Phototherapy and exchange transfusion for neonatal hyperbilirubinaemia

Neonatal academic hospitals' consensus guidelines for South African hospitals and primary care facilities

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The purpose of this document is to address the current lack of consensus regarding the management of hyperbilirubinaemia in neonates in South Africa. If left untreated, severe neonatal hyperbilirubinaemia may cause kernicterus and ultimately death and the severity of neonatal jaundice is often underestimated clinically. However, if phototherapy is instituted timeously and at the correct intensity an exchange transfusion can usually be avoided. The literature describing intervention thresholds for phototherapy and exchange transfusion in both term and preterm infants is therefore reviewed and specific intervention thresholds that can be used throughout South Africa are proposed and presented graphically. A simplified version for use in a primary care setting is also presented. All academic heads of neonatology departments throughout South Africa were consulted in the process of drawing up this document and consensus was achieved.

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The range of different thresholds for the initiation of phototherapy and exchange transfusion in newborn infants in South Africa reflects the same lack of consensus that exists worldwide.[1] There are also no local evidence-based guidelines on how to manage infants who are jaundiced but do not require phototherapy, and there is a worrying misconception among some medical staff that a single total serum bilirubin (TSB) level below the phototherapy threshold is sufficient basis to discharge infants with only visual review thereafter.

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A national guideline for the management of neonatal jaundice will help facilitate uniform care and admission criteria and could ultimately improve the care of jaundiced neonates.

This document is the result of collaboration with the heads of neonatal departments of all South African medical faculties.

International recommendations for the use of phototherapy and exchange transfusion in jaundiced term and near-term infants

The aim of phototherapy and exchange transfusion is to avoid kernicterus. The pathological definition of kernicterus is gross yellow staining in the brainstem nuclei with microscopic evidence of neuronal damage.[2] However, in the literature reviewed, kernicterus was defined by any of the following: postmortem pathological findings, acute clinical findings (bilirubin encephalopathy) and typical chronic neurological sequelae.

In 1952, before the use of phototherapy was established, Hsia *et al.*[3] studied 229 infants with erythroblastosis fetalis. They demonstrated that when TSB levels exceeded 340 µmol/l, the risk of kernicterus increased significantly and at TSB levels above 510 µmol/l the risk rose to 50%, despite exchange transfusion. When they introduced a policy of attempting to keep the TSB level below 340 µmol/l using exchange transfusion, there were no cases of kernicterus in 200 consecutive cases. Twenty years later, Oski and Naiman[4] published a nomogram that was constructed by Diamond and Allen, specifically for use with infants with erythroblastosis fetalis. Despite the introduction of phototherapy, the TSB level above which exchange was obligatory remained at 340 µmol/l for both term and preterm infants.

By 1979 the use of phototherapy was well established. Cockington[5] used Diamond and Allen's nomogram as a basis for recommendations on when to perform exchange transfusion and added recommendations on when to initiate phototherapy. Despite the availability of phototherapy, he did not raise the level of obligatory exchange. However, following a recommendation by Karabus,[5,6] Cockington devised different thresholds according to birth weight and age in hours. He did not suggest different thresholds for infants with other risk factors.

Although he did not define the recommended irradiance level of the phototherapy it must have been low because he used a bank of only 12 white fluorescent bulbs. However, his small study of 85 cases across all weight groups showed the suggested phototherapy intervention levels to be effective at preventing the need for exchange transfusion in most infants. Cockington's charts remain in use in some centres in the UK today[1] and they are recommended in a definitive local text by Harrison.[7]

Since Cockington, there have been several other recommendations, all based on limited evidence.[1] A recent, comprehensive review[8] of the available evidence for the management of jaundiced term and near-term (> 34 weeks' gestation) infants was published in 2004 by Stanley Ip, and the American Academy of Pediatricians' (AAP) Subcommittee on Hyperbilirubinemia.

The report concluded that kernicterus has a 10% mortality and 70% morbidity risk versus the risk of permanent sequelae caused by exchange transfusion of 5 - 10%. The reviewed studies of infants who already have kernicterus showed that the vast majority of term and near-term infants with kernicterus and co-morbidity (e.g. sepsis, haemolysis) had a peak recorded TSB of > 342 µmol/l. The infants with kernicterus who had no associated co-morbidity showed a higher peak with a TSB range from 385 to 923 µmol/l. Although acute kernicterus (bilirubin encephalopathy) can be completely reversible if treated by exchange transfusion,[9] only 14% of the group reviewed by Ip *et al.* are known to have survived without chronic sequelae. However, much of the data were missing, so this number may be higher.

Contrary to the retrospective review of infants with kernicterus, the review of prospective studies of all infants with hyperbilirubinaemia showed many infants who did not develop kernicterus, with bilirubin levels well over 428 µmol/l. There was also no consistent association between peak TSB and intelligence quotient, long-term neurological problems or permanent hearing loss. However, the data from the largest contributing study,[10] the Collaborative Perinatal Project (CPP), were subsequently shown[11] to be significantly confounded by the beneficial effect of exchange transfusion that was done in 53% of infants with TSB > 342 µmol/l and this would have included virtually all infants with peak TSB > 428 µmol/l (phototherapy was not yet widely available at the time of data collection, 1959 - 1966). Thus, while most infants with kernicterus have TSB > 342 µmol/l, most infants with TSB > 428 µmol/l do not have problems if the level of bilirubin is reduced rapidly (i.e. via exchange transfusion).

Ip's review formed the basis of the updated AAP recommendations published in 2004.[12] These recommendations differed from the 1994 AAP recommendations (Table I)[13] in that the TSB levels were plotted onto an hour-based curve (Figs 1 and 2). The availability of high-intensity phototherapy and the acknowledgement of specific risk groups, resulted in relatively raised phototherapy and exchange transfusion thresholds for well term infants and different intervention levels for infants at risk. High-intensity phototherapy is recommended as a first-line intervention, but immediate exchange is recommended if TSB levels at presentation are greater than 85 µmol/l above the exchange threshold or if bilirubin levels are not expected below the exchange threshold within 6 hours.

The approach to the jaundiced term and near-term infant has been further refined by Bhutani *et al.*,[14] who derived an hour- and age-based bilirubin centile chart from a study of 17 854 live births between 1993 and 1997 (Fig. 3). This chart assigns risk of progression to higher levels depending on the current level of the TSB. Thus 39.5% of infants with TSBs in the high-risk zone after age 18 hours will remain in that zone 24 hours later, 12.9% of infants in the high-intermediate zone will cross into

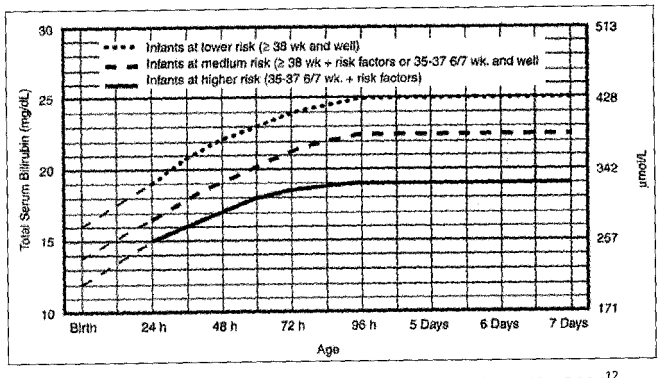

Fig. 1. Exchange transfusion thresholds recommended by AAP, 2004[12] (reproduced with permission).

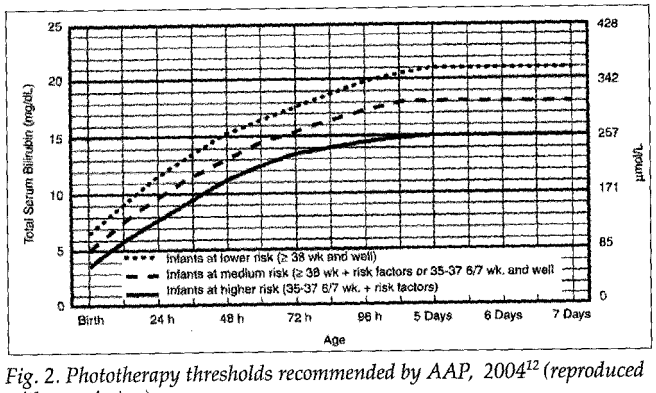

Fig. 2. Phototherapy thresholds recommended by AAP, 2004[12] (reproduced with permission).

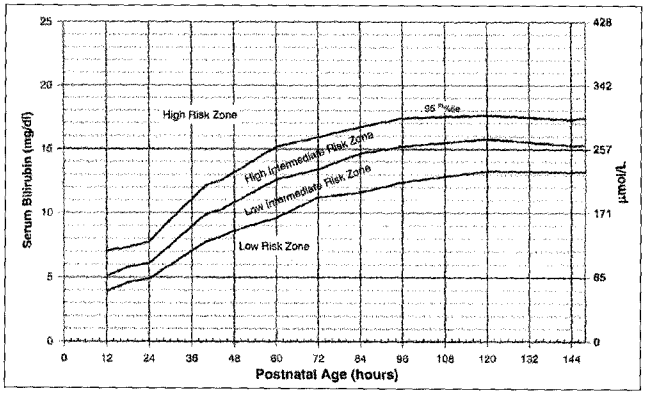

Fig. 3. Risk designation of term and near-term newborn infants, based on their hour-specific bilirubin levels[14] (reproduced with permission).

the high-risk zone and 2.2% of infants in the low-intermediate zone will cross into the high-risk zone. None of the infants in the low-risk zone will cross into the high-risk zone. This information assists discharge planning for infants who are jaundiced, but do not require phototherapy. The application of this chart according to risk zone is recommended[15] as follows: (*i*) high-risk zone – start phototherapy if threshold reached. Repeat TSB in 6 - 12 hours; (*ii*) high-intermediate risk zone – repeat TSB within 24 hours; (*iii*) low-intermediate risk zone – repeat TSB within 48 hours; (*iv*) low-intermediate risk zone – clinical evaluation only within 48 hours.

International recommendations for the use of phototherapy and exchange transfusion in jaundiced low-birth-weight and very-low-birth-weight infants

The management of low-birth-weight infants is less clear than that of term infants. Cockington's guidelines[5] extended to infants less than 1 500 g but had no further weight subdivisions. In 1985, the National Institute for Child Health and Human Development (NICHD) published thresholds[16] for infants who weighed less than 1 250 g, but they did not provide a time component (Table II). In 1994, Watchko and

Table I. AAP 1994: Management of hyperbilirubinaemia in the healthy term newborn[13]

	TSB level (μmol/l)			
Age (h)	Consider phototherapy	Phototherapy	Exchange transfusion if intensive phototherapy fails	Exchange transfusion and intensive phototherapy
< 24	Jaundiced infants this age are not considered healthy and require further evaluation			
25 - 48	≥ 170	≥ 260	≥ 340	≥ 430
49 - 72	≥ 260	≥ 310	≥ 430	≥ 510
> 72	≥ 290	≥ 340	≥ 430	≥ 510

Table II. Varying recommendations for exchange transfusion in preterm infants: Birth weight (g) v. bilirubin (μmol/l) thresholds[16,18,20-23]

Birth weight, g (gestation)	NICHD 1985	Ahlfors 1994	Maisels in Avery *et al.* 1999	Ives in Rennie and Roberton 1999	Cashore 2000	NICHHD Trial 2002
Risk factor adjustment	Subtract 40 μmol/l	Subtract 40 μmol/l	'Use lower values'	Subtract 40 μmol/l	'Use lower values'	Not specified
500 - 749	220	220	220 - 275	200	204 - 255	220
750 - 999 (< 28 wks)	220	220	220 - 275	200	255	255
1 000 - 1 249 (28 - 31 wks)	220	220	220 - 275	250	255 - 306	Not specified
1 250 - 1 499 (32 - 34 wks)	255	255	220 - 275	300	289 - 340	Not specified
1 500 - 1 999 (35 - 36 wks)	289	290	275 - 300	350	Not specified	Not specified

* wks = weeks.

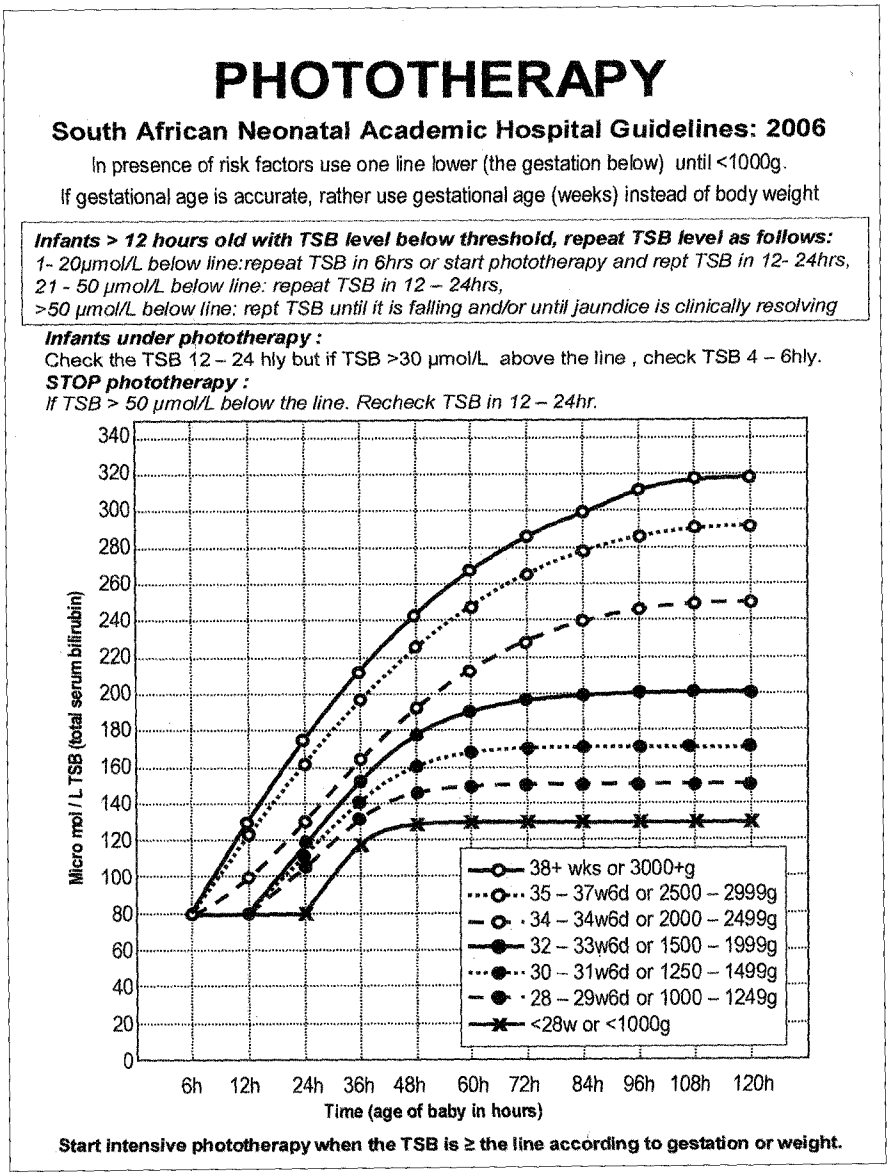

Fig. 4. Phototherapy guidelines for all gestational ages.

Claasen[17] compared the 1985 NICHD criteria with a retrospective review of postmortem records and 56% of the 78 infants who did not have kernicterus had bilirubin levels greater than that suggested as exchange criteria by the NICHD. In 2000, Cashore[18] suggested elevated thresholds (Table II) and extended the weight range as low as to 500 g. However, a wide range was given and no time component provided.

In 2003, the review by Watchko and Maisels[19] quotes a wide range of TSB levels (170 - 306 µmol/l) in preterm infants < 1 500 g with kernicterus. These levels are considerably lower than those reported in earlier studies of preterm infants who generally weighed more than 1 500 g. Although co-morbid factors such as sepsis, haemolysis and hypoxia are thought to be responsible for kernicterus at such low levels, the only group that have been shown to be at increased risk of neurological deficit are those with grade 1 intraventricular haemorrhage or higher. A review of studies that tried to find an association between peak TSB and subsequent neurological abnormality, failed to show a consistent association. Thresholds recommended by Maisels,[20] Ives,[21] Ahlfors[22] and the NICHHD Neonatal Network trial[23] show a range of interventions with considerable overlap (Table II).

South African recommendations for the use of phototherapy and exchange transfusion in hospitals

When creating charts to guide the use of phototherapy and exchange transfusion in South African hospitals and primary care units, we aimed to provide intervention levels that would be based on available evidence and would also be safe according to available resources. We also aimed to provide guidance on when phototherapy should be stopped and when TSB levels should be repeated in jaundiced infants who do not require phototherapy.

The nomogram from Bhutani *et al.*[14] shows that term and near-term infants enter a high-risk zone at a level slightly below the AAP 2004 upper phototherapy threshold.[12] The AAP 2004 guidelines suggest the use of high-intensity phototherapy from the start and also suggest a lower threshold for babies who are haemolysing or have other risk factors for early-onset kernicterus. High-intensity phototherapy has been defined as that which provides an irradiance of at least 30 µW/cm²/nm in the 430 - 490 nm band.[12] Phototherapy at this level resulted in a 45% drop in TSB levels in term infants with non-haemolytic unconjugated hyperbilirubinaemia, and increasing the intensity did not result in significantly faster rates of fall of bilirubin levels.[24]

However, high-intensity phototherapy is not always available and haemolytic disease might only be diagnosed after laboratory evaluation and/or response to phototherapy. Our phototherapy

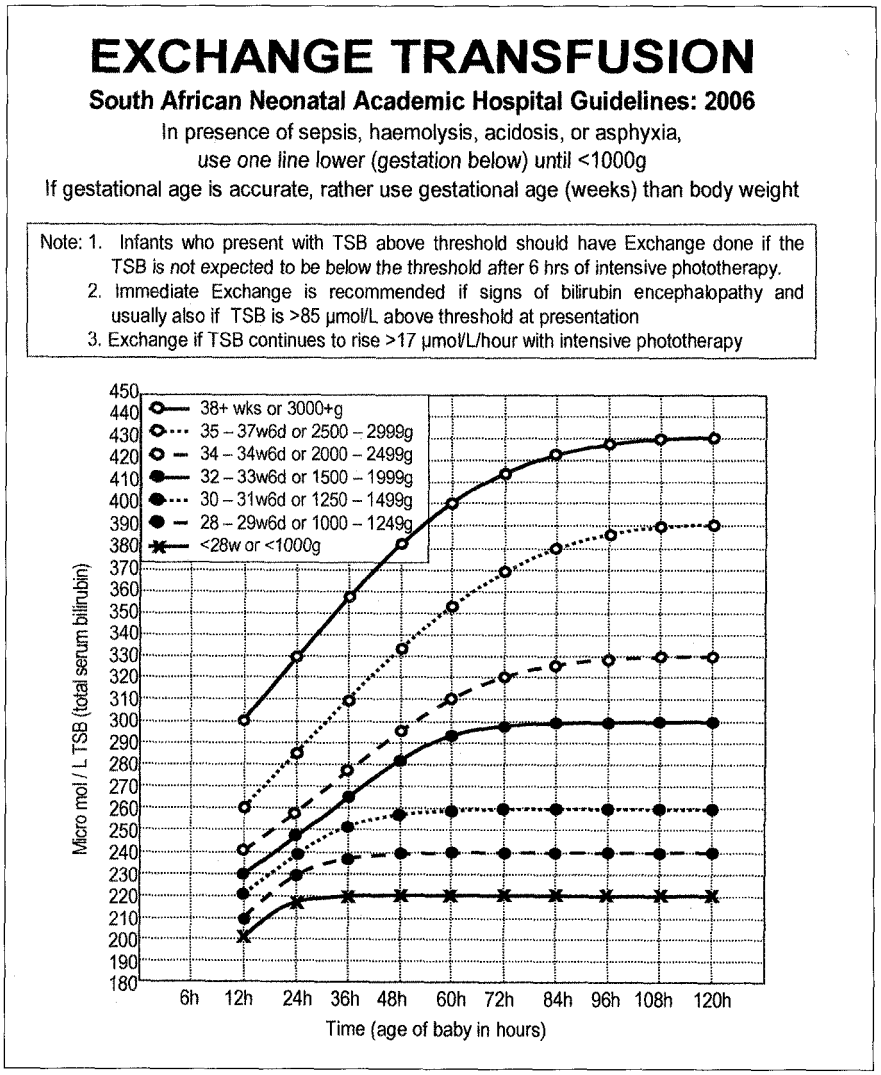

Fig. 5. Exchange transfusion guidelines for all gestational ages.

recommendations therefore have a lowered threshold for well term infants: 30 µmol/l lower in the first 36 hours and 20 µmol/l lower thereafter. We also recommend that if the TSB level is between 1 and 20 µmol/l lower than the phototherapy threshold then the TSB level should be repeated in 6 hours or phototherapy should be commenced early and the TSB level repeated within at least 24 hours. Infants who require phototherapy should have the TSB checked at least 24-hourly, but if the TSB is > 30 µmol/l above the phototherapy threshold then the TSB should be checked 4 - 6-hourly.

We have formally adopted the AAP thresholds for exchange transfusion in term and near-term infants without any alteration. The thresholds we recommend for preterm infants are based on a combination of guidelines (Table II) that were summarised in the most recent review by Watchko and Maisels,[19] and we have displayed the recommendations for exchange transfusion for term and preterm infants on one chart.

The final charts for hospital use (Figs 4 and 5) are displayed graphically. Gestational equivalents are provided because more mature growth-restricted infants can be treated at relatively higher thresholds.

Comparison of the top line of phototherapy chart with Bhutani's chart shows the following approximate relationship after 12 hours' age: (*i*) high-risk zone – starts 20 µmol/l lower than phototherapy threshold; (*ii*) high-intermediate risk zone – 21 - 50 µmol/l lower than phototherapy threshold; (*iii*) low-intermediate risk zone – starts 51 - 100 µmol/l lower than phototherapy threshold; (*iv*) low-intermediate risk zone – > 100 µmol/l lower than phototherapy threshold.

We therefore suggest that this relationship be used to guide timing of repeat TSB levels and this is shown on the phototherapy chart.

Simplified phototherapy charts for primary care

The difference in resources and experience between primary care facilities and hospitals prompted us to develop simplified phototherapy charts for infants ≥ 2 kg and > 35 weeks' gestation (Fig. 6). These charts are weight-specific and replicate the top two lines of the hospital charts, with the other intervention thresholds 20 µmol/l and 50 µmol/l below the phototherapy threshold drawn in. They also include recommendations for referral to higher levels of care.

Recommendations for stopping phototherapy

The AAP recommends that infants who are admitted for phototherapy continue until the TSB is < 240 µmol/l,[12] a level that is 100 µmol/l below the photography threshold for well 5-day-old infants. They comment that discharge need not be delayed to observe the infant for rebound of TSB levels after phototherapy is stopped, but TSB should be rechecked in 24 hours. This decision is informed by three studies[25-27] that applied this cut-off point. The maximum rebound for term and near-term infants when this level is adhered to was 60 µmol/l.[27] When low-birth-weight infants were studied,[26] arbitrary levels of 130 µmol/l and 75 µmol/l were chosen to stop phototherapy in infants 1 - 1.8 kg and less than 1 kg, respectively

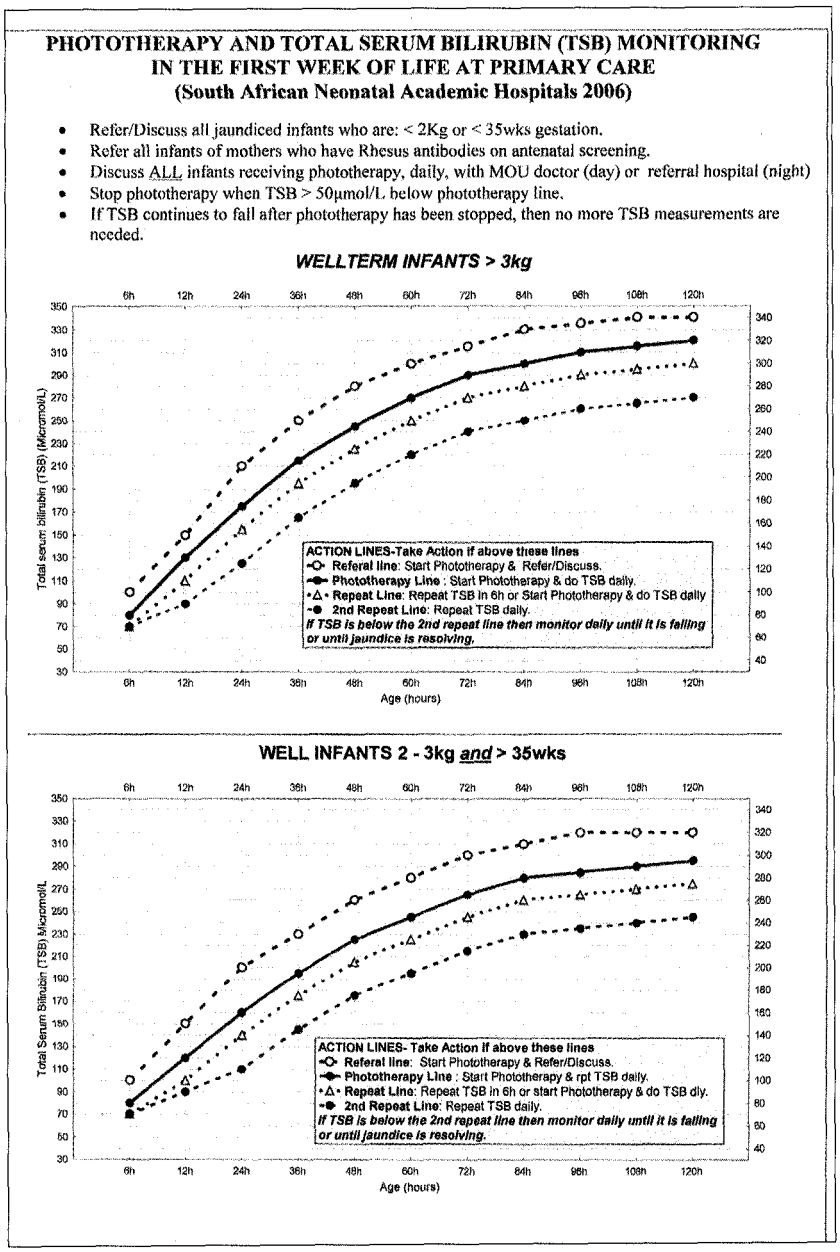

Fig. 6. Phototherapy guidelines for use in primary care.

and the maximum rebound was 30 µmol/l. Based on these data, our safe, practical recommendation is to stop phototherapy at TSB ≥ 50 µmol/l below the phototherapy threshold for all infants and to check the TSB again in 12 - 24 hours.

Final comments

The consensus guidelines presented here provide clear thresholds for the initiation of intensive phototherapy and exchange transfusion at hospital level, for the timing of repeat TSB levels and for the cessation of phototherapy. A simplified version has been provided for use at primary care centres with the aim of streamlining the referral system.

The comments and review from Professor M J Maisels are gratefully acknowledged.

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