Neonatal jaundice screening

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Abbreviations

AAT	α1-Antitrypsin
AST	Aspartate aminotransferase
ABE	Acute bilirubin encephalopathy
BIND	Bilirubin-induced neurologic dysfunction
CBE	Chronic bilirubin encephalopathy
CMV	Cytomegalovirus
CNS	Central nervous system
CRP	C reactive protein
EM	Electron microscope
ET	Exchange transfusion
ETCO	End-tidal carbon dioxide
ERCP	Endoscopic retrograde cholangiopancreatography
G6PD	Glucose-6-phosphate dehydrogenase
GGT	Gamma-glutamyltransferase
Gal-I-P	Galactose-1-phosphate
LED	Light emitting diode
MATLAB	MATrix LABoratory
MRI	Magnetic Resonance Imaging
NC	Neonatal cholestasis
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
PFIC	Progressive familial intrahepatic cholestasis
RBC	Red blood cell
TSB	Total serum bilirubin
TcB	Transcutaneous bilirubin
UGTA1	Uridine disphosphogluconurate glucuronosyltransferase
UTI	Urinary tract infection
VIS-NIR	Visible- Near Infrared
VLFCA	Very long chain fatty acid
WBC	White blood cell
WHO	World Health Organization
WSN	Wireless Sensor Network

Contents

Summary

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Neonatal jaundice is a yellow discoloration of the skin of newborns which appears as a result of the imbalance between bilirubin production and elimination. It occurs in 60-85% of newborns and in majority of cases resolves within a few days. However, misdiagnosis of pathologic neonatal jaundice as benign physiologic jaundice delays the detection of potentially serious medical conditions or complications. High levels of unconjugated bilirubin in blood exert a neurotoxic effect on the central nervous system, leading to bilirubin encephalopathy, while conjugated hyperbilirubinemia indicates potentially serious hepatic disorder or a systemic illness. Unfortunately, severe neonatal jaundice is still recognized as a "silent" cause of numerous cases of neonatal morbidity and mortality worldwide. Therefore, the goal of neonatal jaundice screening programs is the prompt detection of the neonatal jaundice cases, giving extra time to health care personel for preemptive actions with an aim of reducing infant's mortality and morbidity caused by severe hyperbilirubinemia. The objective of this paper is giving an overview of neonatal jaundice, including its pathophysiology and etiology, clinical manifestations and complications associated with it, management and interventions as well as current guidelines and recommendations for screening and management with a short review of technical advances in the area. Ultimately the aim of the paper includes a proposal for a novel approach to early detection of neonatal jaundice.

Keywords: *neonatal jaundice; screening; hyperbilirubinemia; neonatal cholestasis; artificial intelligence algorithm; data analysis*

Sažetak

Probir novorođenačkih žutica

Haris Ahmić

Novorođenačka žutica jest pojava žutog obojenja kože u novorođenčadi koje se javlja kao posljedica poremećaja proizvodnje i lučenja bilirubina. Pojavljuje se u 60-85% novorođenčadi, a u većini slučajeva nestaje kroz nekoliko dana. Međutim, krivo dijagnosticirana benigna fiziološka žutica umjesto patološke novorođenačke žutice, odgađa otkrivanje potencijalno opasnih bolesti i njihovih komplikacija. Visoka razina nekonjugiranog bilirubina u krvi ima neurotoksični učinak na središnji živčani sustav, što vodi do bilirubinske encefalopatije. S druge strane, konjugirana hiperbilirubinemija upućuje na mogući ozbiljan poremećaj jetre ili na sustavnu bolest. Nažalost, novorođenačka se žutica još uvijek smatra "skrivenim" uzrokom velikog broja slučajeva novorođenačke smrtnosti u svijetu. Slijedom toga, cilj probira novorođenačkih žutica jest pravovremeno otkrivanje slučajeva same žutice, što bi dalo više vremena zdravstvenom osoblju za poduzimanje proaktivnih radnji s ciljem smanjenja smrtnosti novorođenčadi uzrokovane hiperbilirubinemijom. Cilj ovog rada je prikazati pregled novorođenačke žutice, uključujući njezinu patofiziologiju, etiologiju, kliničke manifestacije i komplikacije povezane s njom, njezino liječenje i obradu, trenutačne smjernice i preporuke za njenu detekciju i liječenje, tehnička dostignuća u području otkrivanja novorođenačke žutice, i na posljetku prezentirati prijedlog za novi pristup ranom otkrivanju novorođenačke žutice.

Ključne riječi: *novorođenačka žutica; probir; hiperbilirubinemija; neonatalna kolestaza; algoritmi umjetne inteligencije; analiza baza podataka*

1. Introduction

Jaundice, term derived from the French word *jaune*, or icterus, term derived from the Greek word *ikteros*, is a yellow discoloration of the skin and conjunctiva (1) due to the accumulation of an excess of bilirubin. Its appearance in the neonatal period, transition phase during the first 28 days of newborn's life throughout which newborns adapt to extrauterine life, is referred to as a neonatal jaundice. Neonatal jaundice is a common condition occurring in up to 60% of term neonates and 85% of preterm neonates (2), (3). However, neither hyperbilirubinemia nor chronic bilirubin encephalopathy belong to reportable diseases, so there are no reliable sources of information providing national annual estimates (4). Majority of cases of neonatal jaundice resolve within a few days without significant complications (5). Although the terms jaundice and hyperbilirubinemia are often used interchangeably, it should be noted that jaundice is observed only when the serum bilirubin is twice the normal upper limit (6). Based on the predominant type of bilirubin, hyperbilirubinemia can generally be classified into unconjugated and conjugated hyperbilirubinemia.

Hyperbilirubinemia poses a serious risk to neonatal health. High levels of unconjugated bilirubinemia exert a toxic effect on the central nervous system (CNS), while conjugated hyperbilirubinemia implies a potentially serious hepatic illness. For example, chronic bilirubin encephalopathy (CBE) is still occurring even though it should be prevented in the majority of cases (2). Therefore, the goal of neonatal jaundice screening programs is prompt detection of neonatal jaundice cases, giving additional time to health care personnel who will, with prompt interventions, reduce infants' mortality and morbidity caused by severe hyperbilirubinemia. In case of biliary atresia as causative agent of neonatal jaundice, for instance, Canadian Pediatric Hepatology Research Group reported that 14 % of Canadian infants with jaundice caused by biliary atresia present to tertiary referral centres after 3 months of age, and that 49 % of infants who underwent surgery at 30 days of age, 25 % of infants who underwent surgery in the period between 31 and 90 days of age, and 15 % of infants who had operation after 90 days of age, lived with their own liver by the age of 10 years (7).

The importance of effective screening is recognized by health care providers declaring the severe neonatal jaundice as a "silent" cause of significant neonatal morbidity and

mortality (8). *Newman et al* reported laboratory results of 50 000 California newborns where 2 % of them had total serum bilirubin (TSB) higher than 20 mg/dl, 0.15 % had levels higher than 25 mg/dl, and 0.01 % had levels higher than 30 mg/dl. It should be noted that data obtained by this report included infants with clinically detected hyperbilirubinemia, therefore representing minimum estimate of the true incidence of severe hyperbilirubinemia (4). In addition, *Bukhani et al* reported that at least 481000 term/near-term neonates are affected by severe neonatal jaundice/ hyperbilirubiemia each year with 114 000 dying and an additional 63 000 surviving with chronic bilirubin encephalopathy. Hence, it is not surprising that Subcommittee on Hyperbilirubinemia of American Academy of Pediatrics emphasizes the importance of universal, systematic assessment for the risk of severe hyperbilirubinemia, close follow-up, and prompt interventions, when necessary (2).

The objective of this graduate thesis is to be a first step in potential future development of new neonatal jaundice screening paradigm based on artificial intelligence algorithms as predictive model for neonatal jaundice detection.

In order to get a clear overview of the neonatal jaundice that will be a cornerstone for development of novel screening paradigm, the remainder of the paper is organized as follows: Section II, III and IV describe pathophysiology and etiology, clinical manifestations, and management of neonatal jaundice. Neonatal jaundice screening programs and recommendations are given in Section V. Finally, technological advances in the area of neonatal jaundice screening, proposal for future work and concluding remarks, are given in section VI and VII, respectively.

2. Pathophysiology and Etiology

2.1. Bilirubin Metabolism

Bilirubin is a yellow tetrapyrrole pigment formed by the breakdown of heme in the reticuloendothelial system (9). Heme oxygenase and biliverdin reductase are two primary enzymes responsible for bilirubin production. Heme oxygenase catalyzes the oxidation of alpha-carbon bridge, leading to formation of biliverdin, which is subsequently reduced by biliverdin reductase to water-insoluble unconjugated bilirubin (10). Water-insoluble bilirubin undergoes conjugation into bilirubin glucuronides that are water soluble and excreted in bile (9). Metabolism of bilirubin consists of several phases: albumin binding of bilirubin in plasma, uptake and storage by hepatocytes, conjugation, excretion and degradation of bilirubin in the digestive tract (10).

Elevated bilirubin in serum results in yellow discoloration of skin and positive urine tests for bilirubin in case of conjugated hyperbilirubinemia. Decreased levels of bilirubin in intestines lead to acholic stool, decreased urobilinogen and negative urine tests for urobilinogen (9).

During pregnancy, placenta is the principal route of elimination of the lipid-soluble, unconjugated bilirubin, while during the neonatal period bilirubin metabolism shifts to the aforementioned processes resulting in excretion of water-soluble conjugated bilirubin into the biliary system and gastrointestinal tract (10).

2.2. Benign Neonatal Hyperbilirubinemia

Benign neonatal hyperbilirubinemia, previously called “physiologic jaundice”, refers to elevated unconjugated bilirubin levels that occurs in nearly all neonates. It occurs as a result of two specific limitations of newborn infant organism, namely, increased turnover of fetal red blood cells and immaturity of the liver resulting in decrease in conjugation of excretion of bilirubin (11). The former is consequence of newborns having more red blood cells (RBCs) and shorter life-span of their RBCs. The latter is the result of deficiency of enzyme uridine disphosphogluconurate glucuronosyltransferase (UGTA1) activity in the earliest period of life, and increased enterohepatic circulation of bilirubin due to limited intestinal bacterial action on conversion of conjugated bilirubin to urobilin (11).

2.3. Unconjugated Hyperbilirubinemia

The two main two mechanisms responsible for significant unconjugated hyperbilirubinemia are an increase in the load of bilirubin metabolized by the liver and a decrease in bilirubin clearance. Increase in bilirubin load is usually related to RBCs (hemolytic anemias, polycythemia, bruising, internal hemorrhage). Decrease in bilirubin clearance is related to genes encoding enzymes catalyzing conjugation of bilirubin (e.g. UGT1A1). Crigler-Najjar and Gilbert syndrome are examples of UGTA1 disorders responsible for unconjugated hyperbilirubinemia. Bilirubin clearance may be impaired by reduced or absent activity of transferase enzymes and other related enzymes or substances blocking or competing for transferase enzymes (2), (10).

Increased enterohepatic circulation is another contributing factor for development of unconjugated hyperbilirubinemia. When compared to adults, newborns intestines are sterile, and consequently, small amount of conjugated bilirubin is converted to urobilin. Intestinal beta-glucuronidase converts conjugated bilirubin into unconjugated bilirubin that is reabsorbed into the circulation through enterohepatic circulation of bilirubin (12).

The American Academy of Pediatrics Subcommitte on Hyperbilirubinemia classifies risk factors for development of unconjugated hyperbilirubinemia into three groups: major risk factors, minor risk factors and decreased risk. Major risk factors include: TSB or transcutaneous bilirubin (TcB) level in the high-risk zone, jaundice observed in the first 24 h, blood group incompatibility with positive direct antiglobulin test, other known hemolytic diseases, elevated end-tidal carbon dioxide (ETCO), gestational age of 35-36 weeks, previous sibling received phototherapy, cephalohematoma or significant bruising, exclusive breastfeeding, particulary if nursing is not going well and weight loss is excessive, and East Asian race. Minor risk factors include: predischarge TSB or TcB level in the intermediate-risk zone, gestational age of 37-38 weeks, jaundice observed before discharge, previous sibling with jaundice, macrosomic infant of a diabetic mother, maternal age more than 25 years and male gender. Decreased risk factors include: predischarge TSB or TcB level in the low-risk zone, gestational age >41 weeks, exclusive bottle feeding, black race, discharge from hospital after 72 h (2).

2.4. Conjugated Hyperbilirubinemia

Conjugated hyperbilirubinemia beyond the first 14 days of life is the biochemical definition of neonatal cholestasis (10). Even though the term neonatal cholestasis (NC) contains the word neonatal, it usually refers to hyperbilirubinemia that is present at birth and manifests within first few months of life, not necessarily during the first 28 days of life. Unlike benign neonatal hyperbilirubinemia, NC is always pathologic and the presence of a severe medical condition must be considered. In addition, despite cholestasis being largely associated with jaundice, it refers to impairment of bile excretion with elevation of bile constituents (conjugated bilirubin, bile salts, cholesterol and alkaline phosphatase) (9).

There are two principal pathophysiologic pathways for conjugated hyperbilirubinemia: functional impairment of hepatic excretory function and bile secretion, and mechanical obstruction of bile flow. Even though clinical pictures of any form of neonatal cholestasis are similar, neonatal cholestasis can be sorted into extrahepatic and intrahepatic disease. The etiology of neonatal cholestasis can be divided into 5 main etiologic groups: obstructive, infectious, metabolic/genetic, toxic and alloimune.

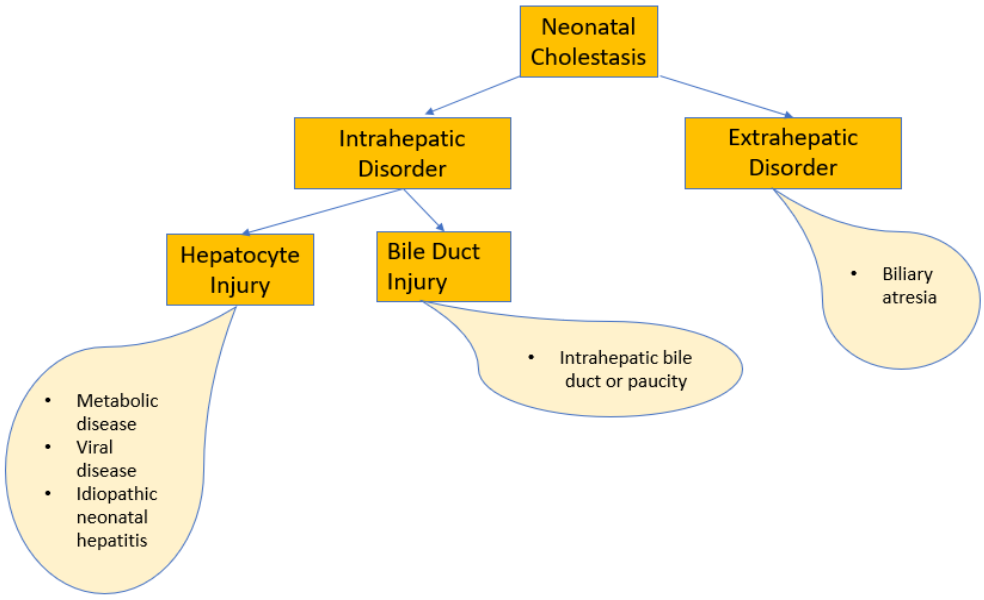

Figure 1. Overview of Neonatal Cholestasis

Classification derived from Nelson Textbook of Pediatrics (10)

Prompt detection of underlying etiology causing NC is important due to the fact that some of the causes are treatable. Among the conditions presenting as NC, biliary atresia and idiopathic neonatal hepatitis are the most common accounting for 35% and 30% of cases, respectively. AAT deficiency (17%), Alagille syndrome (6%), and choledochal cysts (3%) are other common causes of neonatal cholestasis (7).

The following tables represent summary of multiple etiologies of the neonatal cholestasis (*References* (7), (10), (13), (14), (28)):

Table 1 *Extrahepatic disease (obstructive)*

Name of disorder	**Diagnostic approach and potential screening target(s)**
Biliary atresia	Blood: direct (conjugated) bilirubin (15); Ultrasound (gallbladder appearance, cirrhosis and portal hypertension, polysplenia, asplenia); Hepatobiliary scintigraphy; Liver biopsy; Intraoperative cholangiogram
Biliary cyst	Blood: direct (conjugated) bilirubin; serum amylase and lipase levels, serum biochemistry: hypochloremic, hypokalemic metabolic alkalosis (16); Ultrasound; Cholangiogram
Inspissated bile	Blood: direct (conjugated) bilirubin; Ultrasound
Gallstones	Blood: direct (conjugated) bilirubin; Ultrasound
Tumors	Blood: direct (conjugated) bilirubin
Neonatal sclerosing cholangitis	Blood: direct (conjugated) bilirubin; Cholangiogram

Table 2 *Infectious causes*

Causative agent	**Diagnostic approach and Potential Screening Target(s)**
CMV	Blood: direct (conjugated) bilirubin, platelet count, WBC differential (17)
Sepsis	Blood: direct (conjugated) bilirubin, platelet count, WBC differential (17)
Congenital Syphilis	Blood: direct (conjugated) bilirubin, platelet count, WBC differential (17)
E. coli UTI	Blood: direct (conjugated) bilirubin, platelet count, WBC differential (17) ; Urine culture
Rubella	Blood: direct (conjugated) bilirubin, platelet count, WBC differential (17)
Toxoplasmosis	Blood: direct (conjugated) bilirubin, platelet count, WBC differential (17)
Hepatitis B	Blood: direct (conjugated) bilirubin, platelet count, WBC differential (17)
Herpes Simplex	Blood: direct (conjugated) bilirubin, platelet count, WBC differential (17)

**CMV: Cytomegalovirus; UTI: Urinary tract infection; WBC: White blood cell*

Table 3 *Metabolic/ Genetic Causes*

Name of disorder	Diagnostic approach and potential screening target(s)
AAT deficiency	α1-Antitrypsin levels low; *Genetic analysis*
Arthrogryposis–renal dysfunction–cholestasis syndrome	Hepatomegaly; low GGT levels; normal or high AST; *Arthrogryposis; Renal tubular dysfunction; Genetic analysis*
Caroli disease and congenital hepatic fibrosis	Alanine Aminotransferase and AST may be elevated; *Renal dysfunction*; *Hypersplenism*; *Ultrasound images*; *Genetic analysis*
Chromosomal (trisomy 21; Turner syndrome)	*Characteristic features; Karyotyping*
Citrin deficiency	Increased blood or plasma ammonia, serum concetration of citrulline and arginine, plasma threnonine-to serine ratio *(37); Variable liver dysfuntion; Genetic analysis*
Cystic fibrosis	Sweat chloride analysis; *Genetic analysis*
Disorders of bile acid synthesis and conjugation	Urinary bile acid analysis; *Genetic analysis*
Fatty acid oxidation defects	*Newborn screening; Genetic analysis*
Galactosaemia	Non-glucose reducing substances (positive); Gal-I-P uridyl transferase activity low in RBCs*; Genetic analysis; Newborn screening*
Glycogen storage disease type IV	*Liver biopsy; Genetic analysis*
Hereditary fructosemia	Fructose-1-phosphate aldolase B activity low or absent in liver tissue; *Liver biopsy with EM; Genetic analysis*
Mitochondrial respiratory chain disorders	elevated plasma lactate; elevated plasma lactate to pyruvate ratio; raised β-hydroxybutyrate (38); *Genetic analysis*
Neonatal hemochromatosis	*Usually high ferritin, TIBC low; Liver biopsy with iron stain or buccal mucosal biopsy; MRI*
Neonatal sclerosing cholangitis	*Same as in Table 1; Genetic analysis*
Niemann–Pick disease type C	*Abnormal intracellular cholesterol homeostasis in cultured fibroblasts; Fetal ascites; Neonatal liver disease; Pulmonary infiltrates; Genetic analysis*
Peroxisomal disorders	plasma VLCFA high; urinary pipecolic acid excretion, medium and dicarboxylic aciduria, hyperoxaluria, mevolonic aciduria; Electroretinogram; Visual-evoked respones; Brain auditory-evoked responses (39); *Genetic analysis*
PFIC	GGT low to normal in types 1 and 2, high in type 3; *Liver biopsy; Genetic analysis*
Tyrosinaemia	Serum tyrosine and methionine levels high; high serum α-fetoprotein; Succinylacetone detection in urine*; Newborn screening; Genetic analysis*

Urea cycle defects	Serum lactate and pyruvate; Hyperammonemia, Respiratory alkalosis; Citrullinemia; Arginosuccinic aciduria; *Genetic analysis*

**conjugated hyperbilirubinemia finding in all cases of neonatal cholestatic jaundice*

***AAT deficiency: α1-Antitrypsin deficiency; AST: Aspartate aminotransferase; Gal-I-P: Galactose-1-phosphate; GGT: Gamma-glutamyltransferase; EM: electron microscope; MRI: Magnetic Resonance Imaging; PFIC: Progressive familial intrahepatic cholestasis; TIBC: Transferring iron-binding capacity; VLCFA: Very long chain fatty acid;*

In addition, endocrine disorders (hypopituitarism, hypothyrodisim), toxic insults (drugs, endotoxins, total parenteral nutrition-associated cholestasis, herbal products), shock, and intestinal obstruction are also possible causes of neonatal cholestasis (10), (13), (14).

3. Clinical Manifestations and Complications Associated with Neonatal Jaundice

In clinical practice, detection of neonatal jaundice is important because of associated complications arising from elevated levels of serum bilirubin. Accumulation of unconjugated lipid soluble bilirubin is toxic to the brain cells, while accumulation of conjugated bilirubin may indicate potentially serious hepatic disorders or a systemic illness.

3.1. Neonatal Jaundice Manifestations

Jaundice usually appears in the early neonatal period. Based on etiology, neonatal jaundice may be due to benign neonatal hyperbilirubinemia, severe unconjugated hyperbilirubinemia, or conjugated hyperbilirubinemia. Progression follows a cephalocaudal pattern, first appearing on the face, and ultimately on the feet. In case of unconjugated hyperbilirubinemia, skin tends to appear bright yellow or orange, while in case of conjugated hyperbilirubinemia the skin adopts a greenish or a muddy yellow appearance (10). Conjunctival icterus, yellowing of the conjunctiva, usually appears with elevation of TSB levels, and it may be the only visible sign of jaundice on physical examination in patients with dark skin.

3.2. Bilirubin-Induced Neurologic Dysfunction

Bilirubin has a dual action, at low levels it has a beneficial antioxidant effect, and at higher levels it exerts neurotoxic effects leading to bilirubin-induced neurologic dysfunction (BIND) (18). BIND represents a spectrum of neurologic impairment manifesting as visual, hearing, gait, speech, cognitive and language problems (19-22). Excessive unconjugated bilirubinemia leads to passage of unconjugated bilirubin through blood-brain barrier, resulting in apoptosis and/or necrosis of neural cells (23). Areas of the brain most susceptible areas to toxic insult by bilirubin are globus pallidus, basal ganglia, substantia nigra, hippocampus, thalamic nuclei, putamen nuclei, dentate, inferior olives and cerebellum (25).

3.2.1. Acute Bilirubin Encephalopathy

Acute bilirubin encephalopathy (ABE) refers to acute manifestations of bilirubin toxicity observed in the first weeks after birth (2). ABE caused by toxic effects of unconjugated bilirubin manifests as lethargy, hypotonia, poor sucking, irritability, apnea, abnormal

posturing, high pitched cry, seizures and coma (24). Symptoms usually appears during three phases of ABE. In the early phase, lasting through days 3-5 of the disease, subtle nonspecific symptoms such as slight lethargy, hypotonia and hyperreflexia, poor sucking, and poor feeding, are observed. In the intermediate phase, at the end of first week, neonates with ABE present with moderate stupor, irritability, fever, hypo and hypertonia as an alternative symptom, high-pitched cry, back arching and hyperextension of externsor muscles. In the final phase, deep stupor or coma, high-pitched cry, and pronounced retrocollis-opisthotonos are prominent signs (25).

3.2.2. Chronic Bilirubin Encephalopathy

Chronic bilirubin encephalopathy (CBE), kernicterus, refers to chronic and permanent sequelae of bilirubin toxicity (2). During the first year of life hypotonia, hyperreflexia, and delayed motor skills are present. Extrapyramidal symptoms usually appear after a few years. A tetrad of symptoms, consisting of visual symptoms (upward graze palsy), auditory symptoms (sensory neural hearing loss), dental dysplasia abnormalities, and extrapyramidal distrubances (choreoathetosis cerebral palsy), manifest during late infancy and childhood (25).

3.3. Neonatal Cholestasis

Neonates with cholestasis usually present with prolonged jaundice, pale stools and dark urine. Acholic stools are cardinal feature of cholestasis and should be promptly evaluated. Blood biochemistry may differ according to the etiology of disease. Metabolic disorders or sepsis may manifest with neurologic symptoms, such as irritability, lethargy, seizures and poor feeding. Some infants may present with signs of coagulopathy due to deficiency of clotting factors or a vitamin K deficiency. Physical examination findings depend on the etiology of neonatal cholestasis and the duration of disease. Jaundice is observed in almost all cases. Hepatomegaly is common, while splenomegaly may be seen in infants with advanced liver diseases. Other possible clinical findings include growth retardation (congentital infections), syndromic facial dysmorphic features, and mass in right upper quadrant (choledochal cyst) (26).

4. Neonatal Jaundice Management and Interventions

Management of neonatal jaundice is complex due to numerous etiologic entities. There are two goals: prevention of toxic effects of unconjugated bilirubin (usually during the first week of life), identification of the cause of conjugated bilirubinemia (usually after the first week of life) that will yield prompt intervention and improved clinical outcome for the baby. For example, Kasai procedure performed earlier in life has been associated with more successful outcome for patients with biliary atresia and delays the liver transplantation (8). It's important for clinicians to always look for underlying causes along with symptomatic management.

4.1. Management of Unconjugated Hyperbilirubinemia

4.1.1. Phototherapy

Phototherapy's mechanism of action consists of light energy converting the unconjugated bilirubin into water soluble bilirubin that can be excreted. Fibre optic phototherapy, Light emitting diode (LED) phototherapy, BiliBed, conventional phototherapy, single light phototherapy and multiple light phototherapy are available phototherapy modalities (24). Contraindications to phototherapy include: neonates with congenital porphyria, positive family history for porphyiria, and concurrent treatment with photosensitising drugs (5).

4.1.2. Exchange Transfusion

Replacement of neonatal blood with fresh donor blood or plasma is indicated when TSB is above the exchange transfusion (ET) threshold when plotted on the jaundice treatment threshold graph, or TSB is rising more than 0.5 mg/dl per hour despite multiple light phototherapy with known hemolysis or signs of bilirubin encephalopathy (24). Neonates receiving ET should be transferred to neonatal intensive care unit (NICU). If neonate is jaundiced within first day of life, phototherapy should be initiated. If neonate is jaundiced after 24 h of life, treatment modality depends on TSB levels. If TSB is at, or above phototherapy treatment threshold, phototherapy is recommended. If TSB is rapidly rising and TSB is at or above exchange transfusion treatment threshold, ET is recommended (24).

In addition to the aforementioned modalities, unproven modalities or modalities with inconclusive evidence are available. These include intravenous immune globulin, ursodeoxycholic acid, phenobarbital, metalloporphyrins, clofibrate (27).

4.2. Management of Neonatal Cholestasis

Any jaundiced two-week-old infant should be evaluated for neonatal cholestasis. The reason for this is that by the 14th day of life, neonatal liver should be mature enough and physiologic jaundice should be resolved by that day. Neonatal cholestasis indicates investigations for obstructive causes of jaundice. The highest priority during the evaluation is to identify those cases of neonatal jaundice for which specific therapy is available with aim of preventing further damage and decreasing morbidities associated with NC (hypothyroidism, panhypopituitarism, galactosemia, tyrosinemia, etc.) (10).

Diagnostic algorithm for neonates with prolonged jaundice and direct hyperbilirubinemia starts with the assessment of feces and fasting basic blood biochemistry (blood cell count with reticulocytes, total and fractioned bilirubin, coagulation parameters, hemolysis parameters, liver transaminases levels including

Table 4 Tests for Narrowing Differential Diagnosis (10)

Stool color	Presence of bile in instestines
Urine and serum bile acid measurement	Cholestasis; low in case of bile acid synthesis disorders
Hepatic synthetic functions	Severity of hepatic dysfunction
Thyroxine and thyroid-stimulating hormones	Confirmation or exclusion of endocrinopathies
Lysosomal acid lipase enzyme activity	Confirmation or exclusion of lysosomal acid lipase deficiency
Sweat chloride and genetic analysis	Confirmation or exclusion of Cystic fibrosis
Urine and serum amino acids levels	Confirmation or exclusion of metabolic liver disease

Ultrasonography	Assessment of choledochal cyst; signs of biliary atresia
Liver biopsy	Diagnosis of biliary atresia; alternative diagnoses

GGT, plasma bile acids, lipase, glucose, lactate, ammonium and C reactive protein (CRP)). In case of depigmented feces, fasting abdominal ultrasound should be performed with exclusion and assessment for biliary atresia, choledochal cyst and biliary sludge. In the case of pigmented feces, abdominal ultrasound should be performed with the exclusion and assessment of infection, sepsis, hypothyroidism (TSH, thyroxine), progressive familial intrahepatic cholestasis, metabolic disorders and storage diseases.

Liver biopsy, endoscopic retrograde cholangiopancreatography (ERCP), scintigraphy and/or intraoperative cholangiography are potential diagnostic approaches (28).

5. Neonatal Jaundice Screening Guidelines and Recommendations

Professional medical associations worldwide present various neonatal jaundice screening guidelines and recommendations. For instance, World Health Organization (WHO) recommends monitoring and measurement of serum bilirubin in: all babies if jaundice appears on day 1, in preterm babies (<35 weeks) if jaundice appears on day 2, in all babies if palms and soles are yellow at any age. Table 5 shows neonatal jaundice recommendations and guidelines from American Academy of Pediatrics, National Institute for Health and Excellence (NICE), and Canadian Pediatric Society.

Table 5 Neonatal jaundice screening guidelines and recommendations (2), (3), (29)

Canadian Pediatric Society recommendations

- All newborns jaundiced at first day should have TSB measurement
- Infants with severe or prolonged hyperbilirubinemia should be further investigated, including measurement of the conjugated component of bilirubin
- TSB or TcB should be measured in all infants during first 72 h of life
- Follow up should be individualized according to the risk assessment
- Infants discharged within 24 h of life should be visited and assessed by experienced personnel within next 24 hours
- Systematic approach to the risk assessment before discharge is recommended

NICE guidelines

- Bilirubin should not be measured routinely in babies who are not visibly jaundiced
- In babies with suspected jaundice measurement of bilirubin is recommended as soon as possible (within 6 hours)
- Babies ≥35 weeks of age: transcutaneous bilirubinometer should be used. In the case of TcB> 250 micromole/litre TSB should be determined
- Babies <35 weeks of age: TSB is advised

American Academy of Pediatrics

- TSB and/or TcB measurements should be performed on every infants jaundiced in the first 24 hours of life
- TSB and/or TcB measurements should be performed if jaundiced appears excessive for the infant's age
- All bilirubin levels should be interpreted according to the infant's age in hours
- Before discharge every newborn should be assessed for the risk of developing severe hyperbilirubinemia by 2 clinicians
- Jaundice should be assessed by clinicians and nurses whenever infant's vital signs are measured
- Blood typing: all pregnant women should be tested for ABO and Rh (D) blood types, and unusual isoimmune antibodies. If a mother has not had prenatal blood grouping or is Rh negative, a direct antibody test, blood type, and an Rh (D) type on the infant's cord blood are strongly recommended.

6. Technological Advances in the Detection of Neonatal Jaundice

In the following text, a brief overview of novel approaches to measurement of bilirubin is given. When compared to standard measurements of bilirubin, new alternative methods are mainly non-invasive and/or less time-consuming, making them more suitable candidates for widespread screening programs.

6.1. Computer Vision

Kawano, Zin and Kodama (30) developed an automated detector of neonatal jaundice. Their model consists of following phases: extraction of image recordings from neonatal facial area; subsequent extraction of skin area; and estimation of skin color. When compared to TSB gained via standard measurement, this detector was successful in determining changes in skin color of full-term infants, while detection of skin changes in preterm infants failed.

6.2. Neural Networks

Sohani, Makki, Sadati, Kermani and Riazati (31) created a decision support system for neonatal jaundice diagnosis based on Fuzzy neural network algorithm. By combining medical rules, MATrix LABoratory (MATLAB), the Gaussian membership functions and Mandani's fuzzy inference method and controid defuzziciation approach, the developed algorithm had the accuracy of about 78 % for detection of neonatal jaundice. For a more elaborate analysis of this approach, exact number of patients, types of included measurements, and exact rules are needed.

Own, Aal and Abraham (32) proposed intelligent data analysis consisting of retrospective analyses of all cases of neonatal jaundice in NICU and a predictive model based on the collected dataset. From the dataset, 16 predictor variables and 1 target variable were constructed. The disadvantage of the proposed model is that only neonates that have been in NICU had been included.

6.3. Spectrophotometry

Osman, Ahmad and Muharam (33) model used spectrophotometry for the estimation of bilirubin. Concentration of bilirubin in dermis layer of the skin was determined by using LED as a light source and photodiode as a detector. By application of optic theory

and different absorbance of solutions with different concentrations of bilirubin, hardware developed in this study was able to quantify jaundice levels in the form of light intensity and particular voltage output. It should be mentioned that this research was done only in laboratory and using rats' skin.

Kanamail and Periyasamy (34) model also used LED light source and Photodiode to estimate the concentration of the bilirubin in human blood serum. By application of Beer Lambitz law, transmitted light rays were correlated to bilirubin value. Accuracy of this method was ±0.1 and sensitivity was 0.1 mg/dl. This study was performed on 8 healthy adults, so samples including jaundiced neonates have to be included for further evaluation of this method.

Own et al also did study where they developed device based on spectrophotometry for the detection of bilirubin value. Study also used spectrophotometry for the detection of bilirubin value (35). Developed device consisted of white-light source optimized for the Visible-Near Infrared (VIS-NIR) (360-1100 nm), two SMA connectors used for the routing of light, a reflectance probe and USB4000 spectrometer connected to a laptop computer. Model values of hemoglobin, hematocrit and bililrubin were compared to values obtained from laboratory blood tests. While for hemoglobin and hematocrit, model and biochemical results showed high correlation, bilirubin correlation was pure. It is suggested that the results for bilirubin would be more accurate if the data collection was done on more individuals (only 4 individuals).

6.4. Wireless Sensor Network

Hakimi, Hassan, Anwar, Zakaria and Ashraf (36) research proposed wireless sensor network (WSN) technology as a low-cost and real-time monitoring solution for the detection of neonatal jaundice. The idea behind the proposed model is to integrate WSN, which is capable of collecting and analysis of data from sensors, and an optoelectronic sensor to detect the jaundiced baby. The device would be placed on the baby's forehead or sternum, and its information would be presented to medical staff through the Graphical User Interface.

7. Screening Proposal and Concluding Remarks

The objective of the proposed screening program is detecting children with subtle or no visible manifestations of neonatal jaundice. These are the cases omitted by current screening guidelines and recommendations, presenting to tertiary referral centre later in infancy, when the damage to infant's health has already been done. The rationale behind this program is relatively simple: Target parameters in children with and without disease are different. By creating an n-dimensional cross section of healthy and ill children, self-learning artificial intelligence algorithms would for particular input of parameters of new child give prediction whether the child will develop disease.

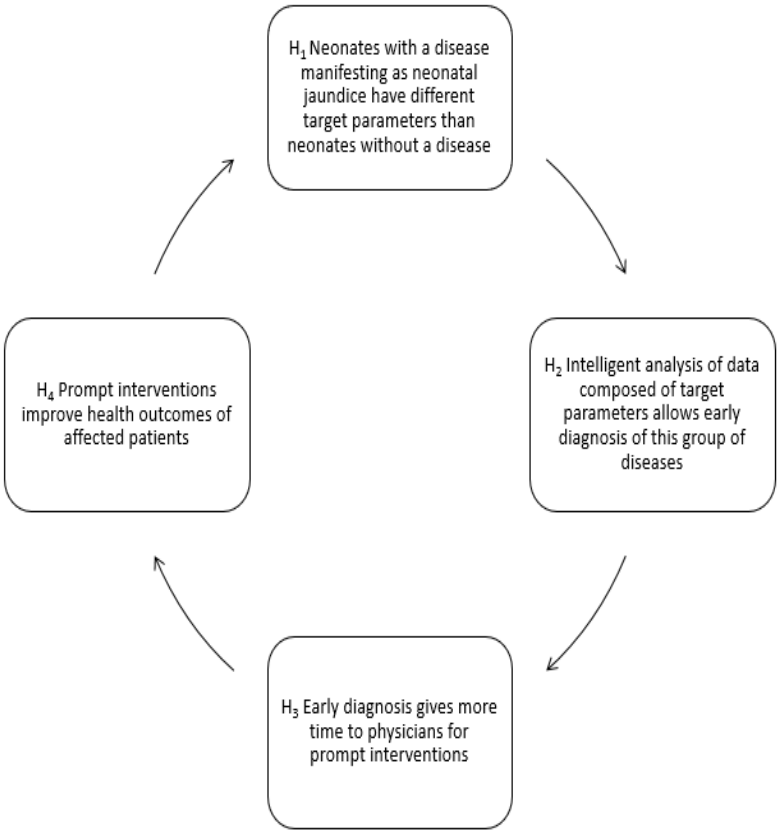

Figure 2. Proposed screening program hypotheses

Based on that prediction, a child without clinical manifestations of disease would be admitted for diagnostic work-up in the hospital, making early diagnosis and well-timed interventions possible. If the predictive model would be calibrated to detect such cases with no or minimal clinical manifestations, cases with more severe clinical picture would be automatically detected.

It is important to mention that prior to the development of a such predictive model, cost-benefit analysis should be done first. In other words, what would change in the infant's health outcome if the predictive program worked perfectly when compared to the current practice in managing neonatal jaundice?

Development of a screening program would be conducted in three phases:

1. The first phase: Data collection

   During the first phase, target parameters of all newborns are going to be collected.

   Selection of target parameters depends on pathophysiologic pathways and their accessibility. As described in the section regarding pathophysiology and etiology of neonatal jaundice, skin color, blood tests, urine analysis and color, and fecal color are potential sources from which target parameters could be obtained. Remnants of blood samples, taken from each newborn for routine metabolic screening, may serve as a backbone for a screening program dataset. Laboratory analysis of initial target parameters requires 0.6 ml of blood volume, so during the blood drawal for metabolic screen, additional 0.6 ml should be taken (40). Subsequently, if the screening program using only parameters obtained from blood would yield good results, urine collection by a visiting field nurse, or a smartphone application that detects changes in the color of skin or feces could serve as additional sources of information.

2. The second phase: Creation of a predictive algorithm

   Once the dataset containing a representative number of children is made, those children that were referred to a tertiary hospital centre with complications associated with neonatal jaundice should be traced back to the dataset and marked as diseased. After this, a predictive program using artificial intelligence algorithms applied on dataset would be created. Dataset collection would not stop, it would be constantly filled with new data records, thus improving the accuracy of the program all the time.

   In the beginning, dataset would contain reference ranges of target parameters from the literature, that would be compared with collected parameters. After 6 months, reference ranges would be callibrated according to the collected

parameters and be tested on parameters obtained during the next 6 months, after which the final version of predictive program should be created.

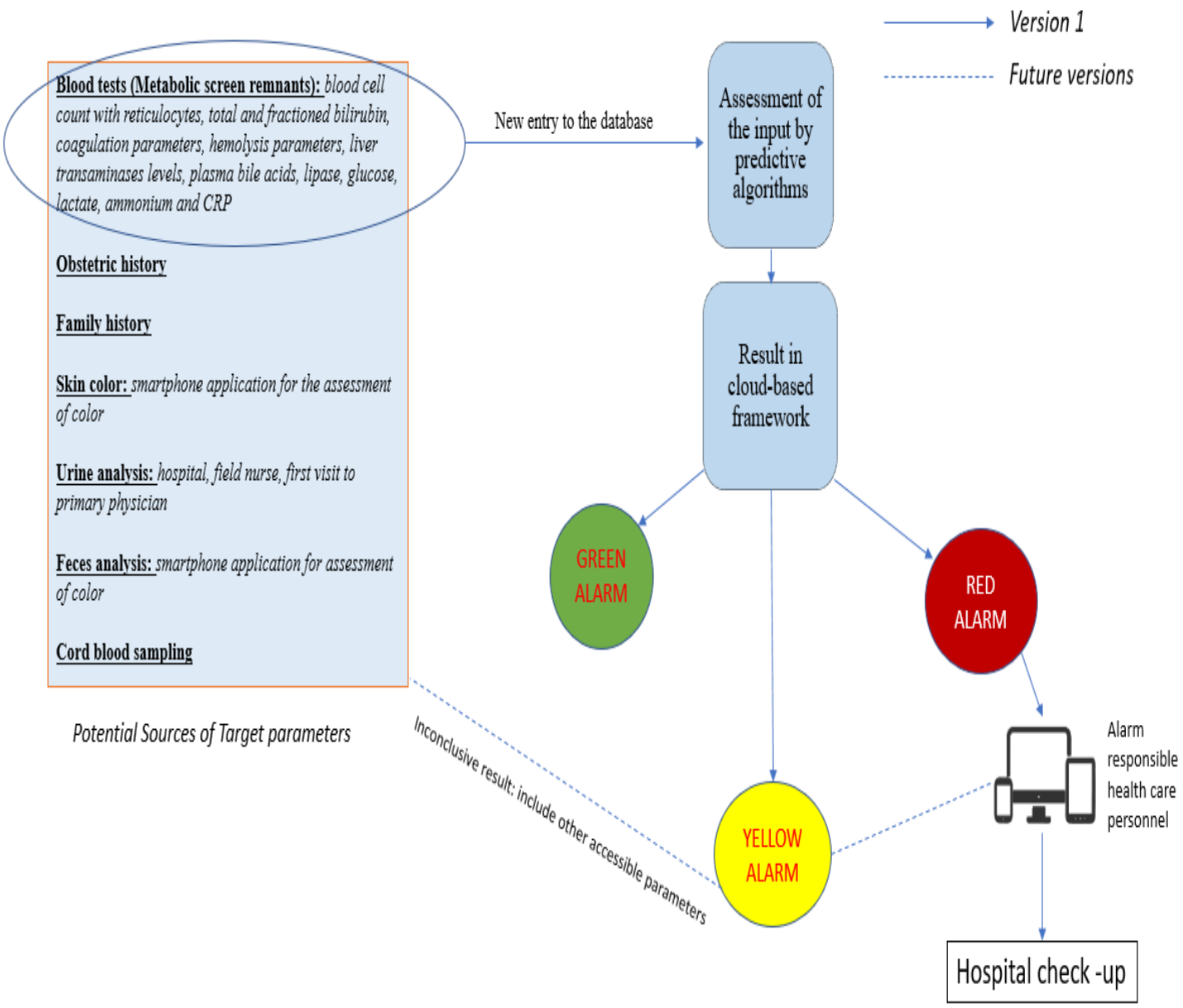

Figure 3. Overview of Predictive Program

3. The third phase: Implementation phase

The predictive program would, upon the new recording input, classify that input into one of three alarming states: critical (red), advisory (yellow) and normal (green). In case of the former two, information would be displayed via Internet of Thing cloud platformon the phones or laptops of the responsible health care personnel. Critical alarm would indicate elaborate diagnostic work-up, while advisory alarm may indicate

other precautionary actions. The alarm time should be in the first two weeks after the birth.

Ultimately, the above-mentioned predictive algorithm, along with its database of target parameters, would have several advantages. Firstly, it would implement technologies available to health care with limited financial resources. Simply put, there would be no need for expensive laboratories or other apparatuses that are almost impossible to obtain due to other high priority challenges of the health care system. Secondly, an algorithm with satisfactory sensitivity and specificity would provide more time for physicians to take preemptive actions for the improvement of the infant's health status. Thirdly, the database would provide an outside-of-the box view of the healthy children and children with neonatal jaundice, that would, by implementing intelligent parameter analysis, potentially open the doors to new research, guidelines and rules related to this area of medicine. Furthermore, other similar problems in neonatology could be upgraded to the existing program.

Data, including medical data, are one of the most valuable assets nowadays. J. Rosenberg, former Senior Vice President of products at Google, said, "Data is the sword of the twenty-first century, those who wield it well, the samurai." In my opinion, unlocking this data and creating a new insight into different aspects of medical science pose a great challenge for future medical advances.

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10. Biography

I was born on 23rd of April in 1994 in Zavidovići, Bosnia and Herzegovina, where I attended primary school. I moved to Zagreb in 2009, where I graduated high school, and in 2013 started my medical studies. I was a demonstrator at the Department of History taking and Physical examination in 2019/2020, and an active participant at the Better Future of Healthy Ageing 2020 (BFHA 2020) conference. My interests lie mostly in internal medicine and artificial intelligence.