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Delirium is likely present in the neonatal intensive care unit and has been largely unrecognized. There are several risk factors for delirium including illness severity, neurosedative exposure, and environmental disruptions that put infants at risk for delirium. Regular use of scoring systems should be considered to improve delirium detection. When identified, initial steps in management should include resolving underlying causes and implementation of standard nonpharmacologic measures. Mounting pediatric evidence suggests that the atypical antipsychotics, as well as the  $\alpha$ -2 agonists, may be additionally beneficial in treating delirium as well as improving the ability to wean off other neurosedative medications.

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Susan S. Cohen and John Flibotte

The incidence of intraventricular hemorrhage (IVH) has overall declined to 15% to 20% of preterm infants with birth weight less than 1500 g. One of the major complications of severe IVH is posthemorrhagic ventricular dilation (PHVD). Nearly 10% of all infants with IVH and 20% of infants with severe IVH will develop progressive PHVD requiring surgical intervention to prevent parenchymal damage in the developing brain. This review focuses on the controversies regarding posthemorrhagic hydrocephalus interventions with a focus on how to interpret recent data from trials that some have seen as heralding a call toward more aggressive intervention.

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Rebecca Hjorten and Joseph T. Flynn

Neonatal hypertension is uncommon but is becoming increasingly recognized. Normative blood pressure data are limited, as is research regarding the risks, treatment, and long-term outcomes. Therefore, there are no clinical practice guidelines and management is based on clinical judgment and expert opinion. Recognition of neonatal hypertension requires proper blood pressure measurement technique. When hypertension is present there should be a thorough clinical, laboratory, and imaging evaluation to promptly diagnose causes needing medical or surgical management. This review provides a practical overview for the practicing clinician

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Jennifer F. Gerardin and Scott Cohen

As the adult congenital heart disease population grows, more women are reaching childbearing age. Women with moderate to complex congenital heart disease have an increased risk of morbidity and mortality than the general population. There is increased risk of prematurity and intrauterine growth restriction in infants. Regular preconceptual adult congenital heart disease care, contraception counseling, and multidisciplinary care during a pregnancy can help minimize the risk during pregnancy for both mother and baby.

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Diana L. Stanescu and Charles A. Stanley

Our lack of basic knowledge about the basic mechanisms of transitional hypoglycemia and other forms of hypoglycemia in newborns underlies the ongoing controversies over standards for managing these conditions. To address this deficiency, the authors evaluated regulation of insulin secretion in fetal, newborn, and adult rats. The results demonstrate that transitional hypoglycemia in normal neonates and persistent hypoglycemia in high-risk infants both reflect altered beta-cell insulin regulation. These findings provide a new foundation for improving detection and management and preventing hypoglycemic brain injury in normal neonates and, especially, in infants with persistent hypoglycemia and genetic forms of congenital hyperinsulinism.

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Jeffrey M. Perlman and Christine Salvatore

Maternal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can present with or without symptoms at the time of birth. Symptomatic mothers are more likely to be associated with preterm births. Population studies demonstrate a consistent association of SARS-CoV-2 infection and a reduction in preterm birth rate. Newborns with positive SARS-CoV-2 test results appear to have minimal burden of illness that is directly associated with a viral infection. Neonatal mortality directly related to SARS-CoV-2 is extremely rare. Maternal vaccination in pregnant women leads to maternal antibody production, and this can occur as early as 5 days after the first vaccination dose.

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Despite dramatic advancements in neonatal intensive care since the 1960s, African-American infants still have more than a two-fold higher first-year mortality rate than non-Latinx White infants. Our essay examines the impact of upstream factors closely linked to the historical and

contemporary context of structural racism in the United States on the African-American women's birth outcome disadvantage. In the process, we propose a paradigm to address the racial health inequity in adverse birth outcome by considering the interplay of racism and social class.

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Megha Sharma, Emily Callan, and G. Ganesh Konduri

Inhaled nitric oxide (iNO) therapy had a transformational impact on the management of infants with persistent pulmonary hypertension of the newborn (PPHN). iNO remains the only approved pulmonary vasodilator for PPHN; yet 30% to 40% of patients do not respond or have incomplete response to iNO. Lung recruitment strategies with early surfactant administration and high-frequency ventilation can optimize the response to iNO in the presence of parenchymal lung diseases. Alternate pulmonary vasodilators are used commonly as rescue, life-saving measures, though there is a lack of high-quality evidence supporting their efficacy and safety. This article reviews the available evidence and future directions for research in PPHN.

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Erin L. Rholl, Katie R. Baughman, and Steven R. Leuthner

In cases whereby the continuation of life-sustaining medical therapies is not in the infant's best interest and does not align with the parents' goals, it is ethically and morally advisable to withhold/withdraw life-sustaining medical therapies. Withdrawing/withholding artificial nutrition hydration is not morally or ethically different from other medical treatments. Determination of what and when to withdraw should occur through shared decision-making considering the parents' values and the infant's physiology and comfort. The practice of physician recommendations followed by parental informed nondissent should be considered in these instances.

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Naomi T. Lavalentha and John D.E. Barks

Mild therapeutic hypothermia has been extensively studied and validated as an effective and safe treatment for term and near-term infants with moderate and severe hypoxic encephalopathy meeting narrow inclusion criteria. Unanswered questions remain about whether cooling treatment can be optimized to improve outcomes even further, and whether it is reasonable to offer treatment to infants excluded from the foundational studies. Consideration of "off-protocol" cooling practices requires methodical review of available evidence and analysis using both a clinical and a research ethical framework.

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Megan Barcroft, Christopher McKee, Darren P. Berman, Rachel A. Taylor, Brian K. Rivera, Charles V. Smith, Jonathan L. Slaughter, Afif El-Khuffash, and Carl H. Backes

Percutaneous-based patent ductus arteriosus closure is technically feasible among infants less than 1.5 kg. However, marked heterogeneity in the type and nature of adverse events obscures current safety profile assessments. Although data on the risks of postdevice closure syndrome remain promising, a lack of comparative trials of surgical ductal ligation and inconsistent surveillance across published studies obscure confidence in present estimates of safety and efficacy. To minimize risk and yield the greatest benefits, clinical studies of patent ductus arteriosus treatment should consider incorporating more robust assessments to ensure that infants at greatest risk for adverse ductal consequences are included.

**Exome and Whole Genome Sequencing in the Neonatal Intensive Care Unit**

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Michael Muriello

The role of genomic sequencing (exome and whole genome) in the neonatal intensive care unit (NICU) has changed with advances in technology and bioinformatics in the last decade. Evidence from 18 retrospective and prospective studies of exome and whole genome sequencing in pediatric intensive care settings has demonstrated an average diagnostic yield of close to 40% and an immediate impact on clinical management in more than 20% of patients tested, and the highest clinical utility was in the perinatal setting. Genomic sequencing, when indicated, should be the standard of care for patients in the NICU.

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Aarthi Gunasekaran, Christa Devette, Samuel Levin, and Hala Chaaban

Necrotizing enterocolitis (NEC) is the most common gastrointestinal (GI) emergency in the neonatal intensive care unit. Despite advances in medical care, mortality and morbidity from NEC have not changed. This is likely due to the lack of a clear understanding of this multifactorial disease, and reliable biomarkers for accurate diagnosis of NEC. Currently, the diagnosis of NEC is made by a combination of nonspecific clinical signs, symptoms, and radiological findings. Though biomarkers have been studied extensively, none offer an acceptable sensitivity or specificity to be used. This review will focus on the available literature on biomarkers for preterm NEC, acknowledging the limitations in studies including the variability of inclusion criteria, and most importantly, the lack of gold standard case definition for NEC.

**Prevention of Necrotizing Enterocolitis**

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Josef Neu

Necrotizing enterocolitis (NEC) is considered to be one of the most devastating intestinal diseases seen in neonatal intensive care. Measures to treat NEC are often too late, and we need effective preventative measures to alleviate the burden of this disease. The purpose of this review is to

summarize currently used measures, and those showing future promise for prevention.

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Natalie G. Allen, Kanthi Bangalore Krishna, and Peter A. Lee

Differences of sex development (DSD) refer to rare conditions in which an individual's sex development is different from typical male or female development. The neonatologist is often the first health care provider to interact with parents of newborns with DSD and must be familiar with the approach to these conditions. In this article, we discuss the definition of DSD, initial workup of the patient with DSD, terminology, and controversies in care.

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Martin Keszler

Extremely preterm infants who must suddenly support their own gas exchange with lungs that are incompletely developed and lacking adequate amount of surfactant and antioxidant defenses are susceptible to lung injury. The decades-long quest to prevent bronchopulmonary dysplasia has had limited success, in part because of increasing survival of more immature infants. The process must begin in the delivery room with gentle assistance in establishing and maintaining adequate lung aeration, followed by noninvasive support and less invasive surfactant administration. Various modalities of invasive and noninvasive support have been used with varying degree of effect and are reviewed in this article.

**Pharmacologic Analgesia and Sedation in Neonates** 243

Christopher McPherson and Ruth E. Grunau

Chronic pain and agitation in neonatal life impact the developing brain. Oral sweet-tasting solutions should be used judiciously to mitigate behavioral responses to mild painful procedures, keeping in mind that the long-term impact is unknown. Rapidly acting opioids should be used as part of premedication cocktails for nonemergent endotracheal intubations. Continuous low-dose morphine or dexmedetomidine may be considered for preterm or term neonates exhibiting signs of stress during mechanical ventilation and therapeutic hypothermia, respectively. Further research is required regarding the pharmacokinetics, pharmacodynamics, safety, and efficacy of pharmacologic agents used to mitigate mild, moderate, and chronic pain and stress in neonates.

**Controversies in Fetal Surgery: Prenatal Repair of Myelomeningocele in the Modern Era** 267

John P. Marquart, Andrew B. Foy, and Amy J. Wagner

Fetal surgery is a constantly evolving field that showed noticeable progress with the treatment of myelomeningocele (MMC) using prenatal repair. Despite this success, there are ongoing questions regarding the optimal approach for fetal myelomeningocele repair, as well as which patients are eligible. Expansion of the inclusion and exclusion criteria is an important ongoing area of study for myelomeningocele including the recent

Management of Myelomeningocele Plus trial. The significant personal and financial burden required of families seeking treatment has likely limited its accessibility to the general population.

**New Horizons in Mild Hypoxic-ischemic Encephalopathy: A Standardized Algorithm to Move past Conundrum of Care**

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Lina Chalak

Hypoxic-ischemic encephalopathy (HIE) presents clinically with a neonatal encephalopathy (NE) whereby the mild spectrum is difficult to classify immediately after birth. For decades trials have focused exclusively on infants with moderate-severe HIEs, as these infants were easier to identify after birth and had the highest risk of adverse outcomes. Twenty years after those trials, the PRIME study finally solved the first part of the conundrum by providing a definition of mild HIE in the first 6 hours. There is strong biological plausibility and preclinical evidence supporting the efficacy of therapeutic hypothermia (TH) but there is a lack of comparative clinical data to establish the risk-benefit in mild HIE. The fundamental question of how best to manage mild HIE remains unanswered. This review will summarize (1) the evidence that neonates with mild HIE are at significant risk for adverse outcomes, (2) the gaps/controversies in management, and (3) an algorithm of care is proposed to ensure standardized management of mild HIE and the direction of future trials.