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Robert H. Lane and Robert M. Kliegman

**Global Challenges, Efforts, and Controversies in Neonatal Care** **749**

Nicole E. St Clair, Maneesh Batra, Jacquelyn Kuzminski, Anne CC Lee, and Cliff O'Callahan

Simple low-cost, evidence-based interventions such as clean delivery practices, immediate warming, umbilical cord care, and neonatal resuscitation could prevent 40% to 70% of newborn deaths globally, but many obstacles preclude the provision of those basic interventions for all newborns, particularly in low-resource regions. Global efforts have led to widespread development of neonatal clinical practice guidelines, training programs, and policies. Because of a shortage of health care resources, standards of care have been redefined to meet the needs of underserved populations. This article provides an overview of the challenges, efforts, and controversies surrounding neonatal health in low-resource settings.

**Prevention of Preterm Birth in Modern Obstetrics** **773**

Kara B. Markham and Mark Klebanoff

Spontaneous preterm labor is a complex process characterized by the interplay of multiple different pathways. Prevention of preterm labor and delivery is also complicated. The most effective interventions for prevention of preterm birth (PTB) are progestin prophylaxis and lifestyle modifications, with cerclage placement also playing a role in selected populations. Interventions such as activity modification, home tocometry, and routine antibiotic use have fallen out of favor because of lack of effectiveness and possibility of harm. The solution to the problem of PTB remains elusive, and researchers and clinicians must collaborate to find a cure for preterm labor.

**Challenges and Controversies in Fetal Diagnosis and Treatment: Hypoplastic Left Heart Syndrome** **787**

Michele A. Frommelt

Today, almost 70% of babies with hypoplastic left heart syndrome (HLHS) will survive into adulthood, although significant long-term morbidity and mortality still exists. Prenatal diagnosis of HLHS is increasingly common, allowing improved counseling, and the potential for fetal intervention if indicated. Exciting progress continues to be made in the area of fetal diagnosis and intervention, specifically catheter intervention for intact atrial septum or severe aortic stenosis. Pediatric cardiologists should be keenly

aware of the flaws of staged palliation for the treatment of HLHS, and need to keep abreast of the emerging data regarding fetal diagnosis and intervention.

**Borderline Viability: Controversies in Caring for the Extremely Premature Infant** **799**

Steven R. Leuthner

Controversy surrounding the decision to resuscitate at the limits or borderline of viability has been at the center of neonatal ethical debate for decades. This debate has led to numerous reports from individual institutions, councils, and advisory committees that all have remarkable consistency in the development of gestational age-based guidelines. This article reviews legal or regulatory concerns that may contradict ethical discussion and guidelines, discriminatory and scientific basis concerns with consensus guidelines, and personal controversy about how to determine best interest. Guidelines are a reasonable place to start in helping determine parental authority and autonomy. The article also addresses controversies raised in counseling and costs.

**Fetal Programming, Epigenetics, and Adult Onset Disease** **815**

Robert H. Lane

How early life events program adult disease is undergoing a transition from the broad field of maternal malnutrition to the current relevant issues of food deserts and prematurity. Although many adult diseases and morbidities associate with various early life events and programming, the morbidities of insulin resistance, cardiovascular disease, and obesity seem to be common end points of many early life events despite potential confounders.

**Comparative Effectiveness and Practice Variation in Neonatal Care** **833**

Joanne Lagatta, Michael Uhing, and Julie Panepinto

Comparative effectiveness research (CER) is a relatively new term for clinical research that directly assists patients, clinicians, and policymakers in making informed decisions to improve health care. In neonatology, there are similarities and differences between CER and existing clinical research and quality improvement literature. This article uses existing examples in neonatal literature to describe CER methodology and list some future directions and challenges in neonatal CER.

**Conquering Racial Disparities in Perinatal Outcomes** **847**

Earnestine Willis, Patricia McManus, Norma Magallanes, Sheri Johnson, and Amber Majnik

Infant mortality rate (IMR) is a reference indicator for societal health status. Trend analysis of IMR highlights 2 challenges to overcome in the United States: (1) US IMR is higher than most industrialized countries and (2) there are persistent racial/ethnic disparities in birth outcomes, especially for blacks. Racial/ethnic infant mortality disparities result from the complex interplay of adverse social, economic, and environmental exposures. In this article, racial/ethnic disparities are discussed, highlighting trends, the role of epigenetics in understanding mechanisms, key domains of

community action planning, and programs and policies addressing the racial gaps in adverse birth outcomes.

**It's Not Your Mother's Marijuana: Effects on Maternal-Fetal Health and the Developing Child**

877

Tamara D. Warner, Dikea Roussos-Ross, and Marylou Behnke

Pro-marijuana advocacy efforts exemplified by the “medical” marijuana movement, coupled with the absence of conspicuous public health messages about the potential dangers of marijuana use during pregnancy, could lead to greater use of today’s more potent marijuana, which could have significant short- and long-term consequences. This article reviews the current literature regarding the effects of prenatal marijuana use on the pregnant woman and her offspring.

**Pain Management in Newborns**

895

Richard W. Hall and Kanwaljeet J. S. Anand

As a standard of care for preterm/term newborns effective pain management may improve their clinical and neurodevelopmental outcomes. Neonatal pain is assessed using context-specific, validated, and objective pain methods, despite the limitations of currently available tools. Therapeutic approaches reducing invasive procedures and using pharmacologic, behavioral, or environmental measures are used to manage neonatal pain. Nonpharmacologic approaches like kangaroo care, facilitated tucking, non-nutritive sucking, sucrose, and others can be used for procedural pain or adjunctive therapy. Local/topical anesthetics, opioids, NSAIDs/acetaminophen and other sedative/anesthetic agents can be incorporated into NICU protocols for managing moderate/severe pain or distress in all newborns.

**Vascular Endothelial Growth Factor Antagonist Therapy for Retinopathy of Prematurity**

925

M. Elizabeth Hartnett

In this article, the growing problem of retinopathy of prematurity (ROP) worldwide, treatments for severe ROP including standard-of-care laser treatment, and the need for new treatments are discussed. Also discussed are the reasons to consider inhibiting the vascular endothelial growth factor (VEGF) signaling pathway in severe ROP and the concerns about broad VEGF inhibition. Finally, the potential role of VEGF in ROP based on studies in animal models of oxygen-induced retinopathy, the effects of anti-VEGF based on basic research data, and the clinical relevance of these data are covered.

**Preventing Herpes Simplex Virus in the Newborn**

945

Swetha G. Pinninti and David W. Kimberlin

Genital herpes simplex virus (HSV) infections are very common worldwide. Approximately 22% of pregnant women are infected genitally with HSV, and most of them are unaware of this. The most devastating consequence of maternal genital herpes is HSV disease in the newborn. Although

neonatal HSV infections remain uncommon, due to the significant morbidity and mortality associated with the infection, HSV infection in the newborn is often considered in the differential diagnosis of ill neonates. This review summarizes the epidemiology and management of neonatal HSV infections and discusses strategies to prevent HSV infection in the newborn.

**Use of Cell-Free Fetal DNA in Maternal Plasma for Noninvasive Prenatal Screening 957**

Amy J. Wagner, Michael E. Mitchell, and Aoy Tomita-Mitchell

Noninvasive prenatal testing (NIPT) using cell-free fetal (cfDNA) offers potential as a screening tool for fetal anomalies. All pregnant women should be offered prenatal screening and diagnostic testing based on current guidelines. Adoption of NIPT in high-risk pregnancies suggests a change in the standard of care for genetic screening; there are advantages to an accurate test with results available early in pregnancy. This accuracy decreases the overall number of invasive tests needed for diagnosis, subjecting fewer pregnancies to the risks of invasive procedures. Women undergoing NIPT need informed consent before testing and accurate, sensitive counseling after results are available.

**Probiotics and Necrotizing Enterocolitis 967**

Josef Neu

One of the most controversial areas in neonatology is whether probiotics should be provided routinely to preterm infants to prevent necrotizing enterocolitis (NEC). This review provides the reader with a brief overview of NEC and current concepts of its pathophysiology, discusses the microbial ecology of the intestine in preterm infants and factors that may lead to a “dysbiosis”, summarizes studies of probiotics in preterm infants, elaborates on the need for regulation in this area, and discusses alternatives to probiotics and what is the future for the prevention of NEC.

**Informing and Educating Parents About the Risks and Outcomes of Prematurity 979**

U. Olivia Kim and Mir A. Basir

The current process of educating and informing parents of the concerns and outcomes of premature infants is suboptimal, mostly because of modifiable factors. Proven methods to improve the transference of information are underused. In most institutions, the task to inform and educate parents is left to individual providers. Effective parent-clinician communication depends collectively on parents, clinicians, and the health care systems. Efforts must focus on improving communication and not on decreasing information provided to parents. If done successfully, we might find new and worthy allies in the trenches of the NICU.

**Ethical Issues in DNA Sequencing in the Neonate 993**

David P. Dimmock and David P. Bick

With the recognition of genetic disorders in the newborn, there is the potential to offer new lifesaving therapies. For other conditions such as hypothyroidism in Down syndrome or hypercalcemia in the 22q11 microdeletion syndrome, the early identification of an untreatable condition permits

prompt screening for potential comorbid conditions. DNA testing for disorders and DNA-based screening are rapidly evolving. With new more powerful tests, there is an increasing ability to see into a potential future and change the outcome for newborns. However, there remain significant ethical and structural issues to be considered before routine implementation of DNA testing.

**Screening for and Treatments of Congenital Immunodeficiency Diseases** **1001**

James Verbsky and John Routes

Although newborn screening (NBS) for inborn errors of metabolism has been successfully utilized in the US for decades, only recently has this screening program expanded to include disorders of immunity. Severe combined immunodeficiency (SCID) became the first disorder of immunity to be screened on a population wide basis in 2008. While NBS for SCID has been successful, the implementation of population-based screening programs is not without controversy, and there remain barriers to the nationwide implementation of this test. In addition, as the program has progressed we have learned of new challenges in the management of newborns that fail this screening.

**Pulse Oximetry in Very Low Birth Weight Infants** **1017**

Richard A. Polin, David A. Bateman, and Rakesh Sahni

Pulse oximetry has become ubiquitous and is used routinely during neonatal care. Emerging evidence highlights the continued uncertainty regarding definition of the optimal range to target pulse oximetry oxygen saturation levels in very low birth weight infants. Furthermore, maintaining optimal oxygen saturation targets is a demanding and tedious task because of the frequency with which oxygenation changes, especially in these small infants receiving prolonged respiratory support. This article addresses the historical perspective, basic physiologic principles behind pulse oximetry operation, and the use of pulse oximetry in targeting different oxygen ranges at various time-points throughout the neonatal period.

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