The Long and Winding Road: Loop Diuretics in Neonatology

First approved for clinical use in 1964, the loop diuretic furosemide remains one of the most commonly prescribed medications in the US. Clinicians leverage its potent diuretic action to treat a multitude of pathophysiologic conditions caused or exacerbated by fluid overload, most typically, congestive heart failure and renal dysfunction. Early use in pediatric populations also focused on acute management of fluid overload such as that associated with congenital heart disease.[1]

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The development of mechanical ventilators suitable for neonates along with improving knowledge about the appropriate use of supplemental oxygen therapy facilitated the advent of modern neonatal intensive care in the 1970s. In those early days, mechanical ventilation and oxygen were the mainstays of treatment of surfactant deficiency and respiratory distress syndrome (RDS). Neonatologists often observed that RDS had the look and feel of heart failure and pulmonary edema: diffusely hazy lung fields on chest radiographs, frothy tracheal aspirates, generalized edema, and a generous cardiothymic silhouette. Published studies from that era noted a relationship between early diuresis and recovery from RDS, as well as an increased risk of bronchopulmonary dysplasia (BPD) in those who did not experience a diuresis.[2-4] The potential for ongoing fluid overload from left to right shunting through a patent ductus arteriosus added further plausibility for diuretic treatment. Furosemide offered a potent pharmacologic complement to the management of RDS in the presurfactant era of neonatal intensive care. So, despite a paucity of systematic study, the use of furosemide and other diuretics in the neonatal intensive care unit (NICU) became rapidly entrenched in neonatology practice, probably reinforced by empiric observations of better respiratory function manifest by a decrease in oxygen requirements, decreased ventilator settings, and diminished work of breathing.

Systematic studies of furosemide use in the NICU started appearing in the late 1970s. These trials showed improvements in lung compliance and diminished requirements for mechanical ventilator support, but the benefit was transient. Translation to standardized clinical practice was hampered by small numbers of patients and variation in study eligibility or outcome variables.[5-8] A meta-analysis published in 2011 failed to demonstrate the value of diuretic therapy for RDS.[9] Similarly, studies of furosemide for the management of BPD showed variable clinical benefit, typically of brief duration.[10,11]

The advent of exogenous surfactant treatment in the early 1990s transformed the outcomes for RDS and probably diminished our collective curiosity about the appropriate role for loop diuretics such as furosemide (and other diuretics) in the NICU. However, the enthusiasm for their use has not gone away, to say the least. Treatment for patients with BPD is now the logical focus given that this remains a vexing problem for neonatologists.[12] Clearly, BPD in the postsurfactant era differs from the classical description of Northway et al.[13] The judicious use of diuretics could be a plausible strategy to address the admixture of alveolar simplification, pulmonary vascular disease, and right-sided cardiac dysfunction seen in many BPD cases.

In the 21st century, several groups have turned to the power of large datasets to reinvestigate the value of diuretic treatment. The latest, appearing in this volume of *The Journal*, is a carefully considered retrospective observational cohort study of loop diuretic exposure among 3252 patients with severe BPD from 43 centers participating in the Pediatric Health Information System database.[14] Furosemide accounted for the majority (98%) of exposure days with the remainder as bumetanide, a more potent drug with the same mechanism of action. The authors found substantial variation (>6-fold) in center-to-center use that could not be explained by case mix. No differences in mortality or timing of discharge could be attributed to the extent of diuretic use. Their findings build on a previous study using the same dataset.[15] Other reports document the similar degrees of variation in large cohorts derived from the Pediatrix Data Warehouse and the Prematurity and Respiratory Outcomes Program (PROP).[16,17]

In the absence of prospective trials, investigators have also used these large datasets to interrogate efficacy. Not surprisingly, the results have been mixed. An analysis of the Pediatrix dataset demonstrated an inverse correlation between the percentage of furosemide exposure-days and BPD or BPD and death.[16] Conversely, Blaisdell et al took advantage of the respiratory support data collected in the PROP cohort and found no short-term improvement in respiratory status.[18] Layered on top of persistent questions of efficacy, is evidence from PROP and an Italian study documenting dosing practices well beyond recommended measures.[17,19] The potential harm of high-dose furosemide treatment, primarily as ototoxicity, is well-documented. Nephrocalcinosis is an additional side-effect especially in premature neonates less than 32 weeks of gestation and exposed to a cumulative dose of more than 10 mg/kg.[20]

Despite more than one-half of a century of clinical experience, it is anything but clear how furosemide and its close relatives should be used in the NICU. Extreme practice variation, exposure to large doses, and a lack of clarity around efficacy suggest we still lack the fundamental knowledge needed to support safe and useful treatment. I suspect the vast majority of neonatologists (myself included) can cite

BPD	Bronchopulmonary dysplasia
NICU	Neonatal intensive care unit
PROP	Prematurity and Respiratory Outcomes Program
RDS	Respiratory distress syndrome

The author declares no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.12.046

examples of the apparent value of these medications for individual patients. However, the accumulated published evidence is cause for concern and offers little guidance for clinicians. Given the challenges of equipoise and expense, it will not be easy to design and conduct prospective studies. However, continuing to expose highly vulnerable patients to furosemide and other loop diuretics without clarity of benefit and risk is concerning. We can and should do better. ■

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In Search of an Ideal Protocol to Distinguish Risk for Serious Bacterial Infection in Febrile Young Infants

The evaluation and management of the febrile young infant is commonly performed in the outpatient setting. The subset of those aged less than 8 weeks of age has traditionally been demarcated from relatively older febrile children by a variety of unique clinical factors affecting risk for serious bacterial infection (SBI). These include inadequately developed host defenses, difficulty in accurately grading patient clinical appearance because of neurologic immaturity, and a unique profile of potential bacterial pathogens causing SBI for which we lack preventative vaccines.

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Consensus regarding appropriate management has evolved over time. Initially, it was customary to perform a full sepsis evaluation and hospitalize all febrile infants aged 0-8 weeks for empiric parenteral antibiotics pending culture results. After determining that the rate of

CSF Cerebrospinal fluid
LP Lumbar puncture
SBI Serious bacterial infection

The author declares no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.10.069