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Review Article: The 120th Japan Pediatric Society Scientific Research Award Winner

Hyperbilirubinemia in preterm infants in Japan: New treatment criteria

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Abstract In 1992, Kobe University proposed treatment criteria for hyperbilirubinemia in newborns using total serum bilirubin and serum unbound bilirubin reference values. In the last decade, chronic bilirubin encephalopathy has been found to develop in preterm infants in Japan because it can now be clinically diagnosed based on an abnormal signal of the globus pallidus on T2-weighted magnetic resonance imaging and abnormal auditory brainstem response with or without apparent hearing loss, along with physical findings of kinetic disorders with athetosis. We therefore revised the Kobe University treatment criteria for preterm hyperbilirubinemic infants in 2017. The three revised points are as follows: (i) newborns are classified under gestational age at birth or corrected gestational age, not birthweight; (ii) three treatment options were created: standard phototherapy, intensive phototherapy, and albumin therapy and/or exchange blood transfusion; and (iii) initiation of standard phototherapy, intensive phototherapy, and albumin therapy and/or exchange blood transfusion is decided based on the total serum bilirubin and serum unbound bilirubin reference values for gestational weeks at birth at <7 days of age, and on the reference values for corrected gestational age at ≥7 days of age. Studies are needed to establish whether chronic bilirubin encephalopathy can be prevented using the 2017 revised Kobe University treatment criteria for preterm infants in Japan.

Key words chronic bilirubin encephalopathy, preterm infant, total serum bilirubin, treatment criteria, unbound bilirubin.

Hyperbilirubinemia management in term newborns

A condition that persistently produces neurological symptoms due to bilirubin toxicity in the neonatal period is diagnosed as chronic bilirubin encephalopathy or kernicterus at autopsy. In the 20th century, chronic bilirubin encephalopathy in term newborns was a major cause of cerebral palsy in infants, as was hypoxic ischemic encephalopathy after asphyxia. Therefore, the objective of neonatal hyperbilirubinemia management in the 1970s and 1980s was to suppress the onset of chronic bilirubin encephalopathy in term newborns.

Established hyperbilirubinemia management strategies in term newborns are listed in Table 1. A transcutaneous bilirubin (TcB) measurement was developed by Yamanouchi *et al.* in 1980 and used as a screen for hyperbilirubinemia.[1,2] Two major sets of treatment criteria based on total serum bilirubin (TSB) alone or TSB and serum unbound bilirubin (UB) were developed and became popular in Japan,[2–4] one of which, using TSB and UB reference values, was developed by Nakamura *et al.* in 1992 (Table 2).[4,5] Treatment methods for hyperbilirubinemia using phototherapy (PT) and exchange blood transfusion (ET) were established.[2] The mechanism of serum bilirubin decrease during PT involves the production of water-soluble bilirubin photoisomer [(*EZ*)-cyclobilirubin] for excretion from the kidney.[6,7] Most perinatal institutions throughout Japan currently possess PT devices; thus, jaundiced newborns who need PT can receive it anywhere in the country. Finally, prevention for anti-rhesus D antigen (RhD) hemolytic disease by treatment with RhD globulin in RhD-negative pregnant women at 28 weeks' gestation and soon after delivery, was also generalized.[8]

The incidence of chronic bilirubin encephalopathy or kernicterus since 2000 is only 0.4 per 100 000 preterm and term live births in Japan.[9] In the past decade, only two term infants have been diagnosed with chronic bilirubin encephalopathy, showing that it is an extremely rare disease. The strategy to prevent the development of chronic bilirubin encephalopathy in term newborns was therefore successful in Japan.[10]

Chronic bilirubin encephalopathy in preterm newborns

Since 2000, the rate of admission of preterm children with athetoid cerebral palsy has increased at a pediatric rehabilitation facility in Japan, suggesting that chronic bilirubin encephalopathy may be present in preterm children.[5] In one clinical study, eight preterm children with athetoid cerebral palsy who were diagnosed with the chronic bilirubin encephalopathy were retrospectively examined in detail by Okumura *et al.* in 2009.[11] They found that chronic bilirubin encephalopathy can be clinically diagnosed based on an abnormal signal of the globus pallidus on T2-weighted magnetic resonance imaging (MRI)

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Table 1 Established hyperbilirubinemia management in term newborns

Screening
Transcutaneous bilirubin measurement[1,2]
Diagnosis
Treatment standard using TSB alone, and TSB and UB in serum[3,4]
Treatment
Phototherapy and exchange transfusion[2]
Prevention
RhD-hemolytic disease in the newborn from an RhD-negative mother by treatment with anti-RhD immunoglobulin[8]

RhD, Rhesus D antigen; TSB, total serum bilirubin; UB, unbound bilirubin.

during infancy, and abnormal findings of the auditory brainstem response (ABR) in the absence of apparent hearing loss, along with physical findings of kinetic disorders with athetosis.[11] Subsequently, we proposed a set of diagnostic criteria for chronic bilirubin encephalopathy in preterm infants (Table 3).[9] In addition, chronic bilirubin encephalopathy in preterm infants often complicates intellectual disability, aspiration pneumonia, dystonia attack, and rhabdomyolysis, which are different from the symptoms in term infants. Currently, there are no clinically established diagnostic criteria for chronic bilirubin encephalopathy. In order to create universal diagnostic criteria for chronic bilirubin encephalopathy in preterm infants, it is necessary to carefully study and analyze a large number of cases along with autopsy cases, and then validate the criteria in the clinical setting.[9]

To investigate the incidence, we conducted a nationwide survey targeting preterm infants <30 weeks of gestational age, who were born in 2011; five of 2,720 preterm infants included in the survey were diagnosed with chronic bilirubin encephalopathy.[12] Because chronic bilirubin encephalopathy in preterm infants is not fully recognized by neonatologists or pediatric neurologists, more undiagnosed cases may exist. Furthermore, chronic bilirubin encephalopathy was estimated to occur in at least 10 preterm infants per year in Japan in recent years.[9]

Why has chronic bilirubin encephalopathy occurred in Japan?

Bilirubin is neurotoxic, and is well-known to cause brain damage in newborns. Preterm infants are particularly vulnerable to bilirubin neurotoxicity due to immaturity of the blood–brain barrier, liver function, and other organ function. Chronic bilirubin encephalopathy or kernicterus can occur even in a low TSB environment in preterm infants, compared with term infants.[4,11,13–17] Therefore, the TSB and UB treatment initiation criteria for preterm infants were set at lower levels than for those in term infants (Table 2).[3,4]

The survival rate of extremely preterm infants has been increasing since 2000 in Japan.[18] The mortality of very low-birthweight infants born after 24 weeks of gestational age is only 5%, which is the lowest mortality rate worldwide.[19] Nonetheless, studies on hyperbilirubinemia management for extremely preterm infants are insufficient in Japan. We believe the major reasons for this are as follows. First, because hyperbilirubinemia was thought not to directly link to mortality, studies on hyperbilirubinemia in extremely preterm infants might not be performed. Second, Japanese neonatologists

Table 3 Proposed diagnostic criteria for chronic bilirubin encephalopathy in preterm infants[9]

History in neonatal period
1. Preterm birth, especially extremely preterm
2. Hyperbilirubinemia while hospitalized in NICU
Physical examination findings in infancy
3. Auditory neuropathy-type hearing impairment with or without deafness
4. Cerebral palsy or delayed motor development with athetosis or dystonia
5. Upward gaze palsy due to oculomotor paresis
6. Dental enamel dysplasia
Examination findings
7. High-intensity signal in the globus pallidus on head MRI in infancy
8. Highly abnormal auditory brainstem response (at ≥90 dB)

A comprehensive diagnosis is reached on the basis of the aforementioned clinical findings. Chronic bilirubin encephalopathy in preterm infants often complicates intellectual disability, aspiration pneumonia, dystonia attack, and rhabdomyolysis, which are different from the symptoms in term infants. (2) This may not be accompanied by markedly elevated total bilirubinemia. High unbound bilirubinemia serves as a reference. (3,4) Hearing impairment and motor disorder are not always of the same severity. (5) and (6) are often not present. (7) A high-intensity signal in the globus pallidus may not be detected if the brain MRI is not performed at an appropriate age, usually <12 months of corrected age. MRI, magnetic resonance imaging; NICU, neonatal intensive care unit.

Table 2 1992 Kobe University treatment criteria for initiation of PT/ET[4,6]

Birthweight (g)	TSB (mg/dL) Hours after birth						UB (μg/dL)
	<24	<48	<72	<96	<120	≥120	Any time
<1,000	5/8	6/10	6/12	8/12	8/15	10/15	0.3/0.8
<1,500	6/10	8/12	8/15	10/15	10/18	12/18	
<2,500	8/10	10/15	12/18	15/20	15/20	15/20	0.6/1.0
≥2,500	10/12	12/18	15/20	18/22	18/25	18/25	

When the TSB or UB level exceeds the reference value, phototherapy or exchange transfusion is initiated. Currently, serum UB can be measured with the UB Analyzer (UA-2™, Arrows, Osaka, Japan). ET, exchange blood transfusion; PT, phototherapy; TSB, total serum bilirubin; UB, unbound bilirubin.

might have the misunderstanding that the blood–brain barrier is fully formed early in life (e.g. after 2 weeks of age) even in extremely preterm infants, and that regular management for hyperbilirubinemia after 2 weeks of age is therefore unnecessary. Indeed, in our retrospective investigation involving 18 extremely preterm infants who developed chronic bilirubin encephalopathy, approximately 90% and 50% had peak TSB after 2 and 4 weeks of age, respectively.[17] Finally, clinical demonstration of neurotoxicity or brain damage using bilirubin was difficult in extremely preterm infants until it was found that chronic bilirubin encephalopathy could be diagnosed using ABR and brain MRI in infancy.[11]

Is aggressive PT effective or harmful for preterm infants?

Because preterm infants can develop chronic bilirubin encephalopathy even if TSB is relatively low,[4,11,13–17] and neonatologists assumed that no major side-effects occur with PT, there is a tendency to perform PT aggressively for preterm infants, even in those with low TSB in Japan (aggressive PT).

In *in vitro* studies, PT can cause oxidative injury to the cell membrane and DNA,[7] and the injury could have a negative effect on extremely preterm infants.[20] To investigate if aggressive PT is effective for the prevention of bilirubin neurotoxicity or harmful for extremely preterm infants, a multi-center cohort study was conducted involving 1,974 extremely preterm infants in the USA.[21] The incidence of death or neurodevelopmental impairment for aggressive PT did not decrease compared with that for conservative PT. Particularly, it was reported that the mortality rate in infants with birthweight 501–750 g slightly increases, even if the neurodevelopmental impairment rate alone was decreased slightly by aggressive PT.[21] This suggests that aggressive PT has a limitation in improving the prognosis for extremely preterm infants, and that aggressive PT may be harmful.

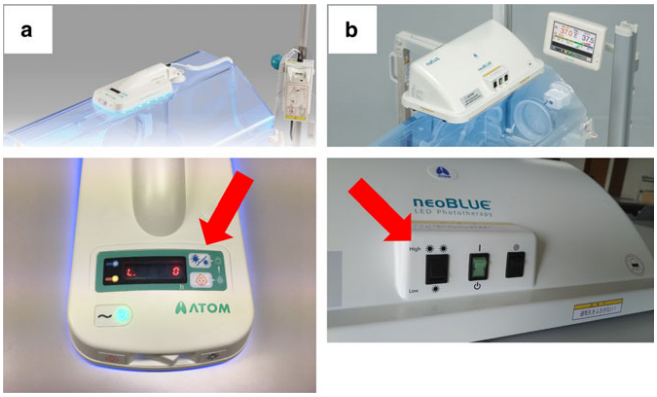

Fig. 1 Current major light-emitting diode phototherapy devices in Japan. (a) BILI-THERAPY™ (Atom Medical, Tokyo, Japan); (b) neoBLUE™ (Natus Medical, Pleasanton, CA, USA). Red arrow, switching button between the low (10–15 μW/cm^2 per nm for standard phototherapy) and high modes (30–35 μW/cm^2 per nm for intensive phototherapy).

Recently, a historical cohort study in California, USA showed that the incidence of infantile cancer in newborns who received PT was slightly higher than that in newborns who did not (32.6 and 21.0 per 100 000 newborns, respectively; relative risk: 1.6).[22] Although the participants of that study were not extremely preterm infants, the risk may be considered when making an initial decision to use PT for newborns with TSB or UB below the current treatment criteria cut-off.[22]

These two reports suggest that the use of PT should be carefully considered, given the carcinogenic risk, and also the negative effects of aggressive PT in extremely preterm infants. That is, PT may have side-effects, as do antibacterials and other drugs.

What are standard and intensive PT?

The efficacy of PT in reducing TSB depends on the spectrum of light emitted, spectral irradiance of the light, exposed body surface area, cause of jaundice, and TSB level at the start of PT.[2] The light irradiance has a dose-dependent effect on TSB decrease. The Subcommittee of Hyperbilirubinemia in the American Academy of Pediatrics defined the standard PT spectral power as 8–10 μW/cm^2 per nm and intensive PT as >30 μW/cm^2 per nm.[2] Because the increased mortality observed in extremely preterm infants who are receiving PT[21] and the injury to cell membranes and DNA by PT in *in vitro* studies[7,23,24] suggest that it is prudent to use less intensive irradiance,[20] it has been recommended to initiate PT at lower irradiance (standard PT), and to increase the level (intensive PT) only when TSB continues to rise.[20] In addition, bilirubin is not only cytotoxic, it also has antioxidant effects for preterm infants, who are susceptible to oxidative stress.[23,25]

In the 20th century, a major light source in Japan was blue fluorescent tubes. Single-surface irradiation was used for mild or moderate hyperbilirubinemic newborns. When newborns developed severe hyperbilirubinemia, double-surface irradiation using two PT devices with fluorescent tubes was performed to avoid ET.[26] In 1998, a light-emitting diode (LED), which is power efficient and produces little heat, was developed as a new light source for PT,[27] and became widespread in Japan thereafter. The LED PT device has a linear relationship between irradiance dose and reduction in TSB level in the range of 20–55 μW/cm^2 per nm without a saturation point,[28] and can easily deliver high irradiance. The LED PT used at a low irradiance of around 10 μW/cm^2 per nm was as effective as conventional single-surface irradiation PT using a halogen lamp.[29] Two major LED PT devices, BILI-THERAPY™ (Atom Medical, Tokyo, Japan) and neoBLUE™ (Natus Medical, Pleasanton, CA, USA) are currently used in Japan. These devices have both low-intensity (10–15 μW/cm^2 per nm in low mode for standard PT) and high-intensity irradiance (30–35 μW/cm^2 per nm in high mode for intensive PT). Additionally, the devices make it easy to switch between low and high mode (Fig. 1). Neonatologists should be aware that intensive PT in preterm infants sometimes causes bronze baby syndrome and neonatal cholestasis.

Why should the 1992 Kobe University treatment criteria be revised?

There are six reasons to revise the 1992 Kobe University treatment criteria (Table 2). First, chronic bilirubin encephalopathy has been identified in preterm infants in Japan. Second, because the 1992 Kobe University treatment criteria did not target preterm infants, specifically extremely preterm infants, there are no treatment criteria values for infants ≥1 week of age. As aforementioned, preterm infants should be managed for hyperbilirubinemia and treated for as long as needed during their neonatal care unit stay, because half of extremely preterm children who developed chronic bilirubin encephalopathy had peak TSB after 4 weeks of age (maximum, 12 weeks of age).[17] Therefore, treatment criteria values until discharge from the neonatal care unit are required. Third, according to the 1992 Kobe University treatment criteria, preterm infants may receive treatment more frequently based on only the suprathreshold UB values, although the TSB level is below the threshold.[30] Fourth, although we chose only the two treatment options of PT and ET, which is introduced when PT is ineffective, intensive PT and albumin therapy are currently available in routine practice before ET is performed.[28,31] Fifth, in 2013, UB reference values for the initiation of ET were proposed for newborns weighing >1,500 g at birth: (i) for serum UB 1.00–1.50 μg/dL, PT and infusion are given with or without albumin or immunoglobulin therapy; and (ii) for serum UB >1.50 μg/dL, ET is performed immediately.[32] Finally, as mentioned in detail, appropriate use of PT is needed because aggressive PT may be harmful.[21,22]

New 2017 revised Kobe University treatment criteria

The Kobe University treatment criteria based on TSB and UB reference values were revised in 2017 (Table 4).[10] The TSB reference values for standard PT (low mode) and ET or albumin therapy were from the Murata–Imura treatment criteria[3] and the 1992 Kobe University treatment criteria,[4] which are currently used in Japan. Because in the 1992 Kobe University treatment criteria, infants often receive treatment based on only the suprathreshold UB value (0.3 μg/dL for PT/0.8 μg/dL for ET in infants weighing <1,500 g; and 0.3 μg/dL for PT/0.8 μg/dL for ET in infants weighing ≥1,500 g at birth), not TSB level,[30] the UB reference values were modified based on the following evidence. Nakamura *et al.* originally reported that 0.8 and 1.0 μg/dL were optimal UB cut-offs for predicting kernicterus in infants weighing <1,500 g and 1,500–2,000 g at birth, respectively.[4] Yokota *et al.* reported that no infants were diagnosed with ABR abnormalities at the time of discharge from the neonatal intensive care unit even when the UB reference value for ET was set at 1.5 μg/dL.[32] The TSB and UB reference values for intensive PT (high mode) were determined based on the median value calculated using the values for standard PT and ET. Furthermore, we investigated TSB and UB data obtained from 6,288 samples in 1,174 infants admitted to Kobe University Hospital in 2012–14, and each TSB and UB value in the new 2017 Kobe University treatment criteria was modified and confirmed based on analysis of patients who exceeded the reference values in the 1992 Kobe University treatment criteria.

The three revised points are as follows. First, given that fetal diagnostic technology in obstetrics has advanced, the gestational age at birth can be diagnosed accurately. In the revised criteria, newborns were classified under gestational age at birth or corrected gestational age, and not birthweight, because gestational age at birth or corrected gestational age is associated with organ maturation. Second, the following three treatment options were created: standard PT, intensive PT, and albumin therapy and/or ET. And third, the initiation of standard PT, intensive PT, and albumin therapy and/or ET is judged based on the TSB and UB reference values of gestational age in weeks at birth for <7 days after birth, and, at ≥7 days of age, the initiation of treatment is judged based on the TSB and UB reference values of the corrected gestational age. For example, when a newborn with a gestational age of 28 weeks and 2 days at birth is 14 days old, we can use the TSB reference values for ≥120 h for 30–31 weeks (14 mg/dL, 16 mg/dL, and 20 mg/dL for standard PT, intensive PT, and albumin therapy and/or ET, respectively) and UB reference values for 30–31 weeks (0.6 μg/dL, 0.8 μg/dL, and 1.0 μg/dL for standard PT, intensive PT, and albumin therapy and/or ET, respectively).

Table 4 New 2017 revised Kobe University treatment criteria[10,†]

GA or CGA (weeks)	TSB (mg/dL) Hours after birth						UB (μg/dL)
	<24	<48	<72	<96	<120	≥120	
22–25	5/6/8	5/8/10	5/8/12	6/9/13	7/10/13	8/10/13	0.4/0.6/0.8
26–27	5/6/8	5/9/10	6/10/12	8/11/14	9/12/15	10/12/15	0.4/0.6/0.8
28–29	6/7/9	7/10/12	8/12/14	10/13/16	11/14/18	12/14/18	0.5/0.7/0.9
30–31	7/8/10	8/12/14	10/14/16	12/15/18	13/16/20	14/16/20	0.6/0.8/1.0
32–34	8/9/10	10/14/16	12/16/18	14/18/20	15/19/22	16/19/22	0.7/0.9/1.2
≥35	10/11/12	12/16/18	14/18/20	16/20/22	17/22/25	18/22/25	0.8/1.0/1.5

[†]For initiation of standard phototherapy (low-mode)/intensive phototherapy (high-mode)/exchange transfusion or albumin therapy). Currently, serum UB can be measured with the UB Analyzer (UA-2™, Arrows, Osaka, Japan). CGA, corrected gestational age; GA, gestational age; TSB, total serum bilirubin; UB, unbound bilirubin.

Treatment protocols using the new treatment criteria

The treatment protocols for the new treatment criteria are as follows (Fig. 2).[10]

1. The initiation of standard or intensive PT or ET is determined according to the TSB and UB reference values classified by gestational age at birth or corrected gestational age (Table 4).
2. When TSB is >5 mg/dL and the serum direct bilirubin level exceeds 10% TSB, UB is evaluated carefully because measurement by UB Analyzer (UA-2™; Arrows, Osaka, Japan) often shows an amount higher than the actual amount due to the influence of direct (conjugated) bilirubin.[33]
3. The case of hemolytic disease is excluded from this flowchart. Treatment according to severity of hemolytic disease is carried out, including globulin therapy (0.5 g/kg i.v. for 2 h).[34]
4. Low-mode PT starts when either TSB or UB exceeds the reference values for standard PT and continues for 24 h. If either TSB or UB after 24 h treatment still exceeds the reference value, low-mode PT is continued. When both TSB and UB are lower than the reference value, PT is discontinued. TSB and UB should be measured 24 h after the discontinuation, and re-elevation of TSB and/or UB is evaluated.
5. When either TSB or UB exceeds the reference value for intensive PT, high-mode PT is started. Simultaneously, the attending neonatologist should pursue the cause of hyperbilirubinemia. Measuring serum albumin and direct bilirubin is essential. TSB and UB should be re-measured 4–8 h after the start of high mode PT.
6. When either TSB or UB exceeds the reference value of ET, (I) high-mode PT is started soon; simultaneously, the attending neonatologist should pursue the cause of hyperbilirubinemia; measurement of serum albumin and direct bilirubin is essential; (II) when only serum UB exceeds the reference value for ET, albumin is given (albumin therapy, 1 g/kg i.v. for 2 h);[31] (III) 4 h after the start of high-mode PT, re-examination of TSB and UB is carried out; (i) ET is conducted if either TSB or UB is not lower than the ET reference value, but if the decrease rate of TSB and UB, calculated from the start of high-mode PT, predicts that they will be below the TSB and UB reference value for ET after 12 h from the start of high-mode PT, ET may be withheld, but re-measurement of TSB and UB should be carried out until they are below the ET reference value; (ii) even if both TSB and UB are lower than the ET reference value, high-mode PT is continued for 24 h.
7. During the PT, ET is considered when the symptoms of acute bilirubin encephalopathy are observed regardless of TSB and UB level.
8. PT is performed at a distance of 30 cm from the body surface. Ten to fifteen $\mu W/cm^2$ per nm for low-mode PT or 30–35 $\mu W/cm^2$ per nm for high-mode PT should be confirmed regularly, every 1–2 months, with the Atom Phototherapy Analyzer II™ (Atom Medical) when using PT with blue light.
9. Regarding the selection of light sources (i.e. blue or green), Itoh *et al.* reported that the effective wavelength of PT is near the green region rather than the blue region, and that safe PT (i.e. by avoiding the wavelength 400–500 nm, which belongs to the blue region), can be used in preterm infants. Green light, however, has side-effects for the observer's vision, and generates bilirubin phototoxicity in human cells *in vitro*.[7] Further studies are needed to identify light sources that are effective and safe for preterm infants.

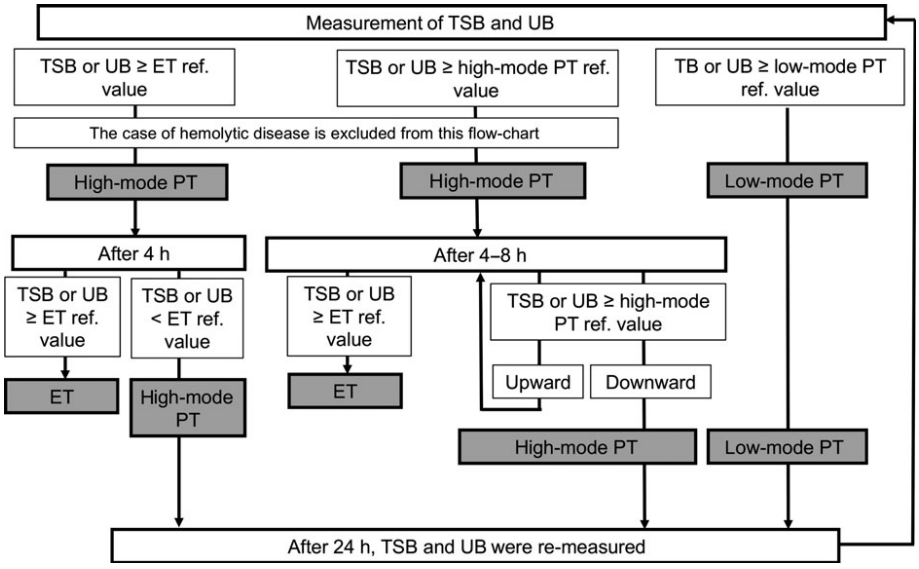

Fig. 2 Flowchart of the revised 2017 Kobe University treatment criteria. ET, exchange blood transfusion; high-mode PT, intensive phototherapy; low-mode PT, standard phototherapy; PT, phototherapy; ref., reference; TSB, total serum bilirubin; UB, unbound bilirubin.

Table 5 Proposed jaundice management protocol for preterm infants[9]

Age	Management
Birth–6 days of age	Measure TB and UB daily
7–13 days of age	Measure TB and UB every couple of days
Thereafter (until discharge from NICU)	Monitor TcB daily, and when TcB is ≥8, measure TB and UB Confirm TB and UB once a week

NICU, neonatal intensive care unit; TB, total serum bilirubin; TcB, transcutaneous bilirubin on JM-105 jaundice meter (Konica Minolta, Tokyo, Japan); UB, unbound serum/plasma bilirubin on UB analyzer (Arrows, Osaka, Japan).

10. A jaundice management protocol for preterm infants is proposed (Table 5).[9] I recommend that preterm infants after 2 weeks of age should be monitored for TcB daily, and TSB and UB measured when TcB is ≥8 mg/dL, and TSB and UB levels confirmed once a week.

Currently, a multicenter collaborative prospective study for preterm infants is ongoing to examine whether chronic bilirubin encephalopathy can be prevented by using the 2017 revised Kobe University treatment criteria.

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Author contributions

I.M. designed this review article, wrote the manuscript, and approved the final manuscript as submitted.

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