data, but that may reflect social and political realities that exist beyond the NICU – perceptions of disability, abortion

politics, individual versus communitarian emphasis, fascination with technology, discrimination, publicity, financial constraints – so that an ethical course of action in one country, one city, or one family might seem perverse elsewhere.

Suggested Readings

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4

Global Neonatal Health

CYRIL ENGMANN AND MANEESH BATRA

KEY POINTS

- In many parts of the world, childbirth remains a risky, life-threatening process.
- Over the past 25 years, decreases in neonatal mortality rates (NMRs) have been slower than those for maternal and child mortality.
- Intrapartum birth asphyxia, sepsis, and prematurity are the most common causes of global neonatal mortality.
- Lower NMRs are strongly associated with increased gross national income, decreased total fertility rates, higher female literacy, at least one antenatal care visit, presence of a skilled attendance at birth, and a higher percentage of birth registrations.

Global Newborn Health – History

It is essential for all those who work with mothers and their babies to understand the global health milieu and the historical factors that have shaped the field as it stands today. More importantly, as neonatologists look to the future, a contextualizing of their work in neonatal and perinatal health and an appreciation of what levers need to be pulled to affect the future of the world's newborns become even more important. Finally, for those who want to influence these processes and contribute to moving the field forward, a deeper understanding becomes necessary (Darmstadt et al., 2014). Today more than ever, the field of global newborn health is much broader and quite distinct from the technologically infused might of neonatal intensive care units (NICUs) in high-income countries. This chapter will discuss the policies, programs, research, advocacy, and common underlying public health themes that affect the newborn globally (Lawn et al., 2014). Armed with this knowledge, the healthcare provider working with mothers and newborns in today's multicultural environments will be better able to understand and provide the culturally and contextually sensitive care necessary to be effective and will have the tools to springboard the future of global newborn health (Engmann, 2011; Engmann et al., 2013a).

Childbirth is a risky, life-threatening process with good maternal and neonatal outcomes far from assured. It is therefore no surprise that newborns have been given special attention (either because they lived, died, or were maimed during birth) throughout history. Some of the earliest recordings of newborns in ancient history date back to the second century AD and are ascribed to the Greek physician and gynecologist Soranus of Ephesus (Dunn, 1995). Other artists from late antiquity and the middle ages depict the

process of childbirth with a mother in the squatting position, a doula/helpmate supporting her, a midwife, and perhaps in the most important role, someone praying, invoking all the extra help possible from the deities (Fig. 4.1).

The *Boke of Chyldren*, written by Thomas Phaire in 1545, was one of the earliest books published in English (Phaire, 1545) while the 17th century treatise by William Harvey remains among the most elegant descriptions of the transition from fetal to extrauterine life (Dunn, 1990). The Talmud and the Old Testament are replete with stories concerning babies. For example, one story describes the birth and early life of Moses, who at 3 months of age was placed in a basket, floated down the River Nile, and subsequently adopted by the Pharaoh's daughter. Another story, perhaps one of the earliest recorded cases of sudden infant death syndrome and baby-snatching, describes two women each with newborn babies who live in the same house. One baby dies in the night, and its mother is accused by the other of waking up and switching her dead baby with the live one. This dispute is brought to King Solomon for adjudication. He recommends that the baby be sawn in two with one-half given to each woman. One woman, the mother of the dead baby, agrees to this proposal, while the mother of the live baby, appalled that her baby will be killed, says its life should be spared and agrees to relinquish her claim to being the mother. This act convinces King Solomon that she is the rightful mother, and he adjudicates the baby should be given to her (Bible: 1 Kings 3:16–28). By AD 315, the Roman Empire had established laws supporting the enslavement of “foundlings” or abandoned babies, in a bid to counter a faltering population growth and infanticide and to promote the adoption or child-rearing of orphans (Spaulding and Welch, 1991). During the 17th century a number of countries started to build “Foundling Hospitals” and by the late 19th century, preterm babies, known as “hatchlings,” were an important draw at exhibitions and public fairs where they were displayed as they lay in incubators known as “hatcheries” (Silverman, 1979).

Various societies have evolved cultural practices such as delayed naming of a child, perhaps in response to high perinatal and neonatal mortality rates (NMRs). In certain Asian cultures, full naming ceremonies are not held until the infant is several months old, while in Jewish tradition, full mourning for the entire year is not required for a neonatal death (Ginzberg et al., 2003). In some African populations, the mother and her newborn baby are not allowed to be seen for the first 7 days after birth except by very close family and friends to ensure the “evil eye” is not put on either the mother or her baby. In other settings, a “naming ceremony”



• **Fig. 4.1** Classical Greek Image of Woman Giving Birth, Depicting Doulas, Midwife, and a Woman Praying for the Safety of Mother and Baby. (From <http://visualizingbirth.org/classical-greek-image-of-woman-giving-birth/>.)

where a baby is provided a name and then publicly introduced to the community does not occur for the first 7 days or sometimes longer. This is to ensure that the baby has decided to stay on earth and thus differentiated itself from being a “spirit child” who will die (Denham et al., 2010). To counter the death of a baby in the family, certain societies in Africa and Asia give the next child a coarse or earthy name to ward away spirits who might otherwise also take the new arrival.

Early in the 20th century, an obstetrician advocated in the *British Medical Journal* for the specialized training of doctors and nurses in neonatal medicine and for the construction of specialized newborn health facilities. He went on to predict that within a short period of time, the specialist in neonatal diseases and the nurse intensively trained and expert in the management of the delicate newborn would be commonplace (Ballantyne, 1923). By the mid-20th century, there was a deepening realization among certain pediatric groups, boards, and societies that the study and practice of pediatrics during the first month of life were distinct and specialized enough to require further training. Furthermore, the need for an in-depth understanding of embryonic, fetal, and neonatal pathophysiologic processes, the role of technology, including ventilators, and the complexities of the medical management of a sick baby led to the creation of neonatology as a distinct subspecialty in the United States. A subboard of the American Board of Pediatrics was created to oversee and shape the current and future knowledge and understanding of the field. The first subboard examination in neonatal–perinatal medicine was offered in 1975 (Philip, 2005).

By the close of the 20th century, there was emerging appreciation in global health policy and programmatic circles that the newborn period provided unusual challenges, with drivers influencing survival that were different to the more traditional child health programs. Another realization was that the newborn was absent from maternal and child health programs. This was because national and international maternal health programs had hitherto assumed that child health programs encompassed close attention to newborn care as newborns grow to become children, while child health programs, believing the mother and neonate to be inextricably linked at

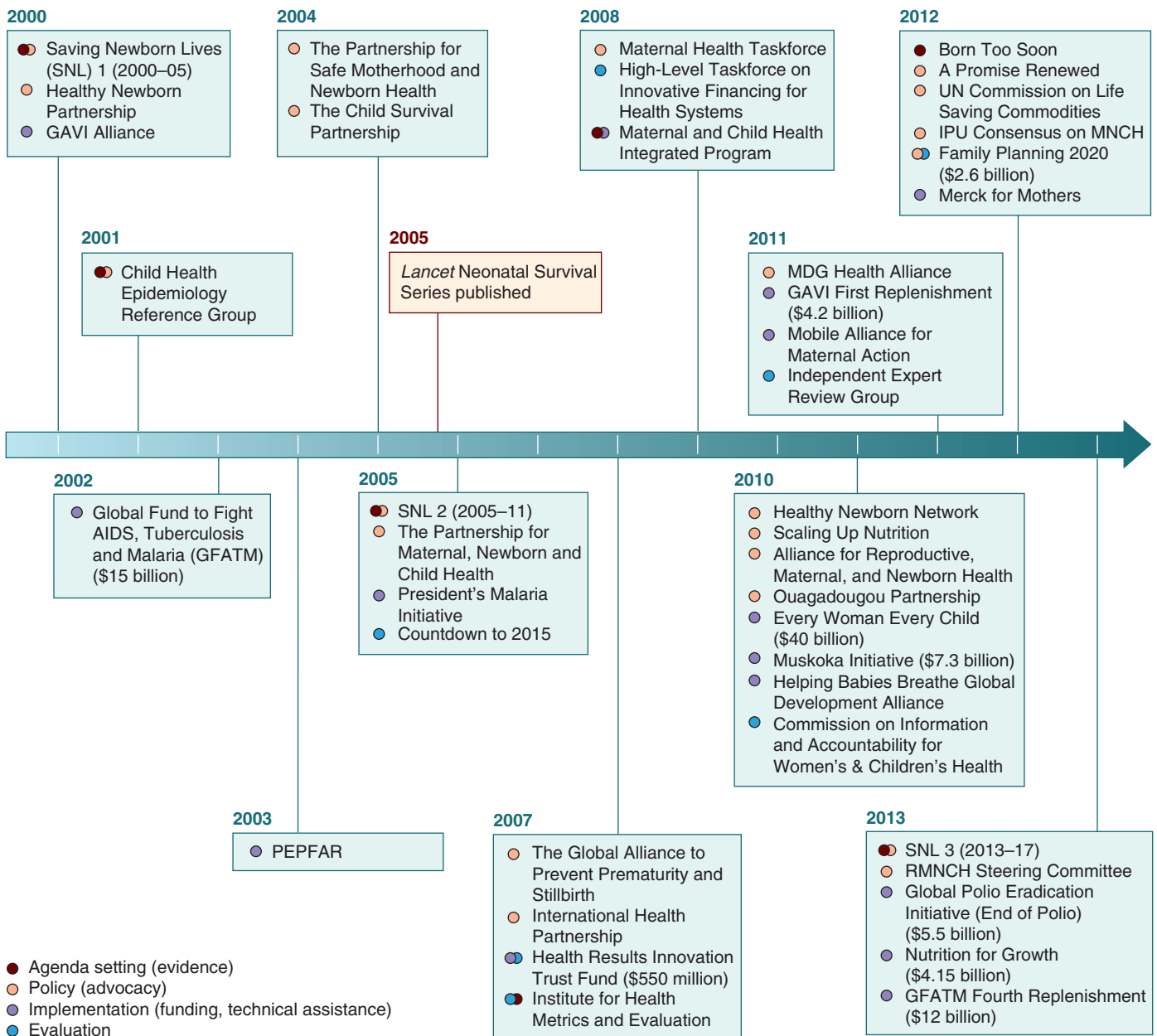
birth, had subsequently assumed that maternal programs included a strong focus on the neonate (Tinker et al., 2010). As a result, there was a paucity of routine newborn surveillance and epidemiologic data collected globally and nationally (The World Health Report, 2005). Programmers, policymakers, and funders started increasing their focus on the neonate. Abhay Bang and colleagues from the Gadchiroli district of India published a landmark series on the effects of a home-based newborn care program and compared these against control village clusters who had no intervention. The program involved a package of interventions that included training of village health workers in neonatal care who then made home visits and managed birth asphyxia, premature birth or low birth weight, hypothermia, breastfeeding problems, and neonatal sepsis (septicemia, meningitis, and pneumonia). In addition, assistance by trained traditional birth attendants, a health promotion program, and fortnightly supervisory visits were provided. The authors reported a decline in NMR from 62 to 25 per 1000 live births in the intervention clusters, whereas in control clusters, they reported an *increase* in NMRs from 58 to 64 per 1000 live births (Bang et al., 2005).

In 2000, the Bill and Melinda Gates Foundation provided funding to the nongovernmental organization (NGO) Save the Children in order to create a special entity called “Saving Newborn Lives.” This group’s remit was to focus and harness newborn stakeholder energies on moving the global newborn agenda forward through research and program work, which would inform advocacy and policy (Tinker et al., 2010). Soon afterwards, Black and colleagues published a child survival series with the first paper provocatively titled “Where and why are 10 million children dying every year?” (Black et al., 2003). This was followed by another seminal publication from the *Lancet* Neonatal Series – which asked “4 million neonatal deaths: When? Where? Why?” (Lawn et al., 2005). These publications highlighted the following: (1) sepsis, intrapartum birth asphyxia, and prematurity were the major drivers of 4 million newborn deaths; (2) most neonatal births and deaths were occurring in low- and middle-income countries, outside of healthcare facilities, and in the home; and (3) there was an absence of district, regional, national, or global data on newborn survival. These seminal papers and the strong advocacy by a handful of newborn champions spurred national governments, United Nations (UN) agencies, NGOs, academic institutions, funding agencies, and other newborn stakeholders to begin developing programs, policies, and research agendas that were newborn focused (Martines et al., 2005) (Fig. 4.2).

Global Newborn Health 2000–2015: Addressing Cause-Specific Neonatal Mortality

Coinciding with increased understanding from seminal publications and with the support of newborn champions, the turn of the 21st century heralded the launch of the Millennium Development Goals (MDGs) (Fig. 4.3).

The MDGs were seen as a focusing and galvanizing effort through which the global community would channel its collective resources and efforts to address major global development issues (*The Millennium Development Goals Report 2015*, 2015). The goals, set in 2000, included eradicating extreme poverty and hunger, achieving universal education, promoting gender equality and empowerment of women, reducing child mortality (death in children under the



• **Fig. 4.2** Key Stakeholders, Events, and Timeline Pertaining to Global Newborn Health From January 2000 to December 2013. *AIDS*, Acquired immunodeficiency syndrome; *GAVI*, Global Alliance for Vaccines and Immunization; *IPU*, Inter-Parliamentary Union; *MDG*, millennium development goals; *MNCH*, maternal, newborn, and child health; *PEPFAR*, President's Emergency Plan for AIDS Relief; *RMNCH*, reproductive, maternal, newborn, and child health and nutrition; *SNL*, Saving Newborn Lives; *UN*, United Nations. (From Darmstadt GL, Kinney MV, Chopra M, et al. Who has been caring for the baby? *Lancet*. 2014;384(9938):179.)

age of 5 years) by two-thirds, reducing maternal mortality by three-quarters, combating HIV/AIDS, malaria, and other diseases, ensuring environmental sustainability, and establishing global partnerships for development (*United Nations Millennium Declaration, Resolution Adopted by the General Assembly, 2000*).

Although these ambitious goals were not all reached by the target date of 2015, the MDG era has arguably seen the greatest improvements in health and development indicators in the history of humankind (*The Millennium Development Goals Report 2015, 2015*). For example, the number of people living in extreme poverty has decreased from 1.9 billion to 836 million; maternal and child mortality have been halved; net school enrolment has reached

91% with sub-Saharan Africa seeing a 20% increase in average literacy rates of women; and in Southern Asia the number of girls enrolled for every 100 boys had increased from 70 to 103 by 2015. Approximately 91% of the world's population is now using improved drinking water sources, compared to 70% in 1990 (*The Millennium Development Goals Report 2015, 2015*).

One of the main themes that the various newborn publications articulated was that most newborn births, and 99% of newborn deaths, occurred in community-based settings such as the home and not in hospitals and health facilities (Lawn et al., 2005; Darmstadt et al., 2009). Furthermore, country case studies showed that a handful of low- and middle-income countries had seen

The Millennium Development Goals (MDGs) are a set of global development objectives to be achieved by 2015 that were unanimously adopted at the United Nations Millennium Summit in September 2000. Attainment of the eight individual goals is to be measured by progress against 18 associated targets.

1	Eradicate extreme poverty and hunger	<ul style="list-style-type: none"> • Reduce by half the proportion of people living on less than a dollar a day • Reduce by half the proportion of people who suffer from hunger
2	Achieve universal primary education	<ul style="list-style-type: none"> • Ensure that all boys and girls complete a full course of primary schooling
3	Promote gender equality and empower women	<ul style="list-style-type: none"> • Eliminate gender disparity in primary and secondary education at all levels by 2015
4	Reduce child mortality	<ul style="list-style-type: none"> • Reduce by two-thirds the mortality rate among children under five
5	Improve maternal health	<ul style="list-style-type: none"> • Reduce the maternal mortality ratio by three quarters
6	Combat HIV/AIDS, malaria, and other diseases	<ul style="list-style-type: none"> • Halt and begin to reverse the spread of HIV/AIDS • Halt and begin to reverse the incidence of malaria and other major diseases
7	Ensure environmental sustainability	<ul style="list-style-type: none"> • Integrate the principles of sustainable development into country policies and programmes; reverse loss of environmental resources • Reduce by half the proportion of people without sustainable access to safe drinking water and basic sanitation • Achieve significant improvement in lives of at least 100 million slum dwellers, by 2020
8	Develop a global partnership for development	<ul style="list-style-type: none"> • Targets cover: trading and financial systems, the special development needs of disadvantaged states, debt sustainability, youth employment, affordable access to essential drugs, and access to information and communications technologies

• **Fig. 4.3** The Millennium Development Goals. *AIDS*, Acquired immunodeficiency syndrome; *HIV*, human immunodeficiency virus. (From http://www.budget.gov.au/2008-09/content/ministerial_statements/image/ausaid-5.gif.)

impressive reductions in national NMRs *before* the creation of the first neonatal intensive units in the country. Sri Lanka, for example, had experienced reductions in mortality from over 50 deaths per 1000 live births in the 1950s to less than 20 deaths per 1000 live births by 1985 when the first NICU in the country was developed (Martines et al., 2005). The Indian state of Kerala also had seen similar impressive reductions in neonatal mortality. Further analysis suggested that in both Sri Lanka and Kerala, sustained inputs and utilization of primary care and government facilities had played major roles in the decrease in their NMRs, not the introduction

of NICUs. In Sri Lanka, for example, by 1996 there was a midwife to patient ratio of 1 : 3000–5000, close to 100% antenatal care coverage, and an 86% facility-based delivery rate. There was no charge to women for their medical care and the average distance from home to a health facility was 1.4 kilometers, with 5 kilometers being the furthest distance of advanced hospitals from those health facilities. Higher maternal educational levels, effective antenatal care provision, and higher contraception prevalence rates were perceived to have contributed significantly to these impressive reductions in NMRs (Lawn et al., 2005).