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Effect of Phototherapy on Length of Neonatal Hospital Stay

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Effect of Phototherapy on Length of Neonatal Hospital Stay

By

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B.S., University of Michigan, 2011

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An abstract of
a thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Effect of Phototherapy on Length of Neonatal Hospital Stay
By Lauren A. White

Neonatal hyperbilirubinemia and neonatal jaundice are two of the most common neonatal outcomes. Hyperbilirubinemia is the accumulation of bilirubin, a product of red blood cell breakdown, manifesting through neonatal jaundice, or a yellowing of the skin and sclera of affected infants. Infants with high serum bilirubin levels, preterm infants, observed jaundice before discharge, and siblings with previous jaundice are at increased risk for hyperbilirubinemia. Hyperbilirubinemia is treated with phototherapy (PT), which involves exposing infants to light, to facilitate bilirubin breakdown and excretion. Healthy term infants are usually discharged from the hospital within 48 hours of birth, but a number of factors can lead to an extended stay. There is limited evidence on how PT treatment affects LOS. Our study utilized data on infants born at two metro Atlanta hospitals over a two-year period to determine if infants receiving PT had increased lengths of stay (LOS). We restricted our analysis to infants with a complete neonatal record, and a hospital stay fewer than 16 days. Fifteen percent (137) of infants received PT. A greater percentage of infants who received PT were small for gestational age, born in hospital 2, and bottle-fed. Infants who did not receive PT had a mean LOS of 2.3±1.8 days, compared to mean LOS of 5.0±3.7 days for infants treated with PT. Four survival analysis models were run to evaluate differences in LOS based on PT treatment. Infants who received PT were 2.6 (95% CI 1.92, 4.20) times more likely to have an extended hospital stay when compared to infants who did not receive PT. When stratified on hospital, which controlled for sociodemographic variables including race and insurance type, hazard ratios did not significantly differ. We concluded that infants who received PT had significantly longer LOS than untreated infants. The results of our stratified analysis suggest that PT does not differentially affect respective hazard ratios on the basis of sociodemographic factors.

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Chapter I: Background & Literature Review

Hyperbilirubinemia and Phototherapy

Neonatal jaundice is one of the most common diagnoses among infants. An estimated two thirds of infants will be clinically jaundiced in their first weeks of life (1). While usually benign, serious neurodevelopmental issues can arise if jaundice is left unmonitored. Some common risk factors for neonatal jaundice are given in table 1 (2). Phototherapy (PT) is the most prescribed treatment for neonatal jaundice, and can be administered in several ways. Proper monitoring, prevention, and treatment are essential for keeping infants healthy.

Neonatal hyperbilirubinemia is distinct from neonatal jaundice. Neonatal jaundice refers to a yellowish appearance of skin and sclera of infants, which is caused by neonatal hyperbilirubinemia. Bilirubin is a byproduct of red blood cell breakdown, and can accumulate in the bloodstream because of liver and gastrointestinal tract immaturity, leading to increased reabsorption (3). In come cases, hemolytic disease such as Rh incompatibility causes hyperbilirubinemia (3). Hyperbilirubinemia is clinically defined by bilirubin levels above 5mg/dL (1). Circulating bilirubin can be measured in two ways: transcutaneously which yields transcutaneous bilirubin (TcB), and via a blood draw and spectrophotometry giving total serum bilirubin (TSB). Bhutani et al. derived a nomogram based on total serum bilirubin levels and post natal age delineating the risk of hyperbilirubinemia for infants weighing at least 2000g at birth, and who were delivered at 35 weeks gestation or later (4).

Current American Academy of Pediatrics guidelines for management of hyperbilirubinemia focus on ten points encompassing prevention, diagnosis, monitoring, treatment, and follow-up (2). Primary prevention relies on encouraging breastfeeding 8-12 times each day for the first several days. Colostrum, a component of breastmilk, encourages gut motility and stool passage which can prevent reabsorption of bilirubin, reducing the risk of hyperbilirubinemia (3). Exclusive breastfeeding has also been associated with an increased risk of hyperbilirubinemia because some infants are slower to reach full feedings, resulting in low caloric intake, weight loss, and delayed stool passage. Generally it is believed that the protective effect outweighs potential negative outcomes, especially when proper monitoring is in place. Protocols to identify high-risk infants include testing mother and baby for ABO and Rh incompatibility, and monitoring all infants for yellowing of the skin. Infants who appear jaundiced in the first 24 hours of life should have a transcutaneous bilirubin or total serum bilirubin measurement. Identifying the cause of jaundice in infants with rapidly rising bilirubin levels, or those undergoing PT is important. High bilirubin levels in the first 24 hours of life are often indicative of hemolytic disease, which requires other pharmaceutical treatment in addition to PT (2).

Infants who do not appear jaundiced during their hospital stay should still undergo a risk assessment for developing hyperbilirubinemia before they are discharged, as some infants do not present with hyperbilirubinemia until several

days after delivery. This assessment involve a TcB or TSB screening, or an assessment of clinical risk factors such as being born preterm, having a sibling who received PT, and poor breastfeeding (2). Readmission for neonatal jaundice has risen 160% over the last ten years, so it is important that infants are properly screened (1). Parents should also be provided with information on hyperbilirubinemia at discharge. With these guidelines in place, infants who are at risk of hyperbilirubinemia should be identified and monitored to ensure the proper care is provided. (2)

Hyperbilirubinemia can be dangerous for infants. When total serum bilirubin exceeds 25mg/dL, infants are at risk for neurological damage(2). Unconjugated bilirubin is able to cross the blood-brain barrier and can accumulate in the brain leading to a number of possible adverse neurodevelopmental outcomes. Lethargy is common among infants with high total serum bilirubin levels, and as levels increase, auditory responses can diminish, and most severely, acute bilirubin encephalopathy or kernicterus can develop(2). An infant affected by acute bilirubin encephalopathy appears lethargic, with poor sucking, and progresses to moderate stupor, irritability and hypertonia. In the most advanced cases irreversible central nervous system damage occurs, with symptoms including backward arching of the neck and trunk, apnea, no feeding, and sometimes seizures and death. Kernicterus is a form of chronic brain damage specifically caused by hyperbilirubinemia, where the brainstem and basal ganglia are stained by bilirubin, accompanied by

neurological deficits such as athetoid cerebral palsy, auditory dysfunction, or intellectual deficits. While rare, a national database spanning ten years reported only 90 cases, kernicterus has 10% mortality, and upwards of 70% long-term morbidity (5).

The AAP offers guidelines for two types of treatment for hyperbilirubinemia. The first, and most widely used treatment is PT. This involves placing the infant under lights at a wavelength that can penetrate the skin, and help breakdown unconjugated bilirubin. Treatment initiation is based on total serum bilirubin levels, and varies depending on gestational age at birth and the presence of other risk factors. Bhutani and colleagues developed a nomogram to define different thresholds for initiation of phototherapy based on serum or transcutaneous bilirubin levels relative to age that is used American Academy of Pediatrics guidelines for hyperbilirubinemia treatment (2, 4). If bilirubin levels do not fall after PT, exchange transfusion is the next treatment. Exchange transfusion involves drawing blood from the baby's body, mechanically removing unconjugated bilirubin, and transfusing the blood back in to the infant (6). Because of its invasive nature, exchange transfusion is only used a last resort following failed intensive PT treatment. A graph similar to the one used for threshold levels for PT is used for exchange transfusion (2). In contrast to exchange transfusion, there are many different ways PT can be administered.

The first randomized controlled trial of PT was published by Lucey et al in 1968, which showed that PT was an effective, safe way to treat hyperbilirubinemia (7). A nurse who often took infants to the outdoor courtyard of the hospital originally identified PT as a potential treatment for neonatal jaundice. She noticed that a jaundiced infants skin had returned to its normal color after being exposed to sunlight, with the exception of an area that was covered by a sheet (8). While the principle of PT remains when treating neonatal hyperbilirubinemia, several types of high-intensity lights have replaced sunlight as a light source.

PT can be administered via a number of different technologies. Banks of lights and spotlights have commonly been used in the past. Currently lighted mattresses and blankets are used. Regardless of the type of light used, the most important component of treatment is the dose, which is determined by the wavelength and irradiance of the light, and surface area of the infant exposed to light. Different types of bulbs can be used, which affect the wavelength and irradiance of the light. Light-emitting diode (LED) bulbs are the newest type used in PT, and are useful because they offer high irradiance, but do not generate much heat, which allows the bulbs to be closer to the infant. Fiberoptic lights are often used in mattress covers and blankets, which are useful because more of the infant's body is exposed to light at one time. Halogen and fluorescent bulb are also used, although today they are not as common as LED lights. Halogen lights only provide high irradiance at the center of the light and also get quite hot,

which can be dangerous for the infant. Fluorescent bulbs can have varying irradiance, which affects the efficacy of the light. (8)

A number of studies have investigated the most effective wavelength, irradiance, and type of light for PT. Maisels & McDonagh suggest that light between 460 and 490m is most effective in treating hyperbilirubinemia (9). This wavelength corresponds to blue-green light, and is most effective because of its ability to penetrate the skin. Irradiance and change in total serum bilirubin are inversely correlated; higher irradiance leads to a faster decline in serum bilirubin (10). Irradiance is related to how close the light is to the infant's body, so blankets and mattresses with LED lights in them are favored because of the short distance between the infant and the light (8). Each of these types of lights can be effective, if light characteristics are accounted for to provide the maximum dose possible to the infant.

Although neonatal jaundice is a common problem, it can be monitored and treated in a number of ways. Prevention and monitoring are the most important components in managing hyperbilirubinemia and jaundice. Guidelines are in place to ensure infants are assessed for risk of developing jaundice both during their hospital stay and before discharge. Treatment can be provided in a number of ways to meet the needs of the infant and family. While serious long-term effects are possible, most infants recover with no last ill effects.

Length of Stay

Infant length of stay (LOS) has been studied with respect to a variety of exposures, and often in relation to monetary cost and resource utilization. Preterm infants are more likely to have an extended hospital stay, as they are born less mature than term infants. Kirkby and colleagues found that most preterm infants were hospitalized longer than their term counterparts because of immaturity rather than illness (11). In accordance with a longer stay, the cost of treating these infants is dramatically increased over the cost of care for a healthy term infants who are usually discharged 24 hours after delivery. Many factors are related to LOS for neonates, making the issue multidimensional.

Infant hospital stays after delivery declined between the 1970s and 1990s. In the 1980s, many insurers refused payment for hospital stays longer than 24 hours for infants born vaginally with no complications (12). In the mid 1990s, legislation by U.S. Congress guaranteed coverage for infants up to 48 hours post delivery (13). Rather than suggest a specific length of say before discharge, the AAP recommends that minimum criteria are met before infants are released, noting it is unlikely that these can be met in fewer than 48 hours (12). Collaboration between obstetrician, pediatrician, and family is important to ensure infants are healthy before discharge.

As mentioned, preterm infants often have a longer hospital stay than term infants. A study of late preterm infants (34-36 6/7 weeks gestation) investigated the frequency of extended hospital stays, and associated morbidities. Forty

percent of preterm infants in the sample had a prolonged hospital stay, defined as the infant remaining in the hospital after the mother was discharged. The authors also found a gradient relationship, where younger gestational age correlated with a greater proportion of infants requiring a prolonged hospital stay. Infants with conditions or interventions were more likely to have prolonged hospital stay. In this study, use of supplemental oxygen, PT for jaundice, hypothermia requiring incubation, IV dextrose for hypoglycemia, nasogastric feeding, antibiotic administration, continuous positive airway pressure use, and assisted ventilation were all significantly associated with prolonged stays after adjustment for gestational age. Additionally, interventions and conditions were more common in infants of younger gestational ages. Although this study focused specifically on late preterm infants, it is likely that similar trends will be apparent with decreasing gestational age, and that specific conditions or interventions will also be associated with prolonged hospital stays in term infants. (14)

Several studies have evaluated LOS and costs associated with caring for preterm infants. A study done in Turkey aimed to quantify the costs accrued in caring for preterm infants born 28-37 weeks gestation (15). The mean LOS for infants was 13.6±13.4 days, and the average cost of hospitalization for each infant was $4187, with a daily cost of $303. A similar study of infants born 32-34 weeks gestation was done in the United States (11). Investigators found mean LOS to be

17.6 days, and an average cost per infant of $31,000. Caring for these 32-34 week infants represented 21.6% of total NICU costs.

Bender et al (2012) evaluated the quality of several different models used to predict infant LOS. They tested two score methods, the morbidity assessment index for newborns, and the score for neonatal acute physiology, perinatal extension, which is used to predict morbidity and death in neonates. They found that accounting for illness severity in the first week of an infant's life improves the ability of models to predict LOS. Accounting for illness severity in addition to birthweight and gestational age alone increased the predictive ability of models.

Additionally, individual LOS is more difficult to correctly predict. The variance in LOS can be affected by birth timing, as an infant born before midnight will have a measured stay one day longer than an infant born at 1:00am. A similar problem can also be caused by gestational age. Gestational age is often rounded down to completed weeks, which suggests that an infant born at 35 6/7 weeks should be physiologically the same as in infant born at 35 0/7 weeks, which is unlikely to be true. Overall, this study demonstrates the great variability both in LOS, and also how it is measured. (16)

The complex nature of LOS leads to great variability in LOS measures. Including components such as birthweight, gestational age, any specific diagnoses or treatment, and insurance. The most important factor is ensuring the infant is healthy and strong enough to leave the hospital.

Neonatal hyperbilirubinemia and jaundice, PT, and infant PT have been frequently studied. Both are complex issues that involve not only standard processes of care but also physician discretion, which can lead to variation in practices. The relationship between neonatal PT and LOS is currently unknown.

Chapter II: Manuscript

Effect of Phototherapy on Length of Neonatal Hospital Stay

By Lauren White

Abstract

Neonatal hyperbilirubinemia and neonatal jaundice are among the most common neonatal outcomes. Hyperbilirubinemia is the accumulation of bilirubin, a product of red blood cell breakdown, manifesting through neonatal jaundice, or a yellowing of the skin and sclera of affected infants. Infants with high serum bilirubin levels, preterm infants, observed jaundice before discharge, and siblings with previous jaundice are at increased risk for hyperbilirubinemia. Hyperbilirubinemia is treated with phototherapy (PT), which involves exposing infants to light, to facilitate bilirubin breakdown and excretion. Healthy term infants are usually discharged from the hospital within 48 hours of birth, but a number of factors can lead to an extended stay. There is limited evidence on how PT treatment affects LOS. Our study utilized data on infants born at two metro Atlanta hospitals over a two-year period to determine if infants receiving PT had increased lengths of stay (LOS). We restricted our analysis to infants with a complete neonatal record, and a hospital stay fewer than 16 days. Fifteen percent (137) of infants received PT. A greater percentage of infants who received PT were small for gestational age, born in hospital 2, and bottle-fed. Infants who did not receive PT had a mean LOS of 2.3±1.8 days, compared to mean LOS of 5.0±3.7 days for infants treated with PT. Four survival analysis models were run

to evaluate differences in LOS based on PT treatment. Infants who received PT were 2.6 (95% CI 1.92, 4.20) times more likely to have an extended hospital stay when compared to infants who did not receive PT. When stratified on hospital, which controlled for sociodemographic variables including race and insurance type, hazard ratios did not significantly differ. We concluded that infants who received PT had significantly longer LOS than untreated infants. The results of our stratified analysis suggest that PT does not differentially affect respective hazard ratios on the basis of sociodemographic factors.

Introduction

Neonatal hyperbilirubinemia and neonatal jaundice are two distinct but related outcomes among infants. The Centers for Disease Control and Prevention estimate that 60% of all infants are clinically jaundiced, while hyperbilirubinemia incidence has been estimated at 19% (17, 18). Bilirubin is a fat-soluble product of the breakdown of red blood cells that can accumulate in neonates causing hyperbilirubinemia. Three common causes of hyperbilirubinemia are increased bilirubin production, decreased bilirubin clearance, and breast feeding-associated jaundice (1). Hyperbilirubinemia most often manifests in the form of jaundice, or a yellowing of the skin and sclera of affected infants, and is clinically defined as a TSB or TcB measure >5mg/dL (1). Select risk factors for hyperbilirubinemia and jaundice include high total serum bilirubin (TSB) or transcutaneous bilirubin (TcB), younger gestational age, and a previous sibling

who was jaundiced (2). If left untreated, bilirubin can accumulate and cross the blood-brain barrier, leading to a number of adverse neurodevelopmental outcomes including diminished auditory response and acute bilirubin encephalopathy, and in extreme cases, kernicterus (2).

The American Academy of Pediatrics developed a flow chart for the management of hyperbilirubinemia in infants ≥35 weeks gestation (2). Hyperbilirubinemia is treated using PT, and there are a number of ways it can be administered. Banks of lights were commonly used at the time our data was collected, but now light-emitting diode (LED) bulbs with higher irradiation, and blankets and mattresses with Fiberoptic lights are used more often now (8). The most important factor in PT is the level of irradiation to which the infant is exposed. Light intensity, and the distance between the light source and infant both contribute to the level of irradiation. LED lights provide high irradiation and minimal heat, allowing them to be placed closer to the infant, and blankets enable infants to be exposed to light on all sides (8). PT works by converting bilirubin into water-soluble compounds that can be easily excreted (1). The duration of PT is dependent on infant bilirubin levels, and can vary from a few hours, to several days. With newer technologies such as blankets and mattresses, more and more infants can receive PT at home. PT is sometimes administered prophylactically for very low birthweight or very preterm infants (19).

As a result of insurance payment policies, most healthy infants are discharged from the hospital 24 hours after birth, although a congressional

mandate guaranteed coverage for up to 48 hours after delivery (12, 13). Rather than impose a timeline on infant discharge, the AAP recommends a number of criteria, including appropriate vital signs, and two consecutive feedings, be met prior to discharge, suggesting these are unlikely to be met in fewer than 48 hours (13). Preterm infants (born <37 completed weeks gestation), and infants born via c-section often have longer lengths of stay prior to discharge to assure infants are healthy. In a recent study, 40% of preterm infants remained in the hospital after their mothers were discharged, and preterm infants often have longer stays due to immaturity rather than illness (11, 14).

Much of the literature on hyperbilirubinemia and PT focuses on methods for measuring bilirubin levels, and identifying the most effective PT technologies. This study aimed to quantify the relationship between PT administration, and the length of infant hospital stay.

Methods

Hypothesis

Based on previous literature, we expect infants who receive PT to have a significantly longer hospital stay than infants who are not treated with PT.

Study Design

Data for this study was originally collected for the Fetal Growth and Development Study, a hospital-based case-control study focused on SGA infants born at two Atlanta area hospitals, one private and one public. All singleton

African-American and White infants born at either hospital between 32 and 42 weeks gestation were eligible. Data collection took place between February 1, 1993 and December 31, 1994. Delivery information (race, sex, gestational age, and birthweight) was abstracted daily from the selected hospital. Each week one of two hospitals was selected randomly in four-week blocks to assume an equal seasonal distribution at each hospital. Data from deliveries at the private hospital (hospital 1)were abstracted from nursery logs, and from obstetric delivery logs at the public hospital (hospital 2). All SGA infants (defined as birthweight less than 10^{th} percentile for gestational age, race, and gender), and a 3% random sample of other infants were selected. After acquiring informed consent, mothers of selected infants completed in-person interviews about lifestyle, medical, and reproductive factors prior to delivery or within 48 hours after delivery. Additional neonatal data on physical examinations, feeding habits, and other relevant information was abstracted from medical records.

Dataset

The analysis dataset was created from the original study cohort (n=1015). Infants with missing neonatal data were excluded due to lack of necessary data, leaving a final cohort of 891 infants. PT was restricted to 15 days or less in an effort to exclude extremely sick infants, for whom PT would likely not be a defining factor in length of hospital stay (n=44).

The exposure of interest was neonatal PT provided in the hospital prior to discharge for hyperbilirubinemia. A binary variable indicating whether or not PT

was ever administered at any time in the first 15 days, the number of days of PT, and highest total bilirubin (mg/dL) were recorded. Length of stay was defined as the number of days between birth and hospital discharge, and was calculated by subtracting birth date from discharge date. In instances where one or both dates were missing, PT was set to missing (n=11).

A number of covariates were selected as risk indicators for both PT and LOS based on a literature review. Covariates included gestational age, birthweight, 5-minute Apgar score, hospital of birth, feeding type, mode of delivery, nursery unit, and abnormal skin examination. Gestational age was determined using clinician's best estimate, recorded on the delivery log, nursery log, or medical records. Small-for-gestational age defined as <10th percentile for birthweight and gestational age was determined based on sex- and race- specific norms for birthweight and gestational age from previous U.S. population-based birth cohort analysis (20).

Analysis

All analyses were completed using SAS Version 9.3 (SAS Institute, Cary, NC). Unadjusted survival curves of LOS were made using Kaplan-Meier methods, stratifying individually on PT, and each covariate. Wilcoxon and log-rank statistics were computed for all curves. Logistic regression and 2x2 tables were used to estimate the relative risk of PT as predicted by each covariate individually.

Cox proportional hazard regression was used to determine the relationship between PT and LOS. Proportional hazard assumptions were tested for each covariate using graphical methods, Shoenfeld goodness of fit residuals, and time-dependent interactions. We used backward elimination model building based on p-values (significance set at p=0.05) to determine the predictive ability of each covariate. Variables violating the proportional hazard assumption on the basis of time-dependence were included as time-dependent interaction terms in models. We used Heaviside models to adjust for differences in baseline hazard over time, and the exact ties option to account for the large number of events occurring in the first three days. Collinearity was assessed for each model. Due to methods used to create LOS variable, all infants achieved the outcome; none were censored. Significance was set to 0.05.

Results

Cohort characteristics

The final cohort consisted of 891 infants. Demographic characteristics are presented in table 2. Cohort infants were, on average, born at normal birthweight and at term. More than sixty percent of infants were below the 10^{th} percentile for gestational age adjusted birthweight as a result of the underlying study design, although mean birthweight exceeded 2500g for both cases and controls.

Fifteen percent (137) of infants received PT. Of infants who received PT, 68.7% were small-for-gestational age, 36.5% were born at hospital 1, 45.5% were

female, 70% were born vaginally, 30% were breastfed, and 70% were in the term nursery.

Phototherapy risk

Table 3 contains risks and risk ratios for PT as predicted by covariates. Infants born at 34-36 weeks gestation were more likely than term infants to receive PT, as were infants born <34 weeks, although there were only 3 infants in this category, limiting the interpretations. Bottle-feeding, birth in hospital 2, an abnormal skin exam, and term-infant nursery unit were all associated with increased risk of PT. There were no significant differences in risk of PT based on gestational age-adjusted birthweight, or 5 minute Apgar score.

Length of stay

Median LOS was 2 days, and did not differ between hospitals. However, mean LOS differed by hospital, and by mode of delivery. Infants born at hospital 1 had an average LOS of 2.1±1.8 days; 1.6±1.4 days for infants born vaginally, and 3.4±2.1 days for infants born via cesarean section. Infants born at hospital 2 had a mean LOS of 3.4±2.9 days; 3.1±2.7 days for infants born vaginally, and 5.3±3.1 days for infants born via cesarean section.

Stratification by PT treatment, gestational age groups, gestational age-adjusted birthweight groups, feeding type, hospital of birth, nursery unit, and mode of delivery led to significant differences in unadjusted PT using Kaplan-Meier methods. There were no differences in LOS when stratifying by normal vs.

abnormal skin examination. Figure 2 shows the survival curve stratified on PT status.

Survival analysis models

Final models and respective hazard ratios are in table 4. All models yielded similar hazard ratios, indicating that infants who received PT were more than twice as likely as infants not receiving PT to have extended hospital stays. The first model used was a Heaviside model divided at 5 days, stratified on hospital, adjusted for unit, interaction of time and unit, 5 minute Apgar score, mode of delivery, and mode of delivery and interaction of time and mode of delivery. Under this model, infants who received PT were 2.60 (95% CI 1.92, 4.20) times more likely to have longer hospital stays when compared to similar infants not receiving PT. The second model was also a Heaviside model split at 5 days, stratified on hospital of birth, and adjusted for gestational age, feeding type, mode of delivery, and an interaction term between mode of delivery and time. This model predicted that infant receiving PT were 2.80 (95% CI 1.08, 3.62) times more likely to stay in the hospital beyond infants who did not receive PT. The third and fourth models were for hospital 1 and hospital 2 respectively. Significant covariate terms varied for each hospital: gestational age and mode of delivery were the only predictors included aside from PT treatment for hospital 1; while nursery unit, mode of delivery, and an interaction term between mode of delivery and time at hospital 2. Infants born at hospital 1 who underwent PT were 2.53 (95% CI 1.81, 3.53) times more likely to stay in the hospital beyond

infants who did not receive PT. Infants born at hospital 2 who received PT were 2.34 (95% CI 1.74, 3.15) times more likely to stay in the hospital beyond infants who did not receive PT.

Discussion

Phototherapy is one of the most common interventions for newborns, and has been thoroughly studied. However, little research has been done on how PT affects PT, particularly using survival analysis methods. Gestational age, birthweight, feeding method, Apgar score, and mode of delivery were consistently associated with PT in previous studies, and most were significant predictors in at least one of our models (19, 21-25). We included nursery unit as a covariate, but also ran equivalent models (model 2) excluding it. It is possible that nursery unit is an intermediate on the pathway between PT and PT, especially if infants are moved to a specific unit after being prescribed PT.

Stratifying on hospital controlled for a number of other demographic covariates. Hospital 1 most often serves white women with private insurance, who generally have higher income and education than women who deliver at hospital 2. Hospital 2 serves mostly Medicaid insured women who are black, and of lower income and education. The two hospitals also had different infant discharge practices. Infants born at hospital 1 were more likely to be discharged within 24 hours for uncomplicated vaginal births and 48 hours for cesarean section births, partly due to insurance reimbursement policies. In contrast, hospital 2 tended to keep infants longer, to ensure they were healthy and

thriving before discharge, as these babies were generally at greater risk for adverse outcomes and complications.

We evaluated the effect of PT on LOS among term infants only, and found a hazard ratio similar to the full cohort. After adjusting for nursery unit, 5-minute Apgar score, and mode of delivery, term infants who received PT were 2.58 (95% CI 1.92, 3.48) times more likely to have an extended hospital stay when compared to infants who did not receive PT.

Breastfeeding has been consistently associated with neonatal jaundice, but less frequently with PT (19, 21, 22, 25-28). Madden and colleagues evaluated PT policies before and after the introduction of a legislative mandate requiring a 48-hour stay for any infants with jaundice or feeding problems. They found breastfeeding was strongly associated with jaundice, but changes in LOS were not related to increases in jaundice-related measures (26). In contrast to this analysis, we found LOS to be significantly associated with PT, although feeding type was only a significant covariate in this association in one model.

While our analysis quantifies differences in LOS based on PT treatment, PT technologies have advanced since our data was collected, limiting our ability to generalize our results to infants receiving PT today. Most of the infants in our cohort received PT with banks of lights or spots, which have lower irradiation, and are thus less effective than newer LED light technologies, and Fiberoptic blankets and mattresses (8, 29). Less effective PT methods also results in longer PT times, which can influence total LOS. Our data on length of PT was limited,

so we were unable to quantify the association between PT duration, and LOS. Nonetheless, the relationship may not be of clinical relevance today because of changing technologies. At the time our data was collected, some infants received PT at home, although this practice has increased over time with the introduction of fiberoptic methods. Our data did not capture any care or therapy provided at home, we are likely underestimating the incidence of phototherapy. Our data did not include information on infants who continued to receive PT at home after discharge, so our findings may not be generalizable to these infants.

Increasing LOS leads to increased healthcare costs. A study of infants born between 32 and 34 weeks gestation found that the average hospital stay was 17.6 days at an average cost of $30,527 (11). Another study done in Turkey, but exchanged to U.S. dollars, found an average infant hospital stay cost of $4187, with a daily cost of $303 (15). Administering PT at home can be a cost-saving measure, reducing inpatient costs. Careful, and possibly more frequent outpatients may be required, but costs will still be reduced compared to inpatient stay.

Stratifying on hospital controlled for a number of other factors including race, insurance type, and other socioeconomic markers. Finding that the risk ratio for extended stay due to PT treatment did not differ significantly between hospitals indicates that these factors may not be involved in this relationship, which is unexpected. Further studies are necessary to determine if these findings are replicable.

There were several other limitations in our data. It is possible that longer hospital stays allow more time for jaundice to be identified and treated. Alternatively, the causative reason for longer stays among infants treated with PT may be PT itself. In addition, we also had limited data on bilirubin levels. We also did not have information on whether or not PT was administered prophylactically, or was medically indicated. Twenty-three of 137 infants (17%) that receive PT had bilirubin levels below the clinical level (5mg/dL) (1). Our data show that infants whose highest bilirubin measurements were sub-clinical had an average LOS of 3.43±2.90 days, which falls between mean LOS for infants who received PT and those who did not (see table 2). Infants who receive PT only prophylactically may have shorter durations of PT, and subsequently shorter lengths of stay compared to infants with a medical indication and need to lower bilirubin levels to a specific value. Very few infants who did not have PT had recorded bilirubin levels, and data was incomplete for many infants who did receive PT. Time of feeding initiation was a common covariate in LOS studies, but we had limited observations including that data. LOS was calculated based on date of birth and date of discharge, and rounded to full days, which leads to noise in models (16). Some of our models used as few as 416 observations due to missing data. Selection bias due to the limitations imposed on the cohort may also affect our findings.

Conclusions

All of our models estimated infants receiving PT had a greater than two-fold increase in likelihood of LOS beyond infants who did not receive PT. Important covariates differed between models, with the exception of mode of delivery, which was present in all final adjusted models. Cost analysis for PT, and possible cost-savings from home administration of PT are will be important, especially in light of insurance overhauls in the U.S. Further studies with more current data, and also those evaluating home PT are important to confirm the findings of this analysis. Long-term studies of potential long-term differences in outcomes may be of interest as well.

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Tables

Table 1. Risk factors for hyperbilirubinemia

Pre-discharge TSB or TcB in high-risk zone
Observed jaundice
Blood group incompatibilty
Preterm birth
Previous sibling jaundiced or received PT
Cephalohematoma or significant bruising
Exclusive breastfeeding
Poor feeding
Large weight loss after birth
East Asian race
Predischarge TSB or TcB in intermediate-risk zone
Macrosomic infant born to diabetic mother
Maternal age ≥25 years
Male gender

Sources (1, 2, 28)

Table 2. Patient Characteristics

	Total		Phototherapy		No Phototherapy	
	Mean	SD	Mean	SD	Mean	SD
Gestational age (weeks)	38.8	1.5	38.2	1.9	39.0	1.4
Birthweight (g)	2885.2	576.7	2663.5	620.3	2925.7	558.7
APGAR 5 minute	8.9	0.5	8.8	0.7	8.9	0.5
Highest bilirubin measure (mg/dL)	9.6	4.3	9.8	4.4	9.2*	4.3
Length of hospital stay (days)	2.7	2.4	5.0	3.7	2.3	1.8
	Count	Percent	Count	Percent	Count	Percent
<5% BW for gestational age	285	33.5	56	19.6	229	80.4
5-10% BW for gestational age	261	30.7	36	13.8	225	86.2
10-90% BW for gestational age	249	29.3	33	13.3	215	86.7
>90% BW for gestational age	56	6.6	9	16.1	47	83.9
Hospital 1	455	53.5	49	10.8	405	89.2
Hospital 2	396	46.5	85	21.5	311	78.5
Female	417	49.0	61	14.7	355	85.3
Male	434	51.0	73	16.8	361	83.2
Vaginal birth	672	79.2	98	14.6	574	85.4
C-section birth	177	20.9	36	20.5	140	79.5
Breastfed	273	41.5	24	8.8	249	91.2
Bottle-fed	385	58.5	71	18.4	314	81.6
Term nursery	642	92.2	74	68.5	568	96.6
Intermediate/ preterm nursery	54	7.8	34	31.5	20	3.4
Phototherapy	137	15.4				

*Only 37 infants without PT had bilirubin measurement

Table 3. Phototherapy risk by patient group with risk ratios and 95% confidence intervals

	PT risk	Risk Ratio	95% CI	
<34 completed weeks	1.00	28.97	10.59	79.29
34-36 completed weeks	0.43	5.38	3.25	8.90
≥37 completed weeks	0.13	1.00		
<5th percentile birthweight	0.20	1.43	0.96	2.13
5-10th percentile birthweight	0.14	1.20	0.98	1.46
10-90th percentile birthweight	0.13	1.00		
>90th percentile birthweight	0.16	1.72	0.94	3.11
Breastfed	0.09	1.00		
Bottle-fed	0.18	1.76	1.29	2.40
Hospital 1	0.11	1.00		
Hospital 2	0.21	2.26	1.54	3.31
Normal skin exam	0.12	1.00		
Abnormal skin exam	0.20	1.87	1.29	2.70
Term nursery	0.12	1.00		
Intermediate/ preterm nursery	0.63	13.05	7.14	23.85
Apgar5 <9	0.26	1.83	0.98	3.39
Apgar5 ≥9	0.16	1.00		

*Only 3 infants were born <37 weeks, all received PT

Table 4. Hazard ratios and respective 95% confidence intervals for selected models.

	HR	95% CI	
Model 1: Heaviside model divided at 5 days, stratified on hospital, adjusted for phototherapy, nursery unit, interaction between nursery unit and time, 5-minuta Apgar score, mode of delivery, and interaction between mode of delivery and time	2.60	1.92	4.20
Model 2: Heaviside model divided at 5 days, stratified on hospital, adjusted for phototherapy, gestational age, feeding type, mode of delivery, interaction between mode of delivery and time	2.80	1.08	3.62
Model 3: Hospital 1, adjusted for phototherapy, gestational age, and mode of delivery	2.53	1.81	3.53
Model 4: Hospital 2, adjusted for phototherapy, nursery unit, mode of delivery, and interaction between mode of delivery and time	2.34	1.74	3.15

Figures

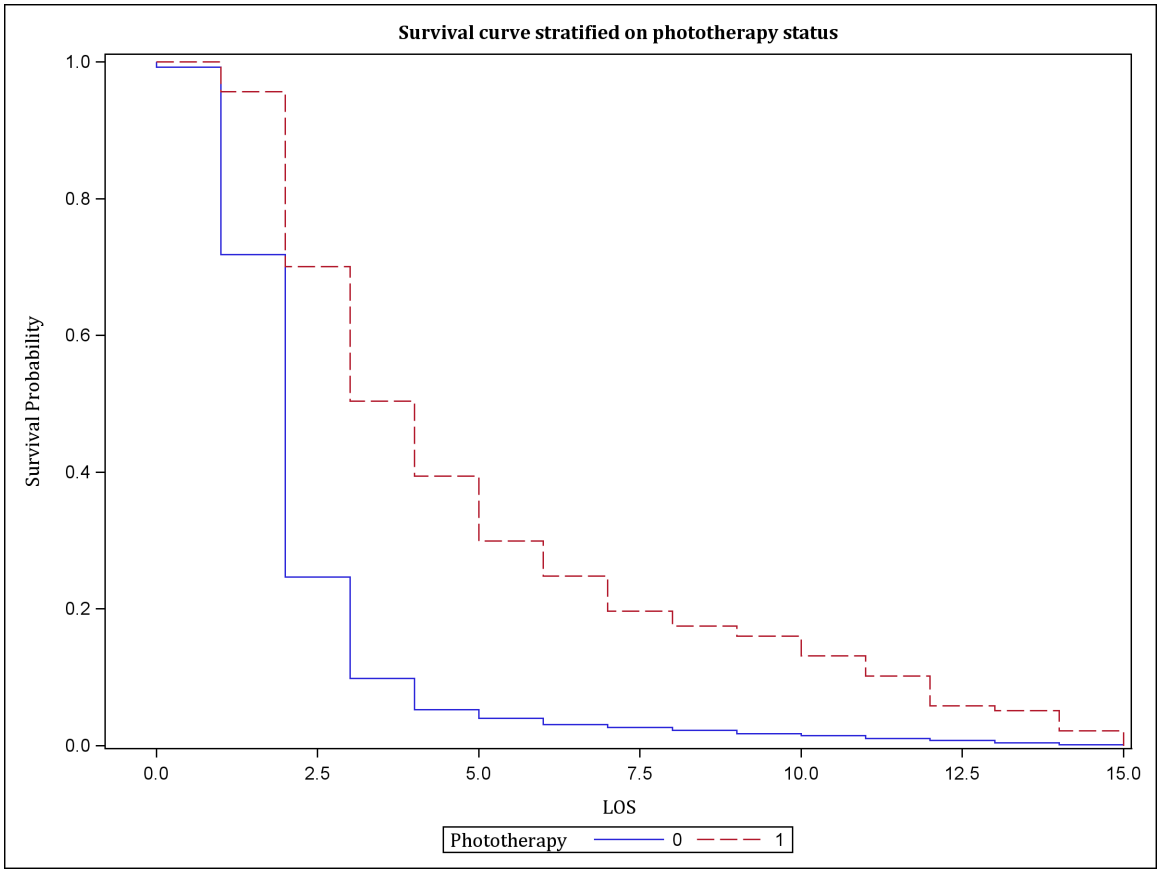

Figure 1. Kaplan-Meier survival curve stratified on phototherapy status. Log-rank statistic=114.0, $p<0.01$.

Chapter III: Implications & Future Research

Implications

There is considerable literature investigating various aspects of hyperbilirubinemia and phototherapy (PT) in neonates. However, the effect of PT administration on infant length of hospital stay (LOS) has not been quantified until now. In our cohort, 137 (15%) of infants received PT. Infants who received PT were had a mean LOS of 5.0±3.7 days compared to 2.3±1.8 days for untreated infants. Kaplan-Meier survival curves and Wilcoxon statistic ($p<0.01$) confirmed significant differences in LOS between infants who received PT and those who did not.

Using survival analysis, we found that infants who received PT had a significantly higher likelihood of longer hospital stays when compared to infants who did not receive PT (HR 2.60, 95% CI: 1.92, 4.20) after controlling for significant covariates. While this result may not be surprising, it is important to know how greatly LOS is affected for infants who receive PT. A number of sociodemographic factors including insurance type, race, and income, were adjusted for by stratifying on hospital of birth. There was little difference in hazard ratios when we evaluated the relationship in each hospital independently, suggesting that these sociodemographic variables may not play an important role between PT and LOS.

As practices evolve, home PT treatment may become more commonplace for infants who otherwise healthy aside from hyperbilirubinemia requiring PT.

Home administration may help drive down some of the costs associated with neonatal hospitalizations, especially among preterm infants who are at greater risk for hyperbilirubinemia, and tend to have more lengthy and expensive hospital stays.

Future research

Specific methods used to administer PT were not available in our data, nor did we have quality data on the duration of PT for treated infants. Future research should investigate whether different types of lights affect LOS differently. Further studies may also evaluate the roles that insurance type, race, and other sociodemographic variables may play. While stratifying on hospital in our study effectually controlled for these variables, we were unable to isolate the individual effects each may or may not have on the relationship between PT and LOS.