Evidence-Based Neonatal Pharmacotherapy

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Dan L. Ellsbury and Robert Ursprung

Despite many years of heavy use in premature and critically ill newborns, surprisingly few medications have been rigorously tested in neonatal multicenter randomized clinical trials. Little is known about the pharmacology of these drugs at various birth weights, gestational ages, and chronologic ages. This article describes a quality improvement approach to evaluating and improving neonatal intensive care unit (NICU) medication use, with an emphasis on adaptation of drug use to the specific clinical NICU context and use of system-based changes to minimize harm and maximize clinical benefit.

Drug Studies in Newborns: A Therapeutic Imperative 11
George P. Giacoia, Perdita Taylor-Zapata, and Anne Zajicek

Although some drugs have been developed for the neonate, drug development for the least mature and most vulnerable pediatric patients is lacking. Most of the drugs are off-label or off-patent and are empirically administered to newborns once efficacy has been demonstrated in adults and usefulness is suspected or demonstrated in the older pediatric population. Few drugs are approved by the Food and Drug Administration for use in this population. The factors that prevent the demonstration of efficacy and safety in the newborn are discussed and a change in the current approach for neonatal drug studies is suggested.

Therapeutic Drug Monitoring—the Appropriate Use of Drug Level Measurement in the Care of the Neonate 25
Thomas E. Young

Neonates and young infants are in a unique and dynamic pharmacokinetic state, in which they undergo relatively rapid maturational changes in drug absorption, distribution, metabolism, and excretion. In addition to these maturational changes, most drug pharmacokinetic studies in neonates show wide interindividual variability despite similar gestational and postnatal ages. Therapeutic drug monitoring is a necessary tool in the neonatal intensive care unit, despite the relative lack of outcome data. This article discusses therapeutic drug monitoring for several frequently used drugs in neonates.
Obstetric Interventions Beneficial to Prematurely Delivering Newborn Babies: Antenatal Corticosteroids, Progesterone, Magnesium Sulfate

Thomas J. Garite and C. Andrew Combs

Although improvements in neonatal care have continued to result in reduced mortality and morbidity of prematurely delivering newborns for decades, the results of a myriad of obstetric efforts and interventions have failed to reduce the overall rate of prematurity or prolong pregnancy at any gestational age. A few new developments or refinements of established interventions give increased hope for an improved obstetric contribution to the problem of prematurity. These include a better understanding of how best to use antenatal corticosteroids, and the newer options of magnesium sulfate to ameliorate or avoid cerebral palsy associated with prematurity and maternal progesterone administration to selected at-risk populations to decrease the likelihood of premature delivery.

Evidence-Based Neonatal Pharmacotherapy: Postnatal Corticosteroids

Kristi Watterberg

Corticosteroids are used in the neonatal intensive care unit primarily to treat two conditions: bronchopulmonary dysplasia (BPD) and hypotension (cardiovascular insufficiency). Historically, high-dose dexamethasone was used for BPD, but its use was later associated with adverse neurodevelopmental outcomes and decreased substantially. Data from randomized controlled trials regarding efficacy and safety of lower-dose dexamethasone therapy are insufficient to recommend its use. Hydrocortisone may be an alternative to dexamethasone, but again data are insufficient to support use. Hydrocortisone therapy is increasingly used to treat hypotension in critically ill newborns; however, the outcomes of this therapy must be evaluated in randomized trials.

Antibiotic Use and Misuse in the Neonatal Intensive Care Unit

Nidhi Tripathi, C. Michael Cotten, and P. Brian Smith

Neonatal sepsis causes significant morbidity and mortality, especially in preterm infants. Clinicians are compelled to treat with empiric antibiotics at the first signs of suspected sepsis. Broad-spectrum antibiotics and prolonged treatment with empiric antibiotics are associated with adverse outcomes. Most common neonatal pathogens are susceptible to narrow-spectrum antibiotics. The choice of antibiotic and duration of empiric treatment are strongly associated with center-based risk factors. Clinicians should treat with short courses of narrow-spectrum antibiotics whenever possible, choosing the antibiotics and treatment duration to balance the risks of potentially untreated sepsis against the adverse effects of treatment in infants with sterile cultures.

The Use of Antiviral Drugs During the Neonatal Period

Richard J. Whitley

Parenteral therapy of viral infections of the newborn and infant began with vidarabine (adenine arabinoside) for the treatment of neonatal herpes simplex virus (HSV) infections in the early 1980s. Acyclovir has become the treatment of choice for neonatal HSV infections and a variety of other
herpesvirus infections. Ganciclovir is beneficial for the treatment of congenital cytomegalovirus (CMV) infections involving the central nervous system (CNS). This article reviews the use of acyclovir and ganciclovir in the treatment of neonatal HSV and congenital CMV infections. A brief summary precedes a detailed discussion of available established and alternative therapeutics.

The Use of Antifungal Therapy in Neonatal Intensive Care

Daniela Testoni, P. Brian Smith, and Daniel K. Benjamin Jr

Invasive fungal infections remain a significant cause of infection-related mortality and morbidity in preterm infants. Central nervous system involvement is the hallmark of neonatal candidiasis, differentiating the disease’s impact on young infants from that among all other patient populations. Over the past decade, the number of antifungal agents in development has grown, but most are not labeled for use in newborns. We summarize the findings of several antifungal studies that have been completed to date, emphasizing those including infant populations. We conclude that more studies are required for antifungals to be used safely and effectively in infants.

Metoclopramide, H₂ Blockers, and Proton Pump Inhibitors: Pharmacotherapy for Gastroesophageal Reflux in Neonates

William F. Malcolm and C. Michael Cotten

Pharmacotherapy for gastroesophageal reflux (GER) in neonates, aimed at interfering with this physiologic process and potentially reducing the negative sequelae that providers often attribute to GER, consists primarily of drugs that increase the viscosity of feeds, reduce stomach acidity, or improve gut motility. Medications used to treat clinical signs thought to be from GER, such as apnea, bradycardia, or feeding intolerance, are among the most commonly prescribed medications in neonatal intensive care units in the United States, despite the lack of evidence of safety and efficacy in this population.

Evidence-Based Use of Indomethacin and Ibuprofen in the Neonatal Intensive Care Unit

Palmer G. Johnston, Maria Gillam-Krakauer, M. Paige Fuller, and Jeff Reese

Indomethacin and ibuprofen are potent inhibitors of prostaglandin synthesis. Neonates have been exposed to these compounds for more than 3 decades. Indomethacin is commonly used to prevent intraventricular hemorrhage (IVH), and both drugs are prescribed for the treatment or prevention of patent ductus arteriosus (PDA). This review examines the basis for indomethacin and ibuprofen use in the neonatal intensive care population. Despite the call for restrained use of each drug, the most immature infants are likely to need pharmacologic approaches to reduce high-grade IVH, avoid the need for PDA ligation, and preserve the opportunity for an optimal outcome.

Evidence-Based Methylxanthine Use in the NICU

Alan R. Spitzer

The introduction of methylxanthines, especially caffeine, for the treatment of apnea of prematurity has been one of the most important and effective
therapies in the neonatal intensive care unit (NICU) to date. Several trials have demonstrated its effectiveness in most NICU infants. It remains a cost-effective intervention with minimal short- and long-term risks when used appropriately. Caffeine also appears to be effective for reducing the risk of bronchopulmonary dysplasia and patent ductus arteriosus, and for decreasing the need for reintubation. For the infant with apnea, currently there does not seem to be any more effective treatment, and caffeine is also more effective and safer than any other methylxanthine.

Pulmonary Vasodilator Therapy in the NICU: Inhaled Nitric Oxide, Sildenafil, and Other Pulmonary Vasodilating Agents
Nicolas F.M. Porta and Robin H. Steinhorn

The perinatal transition from fetal to extraterine life requires a dramatic change in the circulatory pattern as the organ of gas exchange switches from the placenta to the lungs. Pulmonary hypertension can occur during early newborn life, and present as early respiratory failure or as a complication of more chronic diseases, such as bronchopulmonary dysplasia. The most effective pharmacotherapeutic strategies for infants with persistent pulmonary hypertension of the newborn are directed at selective reduction of pulmonary vascular resistance. This article discusses currently available therapies for pulmonary hypertension, their biologic rationales, and evidence for their clinical effectiveness.

The Use and Misuse of Oxygen During the Neonatal Period
Maximo Vento, Javier Escobar, Maria Cerna, Raquel Escrig, and Marta Aguar

This article describes aerobic metabolism, oxygen free radicals, antioxidant defenses, oxidative stress, inflammatory response and redox signaling, the fetal to neonatal transition, arterial oxygen saturation, oxygen administration in the delivery room, oxygen during neonatal care in the NICU, evolving oxygen needs in the first few weeks of life, and complications that can occur when infants go home from the hospital on oxygen.

Hematological Interventions in NICU Care: the Use of rEp, IVIG, and rG-CSF
Robert D. Christensen

This article focuses on the use of rEp, IVIG, and rG-CSF in the NICU. It discusses the most recent studies and the most definitive and clinically relevant evidence, rather than summarizing all published studies. The last section was written for NICU practicing groups that choose to use any of these medications and are seeking a consistent approach for doing so. The section provides the author's approach to the use of rEp, IVIG, and rG-CSF, revealing personal preferences, interpretations, and experiences, and is based on the dictum, "If you are going to use it, use it the same way each time."

Management of Neonatal Thrombosis
Matthew A. Saxonhouse

Neonates have one of the highest risks for thromboembolism among pediatric patients. This risk is attributable to a combination of multiple genetic
and acquired risk factors. Despite a significant number of these events being either life threatening or limb threatening, there is limited evidence on appropriate management strategy. Most of what is recommended is based on uncontrolled studies, case series, or expert opinion. This review begins with a discussion of the neonatal hemostatic system, focusing on the common sites and imaging modalities for the detection of neonatal thrombosis. Perinatal and postnatal risk factors are presented and management options discussed.

**Neonatal Diuretic Therapy: Furosemide, Thiazides, and Spironolactone**

Jeffrey L. Segar

Diuretics are commonly used to treat infants with oxygen-dependent chronic lung disease. However, there are limited data suggesting a beneficial effect of long-term diuretic therapy on pulmonary function or clinical outcome in this population. Furthermore, data available for review were primarily obtained before the widespread use of antenatal steroids or surfactant replacement therapy, before recognition of the new bronchopulmonary dysplasia. If used in this population, limitations of diuretic therapy as well as significant side effects need to be understood and a rationale approach to clinical use developed on a patient-centered basis.

**Neonatal Blood Pressure Support: The Use of Inotropes, Lusitropes, and Other Vasopressor Agents**

Shahab Noori and Istvan Seri

A solid understanding of the mechanisms of action of cardiovascular medications used in clinical practice along with efforts to develop comprehensive hemodynamic monitoring systems to improve the ability to accurately identify the underlying pathophysiology of cardiovascular compromise are essential in the management of neonates with shock. This article reviews the mechanisms of action of the most frequently used cardiovascular medications in neonates. Because of paucity of data from controlled clinical trials, evidence-based recommendations for the clinical use of these medications could not be made. Careful titration of the given medication with close monitoring of the cardiovascular response might improve the effectiveness and decrease the risks associated with administration of these medications.

**Anesthesia and Analgesia in the NICU**

R. Whit Hall

Painful procedures in the neonatal intensive care unit are common, untertreated, and lead to adverse consequences. A stepwise approach to treatment should include pain recognition, assessment, and treatment, starting with nonpharmacologic and progressing to pharmacologic methods for increasing pain. The most common nonpharmacologic techniques include nonnutritive sucking with and without sucrose, kangaroo care, swaddling, and massage therapy. Drugs used to treat neonatal pain include the opiates, benzodiazepines, barbiturates, ketamine, propofol, acetaminophen, and local and topical anesthetics. The indications, advantages, and disadvantages of the commonly used analgesic drugs are discussed. Guidance and references for drugs and dosing for specific neonatal procedures are provided.