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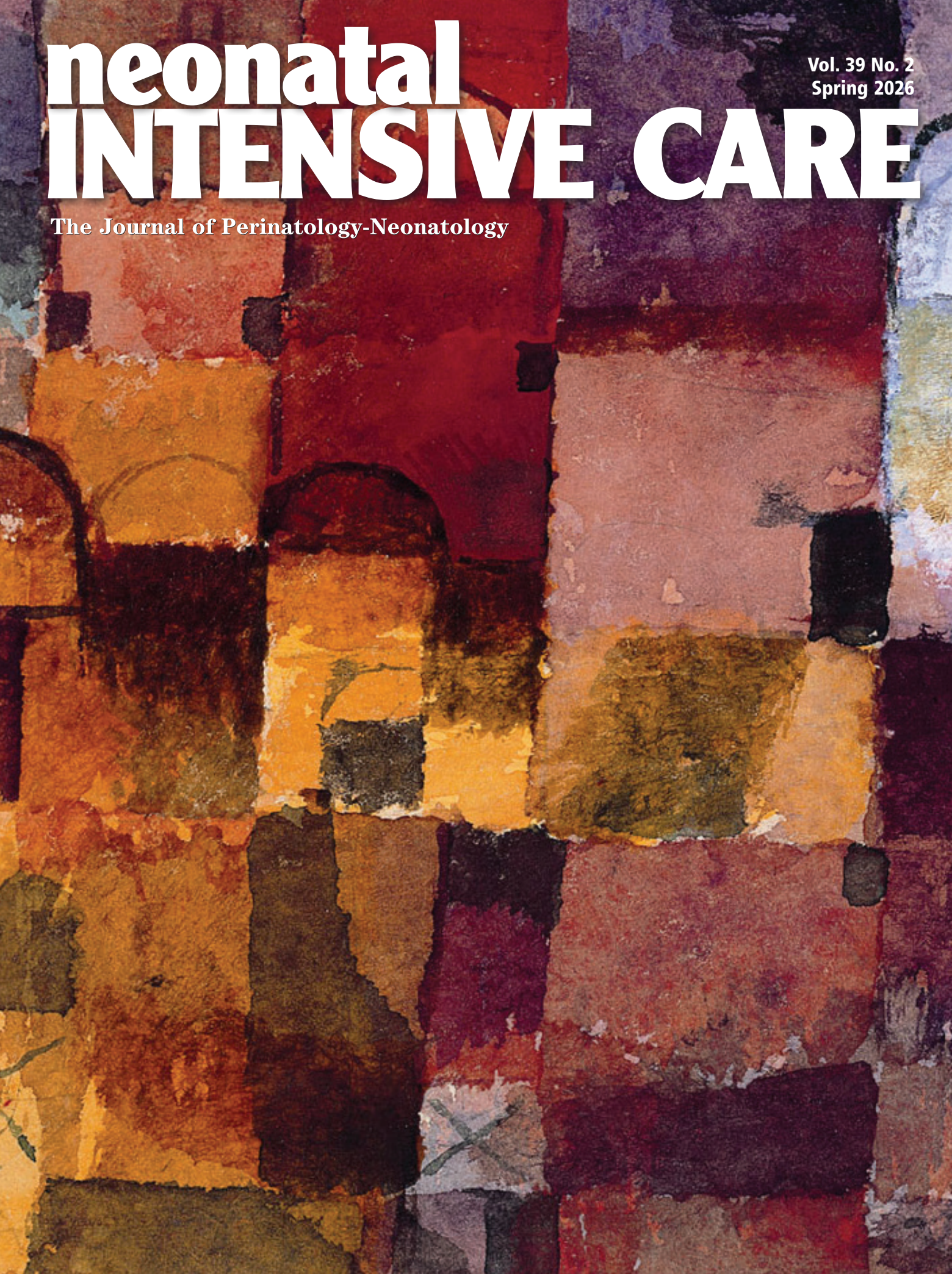

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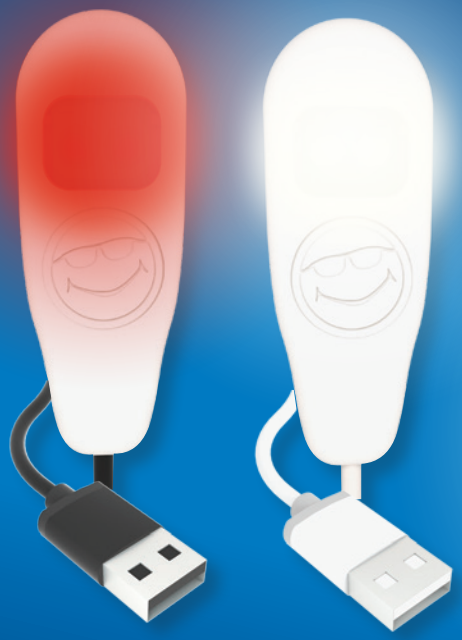

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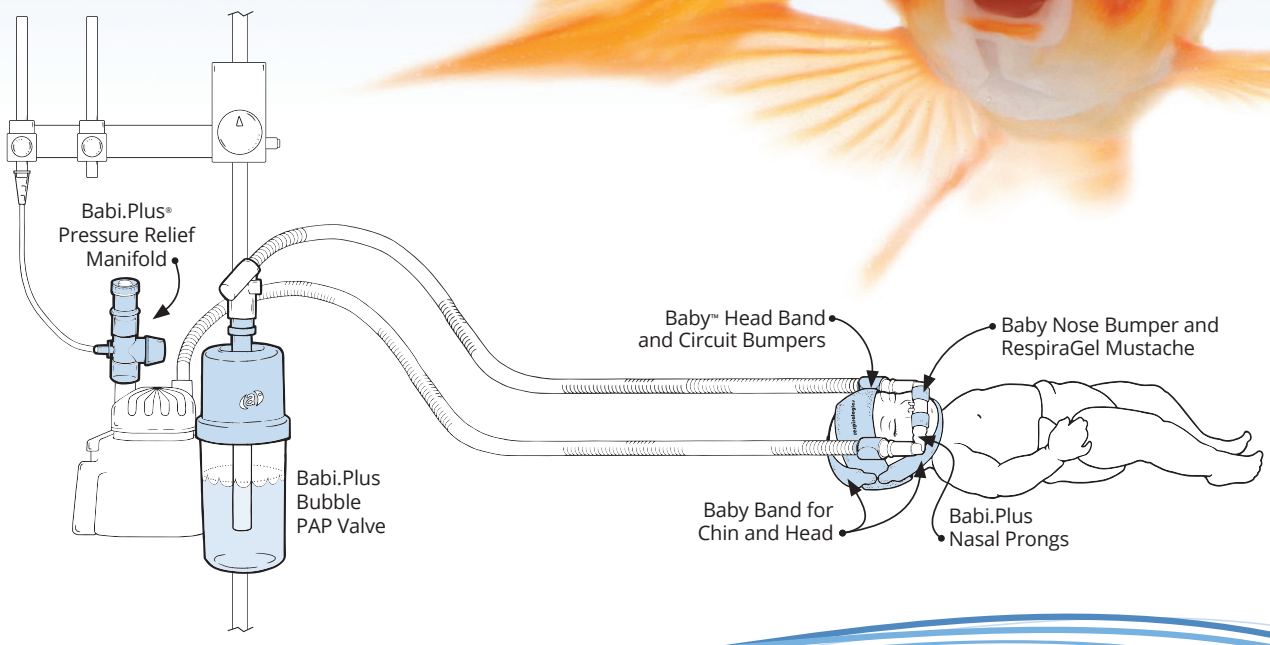

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News

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Differing immune responses in infants may explain increased severity of RSV over SARS-CoV-2

Young infants hospitalized with respiratory syncytial virus (RSV) often become much sicker compared to those infected with SARS-CoV-2, the virus that causes COVID-19. In a study published today in *Science Translational Medicine*, scientists from St. Jude Children's Research Hospital and The Jackson Laboratory (JAX) report that the two respiratory viruses trigger different immune responses. Those differences might explain why these two diseases have different clinical outcomes and require different treatment strategies. During the COVID-19 pandemic, physicians observed that infants admitted with RSV infection often had more severe symptoms than those hospitalized with SARS-CoV-2, despite both being respiratory RNA viruses. To understand these differences, the researchers compared the immune responses of infants hospitalized with either virus to those of healthy infants at a single-cell level. Measurements of proteins, genes and epigenetic signatures in the blood revealed the specific immune cells and signals central to these differences. "We showed, for the first time, that two similar respiratory viruses, RSV and SARS-CoV-2, cause very different types of immune dysregulation in young infants," said co-corresponding author Octavio Ramilo, MD, St. Jude Department of Infectious Diseases chair. "The host response differs depending on the infecting virus at the chemical, cellular and even epigenetic level." The researchers found that severe RSV in infants was linked to unexpectedly low levels of systemic inflammation and a poorly coordinated early immune response, primarily by a special set of immune cells called natural killer cells. This pattern contrasts with the hyperinflammatory immune response profile observed in infants with SARS-CoV-2 infection. "What surprised us most was that the antiviral responses looked similar at first glance, but when we examined how immune genes were regulated, we saw striking differences," said co-corresponding author Duygu Ucar, PhD, Professor at JAX. "RSV appears to reprogram parts of the infant immune system at the epigenetic level; which are molecular switches that control how genes are turned on or off." "These changes may help explain why RSV can lead to more severe disease and possibly influence how the immune system responds in the future," Ucar concluded. To find these differences, the researchers compared immune cells and proteins from blood samples derived from 19 infants hospitalized with RSV infections, 30 infants hospitalized with SARS-CoV-2 infections, and 17 healthy age-matched infants. Most infants in the study were around 2 months old. Comprehensive single-cell analysis of the infants' immune responses revealed that both viruses cause a similar rise in most interferons, antiviral molecules that interfere with viruses, but the analysis also revealed drastic differences. "Most strikingly, we saw infants with RSV had significantly fewer numbers of natural killer cells, compared to those with SARS-CoV-2 infections," said co-first author Asunción Mejías, MD, PhD, MsCS, St. Jude Department of Infectious Diseases. "In those patients, these cells also made less interferon-gamma, a key molecule to defend against viruses, which was strongly correlated with disease severity." "Integrating single cell technologies using advanced computational methods enabled us to not only identify immune response signatures in specific immune cell types but also associate gene expression with potential epigenetic regulators," said co-first author Asa Thibodeau, PhD, Associate Computational Scientist at JAX. "Understanding immune differences at the transcriptional and epigenetic level will guide future studies and better treatments." The RSV response was also marked by lower interferon-gamma expression and reduced activity of key inflammatory signals (IL-1B, NF-KB) that normally help fight infection. In contrast to RSV, SARS-CoV-2 generally causes significant immune dysregulation across multiple cell types. The researchers observed a significant increase in many pro-inflammatory molecules in these infants, such as TNF alpha and NF-κB activity. Clinically, this may explain why anti-inflammatory treatments, such as steroids, help some patients with severe COVID-19, while they have not helped patients with

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RSV, and may even be harmful. "One very practical implication of our work is that we should not routinely give steroids to infants with RSV," Mejías said. "RSV is already immunosuppressive; giving steroids that also suppress immunity may further impair the natural killer cell response combating the virus." RSV remains the primary cause of infant hospitalizations and the number two cause of infant mortality worldwide. The study's results and methodology provide a blueprint for better understanding infant immunity in general. "Globally, five million children die before the age of 5, half occurring in the first months of life due to infection, before vaccines are given," Ramilo said. "With the tools we have developed, we have shown that we can start to uncover what's happening in that early immunological window to begin improving those odds."

Fewer Newborns Receive Hepatitis B Vaccination

The rate of hepatitis B virus vaccinations given to newborns fell by 10 percentage points between 2023 and 2025, to just over 73%, according to new research published in *JAMA*. After the COVID pandemic, attention shifted toward other childhood immunizations, while anti-vaccine media coverage and social media discourse shaped attitudes among parents, researchers wrote. They cited one interview during the study period, in which US Department of Health and Human Services (HHS) Secretary Robert F. Kennedy, Jr, said babies do not need the hepatitis B vaccine and repeated debunked claims the shot raises the risk for autism — messaging that may have influenced parent choices. James D. Campbell, MD, MS, professor of pediatrics at the University of Maryland School of Medicine in Baltimore and vice chair of the American Academy of Pediatrics Committee on Infectious Diseases, said he is disheartened by the decreased rates "because of people sowing doubt." "I always ask people, 'Have you ever taken care of a child with cirrhosis, with liver failure? Have you ever been there in an ICU when an unvaccinated teenager died after two liver transplants because they hadn't had hepatitis B vaccine, a $30 shot?' I can say yes to all of those questions, most people cannot," Campbell said. "The fewer children who are vaccinated, the more of them who will get infected." Nine out of 10 infants infected with the virus at birth will develop hepatitis infections that last over 6 months. The CDC also reported that people with chronic hepatitis B infections have up to 25% risk of dying from hepatitis, cirrhosis, liver cancer, or other diseases caused by the virus. The hepatitis vaccine "can reduce the risk of acquiring what can become a lifelong serious infection that can lead to complications," said Joshua Rothman, MD, MS, an assistant professor in the Department of Pediatrics at the UC San Diego School of Medicine, who led the research. Rothman and colleagues calculated vaccination rates using electronic health records in the Epic Cosmos database representing more than 300 million patient records from 1800 hospitals and 41,500 clinics in the US.

UTI During Pregnancy: Short-Term Link to Preterm Birth

Urinary tract infection (UTI) diagnosed during pregnancy was significantly associated with a higher risk for preterm birth, and the risk was highest within 0-6 days after the diagnosis of UTI and particularly when the infection occurred before 28 weeks of gestation. Researchers conducted an observational study to evaluate how the gestational week at UTI diagnosis and the interval between diagnosis and delivery are associated with the risk for preterm birth. They used data from linked registers in Sweden and included 684,595 deliveries between 2014 and 2020. The analysis included pregnant women with a first recorded diagnosis of UTI identified using standardised diagnostic codes in the national patient register. The outcome was the risk for preterm birth, stratified by gestational week — 22-27, 28-31, and 32-36 weeks. Overall, 19,499 (2.8%) women were diagnosed with UTI during pregnancy. After

adjustments, women diagnosed with UTI at 22-27, 28-31, and 32-36 weeks of gestation had an approximately 18-fold, 13-fold, and 6-fold higher risk for preterm birth within 0-6 days of the diagnosis, respectively, than those without UTI. At 7-13 days after UTI diagnosis, the risk for preterm birth was still raised, approximately 10-fold, 4-fold, and 3-fold higher among women diagnosed with UTI at 22-27, 28-31, and 32-36 weeks of gestation, respectively, than among those without UTI. The elevated risk for preterm birth persisted at least 3 weeks after UTI diagnosis, about 2.5-fold and 3-fold higher at 22-27 and 28-31 weeks of gestation, respectively. Women diagnosed with UTI at 22-27, 28-31, and 32-36 weeks of gestation had extreme preterm birth (2.2% vs 0.3%), very preterm birth (2.8% vs 0.5%), and moderate-to-late preterm birth (7.1% vs 2.5%), respectively, compared with those without UTI. "Our results highlight the importance of raising awareness of the risk of preterm birth among women and healthcare personnel as well as the importance of carefully adhering to the national guidelines," the authors wrote.

AAP Finds No New Evidence Against Hep B Vaccine Birth Dose

A comprehensive review of the medical literature supports the longstanding practice of administering the hepatitis B vaccine to all medically stable infants at birth. The study, published in *Pediatrics*, found no evidence to justify new guidance issued last year by the CDC's Advisory Committee on Immunization Practices (ACIP) discouraging the birth dose for infants born to mothers who test negative for hepatitis B during pregnancy. The review was conducted by researchers with the Vaccine Integrity Project of the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota, Minneapolis. "We did not identify any new evidence that would suggest that there is a concern about safety of the hepatitis birth dose," said Angela Ulrich, PhD, MPH, an infectious disease epidemiologist and researcher with CIDRAP, who led the review. "We also didn't see any concerns about effectiveness, or that safety or effectiveness would improve if that birth dose was delayed or deferred." Since 1991, the CDC had recommended screening for hepatitis B virus (HBV) during pregnancy and giving hepatitis B vaccination to all medically stable infants at birth. In 2025, the Department of Health and Human Services (HSS) Secretary Robert F. Kennedy Jr replaced all 17 ACIP members. The new group voted in December to allow women who screen negative during pregnancy to decide, in consultation with their providers, when or if to vaccinate their child for hepatitis B; and if not at birth, then no earlier than 2 months of age. The committee also suggested considering collecting infant immune titers to guide decision-making for completing the vaccine series. The panel justified its decision on the grounds that rates of perinatal transmission of hepatitis B in the US are "very low" and that screening for the infection "identifies nearly all hepatitis B infections during pregnancy," among other rationales. Kennedy has long questioned the safety and efficacy of the newborn dose, claiming without evidence the thimerosal preservative in the shot causes autism. Last month, Kennedy called the US a "high outlier" in the number of immunizations recommended for all children. Kennedy has also pushed for a clinical trial of the vaccine in Guinea-Bissou, where hepatitis B is rampant. The CIDRAP team conducted a comprehensive review of evidence of the safety, immunogenicity, and efficacy of the birth dose, a delayed first dose, and the potential role of serology for clinical decision-making.

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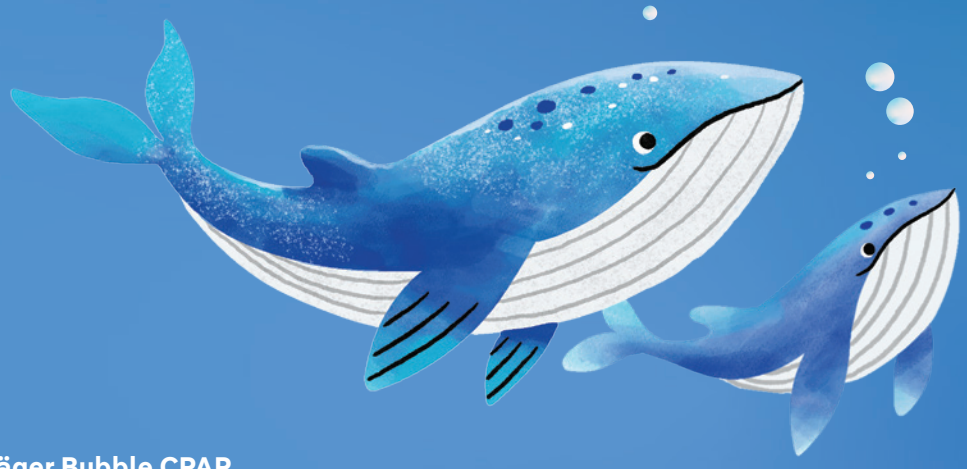

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Incidence of Tracheostomy and Considerations for Care in the Pediatric Cardiac Patient Population

Kristin A King, PhD, CCC-SLP

Airway abnormalities occur in patients with congenital heart disease (CHD) and may pose significant perioperative risks. Given the increased likelihood of airway compromise in this population, Foz et al. (2021) examined the incidence of airway abnormalities and associated risk factors. Their findings indicated that airway abnormalities are more prevalent in premature infants, patients weighing less than 10 kg, and those with specific cardiac lesions or concomitant genetic syndromes.[1] The presence of an airway abnormality in the perioperative period, as well as airway manipulation during and after surgery, increases the risk of requiring a tracheostomy.

The reported incidence of tracheostomy in pediatric patients undergoing cardiac surgery varies based on patient characteristics, the nature of the cardiac defect, and institutional practices. Mastropietro et al. (2016) documented an increase in tracheostomy rates from 0.1% to 0.76% in this population.[2] Additionally, Puchi, Lavin, Eltayeb, and Billings (2023) identified a high mortality rate associated with younger age at the time of tracheostomy and the presence of tracheomalacia in patients with CHD.[3] Although tracheostomy rates remain low, they underscore the severity and complexity of disease in these patients. Children with CHD frequently present with comorbid conditions, including pulmonary hypertension, respiratory muscle weakness, and airway abnormalities, all of which heighten the risk of respiratory failure and the need for prolonged mechanical ventilation.

Risk Factors for Tracheostomy

Several risk factors have been identified as contributing to the need for tracheostomy in pediatric patients following cardiac surgery. These include:

- **Complex Congenital Heart Disease:** Children with more complex cardiac defects, such as single-ventricle physiology or hypoplastic left heart syndrome, are at higher risk for respiratory complications.[4] These conditions often require extensive surgical repair, which can lead to longer postoperative recovery and an increased need for respiratory support.
- **Prolonged Mechanical Ventilation:** The duration of mechanical ventilation postoperatively is a strong predictor of tracheostomy. Children who require prolonged ventilation due to inadequate respiratory function or failure to wean are more likely to undergo tracheostomy. De Araujo et al. (2022) found that the underlying severity of the disease that caused a need for mechanical ventilation was more indicative of a tracheostomy than the length of time of ventilation.[5] They did find that earlier tracheostomy was linked to reduced time on mechanical ventilation and a shorter length of hospital stay but had no effect on mortality.
- **Postoperative Respiratory Complications:** Complications such as diaphragmatic paralysis,[6] pulmonary hypertension,[7] and bronchopulmonary dysplasia[8] are associated with a higher likelihood of requiring a tracheostomy. These conditions exacerbate respiratory insufficiency, making extubation difficult.
- **Surgical Factors:** The type and duration of cardiac surgery also play a role. More complex surgeries that involve longer cardiopulmonary bypass times or multiple procedures can lead to increased respiratory complications.
- **Patient-Specific Factors:** Prematurity, low birth weight, genetic syndromes, and pre-existing respiratory conditions are significant patient-specific factors that increase the risk of requiring a tracheostomy.[1]

Outcomes and Prognosis

The decision to perform a tracheostomy in pediatric cardiac patients is often made when it becomes clear that prolonged mechanical ventilation is necessary. Similar to what is seen in adult literature on the impact of a team, Hansen et al. (2021) found that having a multidisciplinary chronic lung disease team in the neonatal intensive care unit (NICU) was associated with an increased survival rate for infants with tracheostomies.[9] While a tracheostomy may be lifesaving, it is associated with both short- and long-term complications. These include tracheal stenosis, infection, and the potential need for long-term respiratory support. Despite these risks, tracheostomy can lead to improved outcomes in selected patients by facilitating weaning from mechanical ventilation, improving oral feeding, and allowing for discharge from the hospital, especially if the patient is able to use a speaking valve.

The placement of a tracheostomy tube and prolonged mechanical ventilation with an inflated cuff causes a disconnect between the upper and lower airways. The lack of airflow through the upper airway can often lead to multiple negative developmental and functional changes affecting speech and swallowing:

With more than 30 years of experience in medical, academic, and industry settings, Dr King brings a unique perspective of medical speech pathology. Her research, publications, and teachings focus on traumatic brain injury, swallowing disorders, and critical care (tracheostomy and mechanical ventilation) for both pediatric and adult patient populations. She has been an invited speaker both domestically and internationally and has published in peer-reviewed journals. Currently, Dr King is the Vice President of Clinical Education and Research for Passy-Muir, Inc.

reduced subglottic pressure;[10-11] decreased sensation;[12] reduced laryngopharyngeal reflex[13]; decreased ability to manage secretions, requiring more frequent suctioning;[12] decreased sense of taste and smell;[12] inability to vocalize; increased aspiration risk; and muscle disuse and atrophy.[14] A disconnect between respiration and swallowing also may negatively impact the ability to coordinate breathing and swallowing. For pediatrics, long-term tracheostomy placement also has been associated with delayed acquisition of language, delayed social development, and risk of impaired parent-child bonding.[14-16]

A primary method for closing the system to restore more normal physiology and pressures for patients with tracheostomies is the use of a bias-closed position, no-leak valve. When a patient has a tracheostomy, airflow is directed in and out through the tracheostomy tube and bypasses the upper airway. The Passy-Muir® Valve works by closing at the end of inspiration, redirecting 100% of airflow out through the vocal cords and upper airway. Research has shown that this redirection of airflow assists with improving secretion management, increasing sensory awareness, improving swallowing, and restoring natural physiologic PEEP (positive end-expiratory pressure), among other benefits.[12] Brooks et al. (2019) found that, in medically complex infants and children, not only was using a Valve beneficial, but there are predictors of success related to the age and weight at the time of tracheostomy, transtracheal pressure measurements, voicing, and ventilator rate.[17]

Prognosis: The long-term prognosis for pediatric patients who undergo tracheostomy after cardiac surgery varies. Using a valve has been shown to increase the rate of success with feeding and swallowing[14] and lead to earlier decannulation.[18] Some children may eventually be decannulated and achieve normal respiratory function, while others may require long-term tracheostomy care. The presence of underlying conditions, such as chronic lung disease or neurologic impairment, significantly influences long-term outcomes.

Conclusion

The incidence of tracheostomy in pediatric patients undergoing cardiac surgery, while relatively low, reflects the complexity and severity of this population. Identifying risk factors and optimizing management is essential for reducing the need for tracheostomy and improving outcomes or for providing better plans of care should the patient need a tracheostomy. Refining criteria for tracheostomy in this patient population, as well as developing strategies to minimize respiratory complications, will enhance recovery following pediatric cardiac surgery. Through a better understanding of these factors, and knowing when to use a speaking valve, health-care providers can improve the quality of care for children with congenital heart disease, ultimately leading to better long-term outcomes.

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Neonatal Tracheostomy Tubes: To Cuff or Not to Cuff

Megan Quinn, MSN, CPNP-PC

Neonatal tracheostomy

Neonatal patients require tracheostomy tubes for a variety of reasons such as the need for prolonged ventilation, weaning of ventilatory support, and to bypass upper airway obstruction (Walsh and Rastatter, 2018). In recent years, there have been increases in tracheostomy tube placement in the neonatal population for both neurologic and cardiopulmonary diagnoses (Walsh and Rastatter, 2018). With these evolving practices, cuffed tracheostomy tubes have become a commonly considered option for this patient population; however, their risks and benefits must be carefully weighed.

Benefits of cuffed tracheostomy tubes

Cuffed tracheostomy tubes have many benefits for the neonatal patient. The cuff on a neonatal tracheostomy tube is often filled with liquid, either saline or water, depending on the brand of tracheostomy tube. The cuff holds this fluid, which helps create a seal between the upper and lower airway. This can facilitate effective mechanical ventilation.

Many neonatal patients require ventilation via a tracheostomy tube for proper pulmonary support (Walsh and Rastatter, 2018). Ensuring that appropriate pressures can be delivered by the ventilator often requires the seal created by the cuff (Dariya et al., 2022). Minimizing air leaks around the tracheostomy tube helps to provide effective ventilation without requiring higher ventilator settings.

Cuffs can also help to protect against secretions entering the lower airway by acting as a barrier to secretions passing from the oropharynx. Additionally, if there is concern for emesis or regurgitation, it can help to prevent this material from entering the lungs. In this population, the risk of secretions, emesis, breastmilk, or formula entering the lungs is high and this can lead to infections such as pneumonia (Mehta & Chamyal, 2017). While a cuff cannot completely prevent secretions from entering the lungs, it will provide a strong barrier.

Neonatal patients grow rapidly during hospitalization, and their airways grow as well. A cuffed tracheostomy tube can help accommodate this growth by allowing incremental adjustments in cuff inflation, potentially reducing the need for frequent tube size changes. The appropriate inflation volume varies by patient and must balance adequate ventilation and airway protection while avoiding the risk of overinflation (Dariya et al., 2022). Careful monitoring is essential to ensure safe cuff pressures as the child grows.

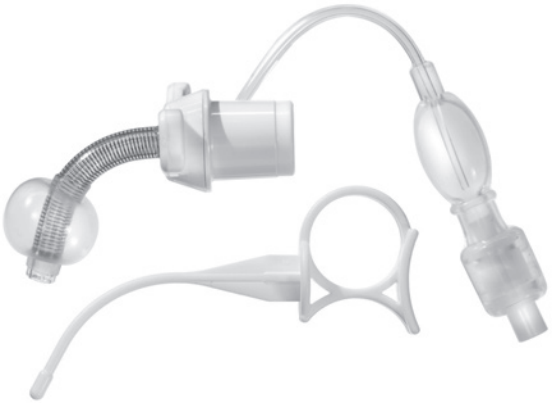

Figure 1. Tracoe Silcosoft Cuffed Tracheostomy Tube.

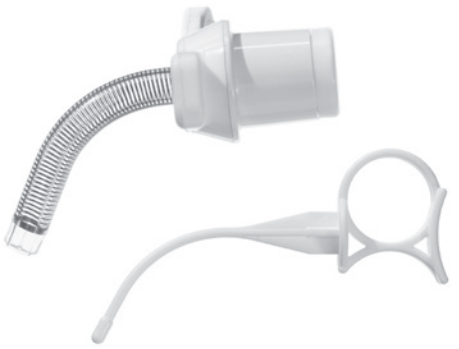

Figure 2. Tracoe Silcosoft Uncuffed Tracheostomy Tube.

Minimal occlusive volume technique is a method used to determine the appropriate cuff inflation volume in a patient. This technique can be utilized in both air and water cuffs. During the procedure, the patient's upper airway is suctioned, and the cuff is fully deflated. Using a stethoscope placed on the suprasternal notch, the cuff is gradually inflated until airflow is no longer heard, then slowly deflated until a small amount of airflow is heard. Finally, a small amount of volume is carefully added to the cuff to achieve minimal occlusion. This method provides a reliable

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estimate of the volume needed to achieve proper cuff inflation (Totonchi et al., 2015). While manometry is considered the gold standard for measuring cuff pressure for air cuffs, it cannot be used with water cuffs; in such cases, the minimal occlusive volume technique has been shown to be an effective alternative (Totonchi et al., 2015).

Risks of cuffed tracheostomy tubes

While cuffed tracheostomy tubes have many benefits for patients and providers, there are risks associated with cuffed tracheostomy tubes.

Underinflation of a tracheostomy cuff can be uniquely harmful. If the cuff is not inflated appropriately, oropharyngeal content can travel past the tracheostomy tube and into the lungs (Sanaie et al., 2019). This can lead to a higher risk of ventilator associated pneumonia (Rose & Redl, 2008). Utilizing a technique like the minimal occlusive volume technique can help ensure that the cuff is inflated to the correct point, but not overinflated.

Additionally, tracheostomy tube cuff overinflation can be very dangerous for neonatal patients. Neonatal airways are, by nature, small. Due to the small diameter of the airway, cuff overinflation can occur easily. Overinflation of a cuff can cause numerous problems such as decreased tracheal capillary perfusion, resulting in decreased blood flow to the trachea, tracheal ischemic damage, tracheal innominate artery fistula, and potentially tracheal rupture (Sangie et al. 2019; Rose & Redl, 2008). Standard cuff pressure should be between 20-30 cm H2O. In cuff pressures of 50 cm H2O, tracheal blood flow can be completely disrupted (Santos Silva de Souza et al. 2022). In a 4 mm neonatal airway, this pressure can be reached with a small amount of extra fluid in the cuff. Once again, minimal occlusive volume technique allows providers to carefully manage cuff inflation, ensuring adequate seal while minimizing the risk of overinflation.

Tracoe Solution

The decision to utilize a cuffed or uncuffed tracheostomy tube is ultimately made by the medical team. They must consider the patient status, size, diagnosis, ventilation needs, and many other factors. Tracoe offers cuffed and uncuffed tracheostomy tubes to support individualized patient care.

Tracoe Silcosoft tracheostomy tubes are soft, made of silicone, and hold their shape well, due to the nitinol spiral reinforcement. Both neonatal and pediatric sizes are available. Importantly, all sizes are available with and without a water cuff, offering flexibility to meet the needs of individual patients.

To learn more about the neonatal tracheostomy tubes available for your patients, please visit Pediatric Tracheostomy Management —Atos Medical (https://www.atosmedical.us/professionals/tracheostomy/tracoe-kids) or email the author: megan.quinn@atosmedical.com

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Forceps: An Obituary to Classic Obstetrics

Born: 1668, Isle of Wight
Died: Slowly

Boris M Petrikovsky, MD, PhD

Introduction

We gather today not in grief, but in hushed respect. The metal hands that once pried open the gates of life — those curved, metal blades — are slipping from our hands like a last breath. They delivered kings and paupers; yanked babies into daylight while mothers screamed and doctors thanked God. Four steps they demanded: engage, lock, traction, release. Clean and effective.

Witnesses say the end began with lawsuits. One forceps nip too deep, one facial nerve twitching, and juries pointed fingers. Rates tumbled. In Sweden they buried them outright; here we still prop them up like taxidermy, just in case.

Obstetricians trained years ago were familiar with different types of forceps: Simpson, Elliot, Luikart, Tucker-McLane, among others (Figure 1). Each type has a particular indication depending on the position of the baby's head and the structure of the maternal pelvis. Depending on fetal head station, forceps deliveries were classified as high, mid-pelvic, or low/outlet.[1]

Figure 1. Learning how to use obstetrical forceps.

In recent decades, the use of forceps (Figure 2) has steadily declined, concurrently with an increase in cesarean rates. The cesarean delivery rate increased by 48% whereas the rate of forceps declined by 93%. As forceps skills are not widely taught to residents, fewer numbers of attending obstetricians are able to teach the use of forceps to the next generation of residents. The fear of lawsuits is mainly responsible for the decline in forceps deliveries in the United States. According to a survey by the American College of Obstetricians and Gynecologists, 41% of the obstetricians surveyed reported that they have altered the way in which they practice because of the risk of medical liability.[2]

Figure 2. Obstetrical forceps.

Do forceps affect the health and well-being of the children? — That is the real question.

In 1996 Dierker et al.[3] compared children delivered by forceps with children delivered by cesarean section. They found no increased morbidity associated with delivery by forceps. Similarly, McBride et al.[4] studied methods of delivery and developmental outcome in 5-year-old children. The children were assessed for gross motor coordination and auditory and visual ability. No deleterious effect of delivery methods was found.

To decrease forceps marks on the baby and maternal lacerations, we've designed "soft forceps" (patent pending) by covering forceps blades with a soft rubber coat. Unfortunately, the decline of forceps use prevents us from making a profit from our invention.[5]

How forceps compare to other forms of assisted vaginal delivery

In studies between two forms of assisted vaginal delivery, perineal lacerations are more common after forceps than after vacuum extraction, and cephalohematomas are more common after vacuum extraction. Vacuum extractors, the other form of assisted vaginal

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delivery, have undergone numerous modifications, but forceps have not been modified.

Classic obstetrical teaching recognizes different indications for obstetrical forceps and vacuum extractions: forceps did not require maternal pushing and were preferred for cases when mother is too exhausted to push or unable due to deep anesthesia. In certain situations, the baby's head is very low and pushing it up during the cesarean section may cause more complications.

Present Day Use of Forceps

Reviewing scarce recent publications on the use of forceps I came across the article on forceps-assisted delivery of a gorilla: a team including zoo veterinarians and human obstetricians used forceps and other human obstetric techniques to deliver a critically endangered 18-year-old Western lowland gorilla at the Philadelphia Zoo after the mother experienced a prolonged labor.[7] The successful delivery of a healthy newborn highlighted the potential for applying human medical principles to reduce mortality rates in the gorilla. It is ironic that a once-essential instrument in skilled human hands is now primarily benefiting the animal kingdom — a real paradox; usually surgical technology is usually tested on animals first and then move on to humans. With obstetrical forceps, the reverse is true.

In 1897, while in London, a rumour spread that the famous writer, Mark Twain, was "dead." The original quote from Mark Twain regarding his supposed death was: "The report of my death was an exaggeration." The same is true of obstetrical forceps which are widely in use in many countries in Africa, Asia and Latin America. The unfortunate permanent reason for forceps demise in the USA and many European countries is that we do not train young doctors in how to use them.

Conclusion

Reviving forceps? Fair question. They're not totally dead — just on life support. In emergencies when cesarean sections are not available, for example in remote areas, they are lifesavers. Training specialists keeps that skill alive; not everyone needs it, but some ob-gyns should master it for those rare, high stakes moments. We can't bury the tool yet — progress means adapting, not forgetting.

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Neonatal Refeeding Syndrome: A Comprehensive Review of Pathophysiology, Risk Factors, Management, and Outcomes

Suzanne Smith, MS, RD, LDN, IBCLC

Abstract

Neonatal refeeding syndrome represents a critical and potentially life-threatening metabolic disturbance that can occur in vulnerable neonatal populations upon the reintroduction of nutrition following a period of starvation or severe malnutrition. This complex condition is primarily characterized by severe fluid and electrolyte shifts, notably hypophosphatemia, hypokalemia, and hypomagnesemia, often accompanied by thiamine deficiency. These imbalances can precipitate devastating consequences, including fluid overload, cardiac arrhythmias, seizures, encephalopathy, and, in severe cases, mortality.

Despite historical recognition of refeeding complications, significant challenges persist in the consistent definition, accurate diagnosis, effective prevention, and standardized management of refeeding syndrome within the neonatal intensive care unit (NICU) setting. The wide variability in reported incidence rates underscores the lack of a unified diagnostic approach, which impedes robust research and comparative analyses. Furthermore, the long-term neurodevelopmental impacts associated with refeeding syndrome highlight the urgency for improved clinical strategies. This review synthesizes current evidence to provide a standardized approach to identifying and managing this often-underdiagnosed condition.

Introduction to Neonatal Refeeding Syndrome

Refeeding syndrome (RS) in neonates is a complex and often underestimated condition that demands a thorough understanding of its definition, historical context, and prevalence within this unique patient group.

Definition and Historical Context

RS is characterized as a potentially life-threatening metabolic disturbance that arises from severe fluid and electrolyte shifts, predominantly hypophosphatemia, hypokalemia, and hypomagnesemia, often coupled with thiamine deficiency.[1-6] These disturbances occur when nutritional support, whether oral, enteral, or parenteral, is reintroduced to individuals who have experienced periods of starvation, severe malnutrition, or significant metabolic stress due to critical illness.[1-6] The clinical manifestations can be severe, including fluid overload, cardiac arrhythmias, seizures, encephalopathy, and even death.[1-6]

The phenomenon of refeeding complications was initially documented during World War II, when individuals recovering from severe famine experienced unexpected morbidity and mortality upon receiving food.[4] While the initial descriptions focused on adult populations, current medical literature now acknowledges a similar syndrome in neonates.[2] It is concerning that despite long-standing knowledge of RS's severe and often fatal effects when refeeding is mishandled, contemporary literature still describes RS as having scarce pediatric evidence, being underdiagnosed, or poorly recognized in young children and neonates.[3] This disparity between historical knowledge and present recognition highlights a critical gap in clinical practice. It suggests that the unique physiological characteristics of neonates, such as their immature organ systems, rapid growth rates, and distinct baseline nutrient stores, are not yet fully integrated into current awareness or diagnostic paradigms. This can lead to delays in diagnosis or even missed cases, thereby compromising timely and effective interventions.

Prevalence and Incidence in Neonatal Populations

The overall incidence of neonatal RS remains undefined and exhibits significant variability across studies, primarily due to inconsistencies in diagnostic criteria and clinical management approaches.[2] This lack of a standardized definition creates a significant challenge for accurately quantifying the true burden of RS in neonates.

Reported incidence rates in preterm infants demonstrate a wide range:

- One study indicated an incidence rate of 38% in preterm infants born before 32 weeks gestation.[4]
- The ProVIDe trial found that 20% of extremely low birth weight (ELBW) infants developed RS.[4]
- Other reports suggest incidence rates as high as 90%, particularly in small-for-gestational-age (SGA) infants, those with intrauterine growth restriction (IUGR), and those receiving aggressive parenteral nutrition (PN) from the first day of life.[4]
- Hypophosphatemia, a hallmark feature of RS, has a higher incidence in IUGR neonates (approximately 40%) compared to appropriately grown very low birth weight (VLBW) infants (9%).[2]
- An estimated incidence of up to 7.4% has been observed in pediatric intensive care unit patients receiving nutritional support.[3]

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- Encouragingly, recent modifications to intravenous nutrition protocols that incorporated increased early phosphate intake and routine biochemical monitoring were associated with a significant decrease in RS incidence from 11.9% to 2.9% in ELBW infants.[1]

The broad range of reported incidence rates (from 7.4% to 90%) is a direct consequence of inconsistencies in the definition of RS across different studies.[2] This "definition dilemma" means that various studies may be measuring distinct clinical phenomena or applying differing thresholds for diagnosis. Such variability severely hampers the ability to accurately determine the true prevalence of RS in neonates, compare clinical outcomes across different research endeavors or institutions, and develop universally effective prevention and management strategies based on robust, comparable evidence. The implication is that until a unified, widely accepted definition of neonatal RS is established, research efforts will remain fragmented, and clinical guidelines may lack the necessary precision to ensure optimal patient care. Furthermore, current prevalence figures may either under- or over-estimate the true burden of the syndrome depending on the specific diagnostic criteria employed.

Pathophysiology and Metabolic Derangements

Understanding the intricate physiological mechanisms and specific metabolic and electrolyte abnormalities is fundamental to comprehending RS in neonates.

Electrolyte Imbalances (Hypophosphatemia, Hypokalemia, Hypomagnesemia)

During periods of prolonged starvation, the body undergoes a metabolic adaptation, shifting into a catabolic state where it primarily relies on endogenous stores of glycogen, amino acids, and fat for energy production.[1-6] Upon the reintroduction of a carbohydrate source, particularly with aggressive feeding, there is a rapid surge in insulin secretion. This hormonal shift prompts a swift transition back to glucose as the predominant fuel source, initiating an anabolic process that demands significant utilization of various minerals and cofactors.[1-6]

The increased insulin levels actively promote the cellular uptake of glucose, potassium, magnesium, and phosphate from the extracellular space into the intracellular compartment.[1] This rapid and substantial intracellular movement leads to a sharp decrease in their serum concentrations, resulting in the characteristic electrolyte imbalances of RS:

- **Hypophosphatemia:** This is frequently considered the hallmark biochemical feature of RS.[1] It occurs due to an increased demand for phosphorus during the anabolic state, coupled with often low total body reserves (even if initial serum levels appear normal), and the direct action of insulin driving phosphorus into cells.[2] The depletion of phosphorus severely impairs cellular energy production, particularly adenosine triphosphate (ATP) synthesis, and compromises oxygen delivery to tissues, which can be life-threatening.[4]
- **Hypokalemia:** This electrolyte disturbance also results from insulin's effect, which shifts potassium intracellularly.[1] Clinically, hypokalemia can manifest as cardiac arrhythmias, muscle weakness, and respiratory depression.[3]
- **Hypomagnesemia:** Magnesium serves as a crucial cofactor in numerous enzyme systems, including those involved in ATP production. Its deficiency can lead to significant cardiac dysfunction, heightened neuromuscular excitability (presenting as tremors, tetany, and seizures), and can complicate the effective repletion of potassium.[1]

While hypophosphatemia is often emphasized as the primary indicator, the available information consistently describes hypokalemia and hypomagnesemia as frequently co-occurring and equally critical.[1] This pattern indicates that these are not isolated deficiencies but rather an interconnected cascade of metabolic disturbances. For example, the depletion of one electrolyte, such as magnesium, can directly exacerbate another, leading to refractory hypokalemia.[1-3] Furthermore, the pathophysiology explicitly links these electrolyte shifts to widespread multi-organ dysfunction, impacting cardiovascular, pulmonary, neuromuscular, hematologic, and gastrointestinal systems.[4] This broader understanding underscores that RS is a systemic crisis, extending far beyond simple laboratory abnormalities, and necessitates a comprehensive, holistic approach to assessment and intervention.

Fluid and Thiamine Deficiencies

Beyond the primary electrolyte imbalances, refeeding syndrome also involves critical fluid and micronutrient deficiencies that contribute to its systemic impact:

- **Fluid Imbalance:** The reintroduction of nutrition can lead to significant sodium retention and subsequent fluid overload.[1] This can result in serious complications such as pulmonary edema and cardiac compromise.[6] The underlying mechanism is likely a decreased renal excretion of sodium and water, primarily driven by hyperinsulinemia during the refeeding process.[2]
- **Thiamine Deficiency:** Thiamine (Vitamin B1) is an essential coenzyme crucial for carbohydrate metabolism. In malnourished individuals, pre-existing thiamine deficiency is common. When a significant carbohydrate load is introduced during refeeding, the increased metabolic demand for thiamine can rapidly deplete its already low stores. This can lead to severe consequences, including lactic acidosis, Wernicke's encephalopathy, cardiac failure, and even death.[3] Consequently, prophylactic thiamine administration is considered a crucial preventive measure, especially before initiating refeeding or administering dextrose-containing fluids.[3]

Risk Factors and Predisposing Conditions in Neonates

Identifying specific vulnerabilities is paramount for proactive prevention and management of RS in the neonatal population.

Specific Vulnerabilities

Neonates, particularly those with certain characteristics, are at a heightened risk for developing RS due to their unique physiological state and nutrient reserves:

- **Preterm Infants:** These infants, especially those born at or before 32 weeks gestation, are inherently at high risk. They are born with minimal nutrient stores, particularly of calcium, phosphate, and other essential micronutrients, as the crucial period for their accumulation occurs during the third trimester of pregnancy.[4]
- **SGA / IUGR:** Infants classified as SGA or with IUGR often experience a state of malnourishment during gestation, frequently attributed to placental insufficiency. This condition results in reduced muscle mass, depleted glycogen stores, diminished adipose tissue, and impaired active transfer of vital electrolytes like potassium and phosphorus across the placenta.[1] Consequently, these infants are significantly predisposed to RS.[1]
- **VLBW / ELBW:** Infants weighing less than 1500g (VLBW) or 1000g (ELBW) have exceptionally high nutrient requirements

Electrolyte Abnormality	Associated Clinical Manifestations (Organ Systems Affected)
Hypophosphatemia	**Neurological:** Weakness, tremors, tetany, seizures, encephalopathy, coma, paralysis, tissue hypoxia. **Cardiovascular:** Impaired cardiac function, hypotension, arrhythmias. **Respiratory:** Respiratory failure (impaired diaphragm contractility). **Hematological:** Hemolysis, leukocyte dysfunction, thrombocytopenia. **Musculoskeletal:** Muscle weakness, myalgias, rhabdomyolysis.
Hypokalemia	**Cardiovascular:** Arrhythmias, ECG changes. **Neurological:** Weakness, paralysis, confusion, lethargy, areflexic paralysis, seizures. **Respiratory:** Respiratory depression/failure. **Gastrointestinal:** Nausea, vomiting, constipation, ileus.
Hypomagnesemia	**Neurological:** Muscle twitching, tremors, tetany, altered mental status, confusion, seizures, coma, paresthesia, weakness. **Cardiovascular:** Cardiac dysfunction, arrhythmias, ECG changes. **Other:** Refractory hypokalemia and hypocalcemia.
Thiamine Deficiency	**Neurological:** Encephalopathy (Wernicke's syndrome, Korsakoff psychosis), nystagmus, neuropathy. **Metabolic:** Lactic acidosis. **Cardiovascular:** Cardiac failure.
Sodium Retention	**Fluid Balance:** Fluid overload, peripheral edema, pulmonary edema. **Cardiovascular:** Cardiac decompensation, hypotension.

Table 1. Key Electrolyte Imbalances and Associated Clinical Manifestations in Neonatal Refeeding Syndrome

Note: This table illustrates the systemic impact of electrolyte and micronutrient derangements in RS, highlighting the multi-organ involvement that necessitates a comprehensive clinical approach.

due to their rapid postnatal growth potential.[1] The incidence of RS-induced hypophosphatemia is notably higher in IUGR neonates (approximately 40%) when compared to appropriately grown VLBW infants (9%).[2]

- **Male Sex and Intraventricular Hemorrhage (IVH):** Studies have identified male infants as having a significantly increased risk of RS (adjusted relative risk 1.31). Furthermore, the risk of RS is significantly higher in infants who experience intraventricular hemorrhage (IVH), with a relative risk of 1.71.[4]

A critical observation arises from the tension between the inherent vulnerabilities of preterm, SGA, IUGR, VLBW, and ELBW infants to nutrient deficiencies and the common practice of employing "aggressive early parenteral nutrition" to promote optimal growth and neurodevelopment.[1-2,4] This creates a notable paradox: the very intervention designed to prevent malnutrition and improve long-term outcomes can, if not meticulously managed, precipitate a life-threatening condition. This highlights that "aggressive" PN, in the context of RS prevention, must be reinterpreted. It should not merely signify high caloric or protein intake but rather emphasize the aggressive and proactive provision of sufficient concurrent electrolyte and micronutrient supplementation from the outset to safely support the rapid anabolic shift. The overarching goal is to effectively meet the high nutrient requirements of these vulnerable infants while simultaneously preventing the dangerous electrolyte imbalances that define RS. This necessitates precise, individualized PN formulations and vigilant monitoring, moving beyond a blanket "slow" approach that might inadvertently compromise essential growth.

Nutritional Practices as Risk Factors

Certain nutritional practices, particularly in the context of neonatal care, can significantly contribute to the risk of RS.

- **Aggressive Parenteral Nutrition (PN):** The early and rapid provision of parenteral amino acids (AA) without adequate concurrent electrolyte and mineral supplementation in the initial days after birth is a major risk factor for RS.[1] High intravenous protein intake without electrolytes, often in the range of 3.5-4.5 g/kg/day, can lead to metabolic complications, including RS.[4]
- **Prolonged Fasting/Poor Intake:** Infants who experience inadequate nutritional intake for 10 days or more, or starvation for at least 3 days, are at increased risk.[5] This category includes neonates who receive only intravenous fluids for extended periods.[2,4]
- **Chronic Illnesses:** Various chronic medical conditions can predispose neonates to RS by causing underlying undernutrition. These include conditions such as congenital heart disease, advanced neurological impairment, malabsorption disorders, and chronic infections.[1,3]

Clinical Manifestations and Diagnostic Criteria

Recognizing the clinical signs and adhering to established diagnostic criteria are crucial for the timely identification and intervention of RS in neonates.

Key Clinical Signs and Symptoms

The clinical presentations of refeeding syndrome typically manifest within the initial days of nutritional reintroduction, commonly between 2 to 5 days after feeding commences.[2] Symptoms can vary from mild to severe and affect multiple organ systems, primarily as a direct consequence of the underlying electrolyte imbalances:

- **Neurological:** Manifestations can include generalized weakness, tremors, tetany, seizures, altered mental status, confusion, disorientation, lethargy, encephalopathy (including Wernicke's syndrome), ataxia, coma, and acute areflexic paralysis.[3]
- **Cardiovascular:** Patients may develop cardiac arrhythmias, signs of cardiac failure, hypotension, decreased stroke volume, and impaired myocardial contractility. Fluid overload can lead to pulmonary edema.[1]
- **Respiratory:** Dyspnea and respiratory failure can occur, often due to impaired diaphragm contractility.[4]
- **Gastrointestinal:** Symptoms may include nausea, vomiting, diarrhea, and paralytic ileus.[2-3]
- **Hematological:** Possible manifestations include hemolytic anemia, leukocyte dysfunction, and thrombocytopenia.[2-3]
- **Other Metabolic Disturbances:** Hypoglycemia, hyperglycemia, and sodium retention can also be observed.[1]

Electrolyte abnormalities and associated clinical manifestations are outlined in table 1.

A significant challenge in diagnosing RS, particularly in neonates, is that its clinical manifestations are often "non-specific" and can "mimic sepsis".[5] This is especially problematic in critically ill neonates, where sepsis is a common co-morbidity and presents with a similar constellation of signs. This non-specificity contributes substantially to the under-recognition of RS, which can delay appropriate nutritional interventions and lead to exacerbated adverse outcomes. This underscores the critical importance of maintaining a high index of clinical suspicion and relying heavily

Severity	Electrolyte Drop (Serum Phosphorus, Potassium, and/or Magnesium)	Associated Conditions	Timing of Onset
Mild	10%–20% decrease from pre-feeding baseline	None specified	Within 5 days of reintroduction of calories
Moderate	20%–30% decrease from pre-feeding baseline	None specified	Within 5 days of reintroduction of calories
Severe	>30% decrease from pre-feeding baseline	AND/OR organ dysfunction resulting from electrolyte decrease AND/OR thiamine deficiency	Within 5 days of reintroduction of calories

Table 2. ASPEN Consensus Diagnostic Criteria for Refeeding Syndrome in Hospitalized Adult and Pediatric Populations.

Note: This table summarizes the ASPEN consensus recommendations for diagnosing RS, which apply to both adult and pediatric populations, including neonates. The criteria are based on a measurable reduction in serum electrolyte levels from baseline within five days of initiating or significantly increasing caloric intake.[7]

on biochemical monitoring, rather than solely on clinical signs, for timely and accurate diagnosis in this vulnerable patient population.

ASPEN and Other Consensus Guidelines for Diagnosis

To standardize the identification of RS, the 2020 American Society for Parenteral and Enteral Nutrition (ASPEN) consensus recommendations provide a framework for classifying severity based on measurable serum electrolyte changes.[7] Under these guidelines, undernourished children are considered at risk, while those who develop a decrease of greater than or equal to 10% in phosphorus, potassium, and/or magnesium within the first five days of increased nutritional support are diagnosed with probable RS.[7] These criteria, which stratify severity from mild to severe based on the magnitude of the electrolyte drop and the presence of organ dysfunction, are detailed in Table 2.

Essential Laboratory Findings

Close and consistent monitoring of blood biochemistry is indispensable during the early refeeding period, typically within the first 2 to 5 days of initiating nutritional support.[1] The key electrolytes that require vigilant monitoring include phosphorus, potassium, and magnesium.[1]

Baseline blood tests should encompass a comprehensive metabolic panel, including urea, electrolytes, creatinine, liver function tests (LFTs), triglyceride levels, and venous blood gas (VBG). Additionally, a thorough nutritional assessment requires specific blood work such as zinc, B12, folate, and iron studies.[20] Hypophosphatemia is the most frequently observed manifestation of RS in neonates, with reported prevalence rates varying widely from 20% to 90% across different studies.[16] An ideal phosphate level is generally considered to be above 4 mg/dL.[1]

Complications and Outcomes Associated with Neonatal RS

RS in neonates carries significant implications, extending beyond immediate metabolic derangements to encompass both acute morbidity and long-term neurodevelopmental consequences.

Short-term Morbidity

RS can lead to devastating consequences if it is not recognized and treated in a timely manner.[1-5] The metabolic shifts characteristic of RS can precipitate or exacerbate a range of severe short-term morbidities in neonates.

- **IVH:** RS is significantly associated with a composite outcome of mortality and IVH in preterm infants born at ≤32 weeks gestation.[4] The risk of developing IVH, including severe forms, is demonstrably higher in premature infants who develop RS.[4]
- **Bronchopulmonary Dysplasia (BPD):** Hypophosphatemia has been linked to a higher risk of BPD, with an odds ratio of 2.38.[2] Some studies have also observed an association between RS itself and an increased risk of BPD in VLBW infants.[4]
- **Sepsis:** Hypophosphatemia has been connected to an increased risk of sepsis in VLBW infants.[4] Notably, a reduction in probable early- and late-onset sepsis was observed in cohorts where increased early phosphate intake was implemented.[1]
- **Other Complications:** Refeeding syndrome can also contribute to an increased duration of mechanical ventilation, the development of patent ductus arteriosus (PDA), and significant growth failure at the time of hospital discharge.[1]

The information clearly indicates that while RS is defined by electrolyte shifts, there is a direct and significant link to severe short-term morbidities such as IVH, BPD, and sepsis.[4] This pattern suggests that the metabolic derangements of RS are not confined to isolated organ systems but rather create a systemic vulnerability that can either precipitate or worsen other common and serious neonatal complications. For instance, the impaired ATP production resulting from hypophosphatemia[4] could lead to widespread cellular dysfunction across various organs, thereby increasing susceptibility to conditions like hemorrhage, lung injury, or infection. This broader implication underscores that the management of RS extends beyond merely correcting laboratory values; it is fundamentally about mitigating a cascade of potentially severe adverse clinical events throughout the neonate's body.

Mortality Rates

RS is recognized as a potentially fatal condition, underscoring the severity of its metabolic disturbances.[1] Studies consistently demonstrate a significant association between RS and an increased risk of mortality in preterm infants. The hazard ratio for death in infants diagnosed with RS was found to be 1.74-fold higher compared to those without RS.[1] Furthermore, mortality rates were notably higher in ELBW babies who developed RS (32%) compared to those who did not (11%).[8] Severe hypophosphatemia, a core component of RS, is also independently associated with an increased risk of death.[8]

Long-term Neurodevelopmental Outcomes

The impact of RS extends beyond acute complications, potentially affecting the long-term neurodevelopmental trajectory of neonates. RS and hypophosphatemia occurring within the first week of life are associated with an increased risk of death or neurodisability in ELBW babies at 2 years corrected age.[9] Suboptimal neurodevelopment is a significant concern in preterm and ELBW infants, affecting 20% to 50% of this population.[9]

Optimizing nutrition, particularly focusing on head growth in the early neonatal period, is identified as a key modifiable

Population Group	Reported Incidence (Range)	Key Risk Factors
Preterm Infants (≤32 weeks GA)	38% (one study)	Gestational age, birth weight, male sex, IVH, placental insufficiency
ELBW Infants (<1000g)	20% (ProVIDe trial)	High intravenous protein intake, low electrolyte supply, SGA status
SGA / IUGR Infants	Up to 90% (some studies); 40% (hypophosphatemia incidence)	Placental insufficiency, reduced nutrient stores at birth, aggressive PN
VLBW Infants (<1500g)	9% (hypophosphatemia incidence in appropriately grown VLBW)	Aggressive early PN without adequate concurrent electrolyte/mineral provision, prolonged fasting/poor intake, chronic illnesses
Pediatric Intensive Care Unit Patients	Up to 7.4%	Severe malnutrition, significant weight loss, prolonged fasting, chronic diseases causing under-nutrition

Table 3. Incidence and Key Risk Factors of Refeeding Syndrome in Preterm Infants

Note: Incidence rates vary widely due to inconsistencies in RS definition across studies. This table consolidates reported figures and associated risk factors from multiple peer-reviewed sources.

factor for improving neurodevelopmental outcomes.[9] While enhanced nutrition and higher protein intakes have been linked to improved head circumference and cognitive outcomes in adolescence, the precise optimal levels of nutritional components for neurodevelopmental benefits remain uncertain. Meta-analyses of randomized controlled trials comparing higher versus lower protein intakes have yielded inconclusive results regarding both growth and neurodevelopmental outcomes.[1] This highlights a critical area for future research to refine nutritional strategies that support both immediate metabolic stability and long-term neurological health. The documented short-term and long-term outcomes associated with neonatal refeeding syndrome are summarized in table 3.

Prevention Strategies for At-Risk Neonates

Effective prevention of RS in neonates hinges on early identification, meticulous risk stratification, and carefully tailored nutritional interventions.

Early Identification and Risk Stratification

The most crucial step in preventing RS is the early recognition of patients who are potentially at risk.[1] While RS is classically associated with overt malnutrition, the available information reveals that critically ill neonates are at risk even without obvious signs of severe chronic starvation. This is due to factors such as baseline frailty, the metabolic stress induced by acute illness, and frequently inadequate nutritional intake.[5] This suggests that RS risk assessment in neonates must extend beyond simple weight-for-age criteria. It is imperative to consider the acute physiological state of the infant, the duration of inadequate intake (even if relatively short), and the specific type of nutritional support being initiated. This "hidden" risk means that RS can occur even in infants who might not fit traditional definitions of malnutrition, necessitating a high index of suspicion in all critically ill neonates.

Key risk factors include:

- Severe malnutrition.[3]
- Significant weight loss (e.g., >10% of body weight, or <80% ideal body weight).[2-3,7]
- Prolonged fasting (>5-7 days) or poor intake.[2-3,7]
- Chronic diseases causing under-nutrition, such as congenital heart disease or advanced neurological impairment.[5]
- Hypoalbuminemia.[2,6]
- Specific to neonates, VLBW/ELBW, SGA/IUGR infants, particularly those born with placental insufficiency, are considered at highest risk.[1]

A comprehensive nutritional assessment should be performed upon admission for all at-risk infants.

Gradual Nutritional Reintroduction Protocols

A gradual and cautious approach to nutritional reintroduction is widely advised to prevent RS.[3] This involves initiating feeding with small amounts of low-calorie fluids and incrementally increasing the calorie content and overall volume of food over several days.[3]

For PN, it is recommended to commence at approximately 50% of the estimated energy requirement, with a gradual escalation over 3-5 days.[2,6] Particular caution should be exercised with glucose intake, aiming for approximately 40% of total energy from glucose, as rapid carbohydrate reintroduction is a primary trigger for electrolyte shifts.[2,6]

There appears to be a tension in the literature regarding feeding rates: "aggressive early PN" is presented as a standard of care for promoting growth in preterm infants, yet "gradual and cautious reintroduction" is the cornerstone of RS prevention.[1-2] This apparent contradiction highlights a critical point: "aggressive" PN, in the context of RS prevention, must be reinterpreted. It should not simply mean rapid caloric escalation. Instead, it implies the aggressive and proactive provision of sufficient concurrent electrolyte and micronutrient supplementation from the outset to support a rapid but safe anabolic shift. The objective is to meet the high nutrient requirements of vulnerable neonates while simultaneously preventing electrolyte imbalances. This approach necessitates precise, individualized PN formulations and vigilant monitoring, rather than a blanket "slow" approach that might inadvertently compromise essential growth and neurodevelopment. While some sources suggest that the "start low, go slow" method has been largely disproven in some contexts, advocating for reaching goal nutrition rates within 24-72 hours, this must be balanced with careful consideration for RS risk.[1,9]

Prophylactic Electrolyte and Micronutrient Supplementation

Prophylactic measures are essential to prevent the onset of RS.

- Any pre-existing electrolyte abnormalities should be corrected prior to the commencement of PN, with the aim of achieving levels within the mid-normal range.[2,7]
- Thiamine administration is crucial before initiating refeeding, particularly if dextrose-containing fluids are to be used.[3] A recommended neonatal dose of 350-500 mcg/kg/day should be administered for at least 5-7 days or longer in high-risk patients.[3,10]
- Consideration should also be given to providing multivitamin and mineral supplements.[2,7,10]
- The early addition of phosphate, ideally in a 1:1 molar ratio with calcium, is recommended during the first week of life for neonates at greatest risk for RS.[7] Adjust to 1.3:1 Ca:Phos

Strategy Category	Key Actions and Considerations				
Prevention	Early Identification: Proactively identify at-risk neonates (VLBW, IUGR, preterm, male sex, IVH).	Gradual Nutritional Reintroduction: Start low and advance calories gradually over 3-5 days (e.g., 50% of estimated energy needs initially for PN) Be cautious with initial glucose intake. Avoid aggressive refeeding, especially high protein (>3.5 g/kg/day).	Prophylactic Micronutrient Supplementation: Consider thiamine supplementation prior to feeding. Consider multivitamin/mineral supplements.	Early Electrolyte Provision: Provide adequate phosphorus and potassium from the start; higher sodium phosphate in the first week is associated with lower risk.	PN Ratio Adjustments: Adjust parenteral calcium and phosphorus ratios (e.g., ≤1 mmol:mmol) to minimize imbalances with higher amino acid delivery.
Management	Close Electrolyte Monitoring: Frequent serum monitoring of phosphorus, potassium, and magnesium (e.g., 6-hourly initially, then daily if levels are trending down). Maintain ideal phosphorus levels (>4 mg/dL).	Fluid Balance & Weight: Implement strict fluid balance monitoring and daily weight measurements.	Clinical Monitoring: Monitor for clinical signs of complications, such as bradycardia.	Stepwise Electrolyte Repletion: Prioritize PN adjustments and enteral repletion; use IV electrolyte repletion as a third-line intervention.	Slow Refeeding: If symptoms of RS appear, slow down the refeeding rate and reduce carbohydrate intake.

Table 4. Summary of Evidence-Based Prevention and Management Strategies for Neonatal Refeeding Syndrome.

ratio thereafter.[2] It should be noted that even if a 1:1 ratio is used in initial fluids it does not completely eliminate the risk of hypophosphatemia. Studies have shown that increased early phosphate intake combined with routine biochemical monitoring is associated with a lower incidence of RS and hypophosphatemia.[1]

- Adjustments to parenteral calcium and phosphorus ratios, specifically aiming for ≤1 mmol:mmol, have been proposed to mitigate hypercalcemia and hypophosphatemia when higher early doses of amino acid delivery are provided.[1-2]

Evidence-Based Management Protocols

Once RS is diagnosed, active management protocols are crucial to stabilize the patient and mitigate adverse outcomes. These protocols focus on adjusting nutritional support, meticulously managing fluids and electrolytes, and implementing vigilant monitoring strategies.

Adjustments to Parenteral and Enteral Nutrition

In instances where RS develops, immediate adjustments to nutritional intake are necessary.

- Caloric intake should be temporarily reduced or maintained at its current level. Some guidelines suggest temporarily discontinuing PN and switching to intravenous (IV) fluids containing 5% dextrose, followed by thorough correction of electrolyte abnormalities before PN is restarted.[2,7] If electrolytes are difficult to correct or show a precipitous drop after initiating nutritional support, reducing calorie/protein intake by 50% for 24 hours is advised. Subsequently, dextrose and calories can be advanced cautiously by approximately 33% of the goal every 24–48 hours.[2,7]
- Complete cessation of nutrition support for 24–48 hours may be considered if electrolyte levels are severely or life-threateningly low, or if they continue to decline despite replacement efforts.[7]
- Consider adopting a tiered approach to manage at-risk patients:
  - *First:* Initiate Neonatal Stock PN with Phosphate at birth.
  - *Second:* Implement custom PN adjustments, focusing on amino acids and the Calcium:Phosphorus (Ca:P) ratio.
  - *Third:* Proceed with intravenous (IV) electrolyte repletion if necessary.
- For enteral feeding, early fortification of preterm milk or use of preterm formula should be considered to provide standard and appropriate enteral sources of calcium and phosphorus.[1]

Fluid and Electrolyte Management and Repletion

Aggressive correction of electrolyte disturbances is paramount in managing RS:[1]

- Intravenous (IV) electrolyte repletion is often required, particularly for severe deficiencies.[1-2,7]
- Enteral supplementation, achieved through routine fortification of preterm milk or formula, or via additional enteral supplements, is also a viable option. One expert group suggests enteral therapy as the safest method for electrolyte repletion.1,[3]
- Fluid management must be individualized to each patient's specific needs, and systemic restriction of fluids and sodium should generally be avoided.[7]

While specific medical interventions are detailed, several sources emphasize that a "multidisciplinary approach is crucial for the proper management of this condition".[2] This is not merely a general recommendation but highlights the inherent complexity of RS. Successful management requires the coordinated expertise of various healthcare professionals, including neonatologists, neonatal nurse practitioners, clinical dietitians, pharmacists, and nursing staff. The intricate interplay of nutritional, metabolic, and fluid balance issues necessitates a team-based strategy to ensure comprehensive and timely interventions, moving beyond the purview of a single clinician.

Monitoring Strategies

Vigilant monitoring is a cornerstone of RS management:

- Close monitoring of key electrolyte levels—phosphorus, potassium, and magnesium—is critical, especially during the first week of life and typically within the first 2-5 days of refeeding.[1]
- Electrolyte and blood sugar monitoring should be performed every 6 hours once PN is initiated for the first 24-48 hours.[2,7] Daily monitoring is recommended if phosphorus levels show a downward trend.[1]
- Strict fluid balance charting and daily weight measurements are

Table 5. Documented Short-Term and Long-Term Outcomes Associated with Neonatal Refeeding Syndrome.

Outcome Category	Specific Outcomes and Associations			
Mortality	Increased mortality risk (1.74-fold higher in preterm infants with RS).	Higher mortality with hypophosphatemia, especially severe hypophosphatemia.		
Neurodevelopmental Outcomes	Increased risk of neurodisability in ELBW babies.	Association with severe hypophosphatemia and neurodisability.	Impact on head growth and cognitive outcome (improved with optimized nutrition).	
Short-Term Morbidities (Conflicting Evidence)	IVH (some studies show higher incidence, others no significant association).	Bronchopulmonary Dysplasia (BPD) (some studies show increased risk, others no significant difference).	Late-Onset Sepsis (LOS) (some studies show association, others no significant difference).	
Other Morbidities (Associated with Nutritional Challenges)	Prolonged Parenteral Nutrition (PN) duration.	PN-associated cholestasis.	Retinopathy of Prematurity (ROP).	Growth failure at discharge (common in Necrotizing Enterocolitis (NEC), often linked to nutritional challenges).

essential components of monitoring.[2,7]
- Continuous electrocardiogram (ECG) monitoring is vital to detect early cardiac abnormalities, given the significant risk of arrhythmias stemming from electrolyte imbalances.[3,7]
- A comprehensive clinical practice guideline that includes detailed monitoring protocols for at-risk infants is listed in table 4.[1,7,10]

Prognosis and Long-Term Outcomes

The occurrence of neonatal RS can have profound and lasting implications for affected infants, influencing both their short-term survival and long-term developmental trajectory. The documented short-term and long-term outcomes associated with neonatal refeeding syndrome are summarized in table 5.[1-2,4]

Mortality Rates

Studies consistently demonstrate a significant association between RS and an increased risk of mortality in preterm infants. The hazard ratio for death in infants diagnosed with RS was found to be 1.74-fold higher compared to those without RS.[4] Furthermore, mortality rates were notably higher in ELBW babies who developed RS (32%) compared to those who did not (11%).[1] Severe hypophosphatemia, a core component of RS, is also independently associated with an increased risk of death.[9]

Neurodevelopmental Outcomes

The impact of RS extends beyond acute complications, potentially affecting the long-term neurodevelopmental trajectory of neonates. RS and hypophosphatemia occurring within the first week of life are associated with an increased risk of death or neurodisability in ELBW babies at 2 years corrected age.[9] Suboptimal neurodevelopment is a significant concern in preterm and ELBW infants, affecting 20% to 50% of this population.[1]

Optimizing nutrition, particularly focusing on head growth in the early neonatal period, is identified as a key modifiable factor for improving neurodevelopmental outcomes.[1] While enhanced nutrition and higher protein intakes have been linked to improved head circumference and cognitive outcomes in adolescence, the precise optimal levels of nutritional components for neurodevelopmental benefits remain uncertain. Meta-analyses of randomized controlled trials comparing higher versus lower protein intakes have yielded inconclusive results regarding both growth and neurodevelopmental outcomes.[11] This highlights a critical area for future research to refine nutritional strategies that support both immediate metabolic stability and long-term neurological health.

Other Long-term Morbidity

Beyond mortality and neurodevelopmental concerns, RS has been associated with other short-term and long-term morbidities. Refeeding syndrome has been significantly linked to a composite outcome of mortality and IVH.[4] However, findings regarding other specific morbidities remain conflicting across studies. While some research suggests an association between RS and an increased risk of BPD and LOS in VLBW infants, other studies have reported inconclusive or no significant differences.[4]

Conditions often co-occurring with or exacerbated by nutritional challenges, such as NEC, are associated with prolonged PN duration, higher rates of PN-associated cholestasis, and retinopathy of prematurity.[2] Growth failure at discharge is also a common outcome in infants with NEC.[2]

The direct association of RS with increased mortality and neurodisability is a clear and concerning finding. However, the conflicting data regarding its direct causal link to other morbidities like IVH, BPD, and LOS is noteworthy. This suggests that RS might not always be the direct cause of these specific complications. Instead, it could serve as a strong indicator of an infant's overall physiological fragility, severe underlying illness, or suboptimal nutritional management, all of which independently predispose them to a broader spectrum of complications. This perspective implies that addressing RS is crucial not only for its immediate metabolic effects but also as an integral part of a comprehensive strategy to improve overall outcomes in highly vulnerable neonates. It suggests that RS may be part of a "cascade of complications" in critically ill preterm infants, where metabolic instability exacerbates other pre-existing vulnerabilities. Future research is needed to meticulously disentangle these complex interrelationships to determine direct causality versus mere correlation.

Current Research, Gaps, and Future Directions
Despite increasing recognition of neonatal RS, significant research gaps persist, particularly concerning its precise definition, true incidence, and optimal management strategies. These limitations impede progress in improving outcomes for vulnerable infants.

Variability in Definitions and Incidence
A major impediment to advancing the understanding and management of neonatal RS is the substantial variability in its definition across studies and clinical settings.[2] The overall incidence of "Neonatal Refeeding-like syndrome" remains largely unknown, and reported rates vary widely, ranging from 20% in ELBW infants in one trial to as high as 90% in SGA or IUGR infants receiving aggressive parenteral nutrition.[4] This wide disparity in incidence figures is primarily attributed to inconsistencies in the definition of RS used, differences in the characteristics of the study populations, and even variations related to infant sex.[4] The absence of a standardized, universally accepted definition directly hinders accurate estimations of RS incidence and severely impedes the design and execution of well-controlled clinical trials, which are essential for generating robust evidence.[5]

This definitional inconsistency is not merely a minor methodological issue; it represents a fundamental barrier that prevents the entire field from advancing. If the core phenomenon being studied is defined differently by various researchers and clinicians, the collective evidence base remains fragmented and challenging to synthesize into universal clinical guidelines. Therefore, achieving a global consensus on a standardized definition for neonatal RS is arguably the most critical "future direction" for the field.

Need for Standardized Clinical Approaches and Trials
The current evidence strongly underscores the urgent need for standardized clinical approaches to managing RS in the NICU to improve patient outcomes.[1] Without consistent protocols for identification, prevention, and treatment, care remains variable and potentially suboptimal.

Future research must prioritize establishing a unified definition of RS in neonates to ensure consistency across research studies and facilitate direct comparisons of findings. Furthermore, there is a critical need for more rigorously designed, controlled trials specifically focused on neonatal populations to develop and validate effective strategies for RS recognition, avoidance, and treatment.[1,7] While some trials, such as the ProVIDe trial, have contributed valuable data on nutritional interventions in ELBW infants[1], large gaps remain in dedicated neonatal research.

Optimizing Nutritional Strategies for Vulnerable Neonates
A key area for future research involves optimizing parenteral nutrition strategies for vulnerable neonatal populations. Significant knowledge gaps persist regarding the precise macro- and micronutrient requirements necessary to support optimal growth and, crucially, how these nutritional interventions relate to important long-term outcomes, particularly neurodevelopment.[1]

Challenges in bridging these knowledge gaps include inconsistent reporting of nutritional intakes and growth parameters in existing studies, the prevalence of small trials with short-term outcomes, and the use of a variety of different methods for monitoring growth.[1] To overcome these obstacles, the path forward requires a concerted effort towards consensus-building around key research questions. This includes developing standardized methods for data reporting from neonatal nutritional trials and fostering the development of large, collaborative consortia capable of undertaking impactful, multi-center trials.[1] Such collaborative efforts are essential to generate the high-quality evidence needed to refine nutritional guidelines and improve the long-term health and developmental trajectories of preterm and at-risk neonates.

Conclusions
Despite historical awareness, neonatal refeeding syndrome (RS) remains a complex, underdiagnosed challenge. The wide variability in reported incidence underscores the urgent need for a unified, neonatal-specific definition to facilitate accurate research and clinical comparison.

RS pathophysiology involves interconnected shifts in phosphorus, potassium, and magnesium, triggering a systemic cascade of organ dysfunction. Diagnosis is frequently complicated by non-specific clinical symptoms that mimic other critical conditions, such as sepsis. Highly vulnerable populations—including preterm, SGA, IUGR, VLBW, and ELBW infants—are at heightened risk due to minimal nutrient stores and rapid growth potential. This creates a clinical paradox: aggressive parenteral nutrition intended to support growth can precipitate RS unless meticulously balanced with proactive electrolyte and micronutrient supplementation.

The impact of RS is severe, linked to increased mortality, short-term morbidities like IVH and BPD, and long-term neurodevelopmental impairment. To improve the developmental trajectory of these infants, a concerted effort is required to:

- Standardize Definitions: Adopt a universal, consensus-based definition for consistent diagnosis.
- Enhance Awareness: Maintain a high index of clinical suspicion and implement robust screening for all at-risk neonates.
- Refine Protocols: Implement individualized nutritional strategies that prioritize both caloric adequacy and metabolic stability through proactive supplementation.
- Strengthen Monitoring: Utilize comprehensive biochemical monitoring to detect and correct electrolyte abnormalities promptly.
- Foster Collaboration: Employ a multidisciplinary approach involving neonatologists, nutritionists, pharmacists, and nurses.
- Prioritize Research: Conduct multicenter trials to determine optimal nutrient requirements and long-term outcomes.

By addressing these areas, the clinical community can significantly improve the identification, prevention, and management of neonatal RS, enhancing the health and developmental trajectory of vulnerable infants.

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Ultrarapid Genomic Testing in the NICU: Delivering Clarity When Every Second Counts

Shruti Sureshkumar, MSc, GC

Caring for critically ill newborns in the Neonatal Intensive Care Unit (NICU) requires rapid and precise decision making. Many infants admitted with multisystem involvement, unexplained neurologic symptoms, metabolic instability, or structural anomalies may have an underlying genetic condition. Rare genetic disorders including aneuploidies, copy number changes, and Mendelian conditions such as inborn errors of metabolism constitute a substantial proportion of NICU morbidity. Current estimates indicate that **30%–50% of neonatal deaths and severe morbidities are attributable to genetic causes** (PMID: 29790870).

Because clinical features may be subtle or evolve over time, timely access to comprehensive molecular testing can significantly redirect management. Approximately **80% of rare diseases are genetic**, and nearly **70% present in childhood**, with **~3% manifesting in the neonatal period** (PMID: 40033553). Establishing a diagnosis early enables targeted therapies, avoidance of unnecessary interventions, more accurate prognostic discussions, and informed family counselling.

Yet, historically, reaching a diagnosis has been lengthy. For many families, the diagnostic odyssey often lasts 4–8 years. In the NICU, such delays can be even more consequential. For example, one study demonstrated that although genetics consults during NICU hospitalization identified a diagnosis in 26% of infants, most are confirmed only after discharge (PMID: 28488422). In critically ill neonates, disease progression can rapidly limit or alter therapeutic options, making speed essential.

Biochemical assessment as the first step

During the initial hours of NICU evaluation, clinicians focus on stabilization while narrowing potential etiologies. Biochemical screening remains an important early tool, especially for suspected metabolic disease providing key insights on underlying genetic conditions and guiding immediate management.

Shruti is a BGCI certified genetic counselor with a Master's degree in Biomedical Genetics. She comes with years of experience in laboratory genetic counseling, specializing in prenatal and pediatric genetics, NGS, and rare disorders. As a Product Manager at Revvity Omics, Shruti leverages her technical leadership and product knowledge to support the development and delivery of cutting-edge omics solutions for various clinical and research applications. Shruti is passionate about advancing the science and practice of genetic counseling and improving the health and well-being of individuals and families.

Parallel collection of samples for genomic sequencing at this early stage ensures that if metabolic or clinical suspicion points toward a specific genetic etiology, confirmatory testing is already underway. This integrated workflow streamlines testing, reducing it from weeks or months to a more efficient process for faster diagnosis and clearer insights into how genotype affects phenotype.

Ultrarapid whole genome sequencing: Changing the diagnostic landscape

Ultrarapid Whole Genome Sequencing (urWGS) has emerged as a transformative tool for critically ill neonates. Multiple peer reviewed studies now demonstrate diagnostic yields in the range of **50%–70%** in appropriately selected NICU populations (PMID: 26684335, 25473036). These yields exceed those of traditional sequential testing, and importantly, the results often guide prompt actionable interventions, including targeted dietary management, precision immunological or hematological therapies, optimized seizure management, or urgent surgical intervention.

What once required weeks can now be delivered in days. Clinical urWGS services increasingly provide results **within eight days**, and in select cases, even sooner. Revvity Omics' urWGS platform integrates analysis of nuclear genome variants, chromosomal and gene level copy number changes, mitochondrial genome variants, tandem repeats, and SMN1 copy number in one assay, reducing the need for multiple investigations.

In the NICU, speed is directly tied to survival and outcomes. Establishing the molecular diagnosis early allows the care team

to align treatment that is targeted to provide the most benefit to the infant, while minimizing unnecessary procedures and optimizing resource allocation, ultimately leading to healthcare cost savings in the long run.

The added value of Biochemical–Genomic Integration

Combining biochemical data with urWGS strengthens interpretation and enhances clinical confidence. Revvity Omics provides **StepOne Biochemical Profile,** an optional enhancement with the urWGS, offering rapid biochemical screening for more than seventy rare diseases using only a few drops of blood.

Newborn screening has long demonstrated the population level benefits of early detection. Integrating this screening approach with individualized ultrarapid genomic testing extends that principle into the NICU, offering clinicians both metabolic signatures and molecular results in a synchronized workflow.

Trio sequencing: Improving accuracy and reducing uncertainty

Trio analysis clarifies inheritance patterns, distinguishes de novo variants from inherited causes, and enables phasing of compound heterozygous variants. This greatly reduces the number of variants of uncertain significance and supports faster movement from suspicion to confirmed diagnosis.

Streamlined consent and sample pathways for Trio urWGS are essential when infants present with:

- Unexplained critical illness
- Refractory seizures
- Multisystem involvement
- Congenital anomalies
- Suspected inborn errors of metabolism

Having parental data available from the outset accelerates interpretation and minimizes diagnostic ambiguity.

A model for precision medicine in the NICU

Integrating urWGS with biochemical screening and Trio analysis supports a precision medicine approach tailored to the unique needs of the NICU. This model reduces the time to diagnosis, decreases unnecessary or invasive interventions, and focuses efforts on appropriate therapies or clinical trials. It also supports compassionate care by enabling clearer prognostication early in the infant's course, helping families and clinicians make decisions aligned with the infant's needs and family preferences (PMID: 26684335, 25473036, 29790870, 28488422).

Case Example: Diagnosis delivered in 53 Hours

A recent case highlights the clinical impact of this integrated approach. A three day old male infant presented with hypotonia, congenital anomalies, and metabolic acidosis. Rapid biochemical screening revealed elevated propionylcarnitine (C3), raising suspicion for metabolic pathology. Concurrent urWGS identified a pathogenic variant in PDHA1.

From sample collection to reporting, the total time to diagnosis was **53 hours** (Revvity case summary). The rapid turnaround allowed clinicians to promptly initiate targeted interventions that stabilized the infant and improved his prognosis. Without such speed, the therapeutic window might have closed before a diagnosis was available.

This case exemplifies how ultrarapid genomics can change the trajectory of care for critically ill newborns.

Conclusion

In the NICU, timely genetic evaluation is not only diagnostic but also therapeutic. By integrating ultrarapid whole genome sequencing (proband only or trio analysis), and early biochemical profiling, clinicians now have the tools to move from uncertainty in diagnoses to clarity in a fraction of the time once required. These advances enable precision care, improve outcomes, and support families facing some of the most challenging moments of early life.

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Forecasting Bilirubin Trends to Support Neonatal Jaundice Management with BiliPredics

Anduin Anderle, RN, ANCL-N

Neonatal jaundice is one of the most frequently encountered medical conditions among newborns and is the most common reason for readmission to the hospital within the first month of life.[1]

The condition primarily results from the normal metabolic transition after birth with a transient increase in bilirubin levels and spontaneous remission within the 5-10 days of life.[2,3] However, in about 10% of all newborns, bilirubin levels increase to therapeutically relevant ranges, making phototherapy treatment necessary.[4]

A key challenge for clinicians is assessing jaundice risk during the first hours of life, often before bilirubin levels peak and while newborns are still in the hospital.[5,6] Because many newborns are discharged before significant bilirubin rises occur, some may not receive adequate risk assessment or appropriate follow-up during the critical first days after birth.[4,5]

This gap creates the potential for underdiagnosis, delayed phototherapy and, in rare but serious cases, bilirubin-induced neurologic dysfunction (BIND), including kernicterus.[9]

Current guidelines and assessment methods

The revised American Academy of Pediatrics (AAP) Clinical Practice Guideline for Management of Hyperbilirubinemia provides clear and comprehensive recommendations for discharge and follow-up checks.[10] However, the complexity of the guideline requires dedicated training of all staff to achieve proper adherence.

Furthermore, current bilirubin risk assessment approaches rely on a limited number of clinical parameters, such as gestational age, days of life, and the presence or absence of risk factors.[6] While computer-based bilirubin tools display measured bilirubin values, they do not predict anticipated bilirubin levels or potential risk zone changes.[6,10] Neonates may change risk zones after discharge, moving from a lower-risk zone to a higher-risk zone or vice versa.[6]

BiliPredics: Forecasting bilirubin trends

The Dräger BiliPredics solution is a cloud-based clinical decision support tool that uses a proprietary algorithm to forecast jaundice risk up to 60 hours in advance by considering a large variety of risk factors for which the underlying algorithm has been trained. Leveraging predictive analytics, it helps clinicians identify at-risk newborns before bilirubin levels peak, so intervention can happen earlier, and often without a readmission.[6]

The solution plots already measured bilirubin values in accordance with the 2022 AAP Guideline within locally applied patient information systems and forecasts the individual dynamic progression of bilirubin, helping identify 9 out of 10 neonates that change risk zone after discharge.[6]

The BiliPredics web application is easy to use, displaying intuitive visual graphs for risk tracking, retrospective patient data at-a-glance, as well as updated AAP guidelines and nomogram curves. The application can be used to generate formatted PDF reports that can be shared with families and pediatricians.

Key benefits:
- Forecasts bilirubin progression with fewer tests
- Helps replace readmissions with scheduled follow-ups
- Supports 2022 AAP Guideline
- Displays intuitive visual graphs for risk tracking
- Generates reports that can be shared with families and pediatricians
- Helps to reduce clinician burnout and improve patient safety

Benefits for parents, clinicians and hospitals

For families, early and transparent communication about jaundice risk can help them better understand and prepare for potential care needs. By enabling proactive management, BiliPredics can reduce the likelihood of distressing and disruptive unplanned readmissions, supporting family bonding and peace of mind.

For clinicians, the BiliPredics solution helps streamline workflows and reduce documentation, and provides risk-adjusted forecasts that support informed, individualized care planning. By aligning with the AAP Guideline, BiliPredics can enhance both clinical decision-making and regulatory compliance.

For hospitals and health systems, enhanced discharge planning accuracy and more informed and timely care decisions may help avoid unnecessary phototherapy, extended hospital stays and costly readmissions while contributing to more efficient use of resources reduced overall care costs.

Conclusion

With health-care systems facing mounting financial and staffing pressures, there is a growing need for evidence-based tools

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that improve communication with parents, allow for proactive treatment, and help keep babies safely out of the hospital whenever possible.

BiliPredics offers a transformative advancement. The modern and easy-to-implement electronic clinical decision support tool based on predictive analytics can significantly improve the day-to-day workflow and reduce cost of care while improving the level of care at the same time.

By embracing these technologies, NICUs can help reduce the burden on overstretched staff, enhance family-centered care, and set a new standard for neonatal health outcomes.

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Bridging the Gap Between IFUs, Contracts and Survey Readiness

Anduin Anderle, RN, ANCL-N with Kara Nadeau

The process of cleaning, disinfecting and sterilizing medical devices in the neonatal intensive care unit (NICU), while it seems simple on the surface, is rife with complexities, challenges and controversies.

Per US Food and Drug Administration (FDA) regulations, device manufacturers must specify in their instructions for use (IFU) validated protocols — down to the specific agents or chemistries — proven to reliably reduce microbial contamination to safe levels without degrading their device's materials or performance over time.[1]

The Joint Commission (TJC), in its accreditation role and safety assessment criteria, requires hospitals to comply with manufacturer IFUs when reprocessing their devices. This means using specified disinfecting agents in the reprocessing section of manufacturer IFUs.[2]

Because some of these disinfecting agents are country specific, meaning they are only commercially available in certain markets, those healthcare organizations in different markets may have trouble acquiring them.[3]

In other cases, an agent specified in a manufacturer's IFU may not align with the organization's infection prevention quality initiatives or could be too costly to procure because it is not covered by the organization's group purchasing organization (GPO) contract.[4,5]

Noncompliance presents the risk for survey citations, financial penalties, conditional accreditation and damaged reputations.[6]

Given the complex landscape of disinfection compliance, regulatory expectations and survey readiness, medical devices manufacturers are reevaluating how they can support users through modernizing IFUs (a complex process regulated by the FDA), collaborating with disinfecting agent manufacturers and investing in additional compatibility testing aligned with regulated efficacy and safety standards.[7]

At the same time, it is important for health systems and hospitals that are purchasing medical devices to understand the tremendous regulatory and cost burden manufacturers face when adding a new disinfectant or sterilant to their IFU. Because manufacturers are bound by the FDA to validate each specific chemistry, each addition requires costly testing and sometimes new FDA 510(k) clearance.[8,9,10]

This document outlines the realities of infection prevention today, the pieces of the IFU accountability puzzle and the collaborative steps we can take to improve the future together.

Post-COVID disinfection realities

The COVID-19 pandemic helped to reshape infection prevention practices in hospitals, influencing types of disinfectants and modes of application.

How COVID changed the disinfectant landscape

Manufacturers of disinfectants turned to active ingredients recommended for use against COVID-19 viruses, including chemicals such as quaternary ammonium compounds (QACs), hydrogen peroxide, bleach (sodium hypochlorite) and alcohols.[11] These were chosen based on their ability to inactivate viruses like SARS-CoV-2.[12]

There has been a shift in modalities as well, with increased use of "ready-to-use" disinfecting wipes by hospital staff for routine cleaning of general surfaces and medical devices.[13,14,15,16,17] Hospitals transitioned from bulk reconstituted disinfectants to ready-to-use (RTU) pre-moistened wipes, especially for point-of-care cleaning of non-critical medical devices and surfaces.

This shift was driven by:[18]

- Convenience and speed
- Reduced risk of improper dilution
- Supply chain disruptions requiring rapid deployment of alternatives

While disinfectants were essential preventive agents against COVID-19, researchers point out how the "pandemic crisis was marred by undue hype, which led to the indiscriminate use of disinfectants and sanitizers."[19]

Additionally, hospitals that signed multi-year contracts for

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disinfectants without confirming compatibility with IFUs risk noncompliance with regulations and compromised patient safety.[20,21,22]

Today, with hospitals continuing to use disinfectants implemented during the pandemic to clean medical devices, the question arises — have these agents been validated by the device manufacturers as effectiv and safe?

The accountability puzzle

Hospitals, disinfectant manufacturers and medical device manufacturers are all bound by regulations intended to drive safe and effective cleaning practices.

Regulatory bodies

Oversight of medical device cleaning and disinfecting involves multiple agencies. The FDA governs medical device manufacturers and their IFUs, the Environmental Protection Agency (EPA) governs disinfectant manufacturers and their agents, and hospitals are governed by accreditation agencies (e.g., TJC, DNV).[23,24,25]

Device manufacturers

The FDA requires medical device manufacturers to provide detailed IFUs that specify how to properly clean, disinfect and store each item. These guidelines outline the necessary steps, the level and frequency of disinfection (e.g., sterilization or high-, intermediate-, or low-level disinfection), compatible agents and limits on how often an item may be reprocessed.[26]

The device manufacturer must prove to the FDA:[27]

Shared accountability for IFU compliance

While manufacturers must validate and publish IFUs, hospitals are responsible for following them.

The FDA emphasizes that reducing infection risk is a shared responsibility among:

- Device manufacturers
- Healthcare facilities
- Regulatory bodies

1. **Efficacy:** Manufacturers must demonstrate that their reprocessing instructions reliably reduce microbial contamination to safe levels. This includes:
   - Validated cleaning, disinfection and sterilization protocols
   - Simulated-use testing under worst-case conditions
   - Microbial reduction aligned with Spaulding classification

2. **Compatibility:** Manufacturers must prove that repeated reprocessing does not degrade the device's materials or performance. This includes:
   - Material integrity testing after multiple cycles
   - Functional performance validation
   - Avoidance of chemical damage or wear

3. **Total manufacturer responsibility:** The FDA places full responsibility on manufacturers to:
   - Provide clear, validated, and user-friendly IFUs
   - Include reprocessing validation data in 510(k) submissions (especially for high-risk devices listed in Appendix E)
   - Ensure instructions are technically feasible and understandable
   - Align with ISO 17664 and AAMI ST98 standards

Disinfectant manufacturers

Manufacturers of agents used to clean and disinfect medical devices are regulated by the US EPA. To obtain an EPA registration, a manufacturer must submit specific data about the safety and effectiveness of each product.[28]

Hospitals

TJC requires hospitals to provide access to information needed to support their infection prevention and control programs. Hospital staff members tasked with cleaning and disinfecting medical devices must follow the manufacturers' IFUs to remain compliant. This means using the disinfectant specified in a device's IFU in accordance with the manufacturer's instructions. Using non-validated disinfectants can trigger The Joint Commission (TJC) findings.[29]

Because each patient care device has its own IFU, hospitals are expected to follow them precisely. Even the products used in cleaning, disinfection and sterilization carry IFUs to verify their effectiveness and ensure processes are performed correctly.

As stated by TJC on its website: "Accredited organizations must follow instructions for quality control of the process, including dilution of products, efficacy testing of the solution or process, exposure times, and acceptable temperature and pressure ranges."[30]

Additional regulatory guidance on cleaning and disinfecting medical devices:

- US Centers for Disease Control (CDC) Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008: presents evidence-based recommendations on the preferred methods for cleaning, disinfection and sterilization of patient-care medical devices and for cleaning and disinfecting the healthcare environment.[31]
- The World Health Organization (WHO) General Instructions for Surface Cleaning and Disinfecting in Patient Care Areas: poster/information sheet download.[32]

Regulatory penalties for IFU non-compliance

Hospitals and medical device manufacturers must comply with IFU requirements set forth by regulatory bodies such as the FDA, TJC and the Centers for Medicare & Medicaid Services (CMS).[33,34,35]

Failure to adhere to these standards can result in significant penalties:

Food and Drug Administration (FDA)[36,37,38]
- Civil monetary penalties (CMP) ranging from $10,000 to $20,000 per violation
- Warning letters and product recalls for misbranded or adulterated devices
- Withdrawal of FDA approval and potential criminal prosecution in severe cases

The Joint Commission (TJC)[39,40,41]
- Survey citations and conditional accreditation
- Financial penalties and reputational damage
- Increased scrutiny during inspections for IFU adherence

Centers for Medicare & Medicaid Services (CMS)[42,43,44]
- Corrective action plans and corporate integrity agreements
- Exclusion from Medicare/Medicaid programs
- Reduced reimbursement and operational disruptions

These penalties underscore the importance of following validated IFUs for cleaning and disinfection to ensure compliance and protect patient safety.

The device manufacturer's dilemma

Given the changes to the disinfectant landscape since the pandemic, hospitals often expect flexibility from manufacturers with regards to what disinfectants can be used effectively and safely with their devices. But because medical device manufacturers are bound by FDA regulations that allow for only validated disinfectants to be listed in their device IFUs, flexibility is not feasible.

Consider the following:[45,46,47]

- Each additional disinfecting chemistry added to an IFU requires costly testing and sometimes a new FDA 510(k) device approval process.
- Validation costs: 5-6 figure expense per disinfect chemistry per device.
- Updating IFUs with new chemistries for legacy devices — ones no longer sold by the manufacturer — would requiresignificant resources.

A partnership approach

Hospitals are required to follow the infection prevention and control standards set by their accreditation agencies, which includes strict compliance with the IFUs provided by medical device manufacturers. These IFUs specify which cleaning agents and disinfection methods have been validated for safety and effectiveness, and surveyors expect organizations to demonstrate adherence during inspections.

Manufacturers play an important role by supplying clear, detailed documentation that supports compliance (e.g., survey prep kits, compatibility matrixes, validation rationale). This information helps hospitals align their practices with regulatory expectations and reduces the risk of noncompliance.

3 steps to support IFU compliance and patient safety

1. **Collaborate across all stakeholders**: Supply chain/ procurement, value analysis, infection prevention, EVS, front line clinicians, sterile processing (if high-level disinfection or sterilization is required).
2. **Provide proactive education**: Engage infection preventionists (and sterile processing) to assess medical device IFUs before contracts to purchase are signed.
3. **Take a strategic approach to validation:** Reference TJC requirements for risk assessment.

In situations where a facility wishes to use a disinfectant not listed in the IFU, the infection prevention team may conduct a formal risk assessment, document the findings, and submit the results to its accrediting agency for review.

In a recent article, Vizient outlined three key factors to determine the appropriate compliance approach and ensure patient safety during a risk assessment:[48]

- Determine whether the equipment comes into direct contact with a patient. Devices involved in direct patient care pose a higher risk and require stricter compliance measures.
- Evaluate the prevalence of these items within the facility. If a device or piece of equipment is widely used or exists in large quantities, ensuring compliance becomes a higher priority.
- Lastly, determine how closely the available disinfectant aligns with IFU requirements.

At the end of the day, effective cleaning, disinfecting and sterilizing of medical devices in the NICU is a team sport, requiring collaboration among hospitals, manufacturers, accreditation agencies and industry associations such as the Association for Professionals in Infection Control and Epidemiology (APIC) and International Sanitary Supply Association (ISSA).

Conclusion

As infection prevention grows more complex, the gaps between IFUs, hospital contracts and survey readiness cannot be ignored. Hospitals, device manufacturers and disinfectant suppliers each operate under distinct regulatory frameworks, yet all share responsibility for safeguarding patients.

Moving forward, greater transparency, clearer documentation and stronger partnerships will be essential to balance compliance with practicality. By working together, stakeholders can reduce the burden of conflicting requirements, minimize risk and ensure safe, effective care for the most vulnerable patients in the NICU and beyond.

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How the ULSPIRA Solution™ from Airgas Therapeutics Improved Efficiencies and Provided Staff Relief for a Busy NICU Department

Case Study

The ULSPIRA Solution provides inhaled nitric oxide therapy and clinical applications support for a hospital's busy NICU department.

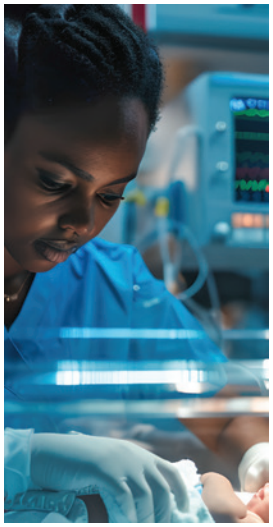
Customer Profile

Inhaled nitric oxide therapy is commonly used in level III and IV NICUs to treat infants suffering from PPHN (Persistent Pulmonary Hyper-tension of the Newborn). When iNO is ordered, the staff needs to start therapy fast. This level III NICU uses state-of-the-art equipment and diagnostics to continually monitor and treat over 500 newborns a year.

Issues

- Concerns with stabilizing the iNO dose when their current system was used with different ventilators
- The therapy delivery device had frequent alarms and a complex backup system
- Lower than expected vendor support and lagging response times
- Monthly device calibrations added workload for the RT staff

> "The Airgas Therapeutics' team took every step to make the transition to the ULSPIRA Solution a smooth one."
>
> – RT in NICU Department



> "Airgas has been a fantastic partner to work with. I feel their product is valuable and helps save lives."
>
> – RT in NICU Department

The Airgas Therapeutics Solution

- **Clinical Reliability**. Stable doses with no fluctuations, even on high-frequency jet ventilation.
- **Simplified Cylinder Management**. Automatic cylinder switchover helps avoid undue pauses that could trigger oxygen desaturation, bradycardia, or the need for manual bagging in fragile neonates.
- **Emergency Safety**. Simple one-switch pneumatic backup. Staff can activate the backup nitric oxide flipping a single switch.
- **Efficiency**. Smart Pre-Use Check reduced system checks from 10+ minutes to around 5 min (valid up to 12 hours). The need for calibrations dropped from 12 to 4 per year.
- **Infection Control**. All-disposable kits and front-facing components help prevent cross contamination.
- **Cost Savings**. Approximately 40% reduction in costs year over year, plus consumable parts included in the contract, yielding a significant financial relief for the hospital.
- **Higher Level of Support**. Responsive service and knowledgeable clinical support, proactive follow-ups and spare monitor provided.

Conclusion

To sum up, the NICU team got exactly what they set out to achieve with the transition to the ULSPIRA Solution™: no more dose fluctuations, greater clinical efficiency, improved customer and clinical support and significant cost savings. In short, what began as a leap of faith turned into a tale of positive change.

Revolutionizing Neonatal Care with the Dräger Babyroo® TN300 AutoBreath Resuscitator

Anduin Anderle, RN, ANCL-N

With approximately 10% of newborns requiring some assistance to begin breathing at birth,[1] labor & delivery (L&D) teams are faced with resuscitating babies in hectic situations where they risk under- or overinflation of fragile lungs.

Access to a user-friendly and precise respiratory support tool at the moment of birth and beyond is critical to reducing the number of respiratory complications that impact poor long-term outcomes and preventable deaths.

The Dräger Babyroo® TN300 configurable open care warmer featuring AutoBreath automatically delivers the desired levels of fractional concentration of inspired oxygen (FiO_2), flow, peak inspiratory pressure (PIP), and positive end-expiratory pressure (PEEP) in precise intervals at an I:E ratio of 1:2. Think T-Piece with an automated rate!

Focus on your patient while AutoBreath delivers set pressures at your set rate

AutoBreath keeps a consistent respiratory rate and shows the applied inflation pressure on the Dräger Babyroo® TN300 Resuscitation Module. This optional feature frees the clinicians' hands to seal and secure the face mask and thus helps to stabilize ventilation. This is especially helpful in high-stress situations or during intra-hospital transfers when babies need further respiratory support after initial stabilization.

Versatile AutoBreath resuscitation circuit

The AutoBreath breathing circuit can be used to provide both automatic and non-automatic (T-piece) resuscitation. This capability allows for a seamless transition to automatic resuscitation without having to change the circuit.

How AutoBreath works

AutoBreath, a gas-powered resuscitator for operator-attended airway management of neonates and infants, consists of a pneumatic oscillator and an adjustable PEEP feature, which allows the operator to control the baseline.

The ventilation cycle of the AutoBreath infant resuscitator consists of an inspiratory and expiratory phase:

Inspiratory phase

- The exhaust port of the expiratory valve is blocked by the operation of the circuit and fresh gas from the Resuscitation Module is forced into the patient's lungs. As the lungs fill, the pressure in the patient airway and fresh gas supply line increases.
- Once this pressure reaches the pressure setting of the adjustable pressure relief valve in the Resuscitation Module, the additional fresh gas flow is relieved by the pressure relief valve and the flow of fresh gas into the baby's lungs ceases.

Expiratory phase

- Expiration begins when the expiratory valve pressure drops to the set PEEP, which is set by the user on the AutoBreath module. During the expiratory phase, gas from the baby's lungs — as well as any gas flow from the resuscitator — vents to the atmosphere.

Conclusion

The Dräger Babyroo® TN300 with AutoBreath provides clinical teams with a user-friendly, reliable, and efficient respiratory support tool for neonatal resuscitation. By automating precise delivery of key respiratory parameters, AutoBreath helps clinicians adhere to resuscitation guidelines, supporting effective respiratory care for babies from the moment of birth and through critical transitions.

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Neotech Products LLC — NeoPulse™ Pulse Oximeter Wrap

Prepared by the of Editors Neonatal Intensive Care

In the neonatal intensive care unit (NICU), pulse oximetry is one of the most frequently used monitoring tools. From the first minutes of life through discharge planning, continuous oxygen saturation monitoring guides respiratory management, ventilator adjustments, oxygen titration, and clinical decision-making in fragile preterm and term infants. Yet while clinicians focus appropriately on data accuracy and alarm management, the physical interface between infant and monitor—the sensor wrap itself—often receives less attention. In extremely low birth weight infants and medically complex neonates, that interface can matter greatly.

The NeoPulse™ Pulse Oximeter Wrap from Neotech Products LLC is designed specifically to address the realities of neonatal skin fragility, long-term monitoring, and the need for both comfort and stability. Constructed from skin-friendly NeoFoam?, the wrap emphasizes softness, lightweight structure, and moisture-wicking properties—features that align closely with NICU priorities around skin integrity and infection prevention.

Why the Sensor Interface Matters in Neonatal Care

Neonatal skin differs significantly from that of older children and adults. Preterm infants in particular have underdeveloped stratum corneum layers, reduced barrier function, and increased transepidermal water loss. Frequent repositioning of sensors, adhesive removal, perspiration accumulation, and prolonged device contact can all contribute to erythema, pressure injury, or skin breakdown.

Continuous pulse oximetry may be required for:

- Preterm infants with bronchopulmonary dysplasia
- Neonates receiving CPAP or mechanical ventilation
- Infants on oxygen weaning protocols
- Postoperative cardiac or surgical patients
- Sepsis evaluations or unstable clinical courses

In these cases, the wrap must provide consistent positioning for accurate signal acquisition while minimizing trauma from repeated application and removal.

NeoPulse™ addresses these competing demands by focusing on three essential NICU concerns: skin protection, stability, and moisture control.

Prepared by the editors of Neonatal Intensive Care. All editorial content is independently authored and does not require advertiser legal review.

Skin-Friendly NeoFoam? and Gentle Contact

The NeoPulse™ wrap is made with NeoFoam?, a soft material engineered to feel gentle against delicate neonatal skin. Softness is not merely a comfort feature in the NICU—it is a protective strategy. Reduced friction and pressure at the contact point can decrease the risk of localized irritation and potential skin injury, particularly in very low birth weight infants.

For nurses and respiratory therapists who reposition sensors frequently to maintain signal quality and reduce pressure points, a material that is both flexible and forgiving may help support skin care protocols already in place within many NICUs.

Stability and Signal Integrity

Accurate oxygen saturation monitoring depends on stable sensor positioning. Movement artifact, slipping, or uneven contact can lead to false alarms, signal dropouts, or inaccurate readings. Alarm fatigue remains a persistent concern in neonatal care environments, where excessive non-actionable alarms can desensitize staff and increase cognitive load.

NeoPulse™ is designed to be lightweight and adjustable, supporting secure placement without excessive compression. The adjustable design allows clinicians to achieve a snug but gentle fit appropriate for different limb sizes and clinical scenarios.

By promoting stability while maintaining comfort, the wrap supports the goal of reliable signal acquisition—a foundational element of neonatal respiratory management.

Moisture Wicking and Odor Control in Long-Term Monitoring

Neonates receiving respiratory support often experience fluctuating temperatures, humidity exposure from incubators or warmers, and perspiration under wraps and dressings. Moisture trapped against the skin can increase maceration risk and create an environment that may contribute to odor or microbial growth.

The moisture-wicking properties of the NeoPulse™ wrap are designed to help manage perspiration, reducing prolonged dampness at the contact site. In units where infants may remain on continuous monitoring for days or weeks, this feature can support broader skin integrity and infection-prevention strategies.

Designed for Practical NICU Workflow

The NeoPulse™ Pulse Oximeter Wrap is available in three sizes, accommodating the varied population seen in modern NICUs—

from extremely preterm neonates to larger-term infants requiring monitoring.

For clinical teams, practical considerations matter:
- Ease of application during routine care
- Compatibility with existing pulse oximeter sensors
- Durability during handling and repositioning
- Efficient replacement during shift changes

A wrap that integrates smoothly into existing monitoring protocols without increasing workload can support both patient care and staff efficiency.

Aligning with Neonatal Best Practices

Current neonatal care emphasizes:
- Prevention of medical device–related pressure injuries
- Gentle handling and minimal skin trauma
- Reduction of unnecessary alarm burden
- Support of developmental and comfort-focused care

A thoughtfully designed pulse oximeter wrap may appear to be a small component of care, yet in the NICU environment, incremental improvements in device interface can contribute meaningfully to overall outcomes and patient experience.

By focusing on softness, adjustability, moisture control, and stability, NeoPulse™ aligns with the day-to-day realities faced by neonatal nurses, respiratory therapists, and neonatologists.

Clinical Relevance in a High-Technology Environment

Neonatal intensive care is increasingly technology-driven, with advanced ventilators, high-frequency oscillatory ventilation, non-invasive respiratory support, and integrated monitoring platforms. Amid these innovations, the human factors of comfort and skin protection remain central.

Monitoring accuracy begins at the point of contact. Products that enhance comfort while supporting signal stability may contribute to more consistent data acquisition and a more manageable alarm environment—two goals shared by NICU teams nationwide.

Improper Medication Is Dangerous—Improper Education Can Be Too: Why the Seven Rights Belong in Family Teaching

Education That Protects, Not Just Informs

Samantha Sobie DNP, APRN, NNP-BC

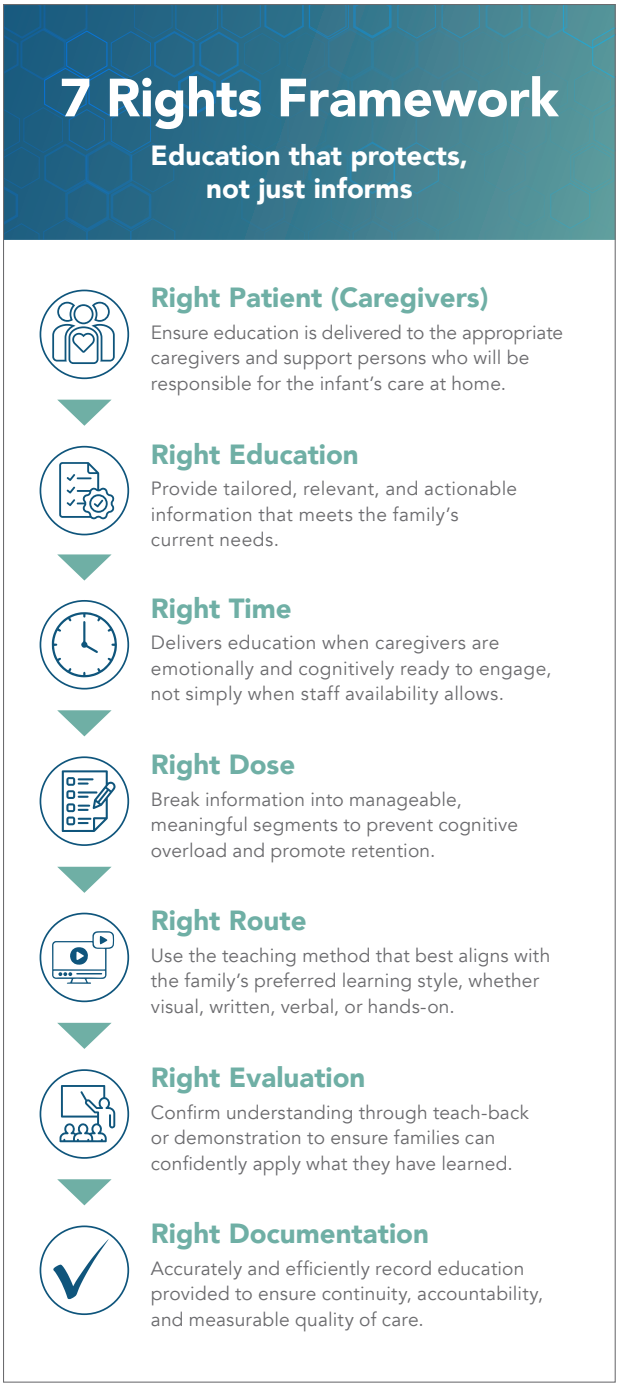
Early in their education, nurses are taught the *Five Rights of Medication Administration*: right patient, right medication, right dose, right time, and right route. This framework is simple, memorable, and deeply ingrained in nursing culture. What if we leveraged this same familiar model to rethink how we deliver education to patients and their families, particularly in high-stress environments?

Education is not a single event. It is layered, emotional, and often delivered under less-than-ideal circumstances. Families are overwhelmed, sleep-deprived, and navigating fear while being asked to absorb complex medical information. In high-acuity environments like the NICU, education is not simply informational; *it is foundational to safety.*

When misunderstood, education can be just as dangerous as improper medication administration. We would never administer a medication without following a standardized safety framework. Yet education, which directly impacts adherence, follow-up, and outcomes, can be delivered inconsistently, at variable times, and without confirmation of understanding.

With its unique requirements, education must be dynamic and personalized to meet families where they are, while also standardized enough to reduce variability and streamline messaging across the care team. Without structure, up to 80% of key information is forgotten, misremembered, or inconsistently reinforced.

A practical and powerful solution is to apply an established clinical framework we already trust: the Five Rights of Medication Administration. By intentionally extending the Five Rights, we create a structured yet flexible approach that promotes comprehension, builds confidence, strengthens continuity of care, and treats education with the same intentionality, consistency, and safety as medication.



Dr Samantha Sobie, is a Neonatal Nurse Practitioner and Clinical Specialist at AngelEye Health with over a decade of experience in the NICU. She earned her Doctor of Nursing Practice from Wayne State University in 2024, where her doctoral work focused on advancing health literacy in NICU education materials to improve family understanding and discharge readiness. Her work centers on optimizing NICU navigation and standardizing discharge processes to better support families across the care continuum.

The First Right: The Right Patient (and Caregivers)

Education should be delivered to the *right audience*. In neonatal care, this means ensuring that the appropriate caregivers are present and engaged for teaching.

For example, an infant may require gavage feedings at home, yet only one parent is at the bedside when education is offered. Recognizing that not all stakeholders are present should prompt us to pause and consider whether teaching should wait until everyone responsible for care is together.

It is equally important to ask families directly: *"Would you like anyone else present for teaching?"* Many families rely on extended support systems such as grandparents, partners, or other caregivers, who all play a significant role once the infant goes home. Respecting cultural norms, family dynamics, and personal preferences around who participates in education helps ensure consistency and shared understanding across the caregiving team.

The Second Right: The Right Education

Not all education is relevant to every family, and more education is not always better.

Providing ten handouts and an hour-long demonstration may satisfy a checklist, but it rarely serves families well. Research consistently shows that attention spans, especially when under stress, are limited. Families often have a short window of intense focus, and our responsibility is to use that time wisely.

Overloading parents with information can unintentionally increase fear and self-doubt. Thoughts like *"This is too much—I'll never get it right"* can overshadow what should be empowering education. Instead, teaching should be tailored, actionable, and immediately applicable to the family's current needs.

A helpful guiding principle is this: *give families what they need today, not everything you know*. Education is cumulative and should be delivered in intentional, manageable layers.

The Third Right: The Right Time

Even the best education will fail if delivered at the wrong time.

Families may rush through teaching simply to "*get it done*," without realizing its future importance. Education should *not* be provided when caregivers are distracted, multitasking, or emotionally preoccupied. For instance, teaching immediately before a feeding is rarely effective, as families are understandably focused on feeding and bonding with their infant.

As bedside nurses, many of us recognize a hard truth: education often occurs when we have time, not when it is ideal for families. While this reality is shaped by workload and staffing constraints, it highlights the need to rethink how and when education is delivered.

This is where technology becomes a critical ally. By leveraging digital platforms, we can provide education asynchronously and remotely, allowing families to engage when they are most receptive, rather than only when staff availability allows.

The Fourth Right: The Right Dose

Is this the right *amount* of education?

Stress and anxiety significantly limit information processing. While families are highly motivated to do what is best for their baby, excessive education can be counterproductive. Cognitive overload makes it difficult to retain and apply information.

The familiar saying applies here: *the only way to eat an elephant is one bite at a time*. Education should be broken into small, meaningful pieces that families can internalize, practice, and master before moving on to the next concept.

The Fifth Right: The Right Route

Education must be delivered through the right *method*.

Families learn in different ways. Some are visual learners, others prefer written materials, videos, audio instruction, or hands-on demonstrations. Simply asking, *"How do you learn best?"* can dramatically improve engagement and retention.

By matching educational delivery to learning style, we respect family preferences and increase the likelihood that information will be understood and used correctly at home.

Expanding the Framework: From Five Rights to Seven

Many clinicians argue that the traditional Five Rights of Medication Administration are incomplete without two additional components: evaluation and documentation. Safe medication practice does not end at delivery; it requires assessing the patient's response and formally recording what was administered.

Those same principles apply to education. If we are extending the Five Rights to guide how we deliver information, we must also extend the expectation of evaluation and documentation.

The Sixth Right: The Right Evaluation and Assessment

Education is incomplete without assessing understanding.

While brief quizzes can be helpful, the time-tested *teach-back* method remains one of the most effective tools. Asking families to demonstrate or explain what they have learned reinforces comprehension and highlights gaps that need clarification.

This approach follows the principle of *"see one, do one, teach one,"* ensuring that families are not just passive recipients of information but confident, capable caregivers.

The Seventh Right: The Right Documentation

Finally, education requires accurate and efficient documentation. Nurses know the saying well: *if it isn't charted, it didn't happen*.

Nurses are no strangers to charting, and education is often the last thing documented. After a hectic 12-hour shift, charting that a family learned how to use a bulb syringe can easily be overshadowed by more urgent documentation demands.

Yet education happens constantly. Every care time and every conversation in the NICU includes teaching. Expecting nurses to manually chart all of this is *unrealistic and unsustainable*.

Once again, technology offers a solution. Automating education delivery and documentation can reduce staff burden, improve compliance, and ensure consistency. By streamlining charting and enabling auto-documentation, nurses gain back valuable time for what matters most: hands-on patient care and meaningful bedside education.

Beyond the NICU: A Universal Teaching Framework

While deeply relevant to neonatal care, this framework extends far beyond the NICU and even beyond healthcare. Delivering the right education, to the right audience, at the right time, in the right dose, through the right route establishes a strong foundation for any effective teaching process. Adding evaluation and documentation elevates education from a task to a measurable, high-quality intervention.

There is a growing imperative to standardize education so families receive consistent, accurate information while still allowing for personalization based on culture, preferences, and learning style. Families in the NICU experience significant stress, and we have a professional obligation to ensure that education is health-literate, validated, and respectful. Healthy People 2030 reinforces this responsibility, shifting the definition of health literacy to emphasize the role of organizations, not just individuals, in ensuring understanding.

This approach also aligns with the NPN Baby's Bill of Rights, which affirms that every infant and family deserves compassionate, developmentally appropriate, family-centered care, including education that prepares them for life beyond the $NICU_3$. Applying the expanded Five Rights framework honors that commitment by ensuring families receive information they can truly understand and use. Standardizing how we approach education while personalizing how it is delivered promotes equity, strengthens confidence, and supports safer transitions home.

Technology plays a critical role in making this level of consistency and personalization sustainable. Platforms such as NICU2Home from AngelEye Health are designed to operationalize the Seven Rights in a standardized way while reducing staff workload. It delivers ~800 NICU-specific, clinically reviewed resources in 70+ languages, beginning at admission and extending through the first year of life. With dynamic content delivery, progress tracking, secure two-way messaging, and discharge checklist functionality, NICU2Home standardizes education, reduces staff workload, and drives measurable improvements in safety and family outcomes.

Innovation is not always about creating something new. Often, it is about applying what we already trust with greater intention. When we reframe education from a task to a safety intervention, we don't just change the trajectory of care; we also safeguard families long after they leave the hospital.

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Neonatal Jaundice Requiring Phototherapy Risk Factors in a Newborn Nursery: Machine Learning Approach

Yunjin Choi, Sunyoung Park and Hyungbok Lee

Highlights

What are the main findings?

- Machine learning algorithms successfully identified the key perinatal factors, including mode of delivery, feeding patterns, maternal BMI, and neonatal birth weight, that are associated with the risk of neonatal jaundice requiring phototherapy.
- Specifically, Cesarean section delivery, increased breastfeeding and formula intake, and lower birth weight were found to significantly increase the likelihood of neonates needing phototherapy for jaundice.

What is the implication of the main finding?

- The development of predictive models leveraging electronic medical records offers a powerful tool for early risk stratification, enabling timely clinical interventions and the more effective management of neonatal jaundice.
- These findings emphasize the critical need for integrating comprehensive maternal and neonatal health data into real-time decision-making tools to help reduce complications and readmissions related to hyperbilirubinemia.

Abstract

Background: Neonatal jaundice is common and can cause severe hyperbilirubinemia if untreated. The early identification of at-risk newborns is challenging despite the existing guidelines.

Objective: This study aimed to identify the key maternal and neonatal risk factors for jaundice requiring phototherapy using machine learning.

Methods: In this study hospital, phototherapy was administered following the American Academy of Pediatrics (AAP) guidelines when a neonate's transcutaneous bilirubin level was in the high-risk zone. To identify the risk factors for phototherapy, we retrospectively analyzed the electronic medical records of 8242 neonates admitted between 2017 and 2022. Predictive models were trained using maternal and neonatal data. XGBoost showed the best performance (AUROC = 0.911). SHAP values interpreted the model.

Results: Mode of delivery, neonatal feeding indicators (including daily formula intake and breastfeeding frequency), maternal BMI, and maternal white blood cell count were strong predictors. Cesarean delivery and lower birth weight were linked to treatment need.

Conclusions: Machine learning models using perinatal data accurately predict the risk of neonatal jaundice requiring phototherapy, potentially aiding early clinical decisions and improving outcomes.

Introduction

Neonatal jaundice is a condition characterized by yellowish discoloration of the skin and sclera in newborns due to elevated bilirubin levels. It occurs in approximately 60% of term neonates and 80% of preterm neonates within the first week of life, typically resolving spontaneously within 2 to 3 weeks [1–3]. However, in some cases, neonatal jaundice can progress to severe hyperbilirubinemia, which may lead to irreversible neurological damage [4]. Therefore, the early diagnosis of jaundice is crucial for preventing severe complications by maintaining bilirubin levels within a safe range and enabling timely interventions, such as phototherapy or treatment of underlying conditions [1,4–6].

Neonatal jaundice is among the leading causes of hospital readmission during the neonatal period [2]. In response, the American Academy of Pediatrics (AAP) in 2022 recommended that all neonates born at ≥35 weeks' gestation undergo bilirubin screening and a clinical risk assessment for severe hyperbilirubinemia prior to discharge. Furthermore, parental education is crucial for empowering caregivers to monitor jaundice at home and seek timely medical care if symptoms progress [7]. Beyond visual inspec-tion, identifying high-risk neonates is essential for the early detection and prevention of severe hyperbilirubinemia.

Studies have identified several key risk factors, including preterm birth, exclusive breastfeeding in the early neonatal period, glucose-6-phosphate dehydrogenase (G6PD) deficiency, ABO

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incompatibility, maternal alloimmunization, maternal obesity, concep-tion via in vitro fertilization and embryo transfer (IVF-ET), delayed cord clamping, and a gestational age of 35–36 weeks. Furthermore, early-term neonates (37 to less than 39 weeks) have a higher likelihood of requiring phototherapy compared to full-term neonates (39 to less than 41 weeks) [8–13].

Although several studies have investigated the risk factors associated with neonatal jaundice [8–13], few have utilized machine learning techniques on large-scale, single-center datasets to identify the risk factors associated with jaundice requiring treatment. Therefore, this study aims to apply machine learning algorithms to analyze the key risk factors for neonatal jaundice, ultimately contributing to improved early diagnosis and preventive strategies.

Methods

This study is a retrospective study applying machine learning techniques to analyze the factors influencing neonatal jaundice in a single tertiary hospital. This study population includes neonates admitted to the well-baby nursery at a single tertiary hospital from 1 Jan-uary 2017 to 31 December 2022 based on electronic medical records. Neonates admitted to the neonatal intensive care unit (NICU) after birth were excluded. To identify the risk factors of the neonatal jaundice requiring treatment, various maternal and neonatal factors were analyzed. Maternal factors included age, weight, BMI, white blood cell count, hemoglobin, platelet count, gestational diabetes, hypertension during pregnancy, maternal conditions such as hypothyroidism, and the use of oxytocin during labor. Neonatal factors included gestational age, prematurity, premature rupture of membrane, prolonged rupture of mem-brane, low birth weight, mode of delivery, Apgar score, meconium pass during delivery, cord neck around, umbilical cord length, delayed cord clamping, urination and defecation at birth, and birth weight. Additionally, neonatal factors such as head circumference, chest circumference, abdominal circumference, weight loss rate of the birth weight, daily formula intake, daily breast milk feeding frequency, daily urination frequency, and daily defecation frequency were extracted. The outcome variable for identifying neonatal jaundice requiring treatment was extracted from nursing records. In the study hospital, when a neonate's transcutaneous bilirubin level was in the high-risk zone, phototherapy was administered following the AAP guidelines, and at that time, nurses recorded "phototherapy initiated" in the nursing records. Therefore, neonates with a nursing record indicating the initiation of phototherapy from birth until discharge were identified. Repeated nursing records for the same neonate were extracted based on the first record.

Data Preparation: Data extraction was performed from the Clinical Data Warehouse of Seoul National University Hospital, using de-identified data to prevent patient identi-fication. To ensure security, data extraction and analysis were conducted using internal servers and an internal analysis cloud. Since the data consisted of mandatory input fields, there were no missing values. However, outliers caused by input errors in weight, height, and vital signs were replaced with the mean values. Data imbalance is typically addressed using two techniques: under-sampling, which reduces the majority class data, and over-sampling, which increases the minority class data. Under-sampling may result in the loss of valuable data, while over-sampling can lead to overfitting. To mitigate these drawbacks, the SMOTE-Tomek method, which combines both under-sampling and over-sampling, has recently been utilized. In this study, due to severe data imbalance, the SMOTE-Tomek technique was applied to prevent overfitting and prediction bias.

Machine Learning: For model development, the data were split into training and test-ing sets in an 8:2 ratio, and model validation was performed using 5-fold cross-validation. Logistic Regression, Support Vector Machine, Random Forest, and XGBoost algorithms were applied and compared. To evaluate the predictive performance and accuracy of the machine learning models, metrics such as accuracy, precision, recall, F1-measure, and the area under the ROC curve were used. The ROC curve area was compared to select the most optimal algorithm. Finally, SHAP values were used to identify the influencing factors and explain the prediction results of the selected algorithm (to explain the prediction result of the selected algorithm, SHAP values were used to identify the influencing factors).

Ethical Considerations: Prior to initiating this study, approval was obtained from the Institutional Review Board (IRB) of Seoul National University Hospital (H-2305-118-1434). Data were extracted from the Clinical Data Warehouse using electronic medical records. Additionally, personal information was anonymized, and any identifiable patient data were de-identified.

Results

A total of 8242 neonates were included in this study, with 1699 (20.6%) requiring pho-totherapy for neonatal jaundice. Table 1 presents the general characteristics of the study population, comparing the phototherapy group ($n = 1699$) with the non-phototherapy group ($n = 6543$). There was no significant difference in neonatal jaundice prevalence based on gender ($p = 0.643$). However, multiple pregnancies were associated with a lower pho-totherapy rate (19.5% vs. 21.5%, $p = 0.031$). Neonates who experienced weight loss ex-ceeding 5% of birth weight had a significantly higher phototherapy rate (27.7% vs. 18.7%, $p < 0.001$). Maternal factors also influenced the phototherapy rates. Infants born to moth-ers with blood type O had a higher phototherapy rate than those with non-O blood types (22.5% vs. 19.9%, $p = 0.012$). Gestational hypertensive disorders (27.7% vs. 19.8%, $p < 0.001$), prior artificial miscarriage (25.6% vs. 20.2%, $p = 0.002$), and cesarean sec-tion delivery (36.5% vs. 7.0%, $p < 0.001$) were significantly associated with increased phototherapy requirements. Regarding neonatal factors, preterm birth (24.0% vs. 19.1%, $p < 0.001$), small-for-gestational-age status (23.9% vs. 19.3%, $p < 0.001$), and lower birth weight (mean ± SD: 2.79 ± 0.54 kg vs. 2.85 ± 0.50 kg, $p < 0.001$) were significantly associated with a higher phototherapy rate. Additionally, neonates in the phototherapy group had a greater number of defecations (6.18 ± 4.97 vs. 5.41 ± 3.27 per day, $p < 0.001$) and urinations (7.11 ± 1.53 vs. 5.90 ± 1.87 per day, $p < 0.001$) compared to the non-phototherapy group.

The evaluation results of the machine learning models are shown in Table 2. The Logistic Regression had an accuracy of 0.754, precision of 0.632, recall of 0.566, F-1 measure of 0.597, and AUROC of 0.823 (95% CI: 0.801–0.845). The Support Vector Machine had an accuracy of 0.790, precision of 0.665, recall of 0.699, F-1 measure of 0.682, and AUROC of 0.870 (95% CI: 0.851–0.890). The Random Forest model had an accuracy of 0.815, precision of 0.710, recall of 0.716, F-1 measure of 0.713, and AUROC of 0.892 (95% CI: 0.874–0.910). The XGBoost model showed an accuracy of 0.828, precision of 0.758, recall of 0.713, F-1 measure of 0.726, and AUROC of 0.911 (95% CI: 0.894–0.927). The ROC curves for each model are shown in Figure 1. A comparison

Table 1. General characteristics.

Characteristics		Non-Phototherapy Group (N = 6543)		Phototherapy Group (N = 1699)		x^2	*p*
Gender	M	3181	79.2%	837	20.8%	0.226	0.643
	F	3362	79.6%	862	20.4%		
Multiple pregnancies	No	3547	78.5%	971	21.5%	4.709	0.031
	Yes	2996	80.5%	728	19.5%		
Weight loss exceeding 5% of birth weight	No	5255	81.3%	1205	18.7%	70.188	<0.001
	Yes	1288	72.3%	494	27.7%		
Maternal country	Korea	6363	79.5%	1641	20.5%	2.113	0.144
	Other	180	75.6%	58	24.4%		
Maternal ABO blood group	Non-O	4819	80.1%	1199	19.9%	6.495	0.012
	O	1724	77.5%	500	22.5%		
Maternal HBsAg positive	No	6437	79.3%	1677	20.7%	0.933	0.379
	Yes	106	82.8%	22	17.2%		
Gestational DM	No	5978	79.6%	1529	20.4%	3.120	0.085
	Yes	565	76.9%	170	23.1%		
Gestational hypertensive disorders	No	5932	80.2%	1465	19.8%	28.827	0.000
	Yes	611	72.3%	234	27.7%		
Maternal thyroid disease	No	6113	79.6%	1566	20.4%	3.344	0.075
	Yes	430	76.4%	133	23.6%		
Premature rupture of membrane	No	5596	78.6%	1521	21.4%	18.279	<0.001
	Yes	947	84.2%	178	15.8%		
Parity	1	4782	78.5%	1310	21.5%	11.296	0.001
	2+	1761	81.9%	389	18.1%		
Prior artificial miscarriage	0	6111	79.8%	1550	20.2%	9.670	0.002
	1+	432	74.4%	149	25.6%		
Prior natural miscarriage	0	4921	79.4%	1275	20.6%	0.020	0.900
	1+	1622	79.3%	424	20.7%		
Induction of labor	No	3165	71.2%	1281	28.8%	396.5	<0.001
	Yes	3378	89.0%	418	11.0%		
Epidural analgesia	No	5564	77.8%	1592	22.2%	88.514	<0.001
	Yes	979	90.1%	107	9.9%		
Delayed cord clamping	No	6380	79.2%	1676	20.8%	7.911	0.004
	Yes	163	87.6%	23	12.4%		
Type of delivery	Normal	4125	93.0%	309	7.0%	1091.884	<0.001
	Cesarean section	2418	63.5%	1390	36.5%		
Vacuum assist	No	5157	76.7%	1566	23.3%	160.01	<0.001
	Yes	1386	91.2%	133	8.8%		
Small for gestational age	No	4788	80.7%	1148	19.3%	21.053	<0.001
	Yes	1755	76.1%	551	23.9%		

Table 1. *Cont.*

Preterm birth	No	4565	80.9%	1076	19.1%	25.881	<0.001
	Yes	1978	76.0%	623	24.0%		
Meconium pass	No	5069	77.3%	1485	22.7%	81.699	<0.001
	Yes	1474	87.3%	214	12.7%		
Meconium staining	No	6128	79.0%	1633	21.0%	14.829	<0.001
	Yes	415	86.3%	66	13.7%		
Cord around neck	No	5262	78.7%	1427	21.3%	11.233	0.001
	Yes	1281	82.5%	272	17.5%		
Cord knot	No	6503	79.5%	1682	20.5%	2.976	0.064
	Yes	40	70.2%	17	29.8%		
Umbilical cord vessels	2 arteries 1 vein	6497	79.4%	1688	20.6%	0.061	0.480
	1 artery 1 vein	46	80.7%	11	19.3%		
Urination during birth	No	5237	79.8%	1324	20.2%	3.704	0.058
	Yes	1306	77.7%	375	22.3%		
Prolonged rupture of membrane [1]	No	6316	79.3%	1645	20.7%	0.347	0.600
	Yes	227	80.8%	54	19.2%		

Characteristics	**Non-Phototherapy Group (N = 6543)**		**Phototherapy Group (N = 1699)**		**F**	***p***
	Mean	**SD**	**Mean**	**SD**		
Birth weight	2.85	±0.50	2.79	±0.54	3.915	<0.001
Birth height	48.01	±2.31	47.47	±2.39	8.537	<0.001
Head circumference	33.85	±5.39	33.70	±1.77	1.098	0.272
Chest circumference	30.57	±2.12	30.43	±2.32	2.281	0.023
Abdominal circumference	28.32	±4.08	28.16	±2.39	1.513	0.130
Number of defecations (per day)	5.41	±3.27	6.18	±4.97	−7.665	<0.001
Number of urinations (per day)	5.90	±1.87	7.11	±1.53	−27.541	<0.001
Number of breastfeeding sessions (per day)	2.57	±3.59	2.21	±3.09	3.766	<0.001
Formula intake (per day)	166.85	±55.79	218.46	±54.3	−34.153	<0.001
Weight loss rate of the birth weight	3.53	±1.87	4.00	±2.00	−9.153	<0.001
Maternal age	40.24	±4.27	40.51	±4.24	−2.302	0.021
Maternal body mass index	27.33	±6.63	28.00	±5.87	3.361	<0.001
Maternal white blood cell count	8.51	±12.23	8.47	±2.19	0.136	0.892
Maternal hemoglobin	11.94	±2.04	12.11	±4.75	−2.240	0.025
Maternal platelet count	207.97	±65.44	212.90	±61.27	−2.807	0.005
Apgar score 1 min	7.88	±0.86	7.77	±0.99	4.339	<0.001
Apgar score 5 min	9.03	±0.56	9.00	±0.59	2.061	0.039
Umbilical cord length	50.20	±33.01	49.11	±26.17	1.251	0.211

[1] birth of over 24 h after rupture of membrane.

of the model evaluation results confirmed that the XGBoost model demonstrated the best predictive performance.

The feature importance based on SHAP values for the XGBoost model, which demon-strated the best predictive performance, is shown in Figure 2. The factor that had the greatest impact on neonatal jaundice was the mode of delivery (mean SHAP value: 1.0054). This was followed by daily formula intake (mean SHAP value: 0.8332), the 1 min Apgar score (mean SHAP value: 0.2201), the daily breastfeeding sessions (mean SHAP value: 0.1616), neonatal height (mean SHAP value: 0.1306), and maternal white blood cell count (mean SHAP value: 0.0971).

Table 2. Comparison of the models.

Models	Accuracy	Precision	Recall	F1-Score	AUROC (95% CI)
Logistic Regression	0.754	0.632	0.566	0.597	0.823 (0.801~0.845)
Support Vactor Machine	0.79	0.665	0.699	0.682	0.870 (0.851~0.890)
Random Forest	0.815	0.710	0.716	0.713	0.892 (0.874~0.910)
XGBoost	0.827	0.739	0.713	0.726	0.911 (0.894~0.927)

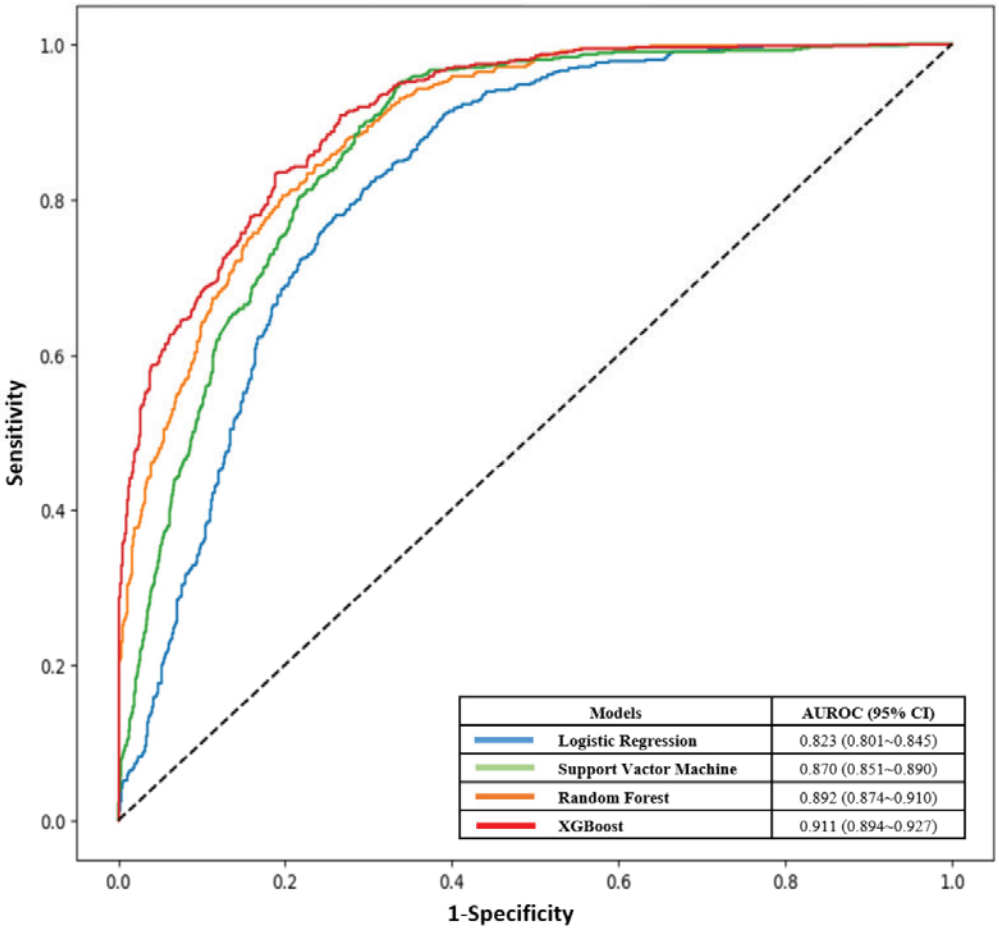

Figure 1. ROC curve of the 4 models.

The SHAP explainable model for the top 20 factors influencing neonatal jaundice is shown in Figure 3. It was confirmed that neonates delivered via cesarean section were more likely to develop jaundice than those born through vaginal delivery. Additionally, higher daily formula intake and more frequent breastfeeding were associated with an increased likelihood of jaundice. Lower 1 min Apgar scores, lower neonatal birth weight, and shorter neonatal length were also linked to a higher occurrence of jaundice. Furthermore, higher maternal white blood cell counts, higher BMI, and older maternal age were associated with an increased likelihood of neonatal jaundice.

Discussion

This study applied machine learning techniques to analyze various factors influenc-ing neonatal jaundice requiring phototherapy. This study revealed a higher incidence of jaundice in neonates delivered by cesarean section compared to vaginally delivered infants. This result stands in contrast to previous studies [14,15] that reported no statis-tically significant association between the type of delivery and the incidence of neonatal jaundice. While bilirubin levels generally reach their peak between 72 and 96 h postpartum, a common practice in numerous hospital settings involves discharging vaginally delivered newborns within 48 to 72 h, whereas neonates born via cesarean section typically remain hospitalized for a duration of 4 to 5 days. This divergence in hospitalization duration suggests that jaundice in cesarean-delivered infants is more likely to be detected during their hospital stay, whereas jaundice in vaginally delivered neonates is likely to be detected after they have been discharged. Thus, delayed detection and treatment of post-discharge jaundice may result in severe neurodevelopmental and long-term health complications [16]. Notably, numerous studies have established that neonatal hyperbilirubinemia significantly impacts neurodevelopment, irrespective of whether the infant is preterm or full-term [17]. Previous research has indicated that early discharge correlates with increased readmis-sion rates for severe jaundice [18,19]. Furthermore, infants discharged following vaginal delivery are reportedly at greater risk of readmission due to hyperbilirubinemia

Figure 2. Feature importance.

[19]. Al-though clinical guidelines and parental education on jaundice detection after discharge are widely implemented, many neonates continue to experience complications from undetected jaundice. This may be attributed to the fact that the immediate postpartum period is a highly vulnerable time for mothers, characterized by psychological, physical, and cognitive challenges [20,21]. Therefore, the effectiveness of education provided during the initial postpartum hospitalization may be limited by maternal factors affecting reten-tion and adherence [22,23]. Additionally, the lack of user-friendly and objective devices for parents to monitor their newborns' bilirubin levels at home presents a significant challenge [24]. Recent studies have highlighted the potential of digital health interven-tions, such as smartphone-based bilirubin measurement, for frequent and noninvasive monitoring [24]. Nevertheless, the widespread commercial application of such technologies faces several limitations. Accordingly, to enable the early identification of neonatal jaundice post-discharge, a sustained effort in parental education from the antenatal stage, coupled with the development and validation of simple yet precise tools for at-home jaundice detection, is essential.

In this study, we found that nutrition-related variables during hospitalization, such as frequency of breastfeeding, daily formula intake, and frequency of urination, were associated with neonatal

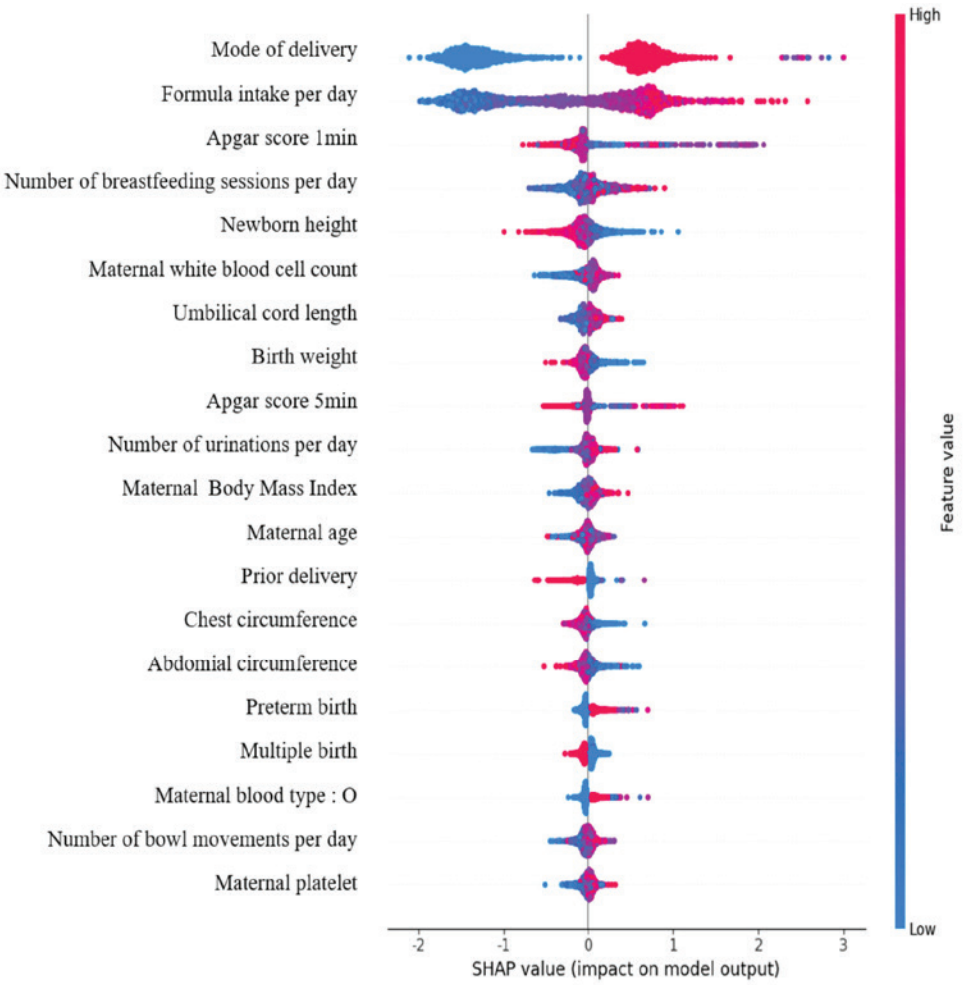

Figure 3. Top SHAP explainable model.

jaundice. Our observation that jaundice was more prevalent in newborns with a higher breastfeeding frequency aligns with the findings from prior research, supporting studies suggesting that frequent breastfeeding may increase the serum bilirubin levels [25,26]. Interestingly, in the present study, we also observed a positive correlation between increased formula intake, urination frequency, and the occurrence of neonatal jaundice. This observation could be explained by the fact that neonates with jaundice received intensified nutritional support through nursing interventions targeting bilirubin reduction [27], as per institutional protocols and clinical guidelines. Consequently, the interpretation of these nutrition-related variables should be approached with caution. While the World Health Organization (WHO) recommends exclusive breastfeeding for the first six months [28], the American Academy of Pediatrics (AAP) guidelines recognize the potential risk of breastfeeding-associated jaundice and advise careful monitoring of nutritional status [29]. Regional and institutional variations in practice [30,31] further underscore the necessity of standardized feeding guidelines. Therefore, further studies are needed to elucidate the intricate relationship between early feeding behaviors and the development of jaundice. Given the retrospective design of this study, prospective validation of the identified key nutritional variables is recommended.

Among maternal variables, both elevated maternal body mass index (BMI) and in-creased white blood cell (WBC) count prior to delivery were significantly associated with neonatal jaundice requiring treatment. These findings suggest that maternal metabolic and immunological status may influence neonatal bilirubin metabolism, consistent with previous studies reporting similar associations [8,32].

Additionally, neonatal factors such as lower birth weight, shorter birth length, and preterm birth were linked to an increased risk of jaundice. These results align with prior research indicating that immature hepatic function and underdeveloped physiology in preterm or growth-restricted neonates contribute to impaired bilirubin clearance [10].

Overall, our findings underscore the critical role of maternal health during pregnancy and the developmental maturity of the neonate in the effective metabolism of bilirubin. While previous studies have typically examined maternal and neonatal factors indepen-dently, this study employed a machine learning-based analysis of electronic medical record (EMR) data to integrate both.

Recently, machine learning-based software for neonatal jaundice prediction has been developed [33]. However, these models primarily utilize neonatal variables and cur-rently focus on validating accuracy, clinical utility, and comparison with existing meth-ods. Most existing machine learning approaches for predicting neonatal jaundice have focused on image-based analyses; however, integrated models utilizing EMR data remain limited [34–37]. This study highlights the potential of predictive modeling using routinely collected perinatal data—information that is readily available at the time of birth.

This study has several limitations. The retrospective design limits the establishment of causal relationships, necessitating prospective research. The use of single-center data may restrict the generalizability of the findings, suggesting the need for multi-center studies with diverse populations. Finally, this study did not account for post-discharge jaundice progression or complications such as neurodevelopmental disorders in neonates. Future research should include data on readmissions and complications for jaundice treatment to refine predictive models.

Implications and Future Directions: Our findings suggest that neonatal jaundice is a predictable condition that can be modeled using perinatal variables from both the mother and infant. These predictors—available at the time of delivery—could be leveraged to develop real-time decision support systems for jaundice risk stratification. Future research should focus on developing and validating large-scale artificial intelligence (AI) models incorporating diverse and comprehensive datasets. In particular, integrating post-discharge outcomes and feeding data may enhance model accuracy and real-world applicability. Such tools would be instrumental in reducing the clinical burden of neonatal jaundice and preventing avoidable complications through early intervention.

Conclusions

This study highlights the potential for developing a neonatal jaundice risk prediction model using machine learning. It is expected to serve as a valuable foundation for early identification and prevention strategies for neonatal jaundice. Moreover, we anticipate the development of strategies that not only prevent readmissions but also empower parents to identify and manage neonatal jaundice after discharge, thereby mitigating a range of potential complications. Further research can refine these findings and contribute to the development of a more sophisticated predictive model, ultimately helping to reduce the clinical burden of neonatal jaundice.

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Institutional Review Board Statement: Prior to initiating this study, approval was obtained from the Institutional Review Board (IRB) of Seoul National University Hospital (H-2305-118-1434, 19 June 2024). Data were extracted from the Clinical Data Warehouse using electronic medical records. Additionally, personal information was anonymized, and any identifiable patient data were de-identified.

Informed Consent Statement: The requirement for informed consent was waived by this institutional review board. Only the researcher can access the data. All methods throughout the study were performed in accordance with the relevant guidelines and regulations.

Data Availability Statement: This study used electronic health record data (de-identified) from the Seoul National University Hospital. The dataset used in this study is not publicly available due to its sensitive nature, and the data use agreement condition. However, aggregated analysis results are available upon request.

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Conflicts of Interest: The authors have no conflicts of interest to declare. The corresponding author also has no conflicts of interest to declare.

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They analyzed numerous sources, including studies of the epidemiology of hepatitis B infection, clinical trials, systematic reviews, vaccine safety data from surveillance and clinical studies, and the potential effect of revised guidelines on individual and public health. Additionally, they reviewed the history of ACIP recommendations and resulting trends in hepatitis B incidence.

Preterm Birth Linked to Higher Disability Risk at Age 12

Children born before 27 weeks of development show higher rates of neurodevelopmental disabilities at age 12, with 37.4% showing moderate-to-severe impairment compared with 4.6% in those born full-term. The infants were at an increased risk for autism spectrum disorder, attention-deficit/hyperactivity disorder, and developmental coordination disorder, with 59% of affected children having multiple disabilities. The study was conducted as part of the Extremely Preterm Infants in Sweden Study, which included all infants born prematurely (before 27 weeks of gestation) from April 2004 to March 2007. At age 12, 462 extremely premature infants who survived were analyzed alongside 373 infants born at term using verified clinical tests and intelligence assessments, which measured cognition, motor function, and behavior. Analysis included diagnoses from national health registers, including the Swedish National Patient Register and the Swedish National Prescribed Drug Register. Parents completed health questionnaires to provide additional information about each child's conditions. Cognitive impairment was the most common disability, affecting one third of children born extremely premature. The prevalence of moderate-to-severe neurodevelopmental disabilities increased from 33.6% at age 6.5 years to 37.4% at age 12 years. Extremely premature children showed higher rates of moderate or severe neurodevelopmental disability than control individuals (37.4% vs 4.6%), with elevated rates of autism spectrum disorder (14.9% vs 2.4%; odds ratio [OR], 7.10; 95% CI, 3.48-15.1), attention-deficit/hyperactivity disorder (21.2% vs 8.9%; OR, 2.77; 95% CI, 1.81-4.26), and developmental coordination disorder (29.4% vs 5.8%). Among premature children with a moderate or severe neurodevelopmental disability, 59% had two or more co-occurring disabilities or disorders than 24.9% with no or mild disabilities. The mean cognitive ability score of those born extremely premature was 89.6 (SD, 15.6), which was lower than that of the control group at 105.1 (SD, 13.0); the mean difference was 15.5 (95% CI, 13.5-17.5; $P < .001$). Overall, 57.4% of children born extremely premature did not have moderate-to-severe neurodevelopmental disability and autism spectrum disorder, while 40.2% were free of autism spectrum disorder, attention-deficit/hyperactivity disorder, and developmental coordination disorder. "Children born extremely preterm remain at high risk for neurodevelopmental disability at 12 years of age and exhibit a high prevalence of cognitive deficits…and behavioral problems, with a high rate of multidomain disability necessitating multidisciplinary follow-up," the researchers of the study reported.

Should Prenatal Growth Restriction Inform Adult Screening?

Neonates who survive fetal growth restriction and extreme prematurity face measurable cardiopulmonary sequelae that persist into adolescence and adulthood, yet birth history is often overlooked in routine pediatric and adult care. Experts warn that systematic documentation of early life risk factors is essential to guide long-term surveillance and prevention strategies. Specialists in Italy gathered to examine the future of neonatal care, informed by *The Lancet Child & Adolescent Health* Commission on the Future of Neonatology. Set against declining birth rates, discussions focused on the Italian context and its specific challenges, concerns raised by the Italian Society of Neonatology (SIN). "Today, more than ever, advances in medicine allow the survival of extremely premature neonates and those with very low birth weight," said Massimo Agosti, MD , neonatologist, president of the SIN, Italy. "At the same time, rising maternal age translates into more neonates born with complex health conditions. As neonatologists, we must set new goals: not only to save lives but to manage the long-term consequences of early health insults through collaboration with pediatricians and physicians caring for adults." Fetal growth restriction (FGR) is diagnosed when estimated fetal weight on ultrasound falls below the 10th percentile for gestational age. Placental insufficiency is the most common cause, leading to chronic hypoxia that limits attainment of genetic growth potential. "This condition activates adaptive hemodynamic mechanisms aimed at preserving the heart and brain," said Tullio Ghi, MD, PhD, professor of obstetrics and gynecology, Università Cattolica del Sacro Cuore, and director, Unità Operativa Complessa di Ostetricia e Patologia Ostetrica, Policlinico Agostino Gemelli, Rome, Italy. "In response to increased workload, the cardiac walls initially undergo functional changes, followed by structural remodeling detectable on prenatal ultrasound. Assessment of myocardial deformation shows higher velocity during the cardiac cycle in fetuses who are small for gestational age compared with those with normal growth." Over time, the structure of the heart changes, becomes more globular and less elongated. By 6 months of age, infants born with low birth weight demonstrate differences left ventricle per unit of time and the thickness of the intraventricular septum compared with those of infants born at a normal weight. Cardiac differences persist during childhood infants born with low birth weight have a thicker carotid artery wall. In adolescence, these individuals show less resistance to fatigue during physical activity, and the increased cardiovascular risk persists in adulthood.

Non-Narcotic Analgesics Allergy Labels Linked to Adverse Maternal and Fetal Outcomes

A non-narcotic analgesics allergy label (NNAAL) is associated with several adverse perinatal outcomes, indicating a need for additional maternal evaluation, according to new research being presented at the 2026 AAAAI Annual Meeting. "There is a paucity of information regarding the effect of a non-narcotic analgesics allergy label on maternal and fetal outcomes," said lead author Chang Su, MD. "Our study showed that having such a label can be associated with various adverse maternal and fetal outcomes. These findings are potentially practice-expanding because evaluating women of childbearing age who have a history of non-narcotics analgesics allergy could lead to delabeling for approximately 80% of patients and potentially improved perinatal outcomes." In this study, researchers conducted a retrospective analysis using the Study of Outcomes in Mothers and Infants, a population-based cohort of all births in California between 2016 and 2021. Both maternal and fetal outcomes were examined by NNAAL status using logistic regression to calculate relative risks (aRRs) and 95% confidence intervals (CIs) adjusted for maternal characteristics. Of the 2,244,210 singleton livebirths included in the study, 10,460 were born to mothers with NNAALs with a significantly higher proportion of mothers with NNAALs being more than 34 years old. Maternal NNAALs were significantly associated with increased rates of eclampsia (aRR 1.5, 95% CI [1.06, 2.12]), preterm birth (aRR 1.21, 95% CI [1.14, 1.28]), NICU admission (aRR 1.17, 95% CI [1.10, 1.25]), infants with neonatal withdrawal syndrome (aRR 1.51, 95% CI [1.24, 1.84]), longer infant hospital stay times ($p < 0.0001$)

and a decreased rate of infants who were large for their gestational age (aRR 0.92, 95% CI [0.87, 0.98]). However, NNAALs were not associated with maternal preeclampsia, infants who were small for their gestational age, major structural birth defects or an APGAR score of less than seven. By exploring the relationship between maternal NNAALs and maternal and fetal outcomes, this study highlights an important need for proactive allergy evaluations of patients with NNAALs and delabeling efforts that may improve perinatal outcomes. Visit aaaai.org to learn more about asthma, allergies and pregnancy. Research presented at the 2026 AAAAI Annual Meeting, February 27 – March 2 in Philadelphia, PA, is published in an online supplement to *The Journal of Allergy and Clinical Immunology* (JACI). The American Academy of Allergy, Asthma & Immunology (AAAAI) is the leading membership organization of more than 7,100 allergists, asthma specialists, clinical immunologists and other professionals with a special interest in the research and treatment of allergic and immunologic diseases. Established in 1943, the AAAAI is the go-to resource for patients living with allergies, asthma and immune deficiency disorders.

Japan Approves Prolacta Bioscience's 100% Human Milk-Based Fortifiers as a Prescription Drug for Vulnerable Infants

Prolacta Bioscience announced that Japan's Ministry of Health, Labour and Welfare (MHLW) has approved PreemieFort Enteral Solution, a 100% human milk-based fortifier, as a prescription drug for very low birth weight infants, infants with congenital gastrointestinal disorders or congenital heart diseases, and those recovering from gastrointestinal surgery. This regulatory milestone was achieved in partnership with the Clinigen Group, which serves as Marketing Authorization Holder and distributor in Japan. PreemieFort is currently marketed under the brand names "Prolact+" in the US and Canada. The landmark regulatory decision validates the critical role of Prolacta's 100% human milk-based fortifiers for the most fragile infants and sets a powerful precedent for neonatal intensive care units (NICUs) worldwide. "Japan's approval of PreemieFort as a prescription drug reflects the strength of the clinical evidence and the pharmaceutical grade processing that stands up to the rigor of Japan's stringent regulatory and quality requirements," said Scott Elster, CEO of Prolacta Bioscience. "The pivotal Japanese clinical study adds to the extensive evidence supporting the benefits of Prolacta's exclusive human milk-based diet for critically ill and fragile premature infants." Clinical evidence generated in Japan from the JASMINE trial ("A Randomized, Controlled Study to Assess Growth and Safety of the Exclusive Human Milk Diet (EHMD) in Very Low Birth Weight (VLBW) Infants") informed Japan's world-class Pharmaceuticals and Medical Devices Agency's (PMDA) review. The Japanese-led phase III, randomized, controlled, open-label, multicenter trial evaluated growth and safety associated with Prolacta's 100% human milk-based fortifiers, demonstrating significantly better growth in VLBW infants with no change in morbidity or mortality. Japan is recognized as a global leader in neonatal care, with among the highest preterm survival rates and lowest rates of necrotizing enterocolitis (NEC),[1,2] a life-threatening intestinal disease primarily affecting premature infants. By granting pharmaceutical approval to PreemieFort, Japan is affirming that Prolacta's human milk-based fortifiers, free from cow milk, are not simply a nutritional choice but an Rx medicine in the NICU. Japan's approval includes three Prolacta products — **PreemieFort Enteral Solution 6, PreemieFort Enteral Solution 8** (Prolact+6 and Prolact+8 human milk-based fortifiers in the US and Canada), and **PreemieFort Enteral Solution CF** (Prolact CR human milk caloric fortifier in the US and Canada) — which provide concentrated nutrition to support growth by delivering essential calories and nutrients, while retaining the highest level of human milk bioactivity. The approval demonstrates clinical confidence in the benefits and safety of PreemieFort human milk-based fortifiers across a wider range of vulnerable infants with complex nutritional needs. "In the NICU, what we feed our smallest patients can influence their entire life," said Kate Tauber, MD, MA, professor of pediatrics and director of the Human Milk Program at Bernard and Millie Duker Children's Hospital. "Human milk-based fortifiers should be held to the same expectations as other therapies, consistent, tightly controlled, and safe. Prolacta's commitment to pharmaceutical-quality manufacturing requirements helps protect vulnerable infants and supports better outcomes." Prolacta maintains the industry's strictest quality and safety standards for screening, testing, and processing donor milk — standards that extend through pharmaceutical grade product manufacturing. Together, these controls earned Japan's prescription drug approval, one of the world's highest regulatory benchmarks.

No Benefit for Magnesium Sulfate in Periviable Deliveries

Providing magnesium sulfate to pregnant patients before delivery in the periviable period of 22-24 weeks' gestation was not linked to better neurodevelopmental outcomes in the newborn after accounting for receipt of prenatal corticosteroids, according to research presented at the Society for Maternal-Fetal Medicine (SMFM) 2026 Annual Pregnancy Meeting. "The lack of association was consistent across all gestational weeks," Margaret Page, MD, a maternal-fetal medicine fellow at The University of Alabama at Birmingham, reported. "Management of pregnant patients at risk of periviable delivery should prioritize antenatal corticosteroid administration." Babies born in the periviable period, between 20 weeks and 24 weeks 6 days , have a high risk for death or severe neurodevelopmental impairment. Research has shown that, for women at high risk for preterm birth who are expected to give birth within 24 hours, prenatal administration of magnesium sulfate reduces the risk for cerebral palsy in the newborn. Page and her colleagues conducted a secondary analysis of data from the National Institute of Child Health and Human Development Neonatal Research Network Generic Database and Follow-up Study to see if an association existed between the prenatal magnesium sulfate exposure in the periviable period and the risk for severe neurodevelopmental impairment or death. The original prospective observational study tracked newborns from 2012 to 2022 from 15 centers, including comprehensive neurodevelopmental follow-up through 2025. The follow-up involved a basic neurologic exam and a Bayley III exam when the children were 22-26 months old. Page and her colleagues included in their analysis all 4179 singletons or twins born between 22 weeks and 24 weeks 6 days gestation, excluding those who died within 12 hours after birth without delivery room resuscitation and those lost to follow-up. They compared outcomes of death and severe neurodevelopmental impairment between the 3242 of infants (78%) exposed in utero to magnesium sulfate to the 937 unexposed infants (22%). Severe neurodevelopmental impairment was defined as a gross motor function classification system level of 4 or 5, a motor or cognitive composite score below 70 on the Bayley exam, blindness in both eyes, or severe hearing impairment in both ears.

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