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Kernicterus and Bilirubin-Induced Neurological Dysfunction: Pathophysiology, Risk Stratification, Pharmacotherapeutic Management and Strategies for Prevention: A Narrative Review

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ABSTRACT

Kernicterus is a severe and potentially permanent neurological disorder caused by bilirubin induced neurotoxicity, most often following severe unconjugated hyperbilirubinemia in newborn infants. The clinical spectrum, now grouped under bilirubin-induced neurologic dysfunction (BIND), ranges from transient, subtle neurological signs to acute bilirubin encephalopathy and chronic bilirubin encephalopathy (kernicterus), which is characterised by athetoid cerebral palsy, auditory dysfunction, upward-gaze abnormalities and dental enamel hypoplasia. Unbound (free) unconjugated bilirubin crosses the immature or compromised blood–brain barrier and accumulates in vulnerable regions, notably the globus pallidus, subthalamic nucleus, hippocampus, cerebellum and brainstem auditory and oculomotor nuclei. Prematurity, isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, sepsis, hypoalbuminemia and clinical instability increase susceptibility, so risk depends on more than the total bilirubin concentration alone. Intensive phototherapy is the cornerstone of treatment, converting bilirubin into water-soluble photoisomers that are excreted without hepatic conjugation. Double-volume exchange transfusion is reserved for severe hyperbilirubinemia, signs of encephalopathy or failure of intensive phototherapy, and intravenous immunoglobulin has a selective role in isoimmune hemolytic disease. Drugs that displace bilirubin from albumin, such as ceftriaxone and sulfonamides, require careful avoidance in jaundiced neonates. Prevention rests on antenatal and neonatal risk assessment, anti-D prophylaxis, support of feeding, universal pre-discharge bilirubin screening, timely treatment and structured post-discharge follow-up. The 2022 American Academy of Pediatrics guideline bases treatment thresholds on gestational age, hour-specific total serum bilirubin and neurotoxicity risk factors. This review summarises current knowledge of pathophysiology, risk stratification, pharmacotherapeutic management and prevention, and highlights the role of the clinical pharmacist.

Keywords: Kernicterus; bilirubin encephalopathy; bilirubin-induced neurologic dysfunction; neonatal jaundice; unconjugated bilirubin; phototherapy; exchange transfusion; hyperbilirubinemia; neurotoxicity.

1. Introduction

Neonatal jaundice is among the most frequent conditions of the newborn period, and some degree of visible jaundice affects most term and late-preterm infants during the first week of life [1,2]. In most infants it is benign and self-limiting. In a minority, however, serum unconjugated bilirubin rises to levels that overwhelm the protective capacity of albumin binding and the blood–brain barrier, producing acute bilirubin encephalopathy (ABE) and, if injury becomes permanent, kernicterus [3,4]. The term *kernicterus*, from the German for “nuclear jaundice”, originally described the yellow staining of the basal ganglia and brainstem nuclei found at autopsy [5].

Kernicterus is largely preventable. Following the introduction of anti-D immunoglobulin, phototherapy and exchange transfusion, it became rare in high-income countries, but case series and registries in the early 2000s documented its re-emergence, particularly among earlydischarged late-preterm and term infants who received inadequate follow-up [6-8]. In low- and middle-income countries (LMICs) the burden remains substantial because of limited access to bilirubin measurement, phototherapy and exchange transfusion, together with a high prevalence of Rh disease and G6PD deficiency [9-11].

Clinical pharmacists contribute to kernicterus prevention in several ways: reviewing neonatal drug regimens for agents that displace bilirubin or cause hemolysis, advising on immunoglobulin products, promoting anti-D prophylaxis, counselling mothers, and supporting guideline-based protocols. This narrative review therefore integrates the pathophysiology, risk stratification, pharmacotherapeutic management and prevention of kernicterus, with emphasis on the 2022 American Academy of Pediatrics (AAP) guideline [12].

1.1 Literature search strategy

This narrative review is based on a search of PubMed/MEDLINE, Scopus and Google Scholar for articles published up to 2025 using the terms "kernicterus", "bilirubin encephalopathy",

"bilirubin-induced neurologic dysfunction", "neonatal hyperbilirubinemia", "phototherapy", "exchange transfusion" and "intravenous immunoglobulin". Clinical practice guidelines, technical reports, systematic reviews, randomised trials and key observational studies in English were prioritised. Reference lists of retrieved articles were also screened. [Authors to confirm databases, date of last search and inclusion criteria before submission.]

2. Epidemiology and Burden

Estimates of the global burden indicate that severe neonatal hyperbilirubinemia affects a large number of late-preterm and term newborns every year, with the greatest burden of death and disability in sub-Saharan Africa and South Asia [10,11]. Rh hemolytic disease, G6PD deficiency, ABO incompatibility, sepsis and delayed or inadequate care are the leading contributors in LMICs [13]. In India, neonatal jaundice is a common cause of admission and readmission to neonatal units, and hemolytic disease and G6PD deficiency are important preventable contributors [14].

In high-income settings, population-based data show that hazardous hyperbilirubinemia is uncommon and that kernicterus is rare, with estimates varying by the surveillance method used [15,16]. Importantly, a high total serum bilirubin (TSB) does not invariably cause kernicterus: in one large cohort, infants with TSB ≥25 mg/dL (428 μmol/L) rarely developed neurological sequelae, which demonstrates that TSB alone is an imperfect predictor of neurotoxicity [17]. Conversely, kernicterus has been reported at relatively modest TSB levels in preterm infants and in infants with hemolysis, sepsis or acidosis [18,19].

3. Bilirubin Metabolism

Bilirubin is the end product of heme catabolism. Heme is converted by heme oxygenase to biliverdin, which biliverdin reductase reduces to unconjugated (indirect) bilirubin, a lipophilic molecule that is poorly water soluble [1,20]. In plasma it is carried bound to albumin and delivered to hepatocytes, where uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) conjugates it to water-soluble mono- and diglucuronides that are excreted in bile. In the intestine, conjugated bilirubin may be deconjugated by β-glucuronidase and reabsorbed (enterohepatic circulation), which is exaggerated in the newborn [1].

Neonates are predisposed to hyperbilirubinemia because of (i) increased bilirubin load from a higher red-cell mass with a shorter red-cell lifespan, (ii) immature hepatic uptake and conjugation, with low UGT1A1 activity, and (iii) increased enterohepatic circulation, particularly when feeding is inadequate [1,2]. Any additional process that raises production (hemolysis) or reduces elimination (for example, genetic UGT1A1 variants, sepsis, hypothyroidism) amplifies the risk [1].

4. Pathophysiology of Bilirubin Neurotoxicity

4.1 Role of unbound bilirubin

Only the fraction of bilirubin not bound to albumin (unbound or free bilirubin, Bf) can readily enter the brain [21]. Albumin has a high-affinity binding site for bilirubin, and binding capacity is reduced by low albumin concentration, acidosis and competition from displacing substances, including certain drugs and free fatty acids [3,21]. Consequently, two infants with identical TSB may have markedly different free-bilirubin concentrations and neurotoxic risk. Although free bilirubin correlates better with neurotoxicity than TSB in experimental and some clinical studies, assays are not widely available and standardised, and TSB remains the basis of treatment thresholds in current guidelines [12,21].

4.2 Entry into the brain and cellular injury

Free bilirubin crosses the blood–brain barrier by passive diffusion, and the barrier is more permeable when it is immature or injured by sepsis, hypoxia, acidosis or hyperosmolality [3,22]. Efflux transporters such as P-glycoprotein and multidrug resistance-associated protein 1 normally limit brain accumulation, and impairment of these defences increases vulnerability [22]. Within neural tissue, bilirubin impairs mitochondrial function, induces oxidative stress, disturbs calcium homeostasis, promotes glutamate-mediated excitotoxicity and activates microglia and astrocytes to release pro-inflammatory mediators, resulting in neuronal dysfunction, apoptosis and necrosis [22,23]. Immature neurons and oligodendrocyte-lineage cells appear particularly sensitive [22].

4.3 Selective vulnerability

Injury is regionally selective. The globus pallidus and subthalamic nucleus are most consistently affected, followed by the hippocampus, cerebellum (including the dentate nucleus) and brainstem nuclei, namely the auditory (cochlear and olivary), oculomotor and vestibular nuclei [5,24]. This distribution explains the characteristic clinical tetrad of chronic bilirubin encephalopathy. On magnetic resonance imaging, acute injury produces increased T1 signal in the globus pallidus, while chronic injury produces increased T2 signal in the same region [24,25].

Figure 1. Sequence of events from increased bilirubin load to kernicterus.

Hemolysis / increased bilirubin production ± reduced hepatic conjugation

↓

Unconjugated hyperbilirubinemia

↓

Reduced albumin binding → increased unbound (free) bilirubin

↓

Crossing of the blood–brain barrier (↑ permeability: sepsis, acidosis, prematurity)

↓

Neuronal and glial uptake: mitochondrial dysfunction, oxidative stress, excitotoxicity, inflammation

↓

Acute bilirubin encephalopathy (reversible if treated promptly)

↓

Permanent neuronal injury in basal ganglia, auditory and brainstem nuclei

↓

Chronic bilirubin encephalopathy (kernicterus)

Schematic synthesised from references [3,4,22].

5. Clinical Spectrum

The term BIND describes the continuum of neurological manifestations attributable to bilirubin, from subtle and possibly transient signs to classical kernicterus [4]. Acute bilirubin encephalopathy evolves through three recognised phases. In the early phase, infants show lethargy, hypotonia and poor suck. In the intermediate phase they develop moderate stupor, irritability, hypertonia, a high-pitched cry and sometimes fever. In the advanced phase there is marked arching of the neck and trunk (retrocollis and opisthotonos), a shrill cry, apnea, seizures and coma, and this phase is generally associated with irreversible injury [4,6,12]. The BIND score (Table 1) grades mental status, muscle tone and cry pattern and can help identify infants requiring emergency intervention [26].

Table 1. Bilirubin-induced neurologic dysfunction (BIND) score.

Clinical sign	Score 0	Score 1	Score 2	Score 3
Mental status	Normal	Sleepy but arousable; decreased feeding	Lethargic, irritable, poor suck	Semi-comatose, apnea, seizures, coma
Muscle tone	Normal	Persistent mild-tomoderate hypotonia	Mild-to-moderate hypertonia alternating with hypotonia; arching	Persistent retrocollis/opisthotonos; bicycling movements
Cry pattern	Normal	High pitched when aroused	Shrill, difficult to console	Inconsolable crying or cry weak/absent

Total score 1–3: subtle; 4–6: moderate (reversible with urgent treatment); 7–9: advanced (likely irreversible). Adapted from Johnson et al. [26].

Chronic bilirubin encephalopathy develops over the first year of life and is classically a tetrad: (i) movement disorder, most often athetoid or dystonic cerebral palsy; (ii) auditory dysfunction ranging from isolated auditory neuropathy spectrum disorder to sensorineural hearing loss; (iii) oculomotor impairment, especially limitation of upward gaze; and (iv) dental enamel hypoplasia of the deciduous teeth [24,27]. Intellect is frequently preserved relative to the severity of motor disability, which can lead to under-recognition of cognitive potential [24]. Isolated or milder BIND, for example auditory neuropathy or subtle neurodevelopmental, behavioural and cognitive deficits, may follow lesser degrees of exposure [4,27].

6. Risk Factors and Risk Stratification

Risk factors for severe hyperbilirubinemia include lower gestational age, East Asian or Mediterranean ancestry, a sibling who required phototherapy, exclusive breastfeeding with suboptimal intake, cephalohematoma or significant bruising, and jaundice within the first 24 hours of life [12,13,28]. Separately, the AAP defines neurotoxicity risk factors that lower the treatment threshold because they increase the likelihood that a given bilirubin level will cause brain injury (Table 2) [12].

Table 2. Neurotoxicity risk factors that lower treatment thresholds (AAP 2022).

Risk factor	Comment
Gestational age <38 weeks	Risk increases progressively with decreasing gestational age; latepreterm infants are particularly vulnerable [7,12,19]
Albumin <3.0 g/dL	Reduced bilirubin-binding capacity increases free bilirubin [12,21]
Isoimmune hemolytic disease	Rh, ABO or minor antigen incompatibility, usually with a positive direct antiglobulin test (DAT) [12,29]
G6PD deficiency	Rapid, unpredictable hemolysis; strongly associated with kernicterus [30,31]
Other hemolytic conditions	For example hereditary spherocytosis, pyruvate kinase deficiency [12]
Sepsis	Increases barrier permeability and may impair albumin binding [3,12]
Clinical instability in the previous 24 hours	Includes acidosis, hypoxia, hypothermia, hypoglycemia and need for respiratory or hemodynamic support [12]

Source: Kemper et al. [12]; supporting evidence as cited in the table.

The 1999 hour-specific bilirubin nomogram demonstrated that the percentile track of a predischarge TSB predicts subsequent significant hyperbilirubinemia [32], and subsequent work showed that combining the pre-discharge measurement with gestational age and other clinical factors further refines prediction [33,34]. The 2022 AAP guideline replaced the earlier riskzone approach with thresholds that depend on gestational age (35 to ≥40 weeks), age in hours and the presence or absence of neurotoxicity risk factors [12,35,36].

7. Assessment and Diagnosis

Visual assessment is unreliable, particularly in infants with darker skin, and cannot be used alone to decide whether bilirubin should be measured [12,37]. Transcutaneous bilirubin (TcB) is a useful screening tool, but TSB is the definitive measurement for treatment decisions, and TcB values approaching the phototherapy threshold or above approximately 15 mg/dL should be confirmed by TSB [12,33]. Evaluation of an infant with significant hyperbilirubinemia should include blood group and DAT, complete blood count and smear, reticulocyte count, serum albumin where indicated, and G6PD testing when clinically appropriate. Direct (conjugated) bilirubin should be fractionated when jaundice is prolonged or the infant appears unwell, since conjugated hyperbilirubinemia requires a different diagnostic pathway [12,28].

Diagnosis of ABE is clinical, supported by the bilirubin level, and can be aided by BIND scoring and, where available, brainstem auditory evoked responses, which may show reversible abnormalities early in the course [4,26]. Magnetic resonance imaging supports the diagnosis of kernicterus, but findings can be subtle or absent, and the appearance changes with time [25]. Chronic bilirubin encephalopathy is diagnosed from the combination of history of severe hyperbilirubinemia, characteristic motor, auditory and oculomotor findings, and imaging [24].

8. Pharmacotherapeutic and Clinical Management

Management is determined by gestational age, postnatal age in hours, the TSB level and the presence of neurotoxicity risk factors. Table 3 summarises the principal modalities.

8.1 Phototherapy

Phototherapy is the principal and most effective treatment. Light in the blue-green range (approximately 460–490 nm) converts bilirubin in the skin and superficial capillaries into configurational isomers and structural isomers (lumirubin) that are water soluble and excreted in bile and urine without conjugation [20,38]. Lumirubin formation is the main route of elimination during phototherapy [20]. Intensive phototherapy is defined by irradiance of at least 30 μW/cm²/nm delivered to as much of the infant's body surface as possible, using bluegreen LED devices, with the infant's eyes protected and thermoregulation, hydration and feeding maintained [12,39]. In extremely low-birth-weight infants, aggressive phototherapy reduced the rate of neurodevelopmental impairment but was associated with increased mortality in infants weighing 501–750 g, which is why preterm thresholds are individualised [40].

Phototherapy should be initiated when the TSB reaches the threshold for the infant's gestational age, hours of life and risk category [12]. After starting, TSB should be rechecked at intervals determined by the proximity to the escalation-of-care threshold. Phototherapy may be discontinued when TSB has fallen at least 2 mg/dL (34 μmol/L) below the level at which it was initiated, with a longer period of treatment considered in infants with risk factors for rebound such as gestational age <38 weeks, age <48 hours at initiation, or hemolytic disease [12]. A follow-up TSB 6 to 24 hours after discontinuation is recommended according to rebound risk [12].

8.2 Escalation of care and exchange transfusion

The 2022 AAP guideline introduced the "escalation-of-care" threshold, set at 2 mg/dL (34 μmol/L) below the exchange-transfusion threshold [12]. When TSB reaches or exceeds this level, the infant should be admitted to a neonatal intensive care setting that can perform exchange transfusion, intensive phototherapy should be continued, intravenous hydration considered when indicated, and TSB, albumin and a crossmatched blood sample should be obtained, with the TSB repeated at least every 2 hours [12]. Exchange transfusion is indicated when TSB reaches the exchange threshold, or in an infant with signs of ABE (such as hypertonia, arching, retrocollis, opisthotonos, fever or a high-pitched cry) regardless of TSB, and when intensive phototherapy fails to produce a fall in TSB [12,41].

Double-volume exchange transfusion rapidly removes bilirubin, sensitised red cells and circulating antibody, and replaces them with compatible donor blood. It is a high-risk procedure that can cause thrombocytopenia, hypocalcemia, hypoglycemia, electrolyte disturbance, infection, necrotising enterocolitis, portal vein thrombosis, cardiac arrhythmia and death, and should be carried out by experienced teams [1,12,41]. After the procedure, TSB should be monitored closely because of rebound, and phototherapy should be continued [12].

8.3 Intravenous immunoglobulin (IVIG)

In isoimmune hemolytic disease, IVIG is believed to block Fc receptors on reticuloendothelial cells and reduce hemolysis. The AAP suggests that IVIG (0.5–1 g/kg over 2 hours, repeated after 12 hours if necessary) may be used in infants with isoimmune hemolytic disease whose TSB is at or approaching the escalation-of-care threshold despite intensive phototherapy [12]. Evidence of benefit is inconsistent. An updated meta-analysis found reduced need for exchange transfusion in some analyses, but the quality of evidence was low, and the effect was less apparent in studies at lower risk of bias [42]. Possible adverse effects include necrotising enterocolitis (a concern with late administration), hypersensitivity reactions and, rarely, transmission of infectious agents, so use should follow institutional protocols [12,42].

8.4 Supportive management and adjunctive agents

Adequate feeding is essential. Frequent breastfeeding (ideally 8–12 times in 24 hours) supports intake and stooling and reduces enterohepatic circulation, with lactation support and, when intake is inadequate, supplementation with expressed breast milk or formula [2,12]. Routine water or dextrose-water supplementation is not recommended because it does not lower bilirubin [12]. Intravenous fluids are indicated for infants who are dehydrated or cannot feed, or at escalation of care [12]. Underlying causes should be treated, including sepsis, hypothyroidism and G6PD-related hemolysis, for which oxidant triggers must be avoided [12,30].

Other pharmacological interventions have been studied but are not part of routine care. The AAP recommends measuring serum albumin to inform neurotoxicity risk, and the bilirubin-toalbumin ratio may be used as an adjunct to, but not a substitute for, TSB [12]. A randomised trial of bilirubin/albumin ratio in preterm infants did not show improved neurodevelopmental outcome compared with TSB-based management [43]. Metalloporphyrins such as tin mesoporphyrin inhibit heme oxygenase and reduce bilirubin production, but they are not licensed for routine neonatal use and remain investigational in most settings [44]. Phenobarbital (enzyme induction) and other agents are not recommended for routine use [2,12].

Table 3. Summary of treatment modalities for neonatal hyperbilirubinemia.

Modality	Indication / role	Key points
Intensive phototherapy	TSB at or above gestational-age and risk-specific threshold	Irradiance ≥30 μW/cm²/nm; maintain feeding and hydration; monitor TSB; check for rebound [12,38]
Escalation of care	TSB ≥2 mg/dL below exchange threshold	NICU-level care; TSB every ≤2 h; albumin, crossmatch; consider IVIG if isoimmune [12]
Exchange transfusion	TSB ≥ exchange threshold, signs of ABE, or failure of intensive phototherapy	Double-volume; experienced team; monitor calcium, glucose, platelets, electrolytes [12,41]
IVIG	Isoimmune hemolytic disease approaching escalation threshold	0.5–1 g/kg over 2 h, may repeat; low-quality evidence [12,42]
Feeding support	All infants; inadequate intake	Lactation support; supplement when needed; avoid routine water supplementation [12]
Investigational agents	Selected research settings	Metalloporphyrins; not routine [44]

TSB, total serum bilirubin; ABE, acute bilirubin encephalopathy; IVIG, intravenous immunoglobulin; NICU, neonatal intensive care unit.

8.5 Drug-related considerations for clinical pharmacists

Drugs can worsen bilirubin neurotoxicity by displacing bilirubin from albumin, by inducing hemolysis in G6PD deficiency, or by inhibiting conjugation. The historical association between prophylactic sulfonamide therapy and kernicterus in premature infants is a classic example of drug-induced toxicity [45]. Studies of drugs used in neonatology show that several agents can displace bilirubin from albumin [46]; ceftriaxone, in particular, is generally avoided in jaundiced neonates for this reason. Sulfonamide-containing agents should be avoided in the neonatal period, and agents known to precipitate hemolysis in G6PD deficiency (for example, primaquine, nitrofurantoin, methylene blue, dapsone and naphthalene-containing mothballs) should be avoided in affected or suspected infants and in breastfeeding mothers when appropriate [30,31]. Table 4 summarises key pharmacist interventions.

Table 4. Pharmacist-led interventions to reduce risk of bilirubin neurotoxicity.

Domain	Intervention
Antenatal	Ensure Rh(D)-negative women receive anti-D immunoglobulin as per protocol (antenatal prophylaxis and within 72 h of delivery of an Rh-positive infant) [10,47]
Medication review	Screen neonatal prescriptions for bilirubin-displacing drugs (e.g., ceftriaxone, sulfonamides) and for oxidant drugs in G6PD deficiency [30,45,46]
Protocols	Support hospital protocols for guideline-based phototherapy, escalation-of-care thresholds and IVIG dosing [12]
Product handling	Verify IVIG weight-based dose, infusion rate and monitoring; ensure availability of blood products and crossmatch [12,42]
Counselling	Educate parents on feeding, jaundice recognition, follow-up and when to seek urgent care [2,12]

9. Prevention of Kernicterus

Prevention requires a systematic, multi-level approach beginning before birth. Rh(D)-negative mothers should receive anti-D immunoglobulin to prevent alloimmunisation, and women with alloimmunisation require specialist fetal surveillance [47]. After birth, the AAP recommends that all infants be

assessed for hyperbilirubinemia risk, that all infants have a TcB or TSB measured before discharge, and that follow-up be arranged according to the infant's bilirubin level relative to the phototherapy threshold [12]. Key elements are summarised below.

- Identify maternal blood group and antibody status; give anti-D immunoglobulin when indicated [47].
- Evaluate all newborns for jaundice at least every 12 hours in hospital and measure bilirubin whenever jaundice appears in the first 24 hours [12].
- Support effective breastfeeding and monitor feeding adequacy, weight loss and stool and urine output [2,12].
- Perform pre-discharge TcB or TSB measurement and interpret it by hour of life and gestational age [12,33].
- Test for G6PD deficiency where prevalence is high or when hemolysis is suspected, and counsel families about triggers [30,31].
- Start phototherapy when guideline thresholds are reached and escalate care promptly [12].
- Arrange post-discharge follow-up based on the proximity of bilirubin to the phototherapy threshold, and avoid early discharge of infants with risk factors without follow-up [12,48].
- Educate parents about jaundice, feeding and warning signs such as lethargy, poor feeding, high-pitched cry and arching [12,41].

Programmes in LMICs additionally require access to reliable bilirubin measurement, low-cost phototherapy devices, exchange transfusion capability, community education and referral pathways [9,13].

10. Outcomes and Long-Term Follow-up

Outcomes depend on the severity and duration of exposure and on how early treatment is started. Early ABE can be reversible with prompt exchange transfusion, whereas advanced ABE is associated with a high risk of permanent sequelae and mortality [4,6]. Survivors of chronic bilirubin encephalopathy require multidisciplinary care including neurology, physical and occupational therapy, audiology (including auditory brainstem response testing and cochlear implantation in selected cases), ophthalmology, dentistry and augmentative communication, with attention to preserved cognition [24,27]. Pharmacological management of dystonia and spasticity is symptomatic, with treatments such as anticholinergics, baclofen, benzodiazepines and botulinum toxin chosen according to individual response, and such therapies need pharmacist input regarding dosing and adverse effects [24]. Infants who had severe hyperbilirubinemia without overt encephalopathy should be offered hearing and neurodevelopmental follow-up [12,27].

11. Challenges and Future Directions

Several issues remain unresolved. First, TSB is an imperfect surrogate for neurotoxic risk, and routine, validated measurement of free bilirubin or bilirubin-to-albumin ratio is not yet standard [21,43]. Second, optimal thresholds for extremely preterm infants remain uncertain because of the balance between benefit and risk of intensive phototherapy [40]. Third, the evidence base for IVIG and adjunctive pharmacotherapy is limited [42,44]. Fourth, access to screening, phototherapy and exchange transfusion in resource-limited settings is inadequate, and low-cost devices, community screening using smartphone-based or point-of-care technologies, and local protocols are priorities [9,11]. Finally, population-specific factors, including G6PD variants and UGT1A1 polymorphisms, merit further research to refine prediction and prevention [3,30].

12. Conclusion

Kernicterus is a preventable but devastating complication of severe neonatal hyperbilirubinemia. Early recognition of infants at increased risk, accurate bilirubin measurement, risk-based treatment thresholds, timely intensive phototherapy and prompt escalation to exchange transfusion when indicated remain the foundation of prevention [3,12]. Pharmacotherapy such as IVIG has a selective role in isoimmune hemolysis, and careful medication review, anti-D prophylaxis and caregiver education are areas where clinical pharmacists can add substantial value. Continued improvement in screening, feeding support, parental education and post-discharge monitoring, together with expanded access to treatment in LMICs, can substantially reduce bilirubin-associated neurological injury [9,12].

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