DEVELOPING CLINICAL DECISION SUPPORT FOR MANAGEMENT OF NEONATAL HYPERBILIRUBINEMIA

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CERTIFICATE OF APPROVAL

This is to certify that the Master's capstone project of

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TABLE OF CONTENTS

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ABSTRACT

Neonatal hyperbilirubinemia is a universal healthcare problem in pediatrics that often requires time-sensitive treatment to prevent irreversible neurologic sequelae. Although providers have guidelines for the effective management of neonatal hyperbilirubinemia, there is great variation in the proper execution of these guidelines. Clinical decision support systems embedded into electronic health records have been shown to improve clinician adherence to guidelines and improve patient care. This capstone project outlines how to develop such a clinical decision support system for the management of neonatal hyperbilirubinemia in the emergency department and inpatient settings. To develop the system, the current guidelines and institutional clinical pathways and workflows were reviewed, and then use cases, Boolean logic and test cases were designed. The results of this capstone project provide a blueprint for the development of an electronic decision support tool. The challenges of putting this tool into practice and next steps for extending this work are also discussed.

INTRODUCTION

Neonatal hyperbilirubinemia is a universal healthcare problem that can lead to development of jaundice and in severe cases may require treatment to prevent neurologic sequelae such as acute bilirubin encephalopathy and kernicterus. Guidelines for the management of neonatal hyperbilirubinemia exist, but there are published reports of poor clinical adherence to the guidelines. At my home institution, The Children's Hospital of Philadelphia, there is also variation in how well providers interpret and apply these guidelines with regards to initiation and discontinuation of phototherapy. This variation has important effects on patient care, including hospital length of stay and appropriate resource utilization. For my capstone project, I explored how to develop a clinical decision support intervention to assist in the management of neonatal hyperbilirubinemia in the emergency department and inpatient settings.

BACKGROUND

Neonatal hyperbilirubinemia is a condition that affects many newborns during the first few weeks of life. It is the result of an imbalance between a newborn infant's increased bilirubin production and impaired excretion, leading to a net excess of bilirubin in the body. This elevated level of bilirubin leads to the yellowing of the skin and other tissues such as the eyes that is commonly referred to as jaundice.

It is estimated that 60% of term infants and 80% of preterm infants will have visible jaundice in the first week of life.[1] The vast majority of these infants will have physiologic jaundice, which is a benign and transient hyperbilirubinemia that usually does not require any treatment. However, other infants will have pathologic jaundice, which will require intervention. In the year 2012 there were 37,832 emergency department (ED) visits and 13,843 hospital admissions in the United States with a principal diagnosis of neonatal hyperbilirubinemia.[2]

Pathologic jaundice can be due to multiple conditions that affect the balance of bilirubin metabolism. Most cases are due to either increased bilirubin production, decreased hepatic uptake as the liver is the main site of bilirubin metabolism, impaired metabolism of bilirubin by the liver, and increased enterohepatic circulation wherein the body reabsorbs bilirubin before it can be excreted.[3] Increased bilirubin production typically comes from the breakdown of red blood cells (RBCs) as bilirubin is a byproduct of hemoglobin degradation, and infants are at higher risk given their increased mass of RBCs, the shorter lifespan of their RBCs,

and the risk of blood type incompatibility issues between mother and infant leading to hemolysis.[4]

The consequence of allowing pathologic jaundice to go untreated is increased risk of severe neurologic sequelae. At high levels, bilirubin overwhelms the ability of the blood's albumin to bind it, allowing the unbound bilirubin to cross the blood-brain-barrier and stain the brainstem nuclei and cerebellum with bilirubin.[5] The neurotoxic effects of bilirubin on the brain can lead to acute bilirubin encephalopathy, and then possibly the chronic, permanent sequelae known as kernicterus. Kernicterus is often fatal in infancy and leaves any survivors neurologically devastated with neurologic signs like movement disorders resembling cerebral palsy, mental retardation, and hearing loss. Fortunately, kernicterus is very rare, with a US Kernicterus Registry only listing 125 voluntarily reported cases between 1992 to 2004.[6] Worldwide incidence of kernicterus is reported to vary anywhere from 1/43,000 to 1/150,000 lives births.[7]

When an infant's degree of jaundice requires intervention, treatments capable of decreasing bilirubin levels include phototherapy and exchange transfusion. Phototherapy involves exposing the patient to blue light that is absorbed by the yellow pigment of bilirubin and converts it into the water-soluble lumirubin that can be excreted in the urine or bile without having to be metabolized by the liver.[8] Phototherapy's effectiveness has led it to become the main form of therapy, though in emergent cases that require rapid removal of bilirubin from the body, exchange transfusion is still used. Initially the first effective therapy for hyperbilirubinemia,

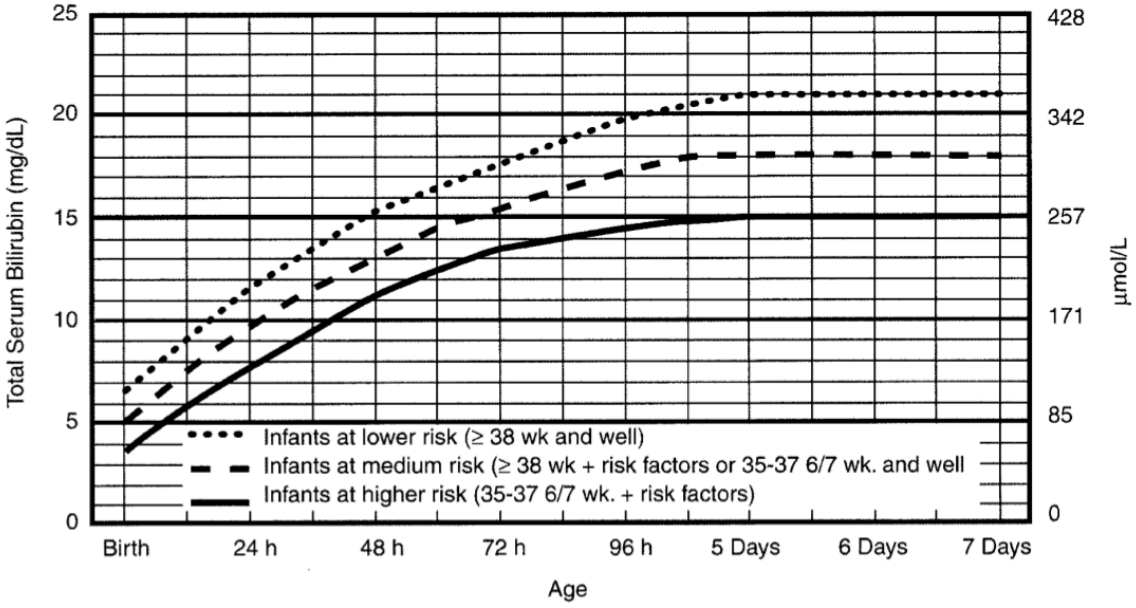
exchange transfusion is a much more invasive procedure that requires removal of the patient's blood in small aliquots with simultaneous replacement with new donor blood.[3]

Current Guidelines for Managing Neonatal Hyperbilirubinemia

The American Academy of Pediatrics (AAP) Subcommittee on Hyperbilirubinemia published the current guidelines on the management of hyperbilirubinemia in the newborn in 2004.[5] These guidelines factor in an infant's gestational age, current hours of life since birth and clinical risk factors to determine the next appropriate steps in management for the patient for a given total serum bilirubin level. Clinical risk factors that are potential contributors to elevated bilirubin levels include isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase deficiency, asphyxia, lethargy, temperature instability, sepsis, acidosis, and low albumin levels. Interpretation of a bilirubin lab value is then achieved by plotting the value on the appropriate nomogram. With regards to treatment decisions, there are separate nomograms for determining the treatment thresholds for phototherapy and exchange transfusion. The phototherapy nomogram is shown below in Figure 1.

Interpretation of this phototherapy nomogram requires the provider to plot the total serum bilirubin lab value against the patient's age in hours at the time the lab was drawn. The provider then chooses the appropriate curve on the nomogram based on the patient's gestational age and if they have any of the previously mentioned risk factors—the presence of any risk factor lowers the threshold at

Figure 1. Phototherapy nomogram in hospitalized infants of ≥35 weeks' gestation



which phototherapy should be initiated. If the total serum bilirubin value exceeds the appropriate curve for that patient, then phototherapy should be initiated. The nomogram for exchange transfusion is similarly shaped but the thresholds are higher than those for the phototherapy, in keeping with its use in more severe cases of hyperbilirubinemia.

Phototherapy should then be continued until the patient's total serum bilirubin value is reduced to below 13 to 14 mg/dL, at which point it can be discontinued. After discontinuing phototherapy, one would expected that a subsequent bilirubin lab value will rebound and be higher than the last value obtained while still on phototherapy. Many providers tend to check a rebound level 6-12 hours after stopping phototherapy, but the guidelines do not recommend delaying discharge to wait for a rebound value.[9] Furthermore, follow-up bilirubin measurement is only

recommended if the patient is less than 3 to 4 days of old at time of discharge or has evidence of hemolytic disease.

These current AAP guidelines were an update to previous guidelines released in 1994 in response to increased reports of kernicterus.[6] This was attributed to data from the 1980s and 1990s that suggested providers were possibly too aggressive in their treatment of hyperbilirubinemia, as well as a push for earlier hospital discharges for newborns that reduced opportunities for early detection of jaundice. Both of these factors contributed to providers being less aggressive in their evaluation and treatment of hyperbilirubinemia.[3,4]

Despite the existence of AAP guidelines on management of neonatal hyperbilirubinemia for over 20 years, there are multiple reports that providers continue to have poor adherence to them. One study examining provider adherence to the 1994 AAP guidelines in the two year period from 1995 to 1996 showed that only 54% of term infants with hyperbilirubinemia received recommended phototherapy at their hospital.[10] A larger study that examined provider adherence over a 12 ½ year period from 1995 to 2007, spanning the periods of both guidelines, showed decreased rates of severe hyperbilirubinemia with a shift towards the majority of infants in their cohort receiving appropriate phototherapy after 2003, but also increasing rates of inappropriate phototherapy use at sub-threshold bilirubin levels.[11]

It is concerning that failure to follow to the guidelines can lead not only to missed opportunities to treat hyperbilirubinemia but also inappropriate admissions for

treatment. Inpatient treatment of these infants should be done only when necessary and as efficiently as possible. These patients, in their first weeks of life, are at higher risk for nosocomial infection owing to the immaturity of their immune systems and lack of protection from their unimmunized status. Treatment using phototherapy is also not without risk as it involves blue light that is capable of causing retinal damage in with prolonged exposure.[12] As a precaution, eye covers are provided as standard prophylaxis for newborns to minimize this risk. Length of hospitalization can also increase parental anxiety and strain on families. Minimizing time under phototherapy and length of stay in hospital thus has multiple benefits beyond just mere cost of care savings.

A Role for Clinical Decision Support

The challenge of getting providers to adhere to clinical guidelines is not unique to the AAP's neonatal hyperbilirubinemia guidelines. A review of potential barriers to provider adherence to guidelines highlights 7 main barriers: lack of awareness, lack of familiarity, lack of agreement, lack of self-efficacy, lack of outcome expectancy, inertia of previous practice and external barriers such as lack of time to access them or absence of reminders to use them.[13] To use the AAP guidelines, a provider must calculate the patient's hours of life at the time every bilirubin lab is drawn, as well as the total serum bilirubin since labs typically report them as two separate components, a direct and an indirect bilirubin. They must then choose the appropriate nomogram and use it correctly, factoring in the gestational age and any clinical risk factors to pick the right threshold for their patient. All of these steps

take time, adding to the challenge of appropriately following the guideline and increasing the opportunities for human error.

One possible way to assist providers in the adherence of the guidelines is to leverage potential capabilities of clinical decision support (CDS) tools in the electronic health record (EHR). CDS tools are able to present clinicians with "knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care."[14] Such a tool would be able to follow programmed rules to retrieve pertinent clinical data and offer it to the clinician to aid in diagnostic or therapeutic decision-making. These CDS tools can take many forms, including reminders for preventative care, alerts to prevent potential adverse events (e.g. drug allergies, drug-drug interactions) or critical results, as well as clinical guideline interpretation.

Such guideline integration into a CDS tool could involve developing alerts to automatically identify patients in clinical situations where a potential guideline might be applicable and then offering recommendations based on the guideline for next steps in patient management such as orders for diagnostic testing or treatment. Reviews of different guideline implementations have shown that such electronic implementations of guidelines can increase guideline adherence and improve clinical outcomes.[15,16] In pediatrics specifically, successful examples of EHR embedded CDS interpreting complex guidelines for providers include interpretation of immunization schedules and asthma guidelines, both of which showed improvements in care delivery.[17,18] The example of CDS for immunizations

schedules in particular highlights the ability of CDS to perform calculations of dates between past immunizations to determine when future immunizations should occur, which not only saves providers time but also reduces the chance for human error of giving a vaccine off schedule.

Given the demonstrated abilities of CDS tools to use existing data in the EHR to follow clinical guidelines, there is potential to assist providers with the AAP guidelines for neonatal hyperbilirubinemia with regards to performing the calculations for age in hours and total serum bilirubin, as well as display all of the bilirubin data on the nomogram itself. The ability to visualize the nomogram in the EHR would give any recommendations familiar context and allow the provider to see the natural history of the patient's course of hyperbilirubinemia.

The State of CDS Tools for Neonatal Hyperbilirubinemia

There are currently several examples of electronic CDS tools to assist in management of neonatal hyperbilirubinemia. These efforts have mainly focused on the simplifying the interpretation of the nomograms for determining whether or not to initiate treatment. The simplest tools are websites with calculators that accept data from a single time point about the patient's age and total bilirubin value, and then outputs information about the patient's risk for developing severe hyperbilirubinemia or thresholds for initiating treatment by phototherapy or exchange transfusion.[19,20] Some websites even provide the ability to see the data plotted on the nomograms and offer recommendations usually based on that single time point.[21,22] Such website tools are easily accessible and free to use, and some

even provide applications for smart phones for offline use. The only peer-reviewed publications about such websites involves BiliTool, which described the development of their tool and survey showing high user approval of the tool, but no evidence of improved patient outcomes or provider guideline adherence.[23]

A major limitation of these website tools is that some still require the user to perform time calculations as well as manual entry of data. The BiliTool does have a way to embed a hyperlink within certain commercial EHRs that can pass a single bilirubin value and the patient's age in hours at time of lab collection to simplify data entry.[24] Embedding the CDS tool within the EHR would have several advantages beyond simplifying data entry, including the ability to offer the tool to the provider in the right clinical context, overcoming the potential guideline adherence barriers of lack of awareness of guidelines and other external barriers such as lack of time.

Two such EHR embedded CDS tools for neonatal hyperbilirubinemia were presented in the last five years at the annual Epic User Group Meeting. The first tool, developed by a group at Kaiser Permanente and presented in 2009, provided single lab value interpretations as part of the bilirubin result and as well as alerts if patient should be on phototherapy or is at risk for developing severe hyperbilirubinemia.[25] It behaved similarly to the website tools but with the ability to offer reminders to providers. More recently, in 2014, another tool developed at the Beaumont Health System was the first to display the bilirubin nomograms in the EHR and offer recommendations based upon the most recent time point.[26] The Beaumont CDS tool

thus provided a way to visualize multiple time points of data, but still only provided decision support on the initiation of phototherapy with future plans to provide follow up guidelines on infant discharge and when to discontinue therapy.

My institution, The Children's Hospital of Philadelphia, has its own method for embedding CDS tools within our Epic EHR system (Verona, WI). This system, called the Care Assistant, uses a web-service approach that functions as a secure website displayed within the EHR but functioning independently of the EHR.[27] The Care Assistant is able to use patient EHR data, such as age, history and laboratory results, as input for many different types of CDS to drive highly tailored care recommendations. Since 2006, this tool has been used at my institution to deliver decision support for immunization administration, asthma care, and otitis media management.[17,18,28,29]

The goal of this capstone project is to conceptualize a CDS tool that can be embedded in our hospital's EHR system to assist providers in the ED and inpatient services with management of hyperbilirubinemia. This Bili Assistant will focus on supporting the use of phototherapy, as treatment by exchange transfusion is a much less frequent event and requires close management by critical care providers without clear guidelines. In addition to providing interpretation of bilirubin values, the tool would seek to provide specific recommendations not only about initiation of therapy, but also when to discontinue therapy.

METHODS

In beginning to develop this hyperbilirubinemia CDS tool, feedback was obtained through discussions with other pediatric clinical informaticians and two neonatal intensive care unit (NICU) physician experts. These clinicians provided insight into the management of hyperbilirubinemia in our hospital's outpatient, emergency department (ED), inpatient and NICU settings. The goal was to determine what decisions the providers would need assistance with, and what information would be provided to them.

When first deciding where this tool might be useful to providers, the typical flow of care of these patients was considered. Typically, a jaundiced infant is first seen in the outpatient primary care setting where testing can occur, and then may be referred to the ED for testing and possibly admission to hospital for treatment. Although there was an identified need for decision support to help outpatient providers determine if patients should be referred to the ED or not, once sent to an ED the patients would always be tested again, regardless of what an initial outpatient bilirubin value showed. Furthermore, the outpatient settings are not consistent in how bilirubin levels are tested, some using blood serum test results and others using transcutaneous bilirubin testing, which approximates the blood serum results but are not supposed to be used to base management decisions (e.g. a high transcutaneous bilirubin value should prompt a blood serum test). Thus, since the treatment decisions would begin based on the ED test result, this tool would not

be developed for the outpatient setting. For the scope of this project, only ED and inpatient settings were considered eligible for this CDS tool.

Review of Current Guidelines and Approaches

To determine the functions of this hyperbilirubinemia CDS tool, the current AAP guidelines for management of hyperbilirubinemia were examined to determine actionable steps that could be incorporated into a CDS tool. Furthermore, the current CHOP ED pathway was considered to ensure the tool followed currently agreed upon standards of care at the hospital. Current inpatient workflow was also considered when developing the CDS tool's recommendations.

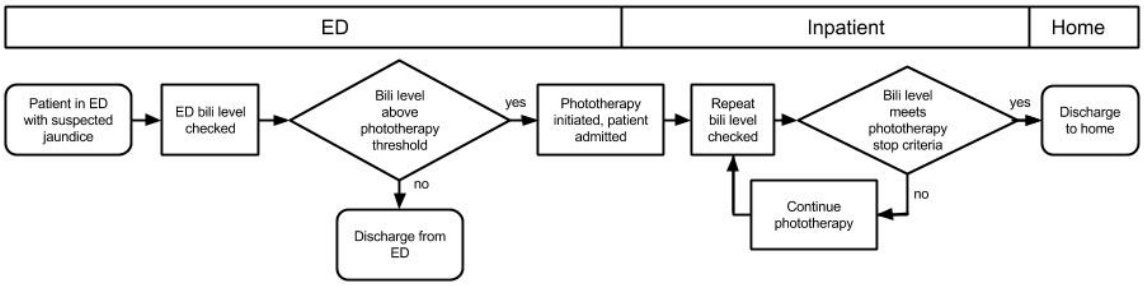
Develop Materials for CDS Tool Development

After discussions with other pediatric clinical informaticians, and review of the current AAP guidelines and existing CHOP pathway, the goal was to produce use cases, Boolean logic and test case scenarios. The use cases were used to outline the steps to be taken for the patient scenarios this tool would be expected to manage. The Boolean logic provides logic to define how the tool will be activated, what decisions must be made and the subsequent actions that should be taken. Test cases follow the use case scenarios and demonstrate the outcomes of the Boolean logic and were validated by review with another pediatric clinical informatician.

RESULTS

In a series of group and one-on-one meetings with other pediatricians and informaticians, we reviewed the current practices of hyperbilirubinemia management at our institution. As recently as 2011, the ED had sought to improve its performance in the care of neonatal hyperbilirubinemia given historical delays in obtaining initial labs and initiation of phototherapy, and so developed a clinical pathway for the ED's management of hyperbilirubinemia.[30] Since the resulting ED pathway was considered the consensus of the ED and NICU physicians, this provided a useful starting point for discussing management of patients after admission since there is not currently a similar pathway for the inpatient management of hyperbilirubinemia. From these discussions, the typical path of a patient through presentation with suspected jaundice to the ED, admission for phototherapy and discharge to home, is briefly outlined in Figure 2.

Figure 2. Process map of patient with hyperbilirubinemia being admitted for phototherapy



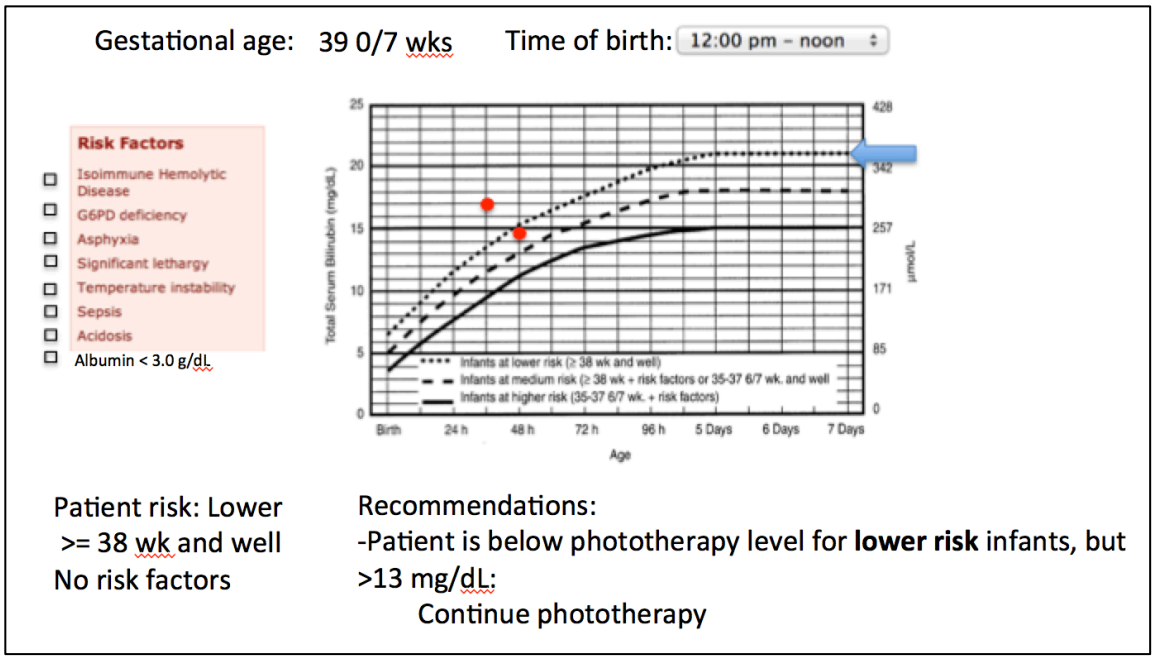
One of the first decisions to result from these discussions was that entry eligibility criteria for the Bili Assistant should be restricted to patients under 21 days of age and greater than 35 weeks gestational age in keeping with the ED pathway. Hyperbilirubinemia seen beyond 21 days of age is more likely to be of pathologic causes that are not amenable to phototherapy and would require more diagnostic work-up beyond the scope of this CDS tool. Infants under 35 weeks gestational age were restricted as the AAP guideline's nomograms were not validated on children under 35 weeks gestational age.[5] It was also decided that the Bili Assistant should only be used outside the NICU, given that patients requiring NICU level management of hyperbilirubinemia were often sicker and might require initiation of exchange transfusion, which is less frequently used compared to phototherapy.

The group identified the some challenges for a hyperbilirubinemia CDS tool in the context of our local EHR and institutional workflows. A major challenge is the lack of a standard place to discretely capture the time of birth, which is involved in determining the patient's age in terms of hours of life, as well as interpreting bilirubin values on the appropriate nomogram. As a standalone children's hospital, our institution does not typically deliver babies and does not follow the Epic EHR's recommended place to store the time of birth, which is a nursing flowsheet row. Instead, the time of birth is recorded in provider notes based on birth hospital discharge papers or parent recall, and this documentation is not stored in a uniform location in the EHR. This makes it impossible for the EHR to automatically use the time of birth in calculations, and would require a provider to input this data in the Bili Assistant.

Another challenge is the poor documentation of patient risk factors used in bilirubin interpretation. As previously mentioned, there are eight potential risk factors that are associated with elevated bilirubin levels, and though some can be explicitly evaluated based on numeric laboratory data (e.g. acidosis, low albumin levels), others are vaguely defined clinical terms (e.g. asphyxia, lethargy, temperature instability). Such clinical terms would likely only be mentioned in a provider notes, and possibly in multiple different ways: temperature instability could be described as fever or hypothermia. Providers agreed that it would be useful to document the specific risk factors identified for the patient to know which ones were being used to interpret bilirubin values.

In discussing potential features the Bili Assistant should have, providers thus thought that a standard place to see and record the time of birth as well as any risk factors would be very useful to overcome the aforementioned challenges. Another desired feature was the graphical display of bilirubin values on the appropriate nomogram with clear identification of which nomogram curve applied to the patient. Such visualization of the bilirubin values in the familiar context of the nomograms was felt to give a provider rapid understanding of how the patient's hyperbilirubinemia was progressing. Finally, the group also suggested explicit recommendations on next steps to take after each bilirubin result, recommendations based on the current ED hyperbilirubinemia pathway and elements of the AAP guidelines. Figure 3 is an example of one low fidelity mockup of a possible Bili Assistant.

Figure 3. Mockup of a possible Bili Assistant used in group discussions



This mockup illustrates some of the features mentioned by the group: visible birth information (gestational age and time of birth), a listing of risk factors, display of the bilirubin values on a nomogram, an indication of which nomogram curve should be used (blue arrow), and the provision of recommendations based on the bilirubin values.

Use Cases

To help define the behavior of the Bili Assistant, use cases were developed based on the most common patient scenarios (see Appendix A). The first use case is of a new patient in the ED, which would require the Bili Assistant to determine patient eligibility criteria, obtain all pertinent patient information to interpret a bilirubin value from that encounter, and display the patient's bilirubin values in the

appropriate context. The end result of this ED encounter would be a decision to discharge the patient to home, admit for phototherapy or admit to the NICU for possible exchange transfusion or other management. The second use case would be a patient that was admitted on phototherapy and provides recommendations for the interpretation of subsequent bilirubin values until the bilirubin value is below the phototherapy stop threshold or is transferred to the NICU. The third use case is for the patient who returns the ED after previously being hospitalized for phototherapy. Although this is a not a common occurrence, this can be associated with hemolytic disease or other pathologic cause of jaundice.[31] As such, providers should be alerted that these patients may require additional diagnostic work-up if they return to the hospital.

Boolean Logic

With the use cases in hand, the Boolean logic that would drive the Bili Assistant was developed. As mentioned with the use cases, key decision points focus upon triggering the Bili Assistant, interpretation of the first bilirubin value to determine discharge versus admission for therapy, and interpretation of subsequent bilirubin values to determine discharge or different therapies. Appendix B contains the Boolean logic and Appendix C has diagrams showing the flow of the logic between functions outlined in Appendix B.

Reviewing the AAP guidelines, one of the key actionable steps is interpretation of bilirubin values in the context of the appropriate nomogram for phototherapy or exchange transfusion. This presents the challenge of transforming each nomogram

into data structures like a table with of the bilirubin value associated with a specific hour of life and the nomogram curve (low, medium or high). The AAP guideline only provides these values as nomogram, without a table of raw data values. An attempt to obtain the values from Dr. Bhutani, the investigator who developed the values, and the AAP were both unsuccessful. Without access the original data, another method would be to use high resolution scans of the nomograms and digitize them to obtain the (x, y)-data for each curve to the nearest hour. To compare the performance of such digitization, the values could be compared to those from existing bilirubin calculators such as BiliTool.

Other actionable steps for patients admitted on phototherapy involved when to consider hemolysis and when to discharge the patient to home in the 'Follow-up Treatment Recommendation' function. In discussion with NICU experts, if subsequent bilirubin values while on phototherapy were stable or rising—though not to exchange transfusion levels—then this should prompt consideration of a Hematology consult in case the patient is undergoing hemolysis. For when to discharge home, the AAP guideline's Appendix 2 recommendation that phototherapy be stopped at bilirubin values between 13 to 14 mg/dL without need for rebound was interpreted as recommending discontinuation of phototherapy when the value is less than or equal to 13 mg/dL.[5]

Test Cases

To assess the Boolean logic and to provide test scenarios for the Bili Assistant, a number of test cases were developed. These test cases assessed the logic's ability to

handle multiple different patient scenarios, testing the Boolean logic on the eligibility criteria and different patient dispositions (e.g. discharge from ED to home, admission to NICU for exchange transfusion, admission for phototherapy, etc.). The test cases would also involve patients with different risk factors to confirm that the appropriate nomogram was being used in each case. See Appendix D for a collection of eight potential test cases with expected variable results. More test cases should be developed in a similar fashion to test edge cases (e.g. patient with 35 0/7 weeks gestational age or a patient's bilirubin level is equal to a threshold value) to see how the Bili Assistant behaves.

DISCUSSION

The conceptualization of the Bili Assistant CDS tool involved multiple steps, from working with pediatric clinical informaticians and NICU experts to decide on the appropriate scope of the tool and how it would fit into our institution's workflow, and then developing common use cases, the logic to drive the tool and test cases to test it. An effective CDS tool should ideally follow Osheroff's 5 rights of CDS: it should present the right information, to the right person, in the right format, by the right channel, at the right time.[32] The proposed Bili Assistant meets these rights and this is how it derives its advantages over existing bilirubin CDS tools.

The main potential advantage of the Bili Assistant over other bilirubin CDS tools is its integration into the EHR. By not requiring providers to leave the EHR to transcribe portions of the relevant clinical data into a separate website or mobile phone application, the Bili Assistant provides can present CDS to the without them having to seek it out. In this way, the Bili Assistant can show clinical information about patient-specific interpretation of the bilirubin value to the provider in the context of the EHR they are already working in, and via the familiar context of the nomogram with recommendations as soon as the lab value is available. Not only would the Bili Assistant be more time efficient by acting on clinical data as it became available, but it could also improve safety by avoiding calculation and transcription errors. Allowing the Bili Assistant to perform all hours of life calculations and plotting bilirubin results internally could help avoid calculation errors, as well as

avoid potential transcription errors if the provider wrote the wrong dates, times or bilirubin values into an external CDS tool.

Another benefit of the Bili Assistant approach is that it provides a longitudinal record of bilirubin values in the context of the nomogram to facilitate provider understanding of patient's course of care. Compared to the other bilirubin CDS tools that only offer interpretation of single bilirubin values at one point in time, providers would be able to see and interpret bilirubin values in the context of the nomogram that they are already familiar with from their training and recognize trends more readily than looking at lab values in numeric format alone. Seeing trends of rapid rise or fall in the bilirubin levels, as well as quickly extrapolating the next bilirubin value from the previous points, could help providers quickly identify which patients are or are not responding to treatment and help them prepare for next steps of care.

Although visualization of the bilirubin values on the appropriate nomogram would be expected to provide the necessary information for providers to care for patients with hyperbilirubinemia, the Bili Assistant's ability to provide specific recommendations might be even more important. A study examining clinician adherence to phototherapy guidelines at two hospitals showed that even when providers had ready access to the phototherapy nomogram in the chart, in 56% of cases phototherapy was delivered when it was in the sub-threshold "optional" range, and in 8% of cases when phototherapy was unnecessary.[33] Although phototherapy itself is considered safe, such excessive use of it can increase hospital

lengths of stay and other costs of care as previously noted. While it was unclear in this study if providers were misinterpreting the nomogram or just being more conservative, it is possible that specific recommendations supported by the institution on how to interpret bilirubin values for decisions of initiating specific treatments, when to seek advice from the NICU, and when to discontinue phototherapy could lead to better adherence to the guidelines.

In conceptualizing the tool, major challenges were also uncovered. The most readily evident challenge is the lack of standard documentation of time of birth in our EHR. Although this information can be obtained from the parents or discharge papers from the birth hospital, it is usually stored in the free text of notes. As it was considered unlikely that nurses and physicians could be expected to document the time of birth in the recommended location in our EHR, the Bili Assistant was expected to accept provider input directly, which could be subject to transcription errors.. The difficulty to recover from such an entry error is another major challenge for the Bili Assistant tool. All of the interpretations of bilirubin values rely upon knowing an accurate time of birth, and if this is entered incorrectly it can lead to incorrect recommendations of care. If the patient's time of birth is actually earlier than the time used (i.e. patient is older than expected), the bilirubin values would need to be shifted to the right on the nomogram, which could mean these values might fall below threshold for phototherapy initiation and a patient might be inappropriately started on phototherapy. On the other hand, if the time of birth is actually later than the time used (i.e. patient younger than expected), the bilirubin values will be shifted to the left on nomogram, which could mean bilirubin values

are actually above the phototherapy threshold and a patient could be discharged to home when they actually needed admission for phototherapy.

A similar consequence of erroneous data entry is seen with risk factor identification. If a provider failed to identify one of the eight risk factors that can contribute to elevated bilirubin values, it would lead to the use of a lower risk nomogram curve (i.e. higher threshold for starting phototherapy), potentially leading to failure to initiate phototherapy when it was needed. Conversely, if the provider incorrectly assigned a risk factor the patient did not have, this would lead to use of a higher risk nomogram curve (i.e. lower threshold for starting phototherapy), potentially leading to inappropriate admission and initiation of phototherapy.

Such errors were considered to be unlikely events by the pediatric informaticians and NICU experts, but if they occurred they could have serious consequences if patients fail to receive recommended treatments. It is difficult for the proposed Bili Assistant in its current state to recover from such errors as the decisions all begin with how the first encounter bilirubin is interpreted. If only one bilirubin existed by the time the error was detected, the provider could just update the time of birth and risk factors, and the system would be able to reinterpret the single value appropriately. However, if the patient has been admitted for phototherapy and the error is not realized until multiple subsequent bilirubin values have been drawn, the question of how the system recover is more complicated. Logic would have to be developed to reinterpret the first bilirubin value again in the context of the corrected patient information. If the recommendation was still that the patient

would be receiving the same treatment, the system could continue to function and interpret the subsequent bilirubin values until the bilirubin value decreased to the stop threshold. However, if interpretation of the first bilirubin indicated that therapy should not have been initiated, then therapy should be stopped and the patient potentially discharged to home.

In addition to these challenges, limitations of this work include the ability to generalize it to other hospitals, even if they are on the same EHR system. The Care Assistant requires significant customization of the Epic EHR by experienced software developers, and a hospital lacking such support staff would not be able to introduce it. It also has not yet been implemented in any EHR other than Epic. Apart from the technical hurdles, the idiosyncrasies of another institution's existing workflows or clinical pathway for the management of neonatal hyperbilirubinemia may make the recommendations of the Bili Assistant inconsistent with standard of care. For example, the hospital may have adopted a different interpretation of some of the AAP guidelines recommendation and thus take more liberal or conservative approaches to some of the decisions outlined in the Bili Assistant's logic. However, this could be overcome by locally changing threshold values or recommendations to match those of the institution's current workflows.

Potential future directions to extend this work conceptualizing the Bili Assistant begins with exploring institutional or external funding support for software developer time to actually program this tool into the EHR. While waiting for development of the Bili Assistant, elements of the logic for the inpatient

management of neonatal hyperbilirubinemia will be used to develop an inpatient clinical pathway, starting in the fall of 2015. Once the Bili Assistant is developed, it could then provide EHR-embedded CDS to supplement the clinical pathway. This would also provide an opportunity to study how the introduction of the pathway could change clinical performance managing neonatal hyperbilirubinemia over time, starting with establishment of the clinical pathway and dissemination of knowledge about the pathway to providers, and then seeing how that compares to when the EHR-embedded CDS tool is introduced.

Other future work could involve extending the logic further, such as including recommendations for the frequency of checking bilirubin values during the inpatient admission, which is currently left to the discretion of providers. The AAP guideline provides an example clinical pathway with suggestions for how often to check bilirubin values, but there are no studies examining frequency of inpatient bilirubin testing to provide evidence for these suggestions.[5] Further expansion of the Bili Assistant's capabilities would be to extend it to the outpatient setting to help with the interpretation of serum bilirubin values to make the initial decision to refer patients to the ED or for possible direct admission to the hospital.

CONCLUSIONS

The management of inpatient hyperbilirubinemia is a complex process that could benefit from an EHR-embedded CDS tool like the proposed Bili Assistant. Developing this conceptualization taught me about the importance of requirements gathering to establish the scope of a decision support intervention, the utility of use cases to inform Boolean logic and the role of test cases. Although the Bili Assistant still needs to be programmed, the work done will already inform the development of an inpatient clinical pathway that the eventual tool will help complement once embedded in my institution's EHR.

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APPENDICES

Appendix A: Use Cases

#1 New Patient in ED

Description: An infant is referred to the ED because of jaundice.

Preconditions:

- A bilirubin has been drawn in the ED and results have returned to the Bili Assistant.
- A prior bilirubin value may or may not be available—this can be plotted but will not be used for the decision support decisions.
- The infant is less than 21 days old.
- The system knows if the infant has received prior phototherapy at the hospital.

Steps:

1. The system triggers Care Assistant for Bili Assistant and sends an alert to the provider.
2. The provider accepts Care Assistant.
3. The system requests patient information including gestational age, date and hour of birth and risk factors, pulling in available data from the EHR.
4. Provider enters missing values/confirms known data.
5. The system plots current total bilirubin value (in red) on two nomograms, one for phototherapy, one for exchange transfusion, highlighting the appropriate risk curve in yellow while others are black.

6. The system displays the recommendation for the next treatment step based on this bilirubin value.

#2 Patient admitted on phototherapy

Description: An infant has been admitted for phototherapy.

Preconditions:

- Prior bilirubin values are available to the system.
- A follow-up bilirubin has been drawn and results are available to the Bili Assistant.
- The system knows that the patient is currently on phototherapy by the order placed for phototherapy.

Steps:

1. The provider is alerted to view the Bili Assistant.
2. The system requests update of patient information.
3. The provider updates or approves patient information.
4. The system plots all prior and current total bilirubin values (with current in red) on two nomograms, one for phototherapy, one for exchange transfusion, highlighting the appropriate risk curve in yellow while others are black.
5. The system displays the recommendation for the next treatment step based on this bilirubin value.
6. The system continues to repeat steps 1-5 while the patient is on phototherapy until the bilirubin value is below the phototherapy stop threshold or is transferred to the NICU.

#3. Return to ED after previous therapy

Description: An infant previously treated for jaundice has returned to the ED

Preconditions:

- A bilirubin has been drawn in the ED and results have returned to the Bili Assistant.
- Multiple prior bilirubin values will be available—these can be plotted but will not be used for the decision support decisions.

Steps:

1. The system triggers Care Assistant for Bili Assistant and sends an alert to the provider. An additional message is shown to indicate to the provider that the patient was previously treated for jaundice and could have a pathologic cause that should be considered in management decisions.
2. The provider accepts Care Assistant.
3. The system requests patient information including gestational age, date and hour of birth and risk factors, pulling in known data from EHR
4. Provider enters missing values/confirms known data
5. The system plots current total bilirubin value (in red) on two nomograms, one for phototherapy, one for exchange transfusion, highlighting the appropriate risk curve in yellow while others are black.
6. The system displays the recommendation for the next treatment step based on this bilirubin value.

Appendix B: Decision Logic for Bili Assistant

1. TRIGGER FOR BILI ASSISTANT

Description. The conditions that will cause the Bili Assistant to appear in the EHR: patient <21 days old and a bilirubin result is present from the current encounter in the ED or inpatient setting. Provider may also trigger the Bili Assistant manually at any time.

Variables.

AGE = Age in days of life (age as calculated automatically in EHR, difference between date of birth & date of encounter)

GA = Gestational age (obtained from EHR Birth History field)

ENC_BILIRUBIN = A bilirubin result from current encounter exists in chart (lab value date time stamp is after start of encounter). This lab value is set by the system looking for the first bilirubin value to return after the start of the encounter. The Bili Assistant will check whenever there is a new result returned to the EHR to see if it contains a bilirubin value.

PHOTO_START: A binary flag indicating whether or not the patient has received phototherapy at the hospital in the past, default FALSE (set by looking back for previous orders)

Logic.

IF AGE < 21 days AND GA >= 35 weeks

THEN

IF ENC_BILIRUBIN = TRUE

THEN

IF PHOTO_START = FALSE

THEN

Action = Present Bili Assistant in EHR to provider

ELSE

Action = Present Bili Assistant in EHR to provider and

NOTIFICATION:

{

Patient has previously been treated for hyperbilirubinemia. Please consider pathologic causes of hyperbilirubinemia in differential diagnosis.

}

END IF

END IF

ELSE (IF AGE >= 21 days OR GA < 35 weeks)

Action = Do not present Bili Assistant in EHR to provider and

NOTIFICATION:

{

The Bili Assistant is designed to aid in the management of bilirubin values in patients <21 days old and >=35 weeks gestation. As this patient does not meet these age criteria, management should be discussed with the NICU.

}

ENDIF

2. BILI ASSISTANT LOGIC

Constants.

PHOTO_STOP = 13 mg/dL, the threshold below which phototherapy should be stopped

PHOTO_NOMOGRAM = a data structure containing bilirubin values for high, medium, and low risk infants at each quarter hour of life

XCH_NOMOGRAM = a data structure containing bilirubin values for high, medium and low risk infants at each quarter hour of life

Variables.

PHOTO_START = A binary flag indicating whether or not the patient has received phototherapy, default FALSE; this is set to TRUE if an order for phototherapy is entered.

DOB = Date of birth (obtained from EHR)

TOB = Time of birth (obtained from provider)

RISK_FACTOR_X = Binary flags for presence or absence of one of 8 risk factors that increase risk of hyperbilirubinemia: (Based on input from provider). Default on each is FALSE

- RISK_FACTOR_1 =Isoimmune hemolytic disease,
- RISK_FACTOR_2 = G6PD deficiency,
- RISK_FACTOR_3 = Asphyxia,

- RISK_FACTOR_4 = Significant lethargy,
- RISK_FACTOR_5 =Temperature instability,
- RISK_FACTOR_6 =Sepsis,
- RISK_FACTOR_7 =Acidosis,
- RISK_FACTOR_8 =Albumin < 3.0g/dL

BILI_LAB = A data structure containing bilirubin laboratory results, including date time (BILI_TIME), unconjugated bilirubin value and conjugated bilirubin value; autopopulated from lab system or EHR or can be added manually

NICU_ADMIT = A binary indicating whether or not the patient has been admitted to the NICU, default FALSE (if admitted to NICU, then beyond the scope of this Bili Assistant). If the patient is admitted to the NICU, then it is set to TRUE and the Bili Assistant will stop being activated.

Calculated values and functions.

RISK_FACTOR(RISK_FACTOR_1, RISK_FACTOR_2, RISK_FACTOR_3, RISK_FACTOR_4, RISK_FACTOR_5, RISK_FACTOR_6, RISK_FACTOR_7, RISK_FACTOR_8) = A binary flag indicating whether or not the patient has any of the 8 risk factors; default FALSE (see below)

PT_RISK(GA, RISK_FACTOR) = the patient's risk level as low, medium or high (see below)

HOL(BILI_TIME) = Hours of life at time of bilirubin test, calculated from date time of a test (BILI_TIME) minus the birthdate and time (from DOB & TOB).

PHOTO_THRESHOLD (HOL, PT_RISK) = Draws from PHOTO_NOMOGRAM returning bilirubin value based on risk level and hours of life

EXCH _THRESHOLD (HOL, PT_RISK) = Draws from EXCH_NOMOGRAM returning bilirubin value based on risk level and hours of life

TSB (BILI_TIME) = Draws from BILI_LAB to return the total bilirubin (conjugated + unconjugated bilirubin) at a specific time.

BILI_TIME_RECENT() = Returns the date time of the most recent bilirubin test in BILI_LAB

BILI_TIME_PRIOR() = Returns the date time of the bilirubin test prior to the most recent test in BILI_LAB

TSB_RECENT = TSB(BILI_TIME_RECENT()); the patient's total bilirubin at time of most recent bilirubin lab result

TSB_PRIOR = TSB(BILI_TIME_PRIOR()); the patient's total bilirubin at time of the lab result prior to the most recent lab result.

HOL_RECENT = HOL(BILI_TIME_RECENT())

RISK_FACTOR(RISK_FACTOR_1, RISK_FACTOR_2, RISK_FACTOR_3, RISK_FACTOR_4, RISK_FACTOR_5, RISK_FACTOR_56, RISK_FACTOR_7, RISK_FACTOR_8)

IF (RISK_FACTOR_1 = TRUE

OR RISK_FACTOR_2 = TRUE

OR RISK_FACTOR_3 = TRUE

OR RISK_FACTOR_4 = TRUE

OR RISK_FACTOR_5 = TRUE

OR RISK_FACTOR_6 = TRUE

OR RISK_FACTOR_7 = TRUE

OR RISK_FACTOR_8 = TRUE)

THEN RISK_FACTOR = TRUE

ENDIF

PT_RISK (GA, RISK_FACTOR)

IF GA >= 38 weeks

IF RISK_FACTOR = FALSE

THEN PT_RISK = Low (i.e. GA >= 38 wks & well)

ELSE PT_RISK = Medium (i.e. GA >= 38 wks w/risk factors)

ENDIF

ELSE (GA < 38 weeks)

IF RISK_FACTOR = FALSE

THEN PT_RISK = Medium (i.e. GA 35-37 6/7 wks & well)

ELSE PT_RISK = High (i.e. GA 35-37 6/7 wks & well)

ENDIF

ENDIF

Initial Treatment Recommendation (PHOTO_START = FALSE).

IF TSB_RECENT >= EXCH_THRESHOLD(HOL_RECENT, PT_RISK)

Action = NOTIFICATION:

{

The patient's bilirubin level is above the exchange transfusion threshold. Discuss with the NICU for admission and further management.

}

ELSE IF TSB_RECENT >= (EXCH_THRESHOLD(HOL_RECENT, PT_RISK)-3)

Action = NOTIFICATION:

{

The patient's bilirubin level is within 3 of the exchange transfusion threshold. Discuss with the NICU for further management to decide if phototherapy is appropriate therapy.

}

ELSE IF TSB_RECENT >= PHOTO_THRESHOLD(HOL_RECENT, PT_RISK)

Action = NOTIFICATION:

{

The patient's bilirubin level is above the phototherapy threshold. Admit to General Pediatrics for continued phototherapy treatment. Obtain additional labs: CBC, Type and Screen.

}

ELSE IF TSB_RECENT >= (PHOTO_THRESHOLD(HOL_RECENT, PT_RISK) -3)

Action = NOTIFICATION:

{

The patient's bilirubin level is below the phototherapy threshold. However, this bilirubin value is within 2-3 mg/dl of the threshold and

so it is an option to provide conventional phototherapy in hospital. Otherwise consider discharge to home with close PCP follow-up in 24 hours.

}

ELSE

Action = NOTIFICATION:

{

The patient's bilirubin value is below the phototherapy threshold. Consider discharge to home with close PCP follow-up in 24 hours.

}

ENDIF

Follow-up Treatment Recommendation (PHOTO_START = TRUE AND NICU_ADMIT = FALSE)

Description. Recommendations based on TSB value after Phototherapy has been started. Will be repeated with each subsequent bilirubin value reported.

IF TSB_RECENT >= TSB_PRIOR (i.e. the value is increasing)

IF TSB_RECENT >= EXCH_THRESHOLD(HOL_RECENT, PT_RISK)

Action = NOTIFICATION:

{

The patient's bilirubin level is above the exchange transfusion threshold. Discuss with the NICU for transfer and further management.

}

ELSE IF TSB_RECENT >= (EXCH_THRESHOLD(HOL_RECENT, PT_RISK)-3)

Action = NOTIFICATION:

{

The patient's bilirubin level is within 3 of the exchange transfusion threshold. Discuss with the NICU for further management to decide if phototherapy is appropriate therapy.

}

ELSE

Action = NOTIFICATION:

{

The patient's bilirubin level is stable/rising.

Continue phototherapy, but consider Hematology consult in case patient is actively undergoing hemolysis.

}

ENDIF

ELSE IF TSB_RECENT > PHOTO_STOP (i.e. the value is decreasing but above stop level)

Action = NOTIFICATION:

{

The patient's bilirubin level is falling, but still above the recommended threshold of 13 mg/dL to stop phototherapy.

Continue phototherapy.

}

ELSE (i.e. the value is at or below the stop threshold)

Action = NOTIFICATION:

{

The patient's bilirubin level is now below the recommended threshold of 13 mg/dL to stop phototherapy.

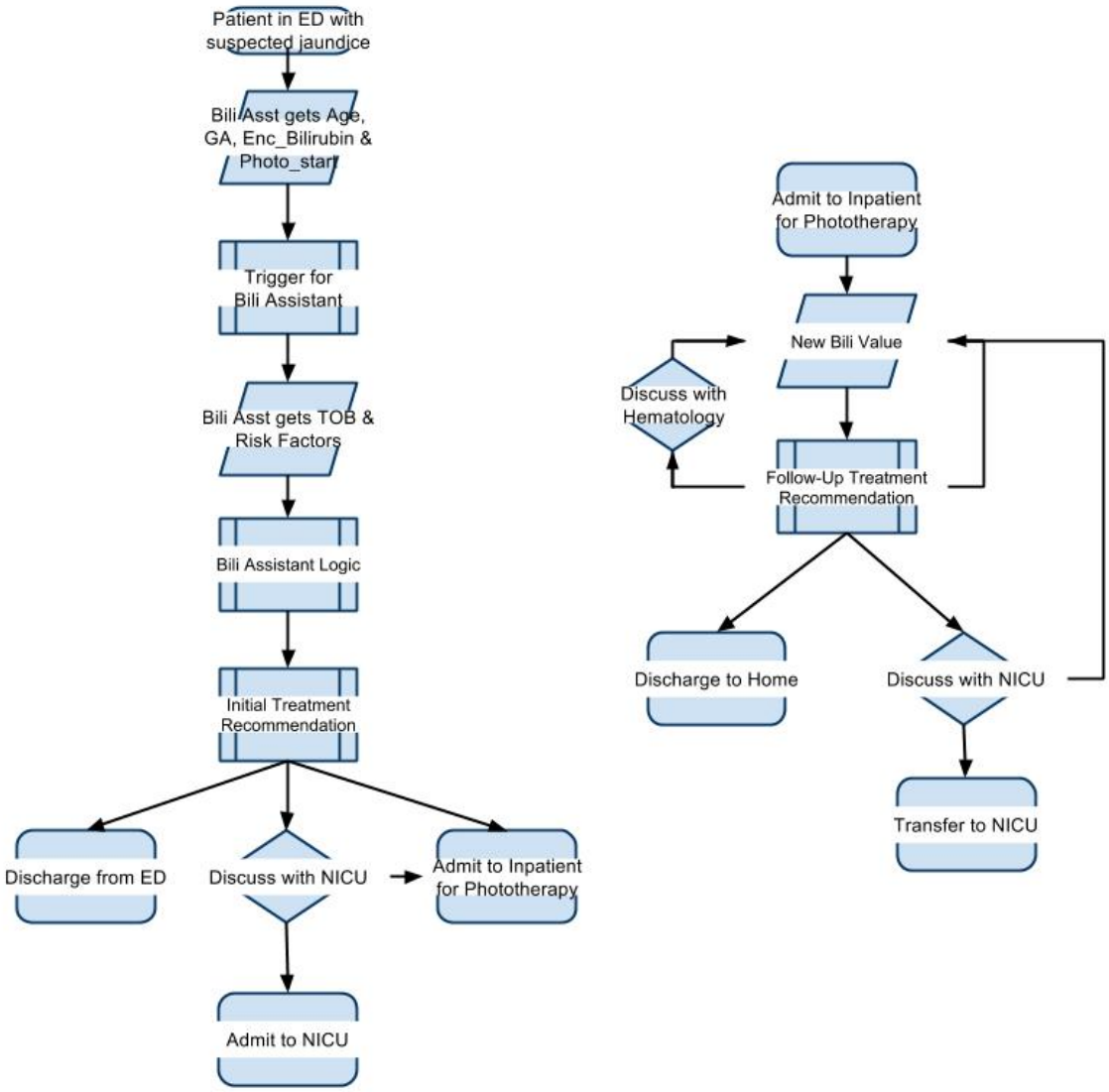
Discontinue phototherapy and it is NOT recommended to delay discharge to check a rebound.

Consider discharge to home and follow-up PCP in 24 hours.

}

ENDIF

Appendix C: Flow Diagram of Boolean Logic Functions



Appendix D: Test Cases

	Case 1: Patient in ED and >21 days old, so Bili Assistant does not present to provider.	Case 2: Patient in ED and GA < 35 weeks, so Bili Assistant stops presenting to provider.	Case 3: Patient in ED, tested & discharged to home.	Case 4: Patient in ED & admitted to NICU for exchange transfusion.
PHOTO_START	FALSE	FALSE	FALSE	FALSE
GA	38 3/7	34 5/7	37 2/7	36 1/7
DOB	6/24/2015	7/2/2015	7/28/2015	8/2/2015
TOB	1:30 am	12:00 pm	1:45 pm	5:50 pm
RISK_FACTOR_1	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_2	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_3	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_4	FALSE	FALSE	FALSE	TRUE
RISK_FACTOR_5	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_6	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_7	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_8	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR	FALSE	FALSE	FALSE	TRUE
PT_RISK	n/a	n/a	low	high
BILI LABS -date time -unconj. Bili (U) -conj. Bili (C)	n/a – Bili Assistant would not initialize regardless of lab value	n/a – Bili Assistant would not initialize regardless of lab value	7/31/15 2 pm U: 12, C: 0.5	8/6/15 9:40 pm U: 23, C: 1.8
NICU_ADMIT	FALSE	FALSE	FALSE	TRUE

	Case 5: Patient in ED, admitted to inpatient for phototherapy, discharged to home.	Case 6: Patient in ED, admitted to inpatient for phototherapy, transferred to NICU for exchange transfusion.	Case 7: Patient in ED, admitted to inpatient unit, recommendation for possible Hematology consultation.	Case 8: Patient previously treated, returning to ED for treatment, tested and discharged home.
PHOTO_START	FALSE -> TRUE	FALSE -> TRUE	FALSE -> TRUE	TRUE (from previous admission)
GA	36 1/7	36 3/7	39 3/7	38 4/7
DOB	9/9/15	8/11/15	8/13/15	7/12/15
TOB	7:15 am	8:30 am	11:40 am	3:00 pm
RISK_FACTOR_1	FALSE	FALSE	FALSE	TRUE
RISK_FACTOR_2	FALSE	TRUE	FALSE	FALSE
RISK_FACTOR_3	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_4	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_5	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_6	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_7	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR_8	FALSE	FALSE	FALSE	FALSE
RISK_FACTOR	FALSE	TRUE	FALSE	TRUE
PT_RISK	medium	high	low	medium
BILI LABS -date time -unconj. bili -conj. Bili	9/15/15, 7:00am U: 18, C: 0.7 9/15/15, 11:10am U: 14.9, C: 0.6 9/15/15, 7:08pm U: 11.5, C:0.6	8/15/15, 2:20am U: 15.3, C: 0.9 8/15/15, 6:30am U: 17.1, C: 1.0 8/15/15, 10:30am U: 18.4, C: 1.1 19.5	8/17/15, 12:45am U: 20, C: 0.7 8/17/15, 7:40am U: 21.2, C: 0.6 8/17/15, 11:55am U: 16.4, C: 0.7 8/17/15, 6:43pm U: 12.3, C: 0.5	7/18/15 6:55pm U: 15.3, C 0.8
NICU_ADMIT	FALSE	FALSE -> TRUE	FALSE	FALSE