The Next Generation in Hyperbilirubinemia Management: A Call for Accurate Point of Care Bilirubin Measuring Tools

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Background

Neonatal hyperbilirubinemia (newborn jaundice) is one of the most common physiological manifestations in newborns[1-3]: Hyperbilirubinemia presents itself in 60% of term neonates and in 80% of preterm neonates[5-6]. It is the primary reason for high readmission rates[4] due to its onset 2-3 days after birth, often after a neonate has been discharged from the newborn nursery. Although modest levels of hyperbilirubinemia are usually benign, reflecting the physiological maturation of the neonate's hepatic system, incorrect or delayed diagnosis could lead to bilirubin-induced neurological dysfunction (BIND). In some cases, it may lead to severe brain damage like cerebral palsy or kernicterus [7-8]. The clinical risk factors for BIND include prematurity, rapid rate of bilirubin rise (usually associated with isoimmune hemolysis), birth asphyxia, sepsis, hypoalbuminemia, and temperature instability[29].

In the current healthcare environment which encourages a decreased hospital stay[9], neonates face a greater risk of readmission for a number of reasons. Therefore, diagnostic assays for bilirubin should be adjusted in order to achieve accurate measures of bilirubin, reduce time to appropriate intervention, and prevent the development of chronic hyperbilirubinemia. An easily accessible, low cost, and accurate assay for bilirubin is essential for proper intervention to prevent the development of severe hyperbilirubinemia, especially with an increasing number of babies being discharged early. A system pairing efficient execution with well-defined quality metrics is the rationale for tackling the prevailing high readmissions due neonatal hyperbilirubinemia.

Inefficient Jaundice Management: Misaligned Priorities in the US Healthcare System

To better understand the need for an easily accessible, low cost, and accurate assay for bilirubin, it is important to first understand the root causes for higher readmission rates. Some of these causes (stemming from misaligned priorities in the current healthcare ethos) that trickle down resulting in inefficient jaundice management are discussed below:

Defensive Practice: The current US healthcare system faces a chronic misalignment of resources and priorities. The current medicolegal system has placed considerable pressure on practicing neonatologists and pediatricians, collectively leading to defensive testing practices. Physicians employ these conservative practices as lawsuits involving newborns sustaining peripartum neurologic injury can result in an average indemnity payment of $440,379, which may or may not be covered by malpractice insurance[13]. One survey of physicians practicing in "high-risk" fields such as obstetrics found that 93% practice defensively some of the time or frequently[23].

Rising Administrative Costs: Healthcare in the United States is not focused on prevention, but on a reactive response to disease. Subsequently, this approach to care (and the associated administrative costs) has contributed to higher newborn mortality rates than most of the industrialized world[11,12]. For example, of the $2.9 trillion spent on healthcare in 2009, $765 billion was considered "waste"; this included categories defined as unnecessary services ($210 billion), excessive administrative costs ($190 billion), inefficiently delivered services ($130 billion) and fraud ($75 billion)[26]. Furthermore, physician and ancillary service expenses continued to increase even when median inpatient admissions declined[21]. Although the US spends more on healthcare than any other nation in the world (18% of gross domestic product)[21,27], the newborn mortality rate in the U.S. was higher than that of Cuba; the overall outcome and life expectancy in the US is ranked much lower than most developed nations[10].

Ineffective Cost Savings Strategy: The cost of healthcare in the US per capita is the highest in the world[28]. This is a direct consequence of several misaligned priorities, as noted earlier. While much of the cost burden is created by chronic disease management in older demographics, costs related to neonatal care is also significant. The average length of stay for later preterm newborns is an average of 3.3 days at a cost of $7200, whereas younger preterm neonates have an average stay of 6.3 days at a cost of up to $202,700[20]. Overall, costs vary inversely with birth weight and gestational age. To survive in an environment with progressively lower reimbursement rates from both Medicare/Medicaid and private insurers, hospitals have started adopting cost containment strategies, resulting in a shorter than average length of stay for patients. For neonates, early discharge reduces the ability to effectively screen for hyperbilirubinemia. The burden of screening moves to the outpatient setting, which has much more variability in patterns of care and available services. These factors ultimately result in higher risk for readmissions due to hyperbilirubinemia[14]. Based on analysis of obstetrical records (which contained no clinical indication for late preterm delivery) it is suggested that patient and provider convenience are contributing to the increasing rate of late preterm delivery[15]. Late preterm deliveries make up a majority of preterm births and as such, face increased risk of complications[16]. Potentially avoidable preterm births accounted for 17% of late preterm birth (34-36 weeks of gestation) in one study[17]; another study suggested that unequal (higher) distribution of delivery occurs on Fridays among late preterm neonates[18]. Cost containment strategies implemented by healthcare facilities have been rendered ineffective by these trends, as the cost of care has increased with greater numbers of late preterm newborns admitted to special care nurseries or the NICU (neonatal intensive care unit).

Sectors of the healthcare community have now recognized that use of innovative technologies can be used to overcome barriers blocking access to care and improve care efficiency, while simultaneously reducing costs. Developments in healthcare IT and digital health are attempting to tackle avoidable admissions and readmissions, medical errors, defensive practice patterns, clinician and patient communication deficiencies, and bloated administrative services. Point of Care Testing (POCT) is one of several technological advances that have the potential to reduce operational inefficiencies and improve patient monitoring along with diagnostic accuracy. It can empower clinicians to quickly access critical laboratory values at the bedside, meaning time to diagnosis and appropriate treatments are minimized, and complications of delayed diagnosis are reduced. The subsequent downstream cost savings per patient cannot be understated.

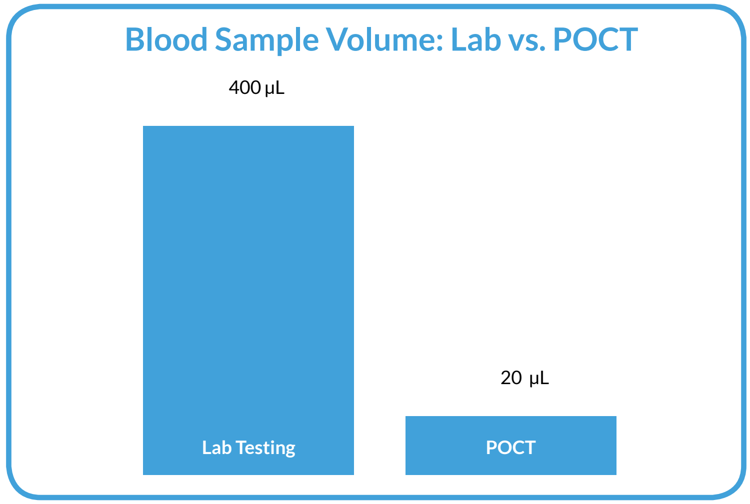

Figure 1: Blood Sample Volume — Lab-based testing vs. POCT device

Impact of Blood-based POCT on Hyperbilirubinemia Management in the NICU

Empowering Clinicians to Make More Confident Treatment Decisions: The emergence of clinical signs of hyperbilirubinemia depends on the rate of bilirubin rise, duration of hyperbilirubinemia, host susceptibility and presence of comorbidities[30,31]. As a result, the recommended methods for assessing hyperbilirubinemia include the measurement of total serum bilirubin (TSB) and/or transcutaneous bilirubin (TcB). These values, when plotted on a standardized hour-specific nomogram, can risk stratify a neonate and indicate need for treatment of hyperbilirubinemia. The premise of using this nomogram relies on bilirubin values being accurate.

The noninvasive nature and quick turnaround time of TcB have made it a good substitute for TSB in order to reduce the total amount of blood draws in neonates. However, the use cases for TcB are limited due to unreliable readings in the following scenarios: during phototherapy or exposure to sunlight because of the bleaching effect of light on the skin, confounding effects of skin melanin content among different ethnicities, and nonlinear deviation of TcB readings when bilirubin levels are greater than 15 mg/dL[33]. Therefore, tracking

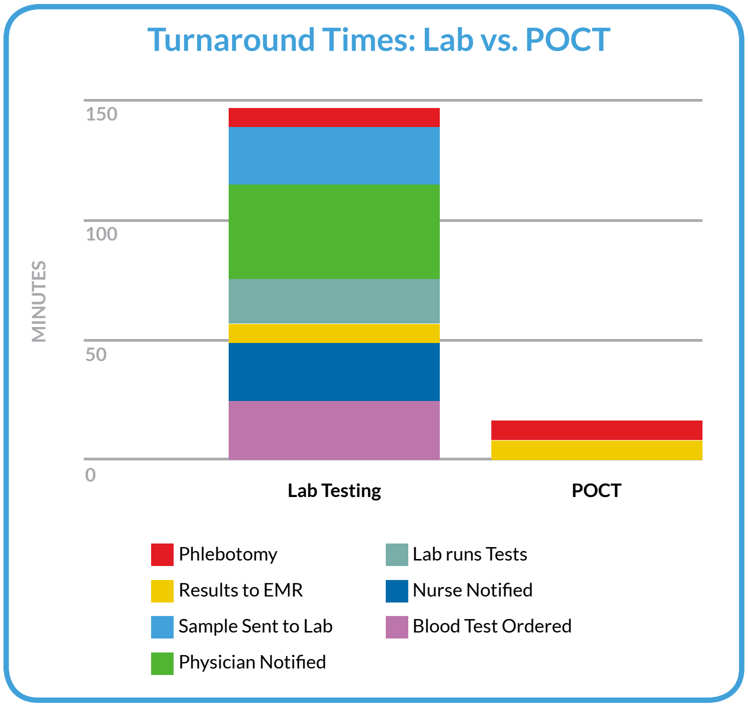

Figure 2: Time to Treatment — Lab-based testing vs. POCT device

the efficacy of phototherapy continues to rely on total serum bilirubin levels. Since 1 in 10 neonates with jaundice achieve bilirubin levels >17 mg/dL[32], TcB will likely underestimate bilirubin levels. It is common clinical practice that significantly elevated TcB levels are confirmed with serum testing. While TSB assays are accurate, they require up to 90 µL blood in currently available POCT systems and up to 0.4 mL in lab-based equipment per test. The TSB testing may need to be repeated every 4 to 12 hours depending upon the acuity of the newborn's condition. For those critically ill neonates in the NICU who require close monitoring of blood bilirubin levels, these blood draws are an immense burden. For a baby weighing 1 kg (2.2 lbs), the maximum blood draw limit per day is 2.5 mL, and 5 mL during a 30-day period[35,36]; any more could trigger the need for a transfusion. Current TSB assays can easily put neonates beyond the threshold for daily maximum blood draws.

An efficient POCT diagnostic device that requires minimal capillary sample blood volumes, similar to glucose meters in the neighborhood of 1 to 20 µL[37], can empower clinicians to make quick treatment decisions with greater confidence. A follow-up test can be done straightaway when needed to double check the consistency of the results reported by a POCT diagnostic device. As a result, clinicians can still practice conservatively with minimal impact to the patient and at reduced cost to the healthcare facility.

More Efficient Patient Management: Patient encounter time can be classified into three categories: administrative time, diagnostic/care time and wait time [33]. Prolonged wait time can have implications on a patient's clinical status, especially in high acuity settings when there is a high probability of deterioration and requirement of additional procedures[33,34].

A blood-based bilirubin POCT device, with a short TAT (turnaround time), can help reduce the waiting time between patient episodes. This means that clinicians can swiftly deploy evidence-based targeted interventions, such as phototherapy, before the need for an exchange transfusion, which involves considerable risks. Figure 2 shows a comparison between time to treatment using lab-based testing and a POCT system (135 mins vs. <15 mins). Additionally, these POCT devices increase patient satisfaction as the newborn and family do not have to wait for lab results performed in the central hospital lab (known to have wait times of approximately 2 hours) prior to discharge.

Decentralization of Blood Testing: A blood-based bilirubin POCT diagnostic device provides not only care efficiency to pediatricians and neonatologists, but also broadens the impact of visiting nurse services. According to guidelines published by the American Academy of Pediatrics[29], every neonate discharged within 48 hours of life should have a follow up appointment 24-72 hours post-discharge. These checkups usually take place in a clinic where blood is drawn and sent to a testing facility. With the help of POCT devices, clinicians can determine bilirubin levels immediately rather than waiting for 24 hours, thereby identifying high risk cases without significant delay. This workflow particularly benefits resource-constrained settings where a patient's family must travel a significant distance to have pediatric-focused lab testing done.

Economic Impact of Blood-based Bilirubin POCT: Several factors influence the economic impact of POCT. These can be compared to the direct and indirect costs of routine laboratory analysis, with implications for economic impact on the quality and timeliness of care as mentioned above. The direct costs include the required staffing to run the tests, cost of reagents, equipment, and resources allocated to transport samples from clinical sites to affiliated laboratories. Indirect costs are associated with delays in time to results, diagnosis, and appropriate treatment,

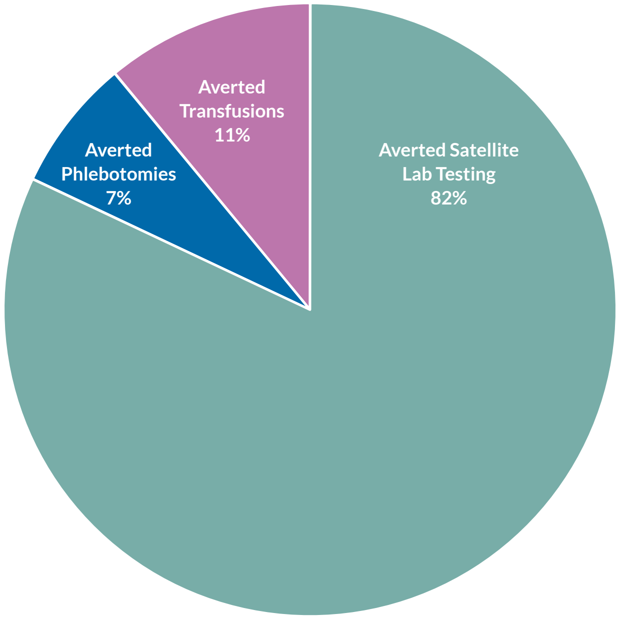

Figure 3: Percentages reflecting averted/saved costs using POCT technology[25]

which in turn impact patient outcomes. Indirect costs are routinely much higher than direct costs[24].

Healthcare facilities using POCT technology can leverage optimal cost savings by targeting indirect costs. Examples of this include reducing infant phlebotomy blood loss and blood transfusions, reducing preanalytical errors by decreasing blood sample exposure to manual manipulation, minimizing resource utilization, and decreasing time to diagnosis and appropriate treatment. This has been illustrated by a study[25] focusing on the effectiveness of neonatal point of care monitors on cost savings in the NICU. This single site study reported that compared to a specialized NICU satellite lab, which was already economically advantageous compared to a centralized lab, POCT may generate significant cost savings on critically ill infants weighing less than 1000 grams – the majority of the NICU demographic who require frequent measurement of bilirubin levels. The distribution of averted costs, which included phlebotomies, satellite blood testing, and transfusions is shown in Figure 3. It should be noted that most of the expense lies in the POCT equipment/rental cost which can be reduced with increased market availability and efficiently calibrated POCT units.

It can be argued that with broader use of POCT devices, an even greater impact will be felt in the outpatient setting. This technology is versatile enough to be used in outpatient clinics, in homes by visiting nurse services, and even in retail clinics. The impact on access and delivery of health care services is significant, especially for families with an at-risk newborn.

Conclusion

There is increasing pressure to reduce costs in the US healthcare system owing to the continual rise in hospital expenditures. This environment has resulted in facilities adopting aggressive cost containment strategies, with an emphasis on reducing length of stays and shifting diagnostic testing to the outpatient setting. As a result, this has strained the effective management of neonatal hyperbilirubinemia. Factors such as early discharge, variable access to pediatric ancillary services, and higher rates of premature birth have increased the risk for readmission of neonates for hyperbilirubinemia. In a high liability specialty like neonatology, this is very problematic and potentially costly. POCT technology has the potential to provide flexibility in diagnostic testing in a variety of clinical settings; however, there is a shortage of accurate POCT assays for bilirubin. These devices can positively impact the economic strain and scarcity of pediatric ancillary services in many facilities. Use of POCT technology can provide confidence to clinicians in their treatment decisions and facilitates the appropriate triage of patients. The immediate availability of accurate bilirubin values can create better efficiency in jaundice management by facilitating more timely intervention for neonates with jaundice — avoiding preventable complications from hyperbilirubinemia, eliminating unnecessary treatment costs, and reducing readmissions.

Please see following page for clinical references.

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