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ORIGINAL PAPER

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Management of hyperbilirubinemia and prevention of kernicterus in 20 patients with Crigler-Najjar disease

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Abstract We summarize the treatment of 20 patients with Crigler-Najjar disease (CND) managed at one center from 1989 to 2005 (200 patient-years). Diagnosis was confirmed by sequencing the *UGTA1A* gene. Nineteen patients had a severe (type 1) phenotype. Major treatment goals were to maintain the bilirubin to albumin concentration ratio at <0.5 in neonates and <0.7 in older children and adults, to avoid drugs known to displace bilirubin from albumin, and to manage temporary exacerbations of hyperbilirubinemia caused by illness or gallstones. A variety of phototherapy systems provided high irradiance over a large body surface. Mean total bilirubin for the group was 16±5 mg/dl and increased with age by approximately 0.8 mg/dl per year. The molar ratio of bilirubin to albumin ranged from 0.17 to 0.75 (mean: 0.44). The overall non-surgical hospitalization rate was 0.12 hospitalizations per patient per year; one-half of these were for neonatal hyperbilirubinemia and the remainder were for infectious illnesses. Ten patients (50%) underwent elective laproscopic cholecystectomy for cholelithiasis. No patient required invasive bilirubin removal or developed bilirubin-induced neurological damage under our care. Visual acuity and color discrimination did not differ between CND patients and age-matched sibling controls. Four patients treated with orthotopic liver transplantation were effectively cured of CND, although one suffered significant transplant-related complications.*Conclusions*. While patients await liver transplantation for CND, hyperbilirubinemia can be managed safely and effectively to prevent kernicterus. Lessons learned from CND can be applied to screening and therapy of non-hemolytic jaundice in otherwise healthy newborns.

Keywords Crigler · Najjar · Hyperbilirubinemia · Kernicterus · Phototherapy

Abbreviations BB: Special blue fluorescent tube · BSA: Body surface area · CND: Type I Crigler-Najjar disease · LED: Light-emitting diode

Introduction

Crigler-Najjar disease type I (CND; MIM# 218800)[1] is an autosomal recessive condition caused by absent activity of hepatic UDP-glucuronosyl-transferase (UGT), a protein encoded by the *UGT1A1* gene on chromosome 2 [15]. The absence of UGT activity results in the progressive accumulation of native insoluble 4Z,15Z-bilirubin in the blood and tissues[2], which associates with high affinity to albumin, red blood cell membranes, and tissue phospholipids [8, 12]. A threshold accumulation of bilirubin within focal brain regions leads to relatively abrupt neural dysfunction fol-

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[1] Except where otherwise noted, we use the abbreviation CND to refer to the severe (type I) phenotype.

[2] Historically, bilirubin in the circulation was measured in serum, which remains the convention in our hospital laboratory. However, many laboratories now measure total bilirubin in anti-coagulated blood. Plasma and serum total bilirubin values from the same blood specimen show no differences, and in CND patients the conjugated fraction is negligible. Therefore, in the present text we simply use "total bilirubin" to denote the total unconjugated bilirubin level as measured in plasma or serum.

lowed by cell death and permanent disability [31, 50, 59]. Crigler and Najjar first characterized fatal hereditary non-hemolytic jaundice in 1952 [19]. They described six infants in three families; five children died of kernicterus by 15 months of age, and the remaining patient died at age 15 years, several months after suffering devastating brain injury.

Crigler-Najjar disease is rare in most populations, but a loss-of-function (type I) *UGT1A1* mutation is prevalent among the Amish and Mennonite groups of Pennsylvania and the Midwestern United States. While the development of effective phototherapy systems has altered the course of this previously lethal disease [18, 34], CND patients remain vulnerable to brain injury throughout their life span [14], and the high disease incidence within our local Plain communities necessitated the development of a systematic treatment protocol. We report here uniformly good neurological outcomes for all CND patients managed under this protocol over the last 16 years.

Patients and methods

Patients

Twenty CND patients, ages 0.8–21 years, were managed over a 16-year period and represent 200 patient-years of follow-up (Table 1). Over this same time period, we were consulted about additional children (not included in the 20-patient cohort) who suffered kernicterus. Data from these cases are included under the section Case summaries to illustrate various concepts. For the 17 patients from Amish or Mennonite communities, only exon 1 of *UGT1A1*was sequenced to determine the homozygous 222C→A genotype. For the three remaining patients, all five exons of *UGT1A1* were sequenced according to previously described methods [40]. Written informed consent to DNA testing was obtained from the parents of all patients.

Table 1 Clinical and biochemical summary of 20 patients with Crigler-Najjar disease

Patient information	Mean (range)	
Current age (years)	11 (0.8–21)	
Age treatment started (days)	6 (2–14)	
Number of non-surgical hospitalizations[a]	1.2 (0–5)	
Clinical parameters	**Percentage of patients (*n*=20)**	
Exchange transfusion[b]	10	
Ursodiol therapy	80	
Cholecystectomy	50	
Liver transplantation	20	
Neurological impairment	0	
Visual impairment	0	
Biochemical parameters	**Means, SD (range)**	**Reference range**
Bilirubin (mg/dl)[c]	16±5 (7–28)	0.2–1.0
Albumin (g/dl)	4.3±0.3 (3.6–4.7)	3.5–5.2
Bilirubin:albumin (mol:mol)	0.44±0.15 (0.17–0.75)	Not applicable
Alanine transaminase (IU/l)	75±36 (28–167)	8–50
Alkaline phosphatase (IU/l)	195±68 (38–282)	34–125
γ-Glutamyl transpeptidase (IU/l)	23±21 (14–108)	6–42

[a]Over 50% of non-surgical hospitalizations were for neonatal hyperbilirubinemia, the remainder were for infectious illnesses. Overall hospitalization rate was 0.12 hospitalizations per patient per year
[b]Exchange transfusions were performed on two patients during the newborn period, before they came under our care in 1989. No exchange procedures were performed within the cohort after 1989
[c]Bilirubin in mg/dl×17.1 = bilirubin in μmol/l; albumin in g/dl×152 = albumin in μmol/l

Clinical management

The mainstay of therapy was an overhead array of ten Philips 40 W special blue (BB) fluorescent tubes[3]. In recent years, two other phototherapy systems were used: portable light emitting diode (LED)-based panels (Stanford PortaBed system [55]) and a custom-made "lightbox" housing 24 fluorescent tubes (combined TL52 and BB). For newborns, a BB- or LED-based light source was placed 10–15 cm from the skin for 15–20 h/day with 60–70% of the body surface exposed. For older children and adults using the BB panel and PortaBed systems, light was positioned 15–30 cm from the skin and delivered at night for 8–12 h with 35–50% of the skin exposed. Mirrors were placed at the sides and head of the bed, and all patients used white sheets. Lightbox therapy was provided for shorter daytime intervals (2–3 h) with about 80% of skin exposed. Ursodiol (15–30 mg/kg/day) and a lipid-rich bedtime snack were used to stimulate bile acid-dependent bile flow and increase hepatic clearance of lumirubin, the water-soluble hepatically-excreted bilirubin photoproduct [21].

Irradiance was measured at the skin surface using three different instruments: the BiliBlanket Meter II (Ohmeda Medical, Laurel, Md.), Joey Dosimeter (Respironics, Pittsburgh, Pa.), and a relatively inexpensive light meter (model LM631, Meterman Test Tools, Everett, Wash.) adapted at Stanford University and calibrated against the BiliBlanket Meter II [55]. The dose of light in watt-hours per nanometer (W-h/nm) was estimated as the product of skin-level irradiance (μW/cm^2/nm), surface area exposed (cm^2),

[3] Overhead BB panels were constructed by Floyd Martin under the guidance of DHM. The BiliBlanket II Meter-based light meter and LED-based PortaBed system were designed and constructed by HJV and colleagues. The LED light panel research and development was financed by a grant from the Dutch Crigler-Najjar Association. The upright lightbox was originally designed and built by Alex Carmichael (Australia) utilizing TL52 tubes. A modified BB tube-based lightbox unit, used for this study, was constructed by FM.

and irradiance time (h). Patients were encouraged to derive additional therapy from natural sunlight, using appropriate UV protection.

The approach to inpatient care is summarized in Table 2. Major indications for hospitalization were neonatal hyperbilirubinemia, infection, and surgical illness. During hospitalizations patients received continuous high-intensity phototherapy, albumin infusions (1–2 g/kg/dose, up to every 12 h as indicated), and a continuous dextrose infusion (7–10 mg/kg/min) to suppress endogenous lipolysis and maintain euglycemia. The molar ratio of bilirubin to albumin (bilirubin:albumin) was monitored with a goal to maintain this value at or below 0.7 (mol:mol) for children and adults, and below 0.5 for term neonates. Drugs which displace bilirubin from its albumin binding site were avoided (see Appendix). Plasmapheresis was available at our hospital at all times.

Vision testing

We were particularly interested in measures of visual system injury, as long-term compliance with eye shields is difficult to achieve with CND patients. Standard Snellen eye charts were used to assess visual acuity in CND patients and unaffected siblings controls, ages 5–15 years. Color vision tests were performed on ten CND patients, all over 10 years of age, using the Farnsworth-Munsell 100-

Table 2 Emergency care for the infant, child, and adult with exacerbation of non-hemolytic jaundice[a](*BR* bilirubin, *ALB* albumin

Continuous high-intensity phototherapy
Fresh Special Blue (BB) or energetically equivalent tubes (e.g. TL52, LED system): maximal emission 400–525 nm (peak: 450–460)
Skin-level irradiance >100 μW/cm^2/nm (measured with Ohmeda BiliBlanket II Meter)[b]
White or reflective bedsheets to minimize light absorption
Reflective surfaces (mirrors, aluminum foil) around patient when possible
Light source*4–8 inches (10–20 cm)* from well-perfused skin
Exposure of *at least* 40% of skin surface to light
Duration of exposure: 24 h per day
Unconjugated bilirubin-albumin molar ratio <0.7 for children and adults, <0.5 for healthy term neonates
Infuse human albumin 1–2 mg/kg/dose up to q6 h as needed based on laboratory monitoring
-BR in mg/dl×17.1= BR in μmol/l; ALB in g/dl×152= ALB in μmol/l
-one gram of albumin binds approximately 8.2 mg BR
-molar ratio of 0.7 is 5.7 mg BR per 1 g serum albumin
Monitor for signs of anaphylaxis and/or pulmonary edema and treat appropriately
Avoid iatrogenic bilirubin displacement
Avoid drugs and drug vehicles that displace bilirubin from the albumin binding site[c]
-avoid drug combinations whenever possible
-intravenous bolus drug dosing is especially dangerous
Maximize elimination of 4Z, 15E-photobilirubin (urine) and lumirubin (hepato-enteral)
Ursodiol 15–30 mg/kg/day to optimize bile salt-dependent bile flow
Regular enteral feeding: milk-based formula in infants, lipid-rich foods in children and adults
Oral calcium carbonate (MW: 100 mg/mmol, 40% elemental calcium): children 40–65 mg/kg/day div QID; adults 25–30 mg/kg/day QID
-TUMS (750 mg) contains 300 mg calcium per tablet
-CaCO3 suspension (1250 mg/5 ml) contains 100 mg calcium per milliliter
Hydration (1–1.5 × daily maintenance) to maintain urine output of >4 ml/kg/day
Dextrose therapy to maintain euglycemia, promote insulin release, and reduce plasma fatty acid levels
Dextrose bolus 250 mg/kg (e.g. D25% 1 ml/kg/dose)
Continuous dextrose infusion of >10 mg/kg/min in infants; >7 mg/kg/min in children and adults
Avoid use of intralipid and parenteral amino acid solutions
Control major physiologic variables that can precipitate kernicterus, including (4H's)
Hypercarbia/acidosis
Hypoglycemia or hyperglycemia
Hypernatremia/hyperosmolarity
Hyperthermia

[a]In any patient with idiopathic jaundice, evidence of hemolysis should be sought and treated. Immunologic: maternal anti-Rho or anti-B antibodies, autoimmune hemolytic disease. Red blood cell enzymopathy: G6PD deficiency, pyruvate kinase deficiency. Ineffective erythropoesis: folic acid, vitamin B12 , or iron deficiency. Physical destruction: disseminated intravascular coagulation (eg. bacteremia). Sequestation: internal hemorrhage or occult tissue hematoma. *For acute hemolysis or ineffective erythropoesis:* Tin mesoporphyrin 6 μmol/kg per dose IM

[b]Different light meters produce variable measurements from the same source (see text and figures for details)

[c]Consult the Appendix for a "Drug Safety" table

Hue test [22]. Five of these subjects were from our cohort (ages 11–19 years) and five were managed at the Sophia Children's Hospital in Rotterdam, The Netherlands (ages 12–18 years). None of the CND patients tested wore eye shields during phototherapy. Three age-matched healthy siblings (ages 13–15 years) were used as controls.

Results

Diagnosis

All seventeen patients of Amish or Mennonite descent were homozygous for a 222C→A mutation in exon 1 of the *UGT1A1* gene that resulted in a stop codon (Y74X) and complete absence of transferase activity. Among the remaining patients, two had severe phenotypes (with genotypes c. [1069C→T] + [1069C→T] and c. [1305-1G→A] + [877_890delinsT]) and one had a milder CN variant (with genotype c. [992A→G] + [992A→G]). Patients for whom records were available began receiving phototherapy at 6±5 days of age, before molecular confirmation of the CND diagnosis. In the newborn period, no patient had evidence of infection, hepatopathy, or hemolysis. Bilirubin rose 3–6 mg/dl/day[4], and the hour-specific bilirubin at presentation was equal to or greater than the 75th percentile for healthy term neonates [6] (Fig. 1a). For high-risk neonates (e.g. sibling affected with CND or parents known to be carriers), mutation detection from cord blood was typically completed within the first 72 h of life.

Phototherapy

We detected no serious health consequences for individuals exposed to >75,000 lifetime hours of high-intensity blue light. For patients homozygous for the Y74X mutation, phototherapy maintained total bilirubin at a mean value of 16±5 mg/dl (range: 7–28 mg/dl)[5] and a bilirubin:albumin molar concentration ratio of 0.44±0.15 (range: 0.17–0.75). Major determinants of individual bilirubin values were the total light dose (irradiance × treated surface area × time)[5] and patient age. Despite consistent light dosing, baseline total bilirubin increased at a rate of 0.8 mg/dl/year (r=0.85, Fig. 1b), such that the bilirubin:albumin molar ratio approached 0.7 by age 20 years. Daily illumination time (8–12 h) and percentage body surface treated (35–50%) were similar among children and adults with CND, whereas irradiance varied considerably.

Using the Ohmeda BiliBlanket II Meter, an overhead bank with ten fresh 40 W BB tubes irradiated skin with 95–115 μW/cm^2/nm at a distance of 20 cm. The Joey Dosimeter measured considerably higher irradiance values from a common light source at a similar distance (Fig. 2a). For fluorescent BB systems, major determinants of skin-level irradiance were source distance, hours of use (tube "freshness"), and the nature of surrounding materials. Energy output was also influenced by the length (2–foot vs. 4 foot) and number of tubes in the array, their axis of orientation to the body, and tube temperature; irradiance was highest when a large number of 40 W (4-foot) tubes were oriented parallel to the long axis of the body and kept cool by a separate system of fans. Tube irradiance diminished by 35–40% after about 1,200 h (4 months) of use, but this was not visually detectable. Families that used light meters on a regular basis more effectively controlled the many variables influencing light dose.

Irradiance provided by the PortaBed (96–105 μW/cm^2/nm) was roughly equivalent to overhead BB light banks. Major advantages of the LED panels were portability, source longevity, and sleep under cover, but the system remains prohibitively expensive at this time. The upright "light box" was most effective, delivering a uniform circumferential irradiance that was 1.5- to 2-fold higher than that achieved with either the overhead BB panel or PortaBed (Fig. 2b). Advantages of the light box system were a high surface area exposure, capacity for a large number of tubes, close proximity of light source to skin, and controlled use of reflective surfaces. Because it constrained the patient during waking hours, it was only practical for about 2 h of use per day. All three systems generated considerable heat, necessitating the use of cooling fans and warranting special attention to patient hydration.

Hospitalizations

The overall hospitalization rate was 0.12 hospital admissions per patient per year, and six patients in the cohort (30%) were never hospitalized. Over 50% of all hospitalizations were for neonatal hyperbilirubinemia and occurred within the first 2 weeks of life. Remaining hospitalizations were for various non-surgical and surgical indications. The major reason for non-surgical hospitalization was infectious illness, which was often associated with transiently increased bilirubin and decreased albumin. Daily light dose could be increased in the hospital by adding a second high-intensity unit and increasing exposure time to >20 h/day. However, given the high efficacy of home phototherapy units, patients were not hospitalized for any intensification of phototherapy per se, but for intravenous albumin therapy, more careful clinical and biochemical monitoring, and the treatment of complicating factors

[4] Our hospital laboratory routinely reports bilirubin values in mg/dl and albumin in g/dl, whereas other laboratories use units of μmol/l. To interconvert these units: Bilirubin in mg/dl × 17.1 = bilirubin in μmol/l; albumin in g/dl × 152 = albumin in μmol/l.

[5] Throughout the manuscript, calculated energy doses are based on direct light meter readings over the spectral range found effective toward photodegrading bilirubin (400–525 nm). This range encompasses the blue light absorption spectrum of bilirubin. These measurements are valid for comparing *relative* light energies. However, for more precise calculation of total light energy striking a biological material, such as the retina, we use "full width at half max" (FWHM), defined as the spectral width at half-maximal light intensity. This is also called the "bandwidth" and for practical purposes takes into account the Gaussian distribution of energy over the detectable range.

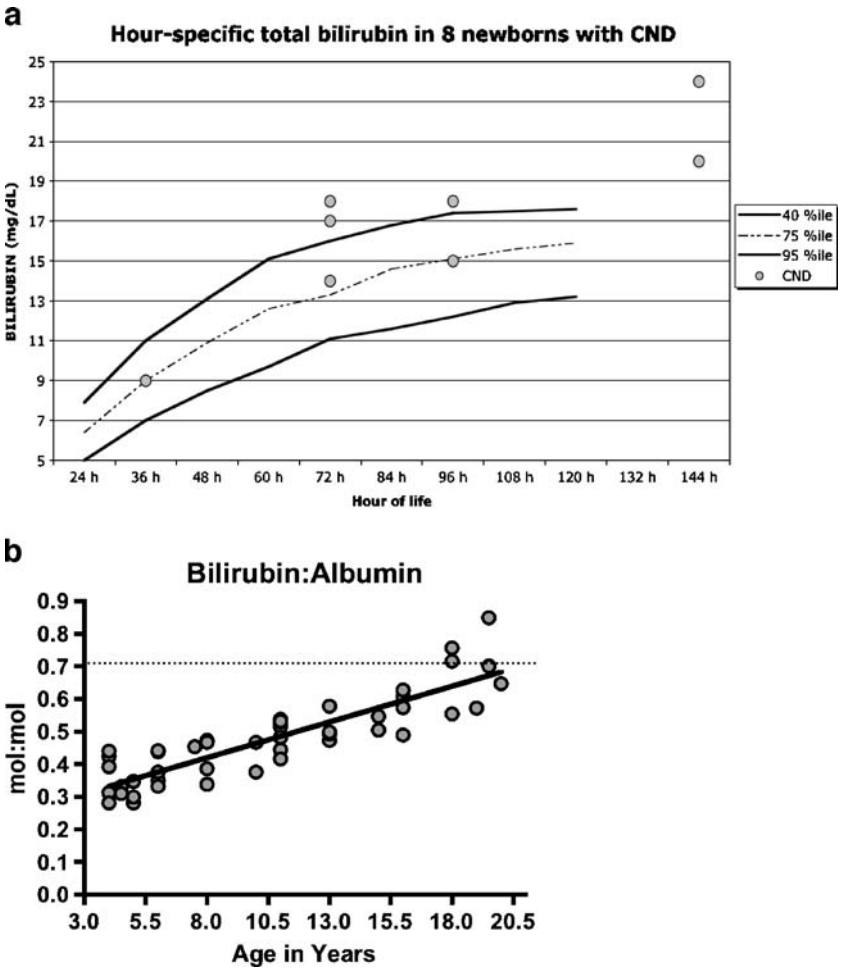

Fig. 1 **a** The rate of rise of bilirubin over the first 96 h of life may be normal in CND patients but continues to rise to dangerous levels by day of life 5. Using the 75th percentile hour-specific bilirubin [6] as a screening cutoff value for predicting severe jaundice (peak bilirubin >17 mg/dl), all of these CND patients would have been identified for targeted follow-up and the early institution of phototherapy. **b** In our CND patients the molar ratio of bilirubin to albumin is elevated from 0.37 to 0.6 during the neonatal period, reaches a nadir by age 4 years, and then rises progressively to adulthood at a rate of 0.022 mol:mol/year (r=0.82). This is due to a progressive 0.82 mg/dl/year (range: 0.68–0.96 mg/dl/year) rise of bilirubin unrelated to patient compliance. Based on the chemistry of bilirubin-albumin binding in healthy individuals, we assign the "safe" bilirubin:albumin molar ratio at or below 0.7 in older children and adults (denoted by the *dashed line*) [8]

(e.g., vomiting, anorexia, dehydration, dysnatremia, etc.). There were no complications of albumin administration, and no patient received plasmapharesis while under our care. Ten of twenty patients (50%) developed cholelithiasis and underwent elective laproscopic cholecystectomy; eight of these patients were being treated with ursodiol prior to developing gallstones.

Neurological outcome

Serial neurological examinations of CND patients showed no evidence of hearing loss, cranial nerve injury, dystonia, cerebellar dysfunction, gait abnormalities, or peripheral neuromuscular disease. Children and adults with CND had normal intellectual function as assessed by school performance and social interactions. Visual acuity was 20/20–30 in both eyes for non-spectacled CND patients over 5 years of age and, compared to unaffected siblings, CND patients did not have an increased need for corrective lenses. The Farnsworth-Munsell color discrimination error score was 58±11 for CND patients and 39±15 for controls (p=0.39, non-significant), where error scores of <100 are consistent with normal color vision.

Liver transplantation

Four patients (ages 12, 14, 19, and 19 years) had whole orthotopic liver transplants performed under standard protocol at the Thomas E. Starzl Institute (Pittsburgh, Pa.). Mean post-transplantation follow-up time was 20 months (range: 12–48 months). Total bilirubin was normal within 24 h of allograft perfusion, but staining of skin and sclerae did not resolve completely for 1–2 weeks. The youngest of these patients had significant post-transplant complications, including CMV hepatitis, EBV viremia, acute and chronic allograft rejection, widespread opportunistic infection of the small bowel, and post-transplant lymphoproliferative disease.

Case summaries

Five clinical cases are grouped by clinical paradigm and briefly summarized. Cases 1, 3, and 5 are patients from the present cohort. Two additional cases (2 and 4) are Amish CND patients from Midwestern states managed elsewhere. Mechanisms of kernicterus are introduced for further discussion (see Figs. 3, 4).

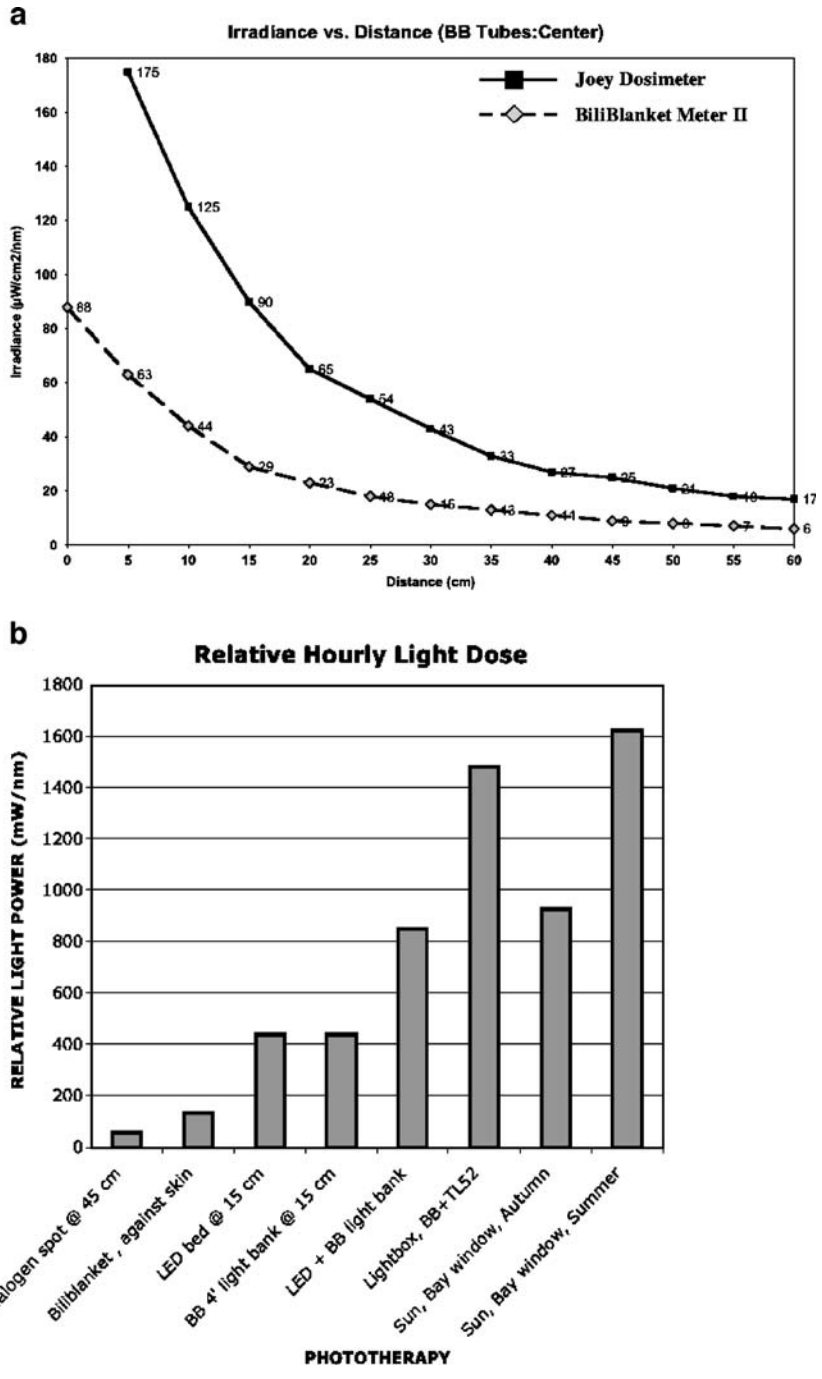

Fig. 2 **a** Using two different light meters, the Ohmeda BiliBlanket Meter II and the Respironics Joey Dosimeter, irradiance measurements were taken at 5-cm increments from an overhead bank of BB tubes (Philips 20 W, 2-foot long) used routinely at a community hospital Neonatal Intensive Care Unit (NICU). BB tubes in use were aged, putting out only about 50% of the power provided by fresh tubes, irradiance decreased as a function of distance from the source, and light meters which should yield roughly equivalent values differed by as much as two- to threefold. **b** The graph displays hourly light power within the 400- to 525-nm bandwidth as the product of skin-level irradiance ($\mu W/cm^2/nm$, BiliBlanket Meter II) and average treatable body surface area with each type of system, estimated for a patient with total body surface area of 1 m^2 (10,000 cm^2). Because irradiance values from the same source vary considerably using different light meters, the graph displays a relative, rather than absolute, comparison of light power

Type I Crigler-Najjar disease in the newborn period

Case 1. Prospective management of CND A Mennonite newborn had a sibling and several cousins homozygous for the Y74X mutation. Phototherapy with an overhead BB light bank was started at home when jaundice was apparent on day of life 3. Cord blood was sent to our clinic for targeted mutation testing, and the diagnosis of CND was confirmed on day of life 6, at which time total bilirubin was 13 mg/dl (222 μmol/l), albumin was 3.7 g/dl (562 μmol/l), and the bilirubin:albumin molar ratio was 0.39. She was managed throughout the first year of life with daily overhead phototherapy and ursodiol (20 mg/kg/day). During that time, total bilirubin ranged from 11.4 to 15.9 mg/dl (194–270 μmol/l) and the bilirubin:albumin ratio ranged from 0.32–0.47. Growth and development were normal, and she had no hospitalizations. She is now 6 years of age, receiving phototherapy 10 h per day, and healthy.

Case 2. Poor neonatal risk assessment, inadequate therapy, and kernicterus In 1997 an Amish infant from the Midwest (not in the 20-patient cohort) was delivered at

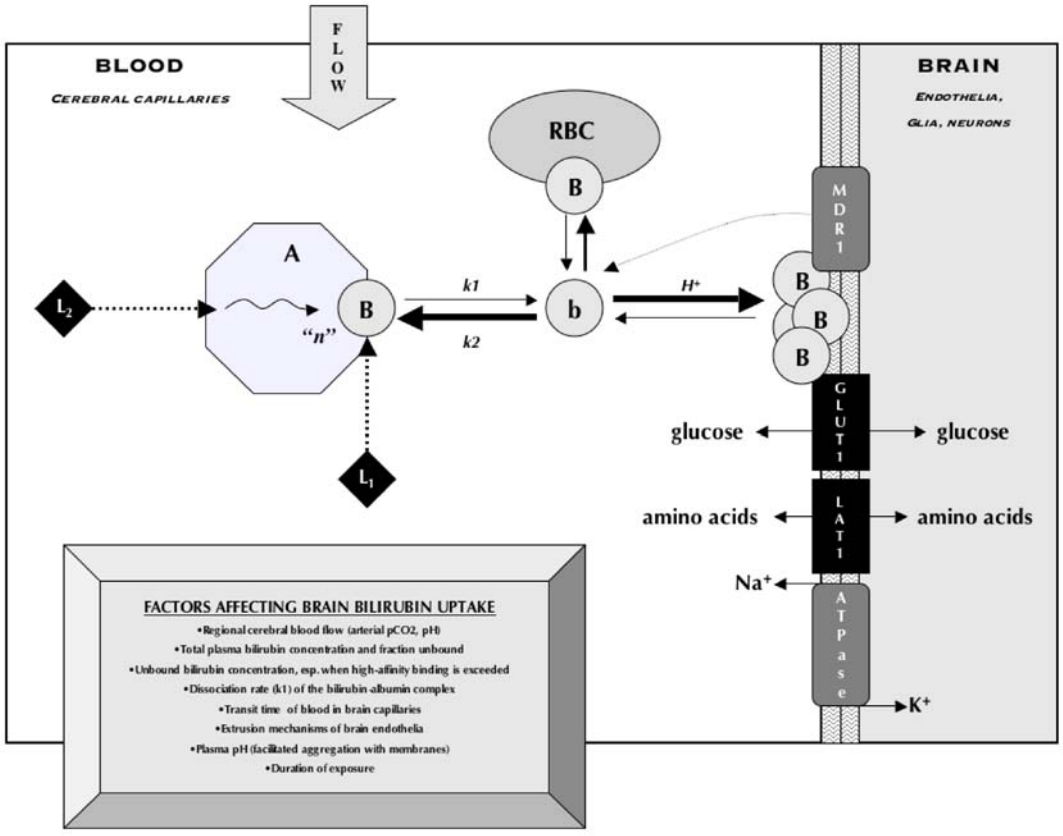

Fig. 3 Bilirubin in the cerebral circulation is bound to albumin and to a lesser extent red blood cells (*RBC*). Unbound bilirubin (*b*) is the fraction that interacts with cerebral membranes, moving continuously between intravascular and extravascular binding sites. Cumulative bilirubin deposition on endothelial membranes interferes with a variety of cellular processes, perhaps by altering the properties of membrane-associated and -embedded proteins such as ion pumps (*NaK-ATPase*), nutrient transporters (e.g.,*GLUT1*, *LAT1*), and metabolic enzymes. The uptake of bilirubin by brain can be expressed by the equation [49]: $D = (F)(B)(t)[1 - fe^{(-k1T)}]$, where D is amount of bilirubin per weight of brain tissue, F is cerebral blood flow, B is total bilirubin concentration (>99% of which is albumin-bound), e is the dimensionless value 2.718, and t is duration of exposure. The last term expresses the relative quantity of bilirubin extracted by the brain for any given total plasma bilirubin value. It depends on the fraction of bilirubin unbound (*f*) and the dissociation constant of the bilirubin-albumin complex (*k1*) relative to the transit time of blood moving through brain capillaries (*T*). Total bilirubin-binding capacity of blood [58] is a function of albumin concentration, the number of high-affinity sites (*n*) per albumin molecule, and affinity of those sites for bilirubin (K_{ab} = k2/k1); where K_{ab} = [B]/(b[nA−B]). A variety of drugs, preservatives, and endogenous anions interact with albumin to either reduce the number of high-affinity binding sites (L_1) or increase the dissociation rate of the complex (L_2; increase k1, decrease K_{ab}). In experimental animals, fractional extraction and brain uptake of bilirubin is invariably 30–50% lower than predicted by this model [59]. This may reflect both the unmeasured effect of erythrocyte binding and the important role of brain endothelial proteins in bilirubin extrusion (e.g. P-glycoprotein, MDR1). Brain bilirubin extrusion matures postnatally and may increase considerably in chronically jaundiced patients

home by a lay midwife. Jaundice was first apparent on day of life 3 but was not measured until he was hospitalized at 14 days of age with lethargy and severe hyperbilirubinemia (48 mg/dl, 821 μmol/l). Liver disease and hemolysis were excluded. Phototherapy decreased total bilirubin to 12 mg/dl over 96 h. He was discharged without phototherapy, and bilirubin again rose to a range of 24–39 mg/dl. He was first examined by us at 7 months of age, and found to be stuporous, irritable, and hypotonic. He had generalized axial dystonia, athetoid movements, poor head control, and feeding impairment. Muscle mass and power were normal, deep tendon reflexes were diminished, and ankle clonus was absent. Babinski reflexes were strongly plantarflexion. Brain stem auditory evoked potentials were absent. A brain MRI showed enlarged cerebrospinal fluid spaces over the frontal and temporal lobes and prominent sulci suggestive of diffuse cortical atrophy. The basal ganglia were normal in size. There were symmetric T2 signal hyperintensities in the internal and external pallidi, nucleus accumbens, substantia nigra, and hypothalamus. At present, he is deaf and has severe generalized dystonia.

Hospital management

Case 3. Prevention of kernicterus in a CND patient during an infectious illness A 7-year-old Amish girl with CND was admitted to our hospital with streptococcal pharyngitis, fever, vomiting, dehydration, rising total bilirubin (31 mg/dl, 530 μmol/l), and a high bilirubin:albumin molar ratio (0.88). She was managed according to an inpatient protocol (Table 1) over a 70-h period. Continuous phototherapy

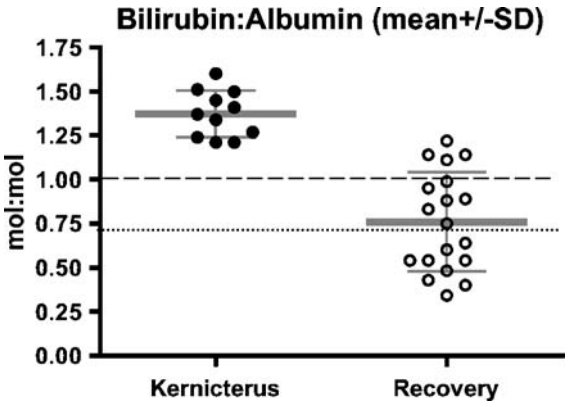

Fig. 4 In vitro studies [8] show a progressive rise in free bilirubin when the bilirubin:albumin molar ratio exceeds 0.7 (*dotted line*) and a sharp rise in free bilirubin when the ratio exceeds 1.0 (i.e., saturation, *dashed line*). Maximum bilirubin:albumin molar ratio was recorded during 19 hospitalizations of our CND patients with transient exacerbation of hyperbilirubinemia (*open circles*). None of these patients developed kernicterus. From our consultation records and published cases, we found 11 cases of brain injury in patients for whom bilirubin and albumin values were available (*solid circles*). Maximum recorded bilirubin:albumin molar ratio was significantly higher in patients that developed kernicterus (1.37±0.04 vs. 0.76± 0.07, $p<0.0001$)

(approximately 13 W-h/nm/day), four albumin infusions (2 g/kg/dose), and enteral ursodiol (30 mg/kg/day) lowered the bilirubin:albumin molar ratio to 0.57. She recovered uneventfully.

Case 4. Acute kernicterus during an infectious illness in a patient with CND An Amish boy with CND (not in the 20-patient cohort) had chronic bilirubin levels of 15–25 mg/dl receiving 6–12 h of phototherapy per day. Albumin levels were not monitored. Bilirubin levels periodically increased to 25–35 mg/dl during illnesses. Growth and development were normal. At 7 years of age he developed streptococcal pharyngitis and was prescribed amoxicillin as an outpatient. The following day his speech became slurred and he stopped eating. Four days later he presented to a Midwestern hospital deeply jaundiced, stuporous and mute, unable to swallow or stand, and febrile. Deep tendon reflexes were increased, he had ankle clonus, and Babinski reflexes were plantarflexion. Total bilirubin was 39 mg/dl (667 μmol/l), albumin was 2.9 g/dl (441 μmol/l), and the bilirubin:albumin ratio was 1.51. Serum chemistries were normal, including glucose (97 mg/dl), bicarbonate (26 mEq/l), and blood urea nitrogen (4 mg/dl). An EEG showed diffuse slowing and paroxysms of generalized polyspike activity. A brain MRI was normal. At the Midwestern hospital, he was managed with continuous phototherapy, intravenous crystalloid, albumin, and phenobarbital. The bilirubin level decreased to his baseline value, but neurological function did not improve. He died at home a few weeks later.

Liver transplantation

Case 5. Liver transplant in a 19-year-old Mennonite man with CND and increasing bilirubin levels The first of our patients to undergo a liver transplant had total bilirubin levels that ranged from 23 to 29 mg/dl (molar ratio to albumin: 0.7–0.9) despite rigid compliance with phototherapy, treatment with ursodiol, and cholecystectomy at age 18 years. Post-transplant, the bilirubin decreased to normal within 48 h, but yellow discoloration of the skin and sclera persisted for 2 weeks. Liver explant showed portal tract fibrosis, inflammation, ductal proliferation, and patchy bridging fibrosis. Crystallized plugs of bilirubin were seen in small degenerating ductules. Centrolobular hepatocytes showed focal hepatocellular giant cell transformation, pseudoacinar formation, leathery degeneration, and cholestasis.

Discussion

Diagnosis and management of CND in the newborn period

Our data demonstrate that CND patients can be detected by universal screening procedures for neonatal hyperbilirubinemia [1, 5, 30] (Fig. 1a). Whether or not a jaundiced newborn has CND does not change their basic need for timely detection and effective treatment; in all of our patients phototherapy was started well before molecular confirmation of the diagnosis (Case 1). Thus, brain injury in neonates with CND does not result from delayed diagnosis per se, but from poor recognition and inadequate treatment of "idiopathic" neonatal hyperbilirubinemia (Case 2).

CND patients can be managed safely to prevent death and disability

Table 3 compares our study to various population measures from five previously published clinical surveys. Crigler and Najjar's classic description preceded the advent of effective phototherapy, and all of their patients developed brain injury and eventually died [19]. The combined data from four recent surveys [37, 52–54] suggest that 23–42% of CND patients suffer neurological injury ranging from mild to severe, 28–50% of patients will need one or multiple exchange transfusions, and 9–38% die of complications related to the disease. In contrast, we had no brain injuries or deaths extending over 200 patient-years and did not perform a single exchange procedure since we began caring for children with CND in 1989. Long-term biochemical data suggest that liver transplantation or some other curative procedure may ultimately be necessary to manage CND patients safely (Fig. 1b, Case 5). Nevertheless, a systematic

Table 3 Historical trends in Crigler-Najjar disease (*NR* not reported, *NA* not applicable)

Reference	Year of publication	Number of Patients	Age in years mean, standard deviation (range)	Bilirubin (mg/dl) mean, standard deviation (range)	Exchange transfusion (%)	Brain damage (%)	Mortality (%)	Liver transplant (%)	Transplant age, mean (range)
Crigler and Najjar [19][a]	1952	6	(0.05–0.9)	24.5 (12.6–44.8)	0	100	100	0	NA
van der Veere et al. [54][b]	1996	57	6.9±6.0	(4.2–42.5)	NR	26	9	37	9.1 (1–23)
Suresh and Lucey [53][c]	1997	42	(<1–21)	20.5±5.5	28	23	0	36	(2.5–16)
Shevel [52][d]	1998	63	NR	NR	NR	59	NR	NR	NA
Nazer [37][e]	1998	12	NR	23.7 (15–37)	50	42	38	17	NR
Present study[f]	2005	20	1±6	16±5 (7–28)	0	0	0	20	16 (12–19)

[a]Crigler and Najjar's original report preceded the advent of exchange transfusion and phototherapy
[b]Brain injured patients (n=8) were transplanted later (14.3±5.9 years) than those without brain damage (n=13, 5.9±5.4 years)
[c]Information is compiled from an international questionaire involving patients from four continents. There is patient overlap with other studies, including our Amish cohort (12 of the 42 patients reported). In the non-Amish subgroup, neurological disability was present in 9 of 30 patients (30%). Mean ± standard deviation bilirubin values (in mg/dl) varied by sub-group: neonatal peak, 26.6±5.8; neonatal typical, 19.8±4.5; postnatal typical, 20.5±5
[d]The 59% incidence of neurological injury is based on an extensive review of 37 published articles (1952–1997) by these authors, who further subdivided adverse outcomes into four discrete patterns of disability
[e]Information from 5 affected siblings, not included in the 12-patient cohort, is included in the paper by Nazer et al. All 5 died with bilirubin-induced brain injury, resulting in a total brain injury rate of 10/17 (59%) and a disease-related mortality of 38%. Four patients required more than one exchange transfusion, for a total of 13 exchange procedures among 6 of the 12 patients reported
[f]Prior to coming under our care, two patients in the cohort required exchange transfusion as neonates, and one patient developed kernicterus. However, the outcomes reported here were observed for patients under our care from 1989 to the present

approach to neonatal screening, light dosing, and kernicterus prevention can assure that children and adults proceed to transplantation in good neurological health.

Providing effective phototherapy

Effective phototherapy for any patient requires education of health care providers and parents, phototherapy systems that are in good working order, a supply of fresh BB tubes or an energetic equivalent (e.g., TL52s, LEDs), and the use of calibrated and affordable light meters [56]. Variables that influence light dose can be monitored intermittently by a nurse, physician, or parent, and allow patients to derive adequate phototherapy from a variety of sources in the hospital or at home. To be meaningful in terms of efficacy, a phototherapy order should specify light source and number, distance from the patient's skin, and nature of surrounding materials (e.g., white sheets and mirrors), with a goal to achieve a measured irradiance over a percentage of skin surface for a specified period of time. A physician's order for phototherapy in "hours per day" is incomplete, and an order for "double" or "triple" phototherapy is uninformative. One good light is usually sufficient, provided it is used correctly.

Surprisingly, many hospital practices use phototherapy systems without regularly monitoring or recording their performance. Data in Fig. 2a was obtained from a 20 W fluorescent BB system in use at the NICU of a local community hospital. It revealed visually imperceptible aging of the tubes. In hospital settings, tubes may only be replaced when they no longer function, such that phototherapy systems operate for long periods emitting well below their energy potential. Furthermore, fluorescent devices are often fitted (1:1) with cool-white bulbs to attenuate the blueness of BB light; this makes the system less effective. Figure 2a also shows that despite measurement within a similar bandwidth and peak sensitivity, irradiance readings from different commercial light meters can vary as much as two- to threefold, while all meters show the decay of energy as a function of distance from the light source. Light power calculations also demonstrate the comparatively low efficacy of fiber-optic blankets and halogen-quartz spotlights, which are inappropriate for managing patients with CND or severe idiopathic jaundice (Fig. 2b). These observations have several practical implications: (1) light meter(s) in use at any facility should be calibrated at a determined distance against each phototherapy system operating at maximum output; (2) any light source should be placed as close to the skin as possible; (3) phototherapy systems should be accompanied by a tag or logbook that records the date of bulb/tube replacements and peak irradiance measurement with fresh lights at a standardized distance; (4) for an infant who genuinely *needs* phototherapy, home treatment with a fiberoptic blanket is inappropriate.

Other factors reduce the dose of light achieved with a given source, including plexiglass barriers, pigmented (light-absorbing) materials, and objects that shield the skin. We find that isolettes are not necessary for well-hydrated term or near-term infants receiving phototherapy. In neonates, the thorax, outer arms, and head constitute the majority of

treatable skin surface, these but may be obscured by unnecessary diapers, monitor leads, and IV boards. We place term newborns with CND in an open crib, naked, lying on an open diaper over bright white sheets. With a BB or LED system placed 10–15 cm from the skin, the newborns appear comfortable, feed well, and maintain core body temperatures of 99°–100°F.

Anticipating and preventing kernicterus

Patients with all variants of CND remain vulnerable to brain injury throughout life, particularly during intercurrent illnesses, after injuries, or during surgery (Case 4). Routine laboratory measurements can only be used to estimate the magnitude of the whole body bilirubin load and its rate of change, but for any individual patient a variety of other clinical and physiological details more fully characterize the potential for brain injury (Figs. 3, 4). These multiple factors vary from one individual to the next and in a single individual depending on age and clinical conditions. It is thus impractical and misleading to assign rigid guidelines for identifying patients "at risk" for kernicterus. Rather, we base treatment decisions on general biochemical indices considered together with particulars of time and circumstance.

Our treatment protocol in Table 2 is based on the pathophysiologic model illustrated in Fig. 3 [3, 12, 39, 49, 58, 59] and is designed to lower total body exchangeable bilirubin and prevent its movement to extravascular sites. In jaundiced infants and adults, the total body bilirubin pool is very large and almost exclusively bound to proteins and lipid membranes, while the lower unbound bilirubin concentration [2, 3] is characterized by continual flux between two competing reservoirs – a finite number of intravascular binding sites and a much larger number of lower-affinity sites on endothelia of brain and other organs. As bilirubin passes through the circulation, the *fraction* deposited in the brain and other tissues depends only on its molar relationship with high-affinity albumin binding sites and the dissociation rate of the bilirubin-albumin complex relative to the time it takes blood to transit a tissue capillary bed [49, 58]. According to this model, when high-affinity bilirubin binding sites on albumin approach saturation, or are occupied by competing ligands, bilirubin can shift rapidly from intravascular to tissue binding sites (Fig. 3).

In clinical practice, the most important factor affecting bilirubin-albumin binding is the presence of organic anions which either compete directly for the bilirubin binding site or allosterically reduce its affinity for bilirubin [58]. Numerous exogenous and endogenous organic anions interfere with bilirubin-albumin binding, including intravenous and oral medications, drug metabolites produced in vivo, commonly used preservatives, and endogenous organic acids and free fatty acids. Drugs which generally *do not* interfere with the binding equilibrium are cationic, glycosylated, or present in blood at protein-bound concentrations of <15 μmol/l [47]. The number and complexity of bilirubin-albumin-drug interactions underscores the point that *all medications and intravenous solutions should be used cautiously in patients with hyperbilirubinemia, and only after a focused review of drug information in the Physicians' Desk Reference, medical literature, and/or a comprehensive pharmacology text*. Based on available resources [3, 4, 7, 9–11, 13, 17, 20, 23, 24, 26–29, 32, 35, 38, 42–47, 57, 58], we compiled a list of commonly used drugs, infusible substances, and endogenous metabolites in the Appendix. Drugs are listed based on probable safety for use in hyperbilirubinemic patients. However, it is important to recognize that in vitro studies are not a perfect predictor of drug-albumin-bilirubin in living patients. For example, drugs in the "variable safety" column show weak displacing activity in vitro which may become clinically significant under certain circumstances. For these compounds, lower dosing and slower infusion rates minimize displacing potential. Important clinical drugs for which no data are available are listed to guide further studies in this important area.

Caring for the aging CND population

Adolescence is a particularly important period of vulnerability for kernicterus in patients with CND. As patients mature, phototherapy increasingly interferes with lifestyle, social opportunities, and the formation of intimate relationships. Baseline total bilirubin increases with age and approaches dangerous levels in young adulthood (Fig. 1b, Case 5). Contrary to other studies [53, 54], we could not identify a relationship between age and compliance with phototherapy as a plausible explanation. The progressive rise in bilirubin is likely influenced by several physiological variables. First, "treatable" body surface area decreases relative to bilirubin volume of distribution as patients age (i.e., plasma in the cutaneous vascular bed accessible with light represents a progressively smaller proportion of total extracellular volume and distributed blood flow). Second, bilirubin distributes to peripheral extravascular binding sites over time, creating a large tissue "reservoir" in equilibrium with the intravascular pool. Evidence of this was found in all four transplanted patients, in whom cutaneous and scleral icterus took up to 2 weeks to dissipate following liver transplantation, despite normal bilirubin levels within 24–48 post-operative hours. Finally, hepatobiliary clearance of lumirubin may become rate-limiting in some patients, as evidenced by cholestatic changes in two of four liver explants.

Whatever the causes of rising bilirubin with age, it is apparent that most of our CND patients will face liver transplantation over the next 5–10 years. Liver transplantation is currently the only clinically robust way to replace *UGT1A1* and hepatic transferase activity [51]. Viral and non-viral gene transfection techniques are far from human trials, and when these methods reach clinical maturity they may not be safer, cheaper, or even more effective than liver transplantation. Fortunately, there is now considerable experience with liver transplantation for primary metabolic disorders as well as reductions in peri-operative mortality and medication-related morbidity over recent years [33, 41, 51]. How-

ever, Patient 7 from our cohort suffered life-threatening post-transplant complications. Thus, despite its metabolic efficacy, liver transplantation is not an easy solution for patients with CND.

Conclusion: lessons learned from CND

Timely recognition of hyperbilirubinemia followed by effective phototherapy makes exchange transfusions and prolonged hospitalizations unnecessary. The core principles of management for neonates with idiopathic hyperbilirubinemia should be the same as those for CND: pre-symptomatic detection, timely risk assessment, scheduled follow-up monitoring, phototherapy guided by measurements of light power, treatment of maximum body surface, and the use of emergency protocols that emphasize bilirubin biodistribution (Table 2, Figs. 1a, 2a, 3, 4) [1]. A precise formulation of kernicterus mechanisms remains obscure, but a great deal is known about bilirubin, its distribution in the body, and interaction with the brain. We believe this knowledge is sufficient to prevent brain injury in most, if not all, jaundiced patients. The most significant obstacle to the prevention of kernicterus is not scientific ignorance, but inadequate education of parents and health care providers, and a failure to translate established concepts into practice [5, 16, 25, 36, 48].

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Appendix

Potential bilirubin-albumin displacing interactions (see text for references)

	SAFETY CLASS (see Note)			
	1	2	3	4
ANTI-INFLAMMATORY/ANTIPYRETIC				
Acetaminophen	•			
Aspirin		•		
Dexamethasone	•			
Ibuprofen			•	
Indomethacin				•
Ketorolac				•
Naproxen	•			
Phenacetin	•			
Prednisolone	•			
Salicylate, sodium		•		
ANTIMICROBIAL				
Acyclovir	•			
Amoxicillin			•	
Amoxicillin-Clavulanate			•	
Amphotericin B	•			
Amphotericin, liposomal				
Ampicillin			•	
Ampicillin-Sulbactam				•
Azithromycin				
Azlocillin				•
Aztreonam		•		
Carbenicillin				•
Cefazolin			•	
Cefalothin	•			
Cefepime				•
Cefixime				•
Cefmetazole		•		
Cefonicid		•		
Cefoperazone		•		
Ceforanide	•			
Cefotaxime			•	
Cefotetan		•		
Cefoxitin				•
Cefpodoxime proxetil				•
Ceftazidime	•			
Ceftizoxime	•			
Ceftriaxone		•		
Cefuroxime	•			
Cefuroxime axetil	•			
Cephalexin				•
Cephapirin	•			
Cephradine	•			
Ciprofloxacin	•			
Clarithromycin				•
Clindamycin	•			
Dicloxacillin		•		
Doxycycline				•
Erythromycin	•			
Erythromycin ES-sulfisoxazole		•		
Fusidic acid	•			
Gangcyclovir				•
Gentamicin	•			
Imipenem	•			
Imipenem-cilastatin	•			
Isoniazid	•			
Levofloxacin				•
Lincomycin	•			
Linezolid				•
Meropenem				•
Methicillin			•	
Metronidazole	•			
Minocycline				•

	SAFETY CLASS (see Note)			
	1	2	3	4
Nafcillin	•			
Nitrofurantoin				•
Oxacillin	•			
Penicillin G	•			
Penicillin V		•		
Piperacillin	•			
Piperacillin-Tazobactam	•			
Rifampin				•
Streptomycin	•			
Sulfisoxazole		•		
Sulphamethoxazole		•		
Sulphasalazine		•		
Tobramycin	•			
Trimethoprim	•			
Trimethoprim-Sulfa (Bactrim)		•		
Vancomycin	•			
CARDIOVASCULAR DRUGS				
Atropine	•			
Bretylium tosylate	•			
Digoxin	•			
Disopyramide	•			
Dobutamine	•			
Dopamine	•			
Edrophonium chloride	•			
Enalapril	•			
Epinephrine	•			
Hydralazine	•			
Isoproterenol	•			
Lidocaine	•			
Nitroprusside	•			
Procainamide	•			
Propanalol	•			
Verapamil	•			
CONTRAST AGENTS				
Diatrizoate sodium				•
Iodate sodium		•		
Iodipamide sodium		•		
Iopanoic acid		•		
Meglumin ioglycamate		•		
Metrizamide	•			
Metrizoate sodium				•
DIURETICS				
Acetazolamide		•		
Bumetanide	•			
Chlorothiazide				•
Ethacrynic acid		•		
Furosemide			•	
Hydrochlorothiazide			•	
Mannitol	•			
Spironolactone	•			
NEUROACTIVE DRUGS				
Aminophylline		•		
Amitryptyline HCl	•			

	SAFETY CLASS (see Note)			
	1	2	3	4
Atomoxetine				•
Bupropion				•
Carbamazepine	•			
Chloral hydrate	•			
Clonazepam	•			
Codeine	•			
Desipramine HCl				•
Diazepam	•			
Ethosuximide	•			
Etomidate				•
Fentanyl	•			
Fluoxetine/Norfluoxetine				•
Inhaled anesthetics	•			
Imipramine HCl				•
Ketamine	•			
Lorazepam	•			
Meperidine	•			
Methylphenidate				•
Midazolam	•			
Morphine	•			
Naloxone	•			
Nortryptyline	•			
Olanzapine				•
Oxazepam	•			
Paroxetine				•
Phenobarbital	•			
Phenytoin	•			
Primidone	•			
Propofol				•
Risperidone				•
Theophylline				•
Thiopental	•			
Valproic acid			•	
Venlafaxine				•
NEUROMUSCULAR BLOCKING AGENTS				
Neostigmine	•			
Pancuronium	•			
Rocuronium				•
Succinylcholine				•
Vecuronium	•			
PRESERVATIVES/METABOLITES [a]				
N-acetyl-DL-tryptophan			•	
N-acetyltyrosine				•
Benzoic acid (benzoate sodium)		•		
Caprylic acid			•	
Hippurate (from benzoic acid)				
2-Hyroxybenzoylglycine		•		
MISCELLANEOUS				
Bicarbonate	•			
Calcium chloride	•			
Calcium gluconate	•			
Carnitine	•			
Clofibrate	•			

	SAFETY CLASS (see Note)			
	1	2	3	4
Heparin	•			
Intralipid/free fatty acids [b]			•	
Magnesium sulfate	•			
Prostaglandin E1	•			
Tin mesoporphyrin				•

1 Probably SAFE for clinical use

2 Considered UNSAFE

3 Safety variable: eg. drug dosing and combinations

4 Insufficient data

a) acetyltryptophan (stabiliser in HSA I), acetyltyrosine (component of some TPN amino acid mixtures), caprylic acid, hexanoic acid (stabiliser in HSA I and II)

b) plasma free fatty acids are increased by fasting and infusions of intralipid, epinephrine, or heparin

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