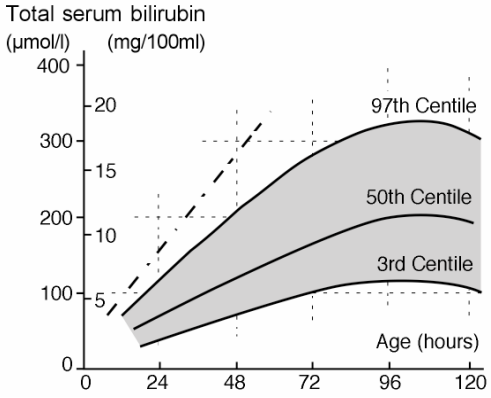
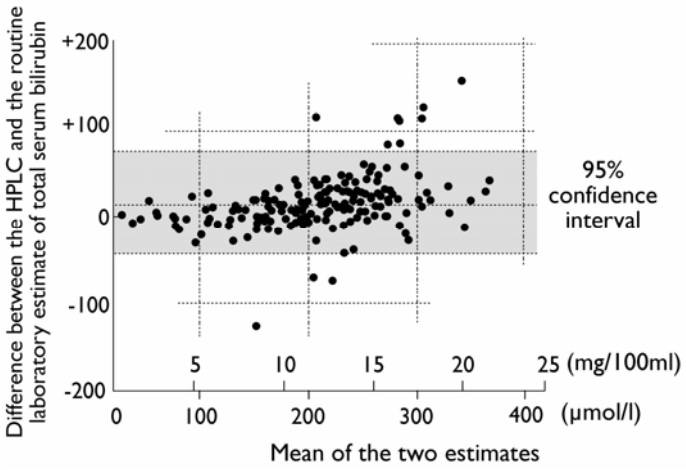
PHOTOTHERAPY (Commentary)

Recognising and managing 'severe' jaundice



Jaundice becomes detectable to the naked eye when the total serum bilirubin level exceeds about 85 μmol/l (5 mg/100ml) and most babies become visibly jaundiced in the first week of life. Unfortunately the terminology used in many texts talks of jaundice being 'moderate' when it exceeds 200 μmol/l and 'severe' when it exceeds 250 μmol/l. On any such definition 'severe' jaundice develops in a third of all breast fed babies in the first week of life ! Such lax use of language undoubtedly triggers a lot of unnecessary investigation. Jaundice is only really 'actionable' in the otherwise healthy term baby when the level exceeds 340 μmol/l (20 mg/100ml) and potentially dangerous when it exceeds 430 μmol/l (25 mg/100ml). Phototherapy would not need to be given so often if it were administered more effectively when given. The graph shown here documents how the bilirubin level varied over time in a large group of mature exclusively breast fed babies – most other 'normative' charts document the levels seen in a population where at least a third of the babies were bottle fed.

Damaging levels are rarely seen in the otherwise well term baby. In a recent Danish study 32 of the 128,344 term and near-term babies born in 2000–2001 developed a total bilirubin level in excess of the value at which national guidelines suggested that exchange transfusion might well be appropriate. Potential blood group incompatibility was a potential factor in half these babies, but in only two was there any overt evidence of haemolysis. The peak bilirubin level seen in these 32 children varied between 385 and 689 μmol/l (mean 492 μmol/l), but only one baby went on to develop permanently disabling kernicterus – a baby whose bilirubin level rose to 651 μmol/l after discharge home. With efficient high-intensity phototherapy only three of these babies were judged to need exchange transfusion (Ebbesen *et al.* 2005). Similarly no term baby with a bilirubin of between 425 and 510 μmol/l (25 to 30 mg/100ml) developed kernicterus during a four year study of 106,627 babies in California in 1995–98, and there was no excess of neurological deficits in these children two years later. In a further population based UK study in 2003–05 kernicterus developed in just 14 of the 108 babies in whom the total bilirubin level *exceeded* 510 μmol/l (Manning *et al.,* 2007). Kernicterus was equally rare in term babies lacking evidence of haemolysis in Zimbabwe unless the serum bilirubin level exceeded 500 μmol/l (Wolf *et al.,* 1999). Experience from the days when Rhesus haemolytic disease was the main cause of severe neonatal jaundice long caused clinicians to fear bilirubin levels in excess of 340 μmol/l or 20 mg/100ml (so called 'vigintiphobia'), but it is now clear that, in the absence of haemolysis, the threshold at which jaundice becomes dangerous in the term baby is much higher than this. Unfortunately it has to be accepted that what constitutes a safe level in a preterm baby still remains, after fifty years, much less clear.



Measuring total serum bilirubin levels It also needs to be realised that blood samples sent for routine analysis do not provide answers that are nearly as accurate as most would suppose. Duplicate reports on the same specimen can sometimes differ by 10%, and if the same specimen is sent to more than one laboratory the results can also, not infrequently, differ by 10%. (Schreiner and Glick, 1982) When, more recently, routine laboratory estimates were compared with those obtained by high pressure liquid chromatography, 5% of the results were found to differ by more than 60 μmol/l (Rubaltelli *et al.,* 2001). In fact, as the Bland Altman plot from that paper shows (see fig), the higher the blood level the greater the

uncertainty attaching to any measurement. It is, therefore, perhaps more helpful to say that 5% of reports issued by any routine hospital laboratory may be out by as much as 30% If measuring the total serum bilirubin level accurately is this difficult, it has to be accepted that assessing how much of this is due to 'direct acting' (conjugated) bilirubin is even more difficult. Hence the advice in this *Formulary* not to take the amount of direct acting bilirubin into account when assessing whether jaundice needs treatment in early infancy.

Non-invasive ways of monitoring jaundice Jaundice appears on the face before it appears on the trunk. What causes this 'cephalopedal' progression of jaundice is poorly understood, but its existence has been reported in a range of studies, and its predictive power confirmed several times (Kraimer, 1969; Ebbesen 1975; Thong *et al.,* 1976; Moyer *et al.,* 2000). How high the bilirubin level has to get before the lower leg starts to look jaundiced seems to depend, however, on whether the baby is being assessed under artificial or natural light. Kraimer, who examined babies under fluorescent light, said it was safe to assume that the level had not reached 270 µmol/l if the lower leg showed no sign of jaundice, but Ebbeson sometimes saw jaundice once the level exceeded 120 µmol/l when the babies were examined by daylight.

Of the various electronic devices that have been developed for measuring just how yellow the forehead of a baby has become only one, the BiliCheck™, has ever been tested against a laboratory estimate obtained using high pressure liquid chromatography. That study showed that this hand held device produced estimates that were just as reliable as those provided by collecting a heel prick blood sample when total serum bilirubin level was anywhere in the range looked at in that study (80 to 300 µmol/l). The more widely used Minolta/Air Shields™ Jaundice meter has not been tested quite as rigorously, but many have shown that it can usefully be used to screen for serious jaundice, minimising the number requiring phototherapy or laboratory confirmation of the actual level (Knudsen, 1996; Kaplan *et al.,* 2008). It has also been shown that, despite differences in skin colour it performs perfectly well in Chinese, Malay and Indian babies (Tan *et al.,* 1996). For clinicians who lack confidence in their own clinical ability to assess jaundice such a device can certainly reduce the number from whom a blood sample needs to be taken (Kaplan *et al.,* 2008). Unfortunately those reporting on the accuracy of such devices have often been strangely ignorant as to how inaccurate standard laboratory estimates can be.

In fact, a very simple devise first described in the *Lancet* by Gosset, a British paediatrician, in 1960 – a small strip of Perspex with a graded colour scale embedded in it – seems to function just as effectively as other more recent gadgets (see fig). Although the original English manufacturer, Thomas Ingram of Birmingham is no longer in business, the device is still easily obtainable from Cascade Healthcare Products, 1826 NW 18th Avenue, Portland, Oregon 97209, in America, for less than $40. Its utility has been put to the test many times (Culley *et al.,* 1960; Schumacher, 1985). Indeed to continues to be used, not only to monitor jaundice in coloured babies in South Africa (Chaibva *et al.,* 1974; Stein *et al.,* 1975) and India (Narayanan *et al.*, 1990) but also by home health nurses in America (Madlon-Kay, 2001). The usual strategy is simply to assess how jaundiced the baby is by pressing the transparent scale over the tip of the baby's nose until it blanches. A few have claimed that, in a coloured baby, it may be better to press the scale over the child's gums. No devise can be used reliably, of course, once phototherapy has been started.

Haemolysis Rapid jaundice is much more likely if excess haemolysis has triggered abnormally rapid bilirubin production (so called 'pathological' jaundice). There is also no doubt that, for any given bilirubin level, the risk of kernicterus is greatly increased by the existence of haemolysis, though the reason for this remains unknown. The speed with which the serum bilirubin level rises in the first 36 hours after birth should alert staff to this possibility. A level above the dashed line in fig 1 should certainly trigger investigation. Check for the presence of isoimmune antibodies in the mother's blood, and get a direct Coombs' test on the baby's blood if haemolytic jaundice is a possibility. Check the baby's blood group (for ABO incompatibility) if the mother is blood group O. Dominantly inherited congenital spherocytosis is one rare cause of excessive haemolysis and early jaundice. G6PD deficiency is common in some racial groups and can occasionally cause severe jaundice, even though the early rise is not usually particularly marked. Bruised babies are also more likely to become significantly jaundiced.

Jaundice and the breast fed baby Healthy, bottle fed, term babies seldom develop serious early jaundice (or sustained low grade jaundice either) and, for many years, most hospital-born babies were at least partly bottle fed. As a result, many paediatricians came to think of the jaundice associated with breast feeding as abnormal when it is the *lack* of jaundice in the bottle fed baby that is actually 'abnormal'. The main reason why 'physiological' jaundice clears more quickly in those who are bottle fed is that they pass stool more often, clearing all the bile-laden meconium from their bowel sooner after birth. In breast fed infants

this reabsorption of bile from the lumen of the gut back into the circulation (enterohepatic recirculation) is particularly pronounced in the early days. The idea that it was a steroid [pregnane-3α,20β-diol] found in the milk produced by some mothers that 'caused' this jaundice, has now been discounted.

There is a condition sometimes called '*lack* of breast milk jaundice' where dangerous jaundice, dehydration and hypernatraemia can occur because the baby fails to get any milk from the breast. While most babies lose weight for a few days after birth, the fall in these babies soon exceeds 10%. Early intervention can often prevent lactation failing altogether. Starvation or dehydration do not, however, account for the early jaundice seen in most breast fed babies – those who become particularly jaundiced do not usually lose more weight than most breast fed babies. It is not, therefore, logical to offer extra water, glucose or formula milk as a routine, or to interrupt lactation even for 'diagnostic' purposes. The jaundice that most of these babies show is normal, does not require diagnosis, and does not call for specific treatment. An unrestricted chance to go to the breast at least once every 3 hours is all that most breast fed babies really need if they have a bilirubin a little above the 98th centile on the 3rd to 5th day of life.

Persisting jaundice The one diagnosis that must not be missed is biliary atresia. The condition is rare (1:14,000 births) but successful surgery depends on early recognition and operative intervention within 6 weeks of birth. The urine will be dark, the stools will be pale (rather than green or yellow) even if they were normal at first, and at least 20% of the total serum bilirubin will be conjugated bilirubin. That apart, over-investigation in the first four weeks will usually only serve to unsettle the mother of an otherwise healthy breast fed baby. Vitamin K (q.v.) *must*, however, be given to any breast fed baby with persisting jaundice because a range of congenital and acquired liver disorders interfere with the absorption of fat and the fat-soluble vitamins leaving babies vulnerable to intracranial bleeding from vitamin K deficiency.

Monitoring the effectiveness of phototherapy treatment The challenge, when giving phototherapy, is to know how effectively it is being given. Nobody would give an antibiotic without knowing with some certainty the dose given, but clinicians give phototherapy all the time without having the faintest idea how much they are giving. Verman and his colleagues have recently described in some detail a very simple way that staff can assess the effectiveness of the treatment they are giving (Verman *et al.,* 2008). If allowance is made for the fact that many devices do not deliver light evenly over the surface of the cot mattress and for the fact that only a variable amount of the child's body is exposed, the technique can be quite complex. In essence however all that needs to be done is expose a sample of jaundiced serum into a series of all-glass microhaematocrit tubes and measure the speed with which unconjugated bilirubin in the sample falls over time. The fall is exponential so it is not difficult to calculate the half life with some accuracy. The speed of fall depends on how jaundiced the sample was to start with but it can be very educational to show how different devises differ in the speed with which they can cause the bilirubin level to fall. Light from a fluorescent 'strip light' or a light emitting diode is usually much more effective than light from a halogen spot light or halogen-sourced fibreoptic device. Some strip lights are more effective than others and the efficacy of old tubes declines slowly over time. Their effectiveness is greatly influenced by how far they are positioned from the child and can be almost doubled by placing lights both above and below the cot (Holtrop *et al.,* 1992; De Carvalho *et al.,* 1999). If units did more to monitor the effectiveness of the strategy they routinely use, efficacy could be greatly improved and the number judged to need exchange transfusion to control jaundice rather than to treat anaemia or remove antibody-coated cells could be greatly reduced. Phototherapy is particularly effective when jaundice is intense, and really concentrated treatment can cause a bilirubin level of 500 µmol/l to fall by 150 µmol/l within 2–4 hours (Hansen, 1997) – the time it usually takes to get an exchange transfusion organised.

A brief history phototherapy For a good account of how clinical acumen led a neonatal nurse to be the first to suspect that sunlight could be used to control neonatal jaundice fifty years ago, how this was confirmed by a trainee general practitioner, and how, given how little the sun usually shines in Romford, England, this soon led to the use of a 'cradle' of fluorescent 'strip lights', see the vivid accounts by Maisels & Watchko, 2000, and by Stokowski *et al,* 2006. Given how very widely this strategy is now used it is interesting to note that it took ten years before a study by Jerry Lucey in America in 1968 led to the sudden widespread adoption of this practise.

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