·专家讲座·
(**Expert Lecture**)

Hyperbilirubinemia in newborns with gestation ≥35 weeks

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1 Introduction

The prevention, detection and management of neonatal jaundice in relatively healthy term and near term infants continue to remain a challenge, partly because jaundice is so common, and kernicterus so rare[1-3]. The term kernicterus is now used interchangeably with both acute and chronic bilirubin toxicity and appears to have a current incidence of approximately 1∶100 000[4-5]. In addition there are many other children who require intensive therapy in order to interrupt the rise in serum bilirubin concentrations[6]. The Canadian Pediatric Surveillance System recently demonstrated, over a 2 year period 148 full term infants who developed severe hyperbilirubinemia and either required exchange transfusion or had a peak serum bilirubin concentration over 425 micromoles[7]. Kernicterus was first recognized in infants with rhesus haemolytic disease, such cases should now be avoidable; however recent reports indicate a relative resurgence of kernicterus in otherwise healthy infants with identifiable risk factors, or occasionally with no identifiable cause[8-9]. To my knowledge, critical hyperbilirubinemia is also encountered often in China and South East Asia and in spite of efforts kernicterus do occur. Therefore, it is important that physicians and health care providers have the necessary skills and knowledge to interpret total serum bilirubin levels and initiate treatment based on the age and condition of the infant.

2 Background

Kernicterus (bilirubin encephalopathy) is a condition characterized by deep yellow staining of the neurons and neuronal necrosis of the basal ganglia and other brain stem nuclei. In the acute phase, the affected infants become lethargic, hypotonic and suck poorly; progression of the disease leads to hypertonia (with opisthotonus and retrocollis) with a high-pitched cry and fever. The surviving infants may later develop athetoid cerebral palsy with or without seizures, developmental delay, hearing deficit, oculomotor disturbances, dental dysplasia and mental deficiency[10-12]. It is possible that milder degrees of hyperbilirubinemia are associated with less severe long-term complications, however, it has been difficult to prove this, and the levels of bilirubin above which such subtle cerebral injury can occur are therefore unknown[9, 13-14]. Prevention of a rare case of kernicterus, remains the underlying justification for the huge effort which is expended to prevent, detect, and treat severe hyperbilirubinemia[15-16]. The societal burden of one affected case runs in the order of hundreds of thousands of dollars. Kernicterus is extremely rare in full term infants whose peak serum bilirubin remains below 340 μmol/L. We therefore define severe hyperbilirubinemia as a total serum bilirubin > 340 μmol/L at any time during the first 28 days of life. Above this level the risk for toxicity progressively increases, although it should be recognized that with levels > 500 μmol/L there are still some infants who will escape kernicterus. The reasons behind this differential susceptibility are unclear, but the risks of kernicterus in the presence of severe hyperbilirubinemia seem to be increased by dehydration, hyperosmolarity, respiratory distress, hydrops, prematurity, acidosis, hypoalbuminemia, hypoxia and seizures[8, 11-12]. Critical hyperbilirubinemia is defined as total serum bilirubin (TSB) >425 micromoles/L.

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3 Epidemiology

It is estimated that 60% of term newborns develop jaundice and 2% reach a TSB > 340 μmol/L[16-17]. In Canada, we estimate that approximately 5 000 term infants develop severe hyperbilirubinemia every year[7]. In China this translates to over 150 000 infants. Several risk factors have been identified for the development of severe hyperbilirubinemia in this population. They are 1) visible jaundice at 24 hours of age, 2) visible jaundice prior to discharge at any age, 3) shorter gestation < 38 weeks, 4) exclusive and partial breast feeding, 5) previous siblings with severe hyperbilirubinemia, 6) external or internal bruising of scalp, face, buttocks or any other part of the body, 7) cephalhaematoma, 8) male sex, 9) maternal age < 25 years of age, 10) ethnic background of Asian, European and Mediterranean origin, 11) dehydration[3, 5, 8, 18]. A large prospective study has been recently preformed demonstrating that prediction of the highest serum bilirubin is possible from the analysis of TSB in the first 24 hours, with a certain degree of accuracy (Butani Nomogram)[19]. It is necessary that each country should develop their own nomograms so that they can use those graphs for prediction and treatment.

4 Who should have bilirubin measurement, how, and when?

A large proportion of full term infants currently have an estimation of serum bilirubin. One option which has been suggested to prevent failures in the system would be a universal screening for all newborns for hyperbilirubinemia followed by interpretation of the total serum bilirubin as a function of the postnatal age in hours of the infant[5,18]. This does not appear to be unreasonable; it could be preformed at a pre-specified time such as when the metabolic disease screening test is carried out. However, there have been no prospective randomized controlled trials to evaluate the cost benefit relationship of universal screening. Furthermore, many of the most severely affected infants will need therapy instituted prior to this time to prevent severe hyperbilirubinemia and its complications. A healthy term infant who is breast feeding well and who is not visibly jaundiced at 48 hours has an extremely low risk of severe hyperbilirubinemia and does not require screening. In order to be able to avoid testing such infants an adequate and appropriate systematic assessment is required for all newborn infants[18].

There are limitations in the clinical detection of jaundice, with thresholds of between 80 and 160 μmol/L being found in different studies[6,8,20]. Most infants with a total serum bilirubin >160 μmol/L will appear clinically jaundiced, which is similar to the treatment threshold in the term infants at 24 hours of age[17,21].

Therefore, all infants should be clinically assessed for jaundice during the first 24 hours and again 24 to 48 hours later by an individual competent in the assessment of the newborn and who has access to testing procedures and treatment facility, whether the infant is still in hospital or has been discharged home.

Bilirubin can be measured transcutaneously using capillary or venous blood samples[21-22]. Transcutaneous measurements have several limitations[18]. They become unreliable after initiation of phototherapy; therefore transcutaneous bilirubinometry cannot be used for repeat measurements after phototherapy is initiated[23]. They may also be unreliable with changes in skin color and thickness, if used to screen infants prior to phototherapy these limitations should be understood[24]. The results are more accurate at lower levels of bilirubin, and therefore use of transcutaneous bilirubinometry as a screening devise may be reasonable pending further information[18]. Visual estimation of bilirubin levels from degree of jaundice is known to be inadequate[25].

Capillary sampling is the method employed by most of the hospitals and institutions in Canada, and is the method used in most of the studies, including the construction of the Bhutani Nomogram[19]. Capillary blood analysis has been reported to give results which are either higher, or lower, than venous samples, thus either can be used to determine the requirement for phototherapy[23-24]. Although early neonatal jaundice is generally due to unconjugated hyperbilirubinemia, it is also possible to have an elevation of the conjugated fraction in some situations such as Rhesus erythroblastosis, liver disease and cholestasis[26]. Infants requiring phototherapy should have consideration of measurement of the conjugated fraction. However, the guidelines and most of the previous information on epidemiology of bilirubin toxicity have used TSB as the standard and this is what should be used when deciding on phototherapy or other form of therapy[1, 11]. An infant with persistent jaundice (> one week) and/or with hepatosplenomegaly should have their bilirubin fractionated[6].

Recommendation: 1) Prior to the discharge of every newborn, there should be a process and protocol in place for assessing the risk of development of significant hyperbilirubinemia in all newborns nurseries; 2)

There should be a systematic approach to the assessment of all infants before discharge for this risk and a follow up program if the infant develops jaundice; 3) All newborn infants who are visibly jaundiced, near term (35-37 weeks) and full term (38-42 weeks), should have a bilirubin level determined; 4) Infants, although not visibly jaundiced but with two or more risk factors should have at least one bilirubin level preformed prior to discharge; 5) Serum bilirubin may be done on either a capillary or venous blood sample; 6) Infants with severe or prolonged jaundice should have further investigations including an analysis of the conjugated component of the bilirubin; 7) A transcutaneous bilirubin measurement may be used if available as a screening device; 8) Infants discharged from hospital prior to 24 hours should be reviewed within the next 24 to 48 hours for development of hyperbilirubinemia.

5 Therapy

5.1 Phototherapy

Phototherapy is defined as the use of a light source for the treatment and prevention of neonatal jaundice[27]. Phototherapy is an effective therapeutic intervention that decreases bilirubin concentration. The effectiveness of phototherapy is related to the area of skin exposed and the intensity of the light at the relevant wavelengths and distance from the source of light[28-30]. More intense phototherapy can be achieved using multiple phototherapy units. Light in the blue-green part of the spectrum is most effective. In general, florescent light is most commonly used[31]. Fibre optic phototherapy systems were introduced in the late 1980's and consist of a light that is delivered from a tungsten-halogen bulb through a fibre optic cable and emitted from the sides and ends of the fibres inside a plastic pad[31]. This pad can be wrapped around the baby's torso. Fibre optic phototherapy is especially useful because the baby can be breast-fed without interruption of phototherapy and therefore the incubator and eye pads are not required[31]. The pad can also be used at home. Halogen spotlights may also be used[31].

The energy from the light induces a configurational change in the bilirubin molecule, making it water soluble. Side effects of phototherapy include temperature instability, dehydration, intestinal hypermotility, diarrhea, and interference with maternal infant interaction, and rarely bronze discoloration of the skin called (bronze baby syndrome)[32]. Although phototherapy increases transepidermal skin water loss, this is not a clinically important issue in full term infants who are drinking well. Some infants with jaundice are dehydrated and rehydration will usually lead to a prompt fall in the serum bilirubin. Enteral feeding should be continued and this will replace missing fluid, supply energy and reduce enterohepatic reuptake of the bilirubin[31-32]. Although, interruption of breast feeding and substitution of formula has been shown to lead to a more rapid decrease in TSB, it is not necessary to stop breast feeding as other treatments such as phototherapy, rehydration will significantly reduce TSB levels despite continuation of breast feeding.

Near term infants have a significantly higher risk for severe hyperbilirubinemia than term infants, and may reach their peak concentrations later, on days 5 and 7 as opposed to 3 and 5 days[33]. Combining the "hour specific" serum bilirubin concentration with a clinical risk factor score appears to further improve prediction of serious hyperbilirubinemia; however the risk score is not significantly better than the use of gestational age alone for predicting severe hyperbilirubinemia. If the TSB concentration measured prior to 48 hours is at or above the 95th percentile, the risk of eventual development of severe hyperbilirubinemia is 0.35 for an infant born at 37 weeks, but only 0.1 for an infant born at 40 weeks gestation[34]. To construct the phototherapy guidelines in Figure 1 therefore, I have calculated these thresholds which will suggest the use of phototherapy for infants with high and low predicted risk of severe hyperbilirubinemia. This figure may be utilized for administrating phototherapy in infants $\geqslant$35 weeks gestation. In order to simplify the risk category one may use two or more risk factors for classification of high risk.

Intensive phototherapy is the use for more than two phototherapy units and has been shown to decrease severe bilirubin at a faster rate. Supplemental intravenous fluids with intensive phototherapy further reduces severe bilirubinemia concentrations and it can be used instead of initiating exchange transfusions if there is a demonstrable effect.

Recommendation: 1) Phototherapy treatment should be given when the TSB level exceeds levels specified for the ages and risk as shown in Figure 1; 2) Additional fluids should be given if the infant is dehydrated. Enteral fluids should be used when possible, as expressed breast milk or formula; 3) Breast feeding should be continued.

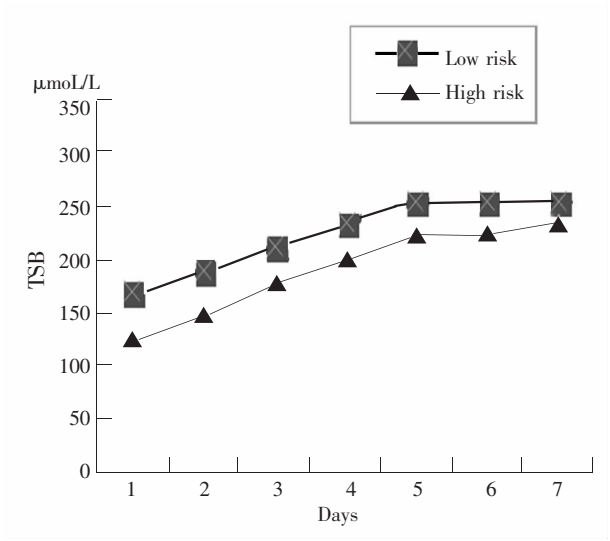

Figure 1 Billrubin management guide lines

5.2 Exchange transfusion

If phototherapy fails to control the rising bilirubin concentrations, exchange transfusion is indicated to lower serum bilirubin concentrations. For healthy term newborns without risk factors, exchange transfusion should be considered when serum conjugated bilirubin is between 375 and 425 μmol/L. Investigations for rare causes of severe hyperbilirubinemia are of no value from blood collected after an exchange transfusion and therefore should be considered prior to performing the procedure and appropriate amounts of blood should be taken and stored for tests such as for red cell fragility, enzyme deficiency (G6PD or PK deficiency) and metabolic disorder tests, haemoglobin electrophoresis, and chromosome analysis.

Exchange transfusion can also be considered for the removal of circulating antibodies. A two volume exchange transfusion will remove >60% circulating antibodies. Some experts use rate of rise of TSB as an indicator for exchange transfusion. A rise of >20 micromole/L/hr may be considered for initiation of exchange transfusion.

Recommendation: 1) Infants with a serum bilirubin level in the severe range should be referred for further investigation and consideration of exchange transfusion; 2) An infant with clinical signs of acute bilirubin toxicity should have an immediate exchange transfusion.

5.3 Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) has been used in the treatment of hyperbilirubinemia particularly in the newborns with Rhesus hemolytic disease and other immune hemolytic jaundice. It acts as a completive inhibitor for those antibodies that cause red cell destruction and release haemoglobin and cause jaundice[35]. Use of IVIG is shown to decrease the need for exchange transfusion, and development of severe jaundice; however, it may not decrease the need for booster transfusion later.

Recommendation: IVIG therapy should be considered as treatment for neonatal jaundice resulting from immune hemolytic jaundice at a dose of 1g/kg.

5.4 Alternative therapies

Hemoxygenase is the rate-limiting step in degradation of haemoglobin to bilirubin. A synthetic analog such as Tin-Mesoporphyrin (SnMP), acting as a competitive inhibitor strongly inhibits the activity of hemoxygenase and suppresses the production of bilirubin and eliminates the need for phototherapy and exchange transfusions for neonates[36]. Such therapies have been more prevalent in countries where autosomal dominant G6PD deficiency is rampant and is not in routinely prescribed in North America although it appears that this therapy is very efficient, further studies are necessary for long term effects.

Phenobarbitone studied as a mean of preventing jaundice did not improve clinically important outcome, however it appears to work better if used antenatally.

Although breast fed infants are at high risk for developing severe hyperbilirubinemia, the risk of kernicterus is very small in comparison with the substantial known benefits of breast feeding[16, 37]. The risk of severe jaundice can be minimized by a program of breast-feeding support[38]. Routine supplementation for breast fed infants is not necessary. The information from a number of studies indicate that unsupplemented breast fed infants experience their maximum weight loss by day 3 and on average lose 6% to 8% of their birth weight[37]. Infants who lose more than 10% of birth weight should have a careful evaluation, including evaluation by an individual with training and experience in support of breast feeding mothers[37-39]. Routine supplementation of water or dextrose water will not prevent hyperbilirubinemia[40].

6 Conclusions

Severe hyperbilirubinemia in relatively healthy term or near term newborns continues to carry a potential threat for complications from bilirubin encephalopathy and bilirubin induced neuronal damage. Careful assessment of the risk factors, systematic approach to detection follow up and estimation along with judicious phototherapy, use of IVIG and exchange transfusion along with appropriate laboratory investigations are required.

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Hyperbilirubinemia in newborns with gestation ≥35 weeks
胎龄≥35 周的新生儿高胆红素血症(摘译)

Koravangattu SANKARAN 著, 姚跃 译

相对健康的足月儿及近足月新生儿黄疸的预防、检测及处理至今仍是一个挑战。足月儿核黄疸(胆红素脑病)近年来发生率约为十万分之一,存在急性及慢性胆红素毒性作用。很多新生儿需要进行强化治疗以阻止血清胆红素水平的上升。

我们将重度高胆红素血症定义为生后 28 d 内任何时间出现血清总胆红素水平大于 340 μmol/L。超过该水平后,胆红素所致毒性的危险递增。尽管如此,仍有部分婴儿血清总胆红素超过 500 μmol/L,但并不出现核黄疸。其易感性不同的原因尚不清楚。但重度高胆红素血症婴儿出现脱水、高渗血症、呼吸窘迫、水肿、早产、酸中毒、低白蛋白血症、缺氧及癫痫时,可能会增加核黄疸发生的可能。当血清总胆红素水平超过 425 μmol/L 时我们称为危重高胆红素血症。

60% 的足月儿会发生黄疸,2% 的足月儿血清总胆红素水平会超过 340 μmol/L。在加拿大,每年约有 5 000 名足月儿发生重度高红素血症,在中国这个数字超过 150 000。重度高红素血症的高危因素包括: 1)生后 24 h 内出现黄疸; 2)出院前出现黄疸; 3)胎龄小于 38 周; 4)纯母乳或部分母乳喂养; 5)前胎有重度高胆红素血症病史; 6)头皮、脸、臀部或者身体其他部位有体表或体内淤血; 7)头皮血肿; 8)男性; 9)母亲年龄小于 25 岁; 10)亚洲、欧洲及地中海裔人群; 11)脱水。

哪些新生儿需要进行胆红素检测? 什么时候检测? 怎样检测呢? 我们的建议是:1) 所有的新生儿病房,都应有在出院前对每个新生儿评估其显著高胆红素血症发生可能的过程和方案; 2) 对有危险因素的新生儿应该在出院前有系统的处理方案,对出现黄疸的婴儿应当有随访计划; 3)所有发生显性黄疸的足月儿及近足月儿都应进行胆红素水平的测定; 4)没有发生显性黄疸,但有一项或两项危险因素的新生儿出院前必须进行至少一次胆红素水平测定; 5)血清胆红素检测可以采集毛细血管微量血或者静脉血; 6)重度或黄疸持续时间较长的婴儿应当进行如结合胆红素分析等进一步的检查; 7)经皮胆红素检测仪可以用来进行初筛; 8)生后 24 h 内出院的新生儿应当在之后的 24 ~48 h 进行高胆红素血症的回访。

高胆红素血症的治疗包括光疗、换血疗法、免疫球蛋白滴注及其他药物干预治疗等。

光疗可以有效降低胆红素浓度。光疗的有效程度与皮肤暴露的面积,相关波长光源的强度,婴儿与光源的距离有关。荧光灯一般是使用最多的。毯式光纤治疗仪由钨-卤素灯作为光源,光纤安置在塑料垫内。光垫可以直接贴于婴儿的皮肤。这样的光疗系统可以使婴儿仍然坚持母乳喂养,并且不需要温箱及眼罩。同时这样的光垫也可以在家中使用。

虽然光疗增加了经皮的失水,但对于喂养正常的足月新生儿来说,并不是很大的问题。对一些脱水的黄疸婴儿补液通常会导致血清胆红素迅速下降,仍应继续肠道喂养。虽然停止母乳喂养已被证实可以迅速降低血清总胆红素水平,但在进行光疗等治疗的同时并非必须停止。即使持续母乳喂养,补液也可明显减少血清总胆红素水平。

为了创建图 1 这个光疗指南,我计算过这些对高危及低危重度高胆红素血症婴儿建议光疗的阈值。该图可用来指导胎龄≥35 周的婴儿的光疗。

关于光疗,我们的建议是:1) 当血清总胆红素超过图 1 根据日龄及危险因素绘制的曲线所示水平时,应当开始光疗; 2)婴儿脱水时应当补液,尽量使用母乳或者配方奶进行肠道喂养; 3)尽量坚持母乳喂养。

光疗失败,可采用换血疗法降低血清胆红素水平。对于没有危险因素的健康足月儿,血清结合胆红素达到 375 ~ 425 μmol/L 时应当考虑换血疗法。部分专家将血清总胆红素上升的速率作为换血指征之一,当血清胆红素每小时上升超过 20 μmol/L就考虑换血疗法。当出现核黄疸症状时,应立即换血治疗。

免疫球蛋白滴注被用于治疗如 Rh 血型不合等免疫溶血性高胆红素血症,剂量为 1 g/kg。免疫球蛋白可以通过抑制体内抗体,减少红细胞的破坏,阻断溶血过程,减少胆红素的生成。静脉滴注免疫球蛋白已被证明可以降低重度黄疸的发生,减少对换血疗法的需要,但不能减少以后因持续轻微溶血而输注浓缩红细胞的需要。

血红素氧合酶是血红蛋白降解形成胆红素过程中的限速酶。锡中卟啉作为血红素氧合酶的人工类似物,竞争性抑制其活性,减少胆红素生成,以降低新生儿对光疗及换血的需求。锡中卟啉治疗在常染色体显性遗传的 G6PD 酶缺乏病高发地区较常见,但在北美并非常规选择。尽管这种方法看上去十分有效,但仍需要更多的研究去了解其远期作用。临床上也常使用苯巴比妥预防黄疸的发生,临床转归并未见明显改善,但在出生前使用效果较好。

尽管母乳喂养是重度高红素血症的危险因素之一,但核黄疸发生的危险与母乳喂养的优点相比微不足道。重度黄疸的危险性可以通过母乳喂养支持降到最低。常规补充水或糖水并不会阻止高胆红素血症的发生。

综上所述,足月儿及近足月儿重度高胆红素血症有发生胆红素脑病及胆红素所致神经元损伤的风险。我们需要仔细地评估危险因素,系统地检测、评估、随访并适时进行光疗,根据实验室检查决定是否使用免疫球蛋白及换血疗法。

(本文编辑 邓芳明)