

Academy of Breastfeeding Medicine

Annotated Bibliography:

Protocol on Jaundice in the Breastfed Infant

Introduction

This review of the literature focuses primarily on basic and clinical research and on clinical guidance published between 1980 and 2005 which relates directly to the relationship of breastfeeding to neonatal jaundice, both early (first 5 days of life) and later. Significant papers prior to this time will also be reviewed. Definitions, clinical manifestations, outcomes, etiologic mechanisms, management and prevention will be reviewed. Broader issues of neonatal jaundice unrelated to breastfeeding, bilirubin metabolism and sequelae of hyperbilirubinemia (bilirubin encephalopathy, kernicterus) will not be reviewed here. The reader is referred to the recent American Academy of Pediatrics Clinical Practice Guideline on Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation (Pediatrics 2004;114:297-316) and to the Technical Report by Ip et al. which accompanies the Clinical Practice Guideline (Ip S, Chung M, Kulig J, et al. An Evidence-Based Review of Important Issues Concerning Neonatal Hyperbilirubinemia. Pediatrics 2004;114:e130-e153).

A total of 34 English language primary research papers were identified from a literature review conducted electronically for the period 1980 to 2005.

Background

Breastmilk Jaundice

Prolongation of neonatal jaundice has been associated with breastfeeding since 1861 (Frerichs, FT. Clinical Treatise on Diseases of the Liver, London, New Sydenham Society, 1861, Vol. 1, p 191.), although not characterized as a syndrome until 1963 and 1964 (Newman AJ, Gross S. Hyperbilirubinemia in breast-fed infants. Pediatrics 1963;32:995 [Level II-2]; Arias IM, Gartner LM, Seifter S et al. Prolonged neonatal unconjugated hyperbilirubinemia associated with breast feeding and a steroid, pregnane-3(α),20(β)-diol, in maternal milk that inhibits glucuronide formation in vitro. J Clin Invest 1964;43:2037-2047 [Level II-2]). In the Arias report, 7 full-term breastfed infants (breastfeeding undefined) of all races were noted to have otherwise unexplained unconjugated serum bilirubin levels ranging from 14.3 to 18.2 mg/dl on the 10th to 19th days of life. The onset of their jaundice was reported to be after 5 days of age, coincident with the appearance of transitional and mature milk. In 4 of these infants, complete cessation of breastfeeding resulting in a decline of serum bilirubin concentrations to adult normal (less than 1.5 mg/dl) within 3 to 6 days. In the infant of one mother who practiced both breastfeeding and artificial feeding, serum bilirubin concentrations did not fall to normal until 12 days later. One mother continued breastfeeding exclusively and this infant's serum bilirubin concentration declined to normal by 35 days of life after having peaked on day 11. The last mother interrupted breastfeeding from days 10 to 15 and this infant's serum bilirubin declined from 16 mg/dl to 5 mg/dl. With resumption of exclusive breastfeeding, the serum bilirubin rose by 1 mg/dl in two days and then gradually declined subsequently. This initial description was elaborated upon by this same group in 1966 (Gartner LM, Arias IM. Studies of Prolonged Neonatal Jaundice in the Breastfed Infant. J Pediat 1966;68:54-66 [Level II-2]) with a description of 20 term breastfed infants who had a very similar spectrum of presentation and response to interruption of breastfeeding. The highest total serum bilirubin noted in this group was 23.1 mg/dl on the 15th day of life. Both of these studies found that the milk of these mothers inhibited the conjugation of a compound believed to be using the same enzyme as bilirubin in vitro. This has subsequently been questioned and the etiology of prolonged unconjugated bilirubinemia in breastfed infants as due to inhibition of hepatic conjugation remains uncertain. A subsequent study in 1983 (Gartner LM, Lee KS, Moscioni AD. Effect of milk feeding on intestinal bilirubin absorption in the rat. J Pediat 1983;103:464-471 [Level II-2]) demonstrated that human milk from mothers of infants with prolonged unconjugated hyperbilirubinemia when introduced into adult rat intestines, markedly increased intestinal absorption of unconjugated bilirubin over a 15 hour period of observation compared with no increase in intestinal absorption with milk from mothers of infants without elevated serum bilirubin concentrations. This observation was confirmed in 1991 in a study of 36 exclusively breastfed, healthy term infants whose serum bilirubin concentrations ranged from less than 1.5 mg/dl to 17 mg/dl during the third week of life. Intestinal bilirubin

absorption in adult rats fed human milk correlated significantly with the infants' serum bilirubin concentrations. This has led to the general acceptance of the concept that prolonged, unconjugated hyperbilirubinemia in breastfed infants is due to a factor in human milk which increases intestinal absorption of unconjugated bilirubin. This entity is now known as breastmilk jaundice. Other hypotheses for the etiology of breastmilk jaundice have been proposed and will be reviewed below.

Starvation Jaundice of the Newborn

A second relationship between breastfeeding and exaggerated neonatal jaundice has become apparent in recent years. Whereas breastmilk jaundice has its onset after 5 days of age and is characterized by a prolonged, but eventually diminishing serum bilirubin, it is clear that some breastfed infants develop an exaggerated serum unconjugated bilirubin concentration earlier in the newborn period (before 5 days), or even later in the newborn period but which does not follow the pattern of breastmilk jaundice. Whereas the infants with breastmilk jaundice are healthy and thriving with good weight gain, another group of infants with otherwise unexplained jaundice are not gaining well or have excessive weight loss. These are breastfed infants who are not getting adequate caloric intake as a result of either maternal or infant problems. In many cases there are deficiencies in frequency of feeding, position and/or latch, or poor effort at nursing by the infant. Some rarer cases may be result from insufficient milk production by mother due to structural or endocrine abnormalities. The common denominator of this group of infants is that they are receiving fewer calories than they need and are suffering from some degree of starvation. It has been recognized for many years now in adults, that starvation of even as brief a period of time as 24 hours despite adequate hydration results in a significant increase in serum unconjugated bilirubin concentrations, usually of about 1 to 2 mg/dl. Similar starvation in adults with inherited abnormalities in bilirubin synthesis, transport or metabolism, even at relatively low levels (2 to 5 mg/dl), known as Gilbert's Syndrome, have even greater increases in serum bilirubin when starving. This is known as starvation jaundice. Animal studies have shown that starvation jaundice results from an increase in intestinal absorption of unconjugated bilirubin. This syndrome in newborns is variously known as Breastfeeding Jaundice, Breast-non-feeding Jaundice, and Starvation Jaundice of the Newborn. Clinical evidence of this phenomenon in newborns will be reviewed below.

Reference	Content	Level of Evidence*
Review of Literature from 1970 to Present		
Wong K, Wood BSB. Breast-milk jaundice and oral contraceptives. Brit Med J 1971;xxx:403-404.	This preliminary or exploratory comparison of minimally, moderately and severely jaundiced, but otherwise healthy full-term, breastfed newborns on the fifth day of life demonstrated a weak but significant association between prior use of anovulatory birth control pills and the likelihood of developing moderate and severe jaundice. Duration of pill use and interval between pill use and birth were not significant. This observation has never been repeated.	II-2
Dahms BB, Krauss AN, Gartner LM et al. Breast feeding and serum bilirubin values during the first 4 days of life. J Pediat 1973;83:1049-1054.	Full-term, healthy newborns, both breastfeeding and formula-feeding were randomly assigned to either a traditional feeding regimens (12 hour fast, glucose water at 12 hours, formula or breastfeeding started at 20 hours; scheduled feedings every 4 hours, no rooming-in, breastfeeders were given formula feedings X2 at night and were supplemented with glucose water or formula after every breastfeed); or to a new hospital regimen (first feeding of breastmilk or formula at 6 hours, feeding on demand averaging 6 to 7 feeds per 24 hours, no supplementation for breastfeeders, rooming-in). No significant differences in mean total serum bilirubin concentrations were seen at 48 to 72 hours of age between breast and formula-fed infants or between old and new regimen, nor were there any significant differences in bilirubin levels above 10 mg/dl. Two infants in the control breastfeeding group and one	I

	<p>in the demand formula-fed group required phototherapy. Mean weight loss was 8% in the demand breastfeeding group on day four, and was less than 5% in the other three groups. There was no relationship between weight loss and serum bilirubin concentrations. 12% of the exclusively breastfed infants developed significant temperature elevation (38.0C.) but this had no relation to weight loss and responded promptly to feeding water or milk. The febrile group of infants had the lowest serum bilirubin concentrations. The authors concluded that breastfeeding, per se, was not a cause of increased jaundice in the first days of life.</p>	
<p>Wood B, Culley P, Roginski C, et al. Factors affecting neonatal jaundice. Arch Dis Child 1979;54:111-115</p>	<p>690 consecutive full-term births in this British hospital formed the cohort for examination of factors associated with development of neonatal jaundice. On day 6, all infants had a serum bilirubin determination. The authors note their surprise at how often they found infants with serum bilirubin levels above 12 and even 15 mg/dl who had not been noted to be clinically jaundiced. Mean total serum bilirubin concentrations on day 6 for the 580 breastfed infants was 8.5 mg/dl, compared with 6.4 mg/dl for the 109 artificially-fed infants. 25% of breastfed infants but only 12% of artificially fed infants had serum bilirubin levels which exceeded 12 mg/dl. Weight loss greater than 5% of birthweight was associated with a significantly higher serum bilirubin concentration and serum bilirubin concentrations in excess of 12 mg/dl in breastfed infants. Only 2.5% of the entire cohort had serum bilirubin concentrations in excess of 18 mg/dl, the level at which phototherapy was instituted, and none reached 25 mg/dl. The authors concluded that breastfeeding itself was a more significant factor in determining 6th day bilirubins than weight loss, but they recommended strong advocacy for breastfeeding.</p>	II-2
<p>Constantopoulos A, Messaritakis J, Matsaniolis N. Breast Milk Jaundice: the role of lipoprotein lipase and the free fatty acids. Eur J Pediat 1980;134:35-38.</p>	<p>321 milk samples were obtained from two randomly selected cohorts of breastfeeding mothers for determination of lipoprotein lipase activity and free fatty acid concentration for comparison with breastmilk from a group of 5 infants with clinically proven breastmilk jaundice. No significant differences were observed between the control and jaundiced infant milks. These negative findings contrast with a report from France which demonstrated increased lipoprotein lipase activity in milk of infants with breastmilk jaundice. Storage of milk may have affected results in both studies. No further studies of this relationship have been reported.</p>	I
<p>Verronen P, Visakaorpi JK, Lammi A, et al. Promotion of breast feeding: Effect on neonates of change of feeding routine at a maternity unit. Acta Paediat Scand 1980;69:279-282</p>	<p>This report examines the effect of a change from traditional newborn feeding practices during postpartum hospitalization to a breastfeeding promotion program which included early skin-to-skin contact in the delivery room, routine rooming-in starting at 12 hours of age, breastfeeding on demand (6 to 7 times per day) after 12 hours of age (every four hours prior to 12 hours of age), one breastfeed at night, avoidance of supplementation unless needed (but 1/3 of infants did receive some supplementation), and printed instructions on breastfeeding. Infants and mothers remained in the hospital for 5 days postpartum. The breastfeeding program group included all healthy, full term infants for two months after establishment of the program (689 infants). The controls were similar, but were from two months prior to establishment of the</p>	II-3

	<p>program (707 infants). No significant difference was observed in clinical jaundice between the breastfeeding program group and the controls, nor was there any difference in serum bilirubin levels in excess of 12 mg/dl or in need for phototherapy treatment. If the infant was clinically jaundiced, a serum bilirubin was determined. Of the approximately 7.5% of infants noted to be clinically jaundiced in each group, the mean total serum bilirubin concentrations in the control group was 13.2 mg/dl, while in the breastfeeding program group it was significantly lower at 12.4 mg/dl. Mean weight loss from birth on day 5 was 5.3% in the breastfeeding program group, a value significantly higher than the 4.5% in the control group. The authors concluded that the more vigorous breastfeeding program did not increase the risk of neonatal jaundice.</p>	
<p>DeAngelis C, Sargent J, ChunMK. Breast milk jaundice. Wisconsin Med J 1980;79:40-42</p>	<p>A study of 251 infants in a university-based ambulatory practice. Temporary interruption of breastfeeding for 24 to 48 hours was recommended when total serum bilirubin concentrations exceeded 12 mg/dl; only one of the mothers failed to resume breastfeeding. Phototherapy was instituted when total serum bilirubin concentrations exceeded 15 mg/dl. 82.1% of the infants were breastfed. 25.7% of the breastfed infants and only 8.9% of formula-fed infants had serum bilirubin values in excess of 10 mg/dl; 19.9% of breastfed infants and only 6.7% of formula-fed infants exceeded 12 mg/dl; 6.8% of breastfed infants and only 2.2% of formula-fed infants exceeded 15 mg/dl, but this highest level was not significantly different. Breastfed infants had their peak serum bilirubin concentrations later (3 to 10 days) compared with formula-fed infants (2 to 6 days). The peak levels and days of peak would probably have been later if interruption of breastfeeding and use of phototherapy had not been instituted. Thirteen (6.3%) of the breastfed infants had total serum bilirubin concentrations exceeding 10 mg/dl for more than 10 days and the longest was 31 days, meeting the criteria of breastmilk jaundice. The authors recommend temporary interruption of breastfeeding when serum bilirubin concentrations come within 3 to 4 mg/dl of the level at which phototherapy would be used. They also suggest alternating formula feeding and breastfeeding at these levels.</p>	II-2
<p>De Carvalho M, Hall M, Harvey D. Effects of water supplementation on physiological jaundice in breast-fed babies. Arch Dis Child 1981;56:568-569</p>	<p>Healthy, full-term infants were randomly assigned to either receive water supplementation ad libitum after each breastfeed (n=120) or to receive no supplementation from birth onward. All babies breastfed on demand and were started on breastfeeding within 3 hours after birth. No difference was noted in peak serum bilirubin values for those infants exceeding 12 mg/dl, age at time of peak, or need for phototherapy during the first week of life. However, this study is compromised by not providing data on the frequency of infants exceeding 12 mg/dl in the two groups. The authors conclude that there is no evidence that water supplementation of breastfeeding infants has any beneficial effect in preventing jaundice or reducing peak serum bilirubin values or need for phototherapy.</p>	I
<p>De Carvalho M, Klaus MH, Merkatz RB. Frequency of breast-feeding and serum bilirubin</p>	<p>This cohort study of 55 healthy term infants from uncomplicated labors and deliveries, who were committed to breastfeeding their infants, were given</p>	II-2

<p>concentration. Am J. Dis Child 1982;136:737-738</p>	<p>optimal breastfeeding instructions which included rooming-in, no supplementation, response to earliest hunger cues, and unlimited frequency and duration of nursing. Feeding frequency and duration were recorded and a total serum bilirubin was determined on the third day of life. The mean serum bilirubin concentration for infants who were breastfed more than 8 times per 24 hours for three days (mean 10.1 feeds/day) were 6.5 mg/dl, in contrast to a significantly higher mean serum bilirubin of 9.3 mg/dl for those who breastfed 8 or fewer times per 24 hours (mean 6.8 feeds/day). Weight loss at three days of age was the same in both groups at 6.5%. Duration of feeds were also the same. Analysis of feeding frequency from 5 to more than 11 feeds per day demonstrated a significant progressive linear decline in third day serum bilirubin with each increase in frequency. The authors recommend frequent and unlimited numbers of feedings during the first days of life. This is one of the most reproduced graphs in all of breastfeeding. (See paper by Yamanauchi et al 1990).</p>	
<p>Nicoll A, Ginsburg R, Tripp JH. Supplementary feeding and jaundice in newborns. Acta Paediat Scand 1982;71:759-761</p>	<p>49 healthy, full-term breastfed infants were randomly allocated to three groups: water supplementation after each breastfeed, glucose water supplement, and no supplement. Total serum bilirubin was determined on day 6. Test weighings before and after all breastfeeds were made on the 6th day during a 9 hour daytime period. A prior survey of 20 British pediatricians revealed that 79% of the infants in their practices received water, glucose water or formula supplementation of breastfeeding, often in the belief that this would prevent jaundice. Results of the supplementation study were that there was no significant difference in weight loss among the three groups on day 5, ranging from 4.0 to 4.3%. Average milk intake on day 5 was the same in all three groups, ranging from 17 to 20 grams/kg. Although there was no statistically significant difference, it is of interest that the unsupplemented group had the highest milk intake. Mean serum bilirubin concentrations on day 6 were not significantly different among the groups, although the group that received water supplementation had a mean total serum bilirubin of 5.4 mg/dl; the glucose water supplemented group was 4.8; and the unsupplemented group was 4.0 mg/dl. There was no evidence of dehydration in the unsupplemented infants. No data is provided on the frequency of breastfeeding each day in each group, an unfortunate omission. Since the numbers of subjects in each group were small, the absence of significant differences is questionable. A larger study population might have shown a significant difference. The authors conclude that fluid supplementation does not reduce physiologic jaundice and "may compromise lactation." They also calculate the cost of providing these water or glucose water supplements at about \$4.00 per child in the United Kingdom in 1980. [Considering three-fold inflation, 60% breastfeeding and the number of infants born in the U.S., this would be a total cost of about \$30,000,000.</p>	I
<p>Kuhr M, Paneth N. Feeding practices and early neonatal jaundice. J Ped Gastro & Nutr 1982;1:485-488</p>	<p>135 consecutive healthy, full-term newborns were enrolled in a study at a community hospital. If jaundice developed, serum bilirubin was determined. 44 breastfed infants were studied on the fourth day for milk volume with pre</p>	<u>II-2</u>

	<p>and post feeding weights. Of the 77 breastfed infants, 37.7% had total serum bilirubin concentrations above 10 mg/dl. Of the 58 artificially-fed neonates, only 10.5% exceeded 10 mg/dl, a significantly lower proportion. Infants ingesting less than 80 cc/kg of milk on the fourth day had a greater incidence of jaundice (44.4%) than those ingesting more than 80% (23.1%). Breastfed infants who ingested more than 100 cc of glucose water during the first three days had a greater incidence of jaundice, although this difference was not significant. Day 4 milk volume was inversely significantly correlated with the volume of glucose water ingested in the first 3 days. Detailed description of breastfeeding management and practice among the study mothers was not provided. The authors conclude that there was no evidence for any benefit in supplementing breastfeeding infants with glucose water and such supplementation was associated with reduced milk volume and increased jaundice.</p>	
<p>Gartner L, Lee, KS, Moscioni D. Effect of milk feeding on intestinal bilirubin absorption in the rat. J Pediat 1983;103:464-471.</p>	<p>Intestinal absorption of unconjugated bilirubin was studied in adult rats to assess the effect of human milk and infant formula on the enterohepatic circulation of bilirubin. Human milk from both mothers of infants with and without breastmilk jaundice were studied. Infant formula completely prevented the intestinal absorption of bilirubin. Human milk from mothers of non-jaundiced infants also prevented the absorption of bilirubin. In contrast, milk from mothers of infants with breastmilk jaundice resulted in absorption of 25% of the instilled bilirubin within the first 5 hours. Whereas bilirubin alone resulted in no further absorption of bilirubin after 5 hours, in the presence of milk from mothers of jaundiced infants, absorption continued for an additional ten hours for a total absorption of 65% of administered bilirubin. Similar results were observed in a closed loop rat model. The authors conclude that normal human milk inhibits intestinal bilirubin absorption, correlating with the observation that adequate milk intake during breastfeeding is associated with a lower serum bilirubin concentration in contrast to the higher serum bilirubin concentration seen in infants ingesting less than optimal volumes of milk. The authors also conclude that some mothers, at least at some times, produce a milk which contains a factor which increases intestinal bilirubin absorption causing the breastmilk jaundice syndrome.</p>	
<p>Butler DA, MacMillan JP. Relationship of breast feeding and weight loss to jaundice in the newborn period: review of the literature and results of a study. Cleveland Clinic Quarterly 1983;50:263-268</p>	<p>183 exclusively breastfed infants and 175 exclusively formula-fed healthy, full-term infants were enrolled in a study of serum bilirubin concentrations over a 5 ½ day period after birth. Serum bilirubin determinations were performed whenever clinical jaundice was suspected and also at the time of the routine metabolic screen at discharge. Peak bilirubin levels in excess of 10 mg/dl were found in 39.8% of breastfed infants and in only 16% of formula-fed infants. 4.4% of breastfed infants and none of the formula-fed infants exceeded 15 mg/dl. Weight loss correlated significantly with serum bilirubin concentrations. From their review of the literature and their own observations, the authors conclude that there are “two separate disorders.” One is the prolonged breastmilk jaundice. The other is the early exaggeration of physiologic jaundice associated with degree of weight loss. They also suggest</p>	<p>II-1</p>

<p>Johnson CA, Lieberman B, Hassanein RE. The relationship of breast feeding to third-day bilirubin levels. J of Family Practice 1985;20:147-152</p>	<p>that many cases represent an overlap of the two entities.</p> <p>This prospective cohort study included 281 full-term, healthy newborns in a university hospital who had a serum bilirubin determination at 3 days of age. Phototherapy was instituted when total serum bilirubin reached 15 mg/dl. Breastfeeding mothers were encouraged to nurse every 2 to 3 hours during the day and every 4 hours at night. Breastfeeding mothers were given sterile bottles and the option of feeding this to their infant after every breastfeed. Mean total serum bilirubin concentrations on day three for formula-fed infants were 5.6 mg/dl, for mixed-fed infants 6.9 mg/dl, and for breast-fed infants 7.5 mg/dl. These differences were significant. The percentages of infants exceeding 12 mg/dl were as follows: formula-fed: 4.4%; mixed-fed 6.9%; breastfed: 18.5%. Statistically significant differences in weight loss were also observed: formula-fed: 3.0%; mixed-fed: 4.7%; breastfed: 5.4%. Breastfed infants with bilirubin levels over 12 mg/dl had even greater weight loss of 6.2%. Further analysis of the data showed that even after adjustment for weight loss, higher serum bilirubin concentrations were significantly associated with breastfeeding. This study did not provide details on the frequency of breastfeeding or on any other characteristics of the breastfeeding practices.</p>	<p>II-2</p>
<p>Osborn LM, Bolus R. Breast feeding and jaundice in the first week of life. J of Family Practice 1985;20:475-480</p>	<p>This is a report of an 18 month prospective cohort study of all 36 week to term breastfed newborn infants weighing more than 2,500g who were born at and treated for jaundice at a university hospital. They were followed in the clinic until all jaundiced had resolved. A control group of 105 non-jaundiced infants or whose serum total bilirubin was never higher than 10 mg/dl was drawn from this same population. Breastfed infants whose serum bilirubin was 15 to 16.9 mg/dl were temporarily switched to formula until their total serum bilirubin declined by 2 mg/dl, when breastfeeding was to resume. Infants with serum bilirubin greater than 16.9 mg/dl were admitted for immediate phototherapy. During the last 6 months of the study, a new protocol for support of breastfeeding was introduced. This new protocol eliminated the initial water feeding and started breastfeeding "at birth,," Encouraged demand feeding 24 hours a day and eliminated formula and water feedings at night, and eliminated all supplementary water feedings after each breastfeed. 71% of all infants were breastfed; of these 5.5% (108 infants) were treated for jaundice with temporary interruption of nursing with or without phototherapy. Three of the infants had hemolytic disease (ABO X 2; G6PD Deficiency X 1). Infants not requiring treatment had a mean weight loss of 3.4%, while those requiring treatment had a weight loss of 4.9%. 48% of infants were exclusively breastfeeding and 20% were receiving mixed feedings at two weeks of age; no differences were seen among the untreated and two treatment groups. Changes in breastfeeding protocol had no effect on the proportion of jaundiced infants or those requiring treatment. The authors concluded that temporary interruption of breastfeeding reduced the need for hospitalization and phototherapy and was just as effective as phototherapy. Furthermore, they found no evidence that interruption interfered with the continuation of breastfeeding. The authors did not provide any detail on the time of initiation</p>	<p>II-2</p>

	of breastfeeding or on frequency of breastfeeding either during the initial period or after introduction of the new breastfeeding protocol.	
Lucas A, Baker BA. Breast milk jaundice in premature infants. Arch Dis Child 1986;61:1063-1067	This study of 186 premature infants weighing less than 1850 g at birth and with a mean gestational age of 31 weeks was randomized to receive either banked human milk or premature infant formula for the first 50 days of life (primary trial) or to receive their mother's own milk with supplementation with either banked human milk or premature infant formula for the first 50 days of life (supplement trial). In the supplement study, mother's own milk was 46% of total milk intake. Both trials demonstrated significantly elevated total serum bilirubin concentrations throughout the 50 day study period for the infants receiving human milk as the only source of nutrition. The duration and peak values of hyperbilirubinemia were greater in the human milk fed group as compared with those receiving infant formula as their exclusive or partial nutrition. Serum bilirubin concentrations in excess of 12 mg/dl were seen in 43% of the infants receiving human milk in contrast to 10% in those receiving only formula. The authors conclude that human milk has a significant and prolonged effect on elevating unconjugated serum bilirubin concentrations in premature infants.	I
Schneider, AP II. Breast milk jaundice in the newborn. JAMA 1986;255:3270-3274	This meta-analysis of 12 pooled studies from 1965 to 1985 comparing jaundice in the breastfed infant with that in the formula-fed infant demonstrated that breastfed infants had a significantly greater risk for both moderate and severe hyperbilirubinemia and higher mean serum bilirubin concentrations compared with formula-fed infants. Moderate jaundice (greater than 12 mg/dl) is 3 times as likely in breastfed infants as in formula-fed infants and severe jaundice (greater than 15 mg/dl) is 6 times as likely to occur. Eleven of 13 studies demonstrated a significantly higher mean serum bilirubin concentration for breastfed infants (7.76 mg/dl) compared to formula-fed infants (6.02 mg/dl). The author concludes that the review of the literature strongly supports the association of jaundice in the first week of life with breastfeeding. This study has one unfortunate deficiency: the author clustered all infants who were said to be breastfed into the breastfed category without any attempt to classify according to the specific nature of the breastfeeding. This deficiency is not entirely the fault of the author because up to that time, very few papers on breastfeeding defined the specific character of the breastfeeding, particularly as to time of onset, frequency, use of supplementation, etc.	II-1
Elander G, Lindberg T. Hospital routines in infants with hyperbilirubinemia influence the duration of breastfeeding. Acta Paediat Scand 1986;75:708-712	29 full-term, healthy infants with total serum bilirubin concentrations of greater than 20 mg/dl were randomly allocated to receive phototherapy in a hospital unit separate from the mother or in a hospital unit with the mother staying with the infant. Mothers of separated infants were free to visit and breastfeed the infant at any time. Mothers of infants receiving phototherapy with the mothers in constant attendance were responsible for providing most of the infant care. For some mothers this was apparently stressful. The duration of phototherapy ranged from one to 8 days. Maternal stress due to separation was assessed by interview and also by measurement of 24 hour urinary cortisol excretion on the 7th day post-partum and three months later. A non-jaundiced control	I

	<p>group drawn from the same population was also studied for breastfeeding and cortisol excretion. Breastfeeding rates were significantly lower in the separated group throughout the 12 week study period compared to both the unseparated group and controls, which were identical. While all three groups showed a gradual decline in breastfeeding rates over the 12 weeks, the rate of decline for the separated group was much greater, especially after 9 weeks. No differences among groups were seen for cortisol excretion. The authors recommend that phototherapy treated infants not be separated from their mothers and that phototherapy be given on the maternity ward rather than moving the child to a different location. Avoiding separation appears to protect breastfeeding.</p>	
<p>Gourley GR, Arend RA. β-glucuronidase and hyperbilirubinemia in breast-fed and formula-fed babies. Lancet 1986;1:644-646.</p>	<p>β-glucuronidase activity in breast milk, formula, serum and stool was examined in breastfed and formula fed infants to test the hypothesis that some breast milk contains increased β-glucuronidase activity which results in more rapid conversion of conjugated bilirubin in the intestine into unconjugated, the form in which bilirubin is absorbed across the intestinal mucosa. Serum bilirubin concentrations were determined at 21 days of age in both groups. Infant formula had almost no β-glucuronidase activity, whereas human milk on the third day post-partum was significant. By 21 days, β-glucuronidase activity in human milk had declined to one-third of the activity on day 3. Infant serum β-glucuronidase activity in breastfed infants was slightly but significantly higher than that in formula-fed infants on the 3rd day of life. Although activity in both groups of infants had declined, breastfed infants on day 21 had three-fold greater serum β-glucuronidase activity than formula-fed infants. Infant fecal β-glucuronidase activity on day 21 was also three-fold higher in breastfed infants compared to formula-fed infants. Breastfed infants with serum bilirubin concentrations in excess of 4 mg/dl had significantly higher fecal β-glucuronidase activity than those with lower serum bilirubin levels. Similarly, breastfed infants with serum bilirubin concentrations in excess of 6 mg/dl at 21 days had significantly higher β-glucuronidase activity in the milk they were ingesting. In one infant, interruption of breastfeeding was associated with a dramatic decline in fecal β-glucuronidase activity and a rise when breastfeeding resumed. The authors suggest that breastmilk β-glucuronidase "seems to be an important factor in the neonatal hyperbilirubinemia of breast-fed babies." It should be noted, however, that other investigators have shown that β-glucuronidase activity in the mucosa of newborn infants is ten-fold higher than in adults or older children. This suggests that endogenous β-glucuronidase (mucosal) may be of much greater importance than that derived from human milk.</p>	<p>II-1</p>
<p>Amato M, Berthet G, Von Muralt G. Influence of fatty diet on neonatal jaundice in breast-fed infants. Act Paediatr Jpn 1988;30:492-496</p>	<p>Human milk lipid was measured by the creatatocrit method in breastmilk samples from mothers of 50 jaundiced and 50 non-jaundiced full-term, healthy newborns who were exclusively breastfed on the 4th to 8th days postpartum. Milk was collected from one breast after the infant had nursed at that breast. Three milk samples were obtained from each mother. Mean creatatocrit was 7.26% in milk from jaundiced babies' mothers and 5.1% in milk from mothers</p>	<p>II-2</p>

	<p>of non-jaundiced infants, a difference which is highly significant. The authors suggest that "high fat content in human milk may be a risk factor for the development of neonatal hyperbilirubinemia. It is not clear from this limited report when the infant's jaundice appeared, peaked and declined, so it is impossible to determine whether the association of the higher fat content is with exaggeration of early physiologic jaundice (first 5 days) or with the pattern seen in breastmilk jaundice, which usually starts after day 5, with the appearance of transitional or mature milk. This is an interesting observation, but far from conclusive.</p>	
<p>Yamauchi Y, Yamanouchi I. Breast-feeding frequency during the first 24 hours after birth in full-term neonates. Pediatrics 1990;86:171-175</p>	<p>140 healthy, full-term newborns who were rooming in were studied for the relationship between frequency of breastfeeding and a number of outcome variables, including the infant's transcutaneous bilirubin on the 6th day of life. Infants were rooming-in and mothers were instructed to feed whenever they "suspected" they were hungry and were also instructed not to limit the duration of nursing on each side. Milk volume was determined by pre and post feed weighings on days 3 and 5. With each increase in frequency of breastfeeding, the proportion of infants with elevated transcutaneous measurements declined. With 9 to 11 feeds per day, there were no infants with elevated bilirubin levels. The authors suggest that many neonatal clinical problems could be prevented by changes in hospital practices. This study suggests that the optimal frequency of breastfeeding, starting with the first day, is more than 8 per 24 hours and likely 10 to 12 per day to prevent excessive neonatal jaundice.</p>	II-2
<p>Alonso EM, Whittington PF, Whittington SH et al. Enterohepatic circulation of nonconjugated bilirubin in rats fed with human milk. J Pediat 1991;118:425-430</p>	<p>Milk from mothers of 36 healthy term infants between 12 and 21 days of age were studied for its effect on intestinal bilirubin absorption in an adult rat model and for its effect on hepatic glucuronosyl transferase activity (conjugating enzyme). In addition the milks were studied for β glucuronidase activity and nonesterified fatty acid concentrations. Infant serum bilirubin concentrations were determined on the day of milk collection. 22 infants had serum bilirubin concentrations above the adult normal range of 1.5 mg/dl, fulfilling the definition of breastmilk jaundice. 13 infants had serum bilirubin concentrations above 5 mg/dl and 2 infants exceeded 15 mg/dl. A significant positive correlation was found between the infant's serum bilirubin concentration and the effect of the milk on increasing rat intestinal bilirubin absorption, confirming the role of human milk in enhancing intestinal bilirubin absorption as the major mechanism of breastmilk jaundice. β glucuronidase activity, nonesterified fatty acid concentrations and inhibition of hepatic glucuronosyl transferase activity failed to show any correlation with infant serum bilirubin concentrations alone and in combination. Thus, this study demonstrated that 2/3 of all healthy breastfed infants during the third week of life have mild to moderate breastmilk jaundice and that this continuation of physiologic jaundice is likely due to a factor in human milk which enhances intestinal bilirubin absorption.</p>	II-1
<p>Gourley GR, Kreamer B, Arnd R. The effect of diet on feces and jaundice during the first 3 weeks of life. Gastroenter 1992;103:660-667</p>	<p>Full-term, healthy infants were fed from birth with either human milk, or one of three infant formulas (whey predominant, casein predominant, or casein hydrolysate (Nutramigen). All stools were collected for the first 21 days of life. Serum bilirubin determinations were performed on infant blood from umbilical</p>	II-1

	<p>cord blood and on days 3 and 21. In addition, transcutaneous bilirubin measurements (Minolta) were made every 3 to 5 days. By day 3, weight loss (5.5%) was significantly greater for the human milk fed infants than for the other groups (1.5 to 2.8%). Day 3 serum bilirubin levels were not significantly different among the four groups (average approximately 7.5 mg/dl). On day 21, the human milk fed infants had a significantly higher mean serum bilirubin concentration (3.6 mg/dl), compared with the other three groups. The casein hydrolysate fed infants had a significantly lower mean serum bilirubin concentration (0.88 mg/dl) than the other two formula-fed infant groups (1.65 mg/dl). Total wet and dry stool weight was lowest for the human milk-fed infants, slightly higher for the casein hydrolysate infant and significantly higher than both for the two regular formula-fed infant groups over the 21 days of study. Although there was no correlation between serum bilirubin concentrations and stool number or wet and dry weights, the decrease in bilirubin only in the human milk group correlated directly with cumulative wet and dry stool weight on day 21. The authors suggest that hyperbilirubinemia in infants fed human milk may be related, in part, to low stool output. This study also indicates that casein hydrolysate formula decreases serum bilirubin concentrations.</p>	
<p>Maisels MJ, Vain N, Acquavita AM et al. The effect of breast-feeding frequency on serum bilirubin levels. Am J Obstet Gynecol 1994;170:880-883</p>	<p>278 term or near term healthy newborns in an Argentine hospital weighing more than 2500 grams were randomly assigned to one of two breastfeeding groups: frequent or demand. Frequent feeding group mothers were instructed to breastfeed at least every 2 hours during the day and no less than every 3 hours at night. Demand feeding mothers were instructed to feed whenever the infant cried or appeared to be hungry. All infants began feeding within one hour of delivery. Dextrose water supplements were given only if requested by the mother. 21% of demand group and 11% of the frequent group mothers gave supplementary glucose water, a significant difference. Rooming in was 24 hours a day. Cord blood and one heel stick between 48 and 72 hours were obtained for serum bilirubin determination. Cord serum bilirubin concentrations were 1.6 and 1.7 mg/dl and were not significantly different. Mean total serum bilirubin was 7.4 mg/dl in the frequent group and 8.0 in the demand group and were not significantly different at an average of 50 and 55 hours respectively. The difference in age at time of blood drawing was significantly higher for the demand group, which would tend to make the values higher. The proportion of infants with serum bilirubin concentrations in excess of 12 mg/dl was not significantly different between the groups. The mean frequency of feeding in the frequent group was 9 (7.5 to 10.5 + 1 SD) per 24 hours and 6.5 (5.5 to 8.0 + 1SD) per 24 hours in the demand group. There was no correlation between frequency of feeding and serum bilirubin concentrations on the third day of life. Mean serum bilirubin levels of infants of mothers who fed 10 or more times per day was 7.2 mg/dl compared to 7.6 mg/dl in those fed 6 times per day or less. The frequent feeders lost 5.5% from birth weight, whereas the demand feeders lost only 4.8%, a significant difference. This is surprising since the frequent feeders did, indeed, feed more</p>	<p>I</p>

	frequently. This lack of difference in serum bilirubin on the third day in relation to frequency of breastfeeding is surprising and at variance from several other studies. The greater loss of weight in the frequent feeders suggests that there was something different about the groups that was not explained with regard to either the breastfeeding effectiveness or the measurement of serum bilirubin.	
Demirkol M, Bohles H. Breast milk taurine and its possible influence on the development of breast milk induced jaundice of the neonate – a hypothesis. From <i>Taurine in Health and Disease</i> . R. Huxtable & DV Michalk, Eds. Plenum Press, New York 1994. pp 405-410.	65 healthy, full-term neonates were followed from birth for 6 weeks for appearance of jaundice, which was then confirmed with daily serum bilirubin measurements. Three day stools were collected during the first week after passage of meconium and again at the end of the first week of life and during the third and sixth weeks. At the midpoint of each stool collection, a milk specimen was obtained from the mother. Twelve infants (18.5%) were diagnosed as having breastmilk jaundice by process of exclusion and the demonstration of a decline in serum bilirubin when breastfeeding was temporarily interrupted and infant formula given. Those without clinical jaundice were considered controls. Stool chenodeoxycholic acid (a bile acid) was significantly decreased during the first week of life in jaundiced infants. No other differences in bile acids were found. At the end of the first week of life, taurine concentrations in milk was significantly higher in mothers of jaundiced babies than in controls and a significant linear correlations was observed between milk taurine concentration and the chenodeoxycholic acid concentration in infant stool. The elevation in breastmilk taurine coincides with the time when breastmilk jaundice begins to develop. The authors suggest that the increased taurine results in taurine conjugates of bile acids which are more soluble than glycine conjugates. It is further hypothesized that increased soluble bile acid conjugates facilitates intestinal bilirubin absorption, resulting in the breastmilk jaundice.	II-2
Maisels MJ, Newman TB. Kernicterus in otherwise healthy, breast-fed term newborns. Pediatrics 1995;96:730-733	6 malpractice law cases of otherwise healthy infants with kernicterus and without hemolysis or any other pathologic cause of jaundice, born between 1979 and 1991, were identified for review. All six infants were breastfed, although details regarding the breastfeeding were not provided. Four were 37 week gestations and were deemed premature. Four had weight loss in excess of 10% (11 to 22%). Peak total serum bilirubin concentrations were 39 to 50 mg/dl on days 4 to 10. All but one were jaundiced at the time of discharge from the hospital on the 2nd or 3rd days of life. The sixth child was born at home. None were jaundiced in the first 24 hours. The authors conclude that “although extremely rare, kernicterus can occur in term or near-term, apparently healthy, breast-fed infants.” They suggest that “closer and more frequent follow-up after birth and discharge from the hospital might prevent some of these unfortunate outcomes.”	II-3
Swand-Comunelli S, Welhoelter J, Harris K et al. Bilirubin levels and weight change in infants with early hospital discharge versus prolonged hospital stay. J Perinat 1996;16:211-214	Two populations of infants from different time periods were studied for development of hyperbilirubinemia. One group of newborns were discharged by 36 hours of age and 75% were breastfed. The other group, from an earlier year, were discharged at 3 to 5 days of age and 67% were breastfed. No significant differences in total serum bilirubin concentrations were found between the early and late discharge populations at comparable ages. On	II-3

	<p>days 2 to 4, serum bilirubin concentrations in the breast and formula-fed infants were almost identical. In contrast, in the prolonged hospital stay group, serum bilirubin concentrations were significantly different at 2 to 4 days, suggesting that breastfeeding techniques in earlier years were less effective. However, on days 5 to 7 in the early discharge group, mean serum bilirubin concentrations in the breastfed infants (9.2 mg/dl) were approximately double that of formula-fed infants (4.5 mg/dl). Total serum bilirubin concentrations in excess of 12 mg/dl occurred in 29% of breastfed infants and only 10% of formula fed infants, a significant difference. However, the differences between breastfed and formula-fed infants at higher bilirubin levels, above 15 and 20 mg/dl were not significant, although slightly higher in the breastfed group. The prolonged hospital stay infants had similar differences between breast and formula-fed infants. No relationship was found to weight changes or any other clinical findings. This later population of 200 infants appears to have a significant incidence of breastmilk jaundice and no evidence of any earlier starvation jaundice. The 29% incidence of serum bilirubins in excess of 12 mg/dl is approximately double that of the Alonso study (abstract 21 above); that difference may be the result of multiple bilirubin determinations over a longer period of time. This suggests that the incidence of breastmilk jaundice, both mild and moderate, may be even greater than the 67% estimated from the Alonso study. The authors concluded that early hospital discharge imposed no adverse effects on serum bilirubin levels.</p>	
<p>Tan KL. Decreased response to phototherapy for neonatal jaundice in breast-fed infants. Arch Pediatr Adolesc Med 1998;152:1187-1190</p>	<p>Three groups of full-term, healthy neonates were studied for response to phototherapy if their total serum bilirubin exceeded 14.9 mg/dl after 48 hours of age or 13.0 mg/dl if less than 48 hours of age. Exclusively breastfed infants (n=34) had a slightly, but significantly, lower rate of serum bilirubin decline than either formula-fed infants or infants on mixed feeding. Although breastfed infants had the greatest weight loss at the time of start of phototherapy (6.1%), their subsequent weight gain during the phototherapy treatment was the same as the other two groups. No infants required further treatment for their hyperbilirubinemia. While the formula and mixed feeding infants had complete loss of clinical jaundice by 7 to 10 days of age, the exclusively breastfed infants were visibly jaundiced for much longer. Some beyond one month of age. The authors suggest that "addition of formula-feeding for totally breast-fed infants would be useful in enhancing the efficacy of phototherapy and reducing the exposure time to phototherapy." The editor's comment was that "the take-home message ...is that a clinician never needs to stop a mother from breast-feeding because of neonatal jaundice caused only by human milk." The slightly lower response to phototherapy may indicate that breastfed infants have increased enterohepatic circulation of bilirubin which renders phototherapy less effective and also results in the observed prolongation of jaundice.</p>	<p>III-2</p>
<p>Gartner LM, Herrarias CT, Sebring RH. Practice patterns in neonatal hyperbilirubinemia. Pediatrics 1998;101:25-31</p>	<p>The American Academy of Pediatrics surveyed 600 randomly identified general office-based pediatrician members and neonatologist members of the Academy as a component of their periodic survey program. The pediatricians</p>	<p>I</p>

	<p>were asked to respond to a series of questions regarding a full-term, healthy breastfeeding neonate whose total serum bilirubin concentration at 36 hours of age was 11.0 mg/dl. Responses were quite wide ranging, although neonatologists were more likely to recommend therapy at lower serum bilirubin concentrations than office-based general pediatricians, who generally followed the guidelines published by the AAP in 1994. The great majority of both generalists and neonatologists would have initiated phototherapy between 13 and 19 mg/dl., though more generalists than neonatologists would have waited until the serum bilirubin was 20 to 25 mg/dl. General pediatricians were equally divided between doing an exchange transfusion at 20 to 25 mg/dl and 26 to 30 mg/dl. More neonatologists would have done the exchange transfusion at 20-25 mg/dl. Approximately 6% of general pediatricians would not have done an exchange transfusion at all, regardless of serum bilirubin concentration. An even wider variation in management was revealed to the question of when to temporarily interrupt breastfeeding. About 40 to 45% of both generalists and neonatologists would have interrupted breastfeeding at 20-25 mg/dl, while approximately 25% would have interrupted at 14-19 mg/dl. Approximately 15% would not have interrupted breastfeeding at all, but 13% said they would have temporarily interrupted at 11 mg/dl.</p>	
<p>Gourley GR, Kreamer B, Cohnen M et al. Neonatal jaundice and diet. Arch Pediatr Adolesc Med 1999;153:184-188</p>	<p>A convenience sample of breastfed and formula-fed healthy, full-term, white, vaginally-delivered neonates were studied with random allocation of formula-fed infants to receive either whey-predominant standard infant formula or casein-hydrolysate formula (Nutramigen). Breastfeeding was exclusive and initiated within 30 to 60 minutes of birth and on demand every 1 to 3 hours. Formula-feeding was started at 30 to 60 minutes of age and was offered on demand every 1 to 3 hours. Infants were monitored closely for clinical jaundice over a three-week period using the jaundice index method. There were 20 infants in each group. The breastfed group had significantly higher jaundice indices starting on day 8 through day 19 compared with infants fed regular formula. Casein hydrolysate-fed infants had significantly lower than regular formula-fed infants from day 3 through day 20. This study confirms the frequent occurrence of breastmilk jaundice starting in the second week of life and continuing through the third week of life. It also demonstrates the effect of casein hydrolysate formula in reducing jaundice. This study suggests that when breastfed infants have serum bilirubin levels sufficiently high to require temporary interruption of breastfeeding, it would be more effective to feed them with casein hydrolysate formula than with regular infant formula.</p>	II-2
<p>Newman TB, Xiong B, Gonzales VM et al. Prediction and prevention of extreme neonatal hyperbilirubinemia in a mature health maintenance organization. Arch Pediatr Adolesc Med 2000; 154:1140-1147</p>	<p>36 week to term neonates weighing more than 2000 g at birth were retrospectively studied for predictors of serum bilirubin greater than 25 mg/dl during the first 30 days of life. Exclusive breastfeeding and a family history of jaundice in a newborn were the two strongest factors significantly predicting serum bilirubin levels in excess of 25 mg/dl.</p>	II-2
<p>Maruo Y, Nishizawa K, Sato H, et al. Prolonged unconjugated hyperbilirubinemia associated with breast milk and mutations of the bilirubin uridine</p>	<p>17 otherwise healthy, full-term, breastfed neonates with prolonged unconjugated hyperbilirubinemia ranging from 10.3 to 31.9 mg/dl during the fourth week of life were diagnosed as having breastmilk jaundice because</p>	II-2

<p>diphosphate-glucuronosyltransferase gene. Pediatrics 2000;106:e59-e61</p>	<p>serum bilirubin concentrations declined when breastfeeding was temporarily stopped and rose with resumption of breastfeeding. By four months of age all infants were anicteric and many had normal serum bilirubin concentrations. Analysis of the enhancer region of the hepatic glucuronyl transferase (conjugation enzyme) gene revealed that 16 of the 17 infants had a mutation for one or more gene sites which results in a reduction in conjugating enzyme activity. This the same defect observed in older children and adults with Gilbert's Syndrome, a life-long, low to moderate unconjugated hyperbilirubinemia. The one infant with normal gene structure was among the infants with the lowest serum bilirubin at four weeks, 12.8 mg/dl. This data suggests that the more severe hyperbilirubinemia of breastmilk jaundice results from the effect of a factor in human milk which enhances intestinal bilirubin concentration in combination with a genetic mutation which reduces hepatic bilirubin conjugating capacity. With maturation of the limited enzyme activity and decrease of intestinal bilirubin absorption, sufficient conjugation occurs to handle the bilirubin load and return serum bilirubin concentrations to normal.</p>	
<p>Bertini G, Dani C, Tronchin M, Rubaltelli FF. Is breastfeeding really favoring early neonatal jaundice? Pediatrics 2001;107:e41-e46</p>	<p>A prospective cohort study of full-term infants in Italy with observation of jaundice and serum bilirubin determinations on all jaundiced infants to assess factors affecting development of jaundice, including breastfeeding and weight loss. Breastfeeding was exclusive and started in the delivery room. Feedings varied from 6 to 12 per day and pacifiers were forbidden. Infants who were breastfeeding and received supplementation with formula were designated as supplemented infants. Infants were observed for the first 3 to 4 days of life, the duration of hospital stay. 24% of infants became jaundiced and 5.1% had a total serum bilirubin concentration greater than 12.9 mg/dl. Analysis revealed that only 2.7% of breastfed infants became jaundiced, the lowest proportion of all factors analyzed. 5.9% of formula-fed infants and 13.1% of supplemented breastfeeding infants had serum bilirubin concentrations in excess of 12.9 mg/dl. Breastfed infants had the smallest weight loss at 72 hours of age (200 g), compared with formula-fed infants (207g) and supplemented infants (264g). Multiple regression analysis revealed a statistically significant association for total serum bilirubin in excess of 12.9 mg/dl with supplementary feeding, vacuum extraction, ABO incompatibility, and increased weight loss, while a negative association was found for C-Section. The authors suggest that the association of exclusive breastfeeding with lower serum bilirubin concentrations in the first 3 days of life is due to initiation of breastfeeding in the delivery room, rooming-in, and breastfeeding on demand. The relatively small weight loss on the 3rd day of life in exclusively breastfed infants supports the conclusion that these breastfed infants were getting adequate milk intake. The authors also conclude the increased jaundice is associated with increased weight loss and suggest that caloric intake is important in the regulation of serum bilirubin. The conclude that "breastfeeding failure and the lack of breastfeeding are major factors in the pathogenesis of neonatal jaundice." Fasting or starvation and not breastfeeding per se is the responsible factor.</p>	<p>II-2</p>

<p>Newman TB, Liljestrand P, Escobar GJ. Jaundice noted in the first 24 hours after birth in a managed care organization. Arch Pediatr Adolesc Med 2002;156:1244-1250</p>	<p>This retrospective case control study compared 140 cases of infants with total serum bilirubin of 25 mg/dl or greater in the first 30 days with a randomly selected population of 631 newborns (controls) in 11 community hospitals. All study infants were 36 or more weeks gestation and at least 2000 g birth weight. 7.9% of all controls were identified in hospital records as having been jaundiced within the first 24 hours of life. Jaundice at less than 24 hours was not associated with breastfeeding.</p>	<p>II-1</p>
<p>Newman TB, Liljestrand P, Escobar GJ. Combining risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns. Arch Pediatr Adolesc Med 2005; 159:113-119</p>	<p>The first retrospective case control study compared 67 cases of infants with total serum bilirubin of 25 mg/dl or greater in the first 30 days with a randomly selected population of 208 newborns (controls) in 11 community hospitals. All study infants were 36 or more weeks gestation and at least 2000 g birth weight. The second study of a similar population included those infants whose serum bilirubin reached 20 mg/dl or greater after 48 hours of age and by the 30th day of life. A previously developed risk index which gave weighted values to 8 clinical variables was used to predict subsequent elevated serum bilirubins. Exclusive breastfeeding at time of hospital discharge at 48 hours of age was given the highest value of 6 points. This index alone and with use of a 48 hour serum bilirubin were assessed for ability to predict subsequent high (treatable) serum bilirubin concentrations. Combined use of the predictor index and the serum bilirubin value before hospital discharge provided the best predictor of subsequent treatable hyperbilirubinemia. Breastfeeding per se was not separately analyzed as an independent predictor.</p>	<p>II-1</p>

Summary of Publications Reviewed

(Numbers in parentheses below refer to citation numbers above; + and – signs indicated presence or absence of association)

No differences in jaundice or hyperbilirubinemia were observed between breast and formula-fed infants during the first 5 days of life in 3 papers (2, 26, 33), whereas 6 papers found a significant association between breastfeeding and early increases in jaundice and serum bilirubin (12, 13, 14, 15, 16, 34).

Greater serum bilirubin concentrations were reported in 8 papers after 5 days of age (3, 21, 24, 26, 28, 29, 30, 31).

Milk from mothers of jaundiced infants after 5 days of age increased intestinal bilirubin absorption (11, 21).

Breastfed infants with inherited defects in hepatic bilirubin conjugation have higher serum bilirubin concentrations during the first three months of life than infants without such mutations (32).

A relationship between increased weight loss from birth and increased jaundice and/or serum bilirubin concentrations was reported in 4 papers (3, 12, 13, 14, and not found in one other paper (26).

Reduced human milk intake was associated with increased serum bilirubin concentrations in the first 5 days of life (10).

Factors considered, but not proven, to cause increased serum bilirubin concentrations in breastfed infants include human milk lipoprotein lipase, free fatty acids (+4), maternal birth control pill use prior to pregnancy (+1), increased β -glucuronidase activity in human milk (+18, -21), increased human milk lipid (+19, -21), increased taurine in human milk (+24).

Attempts to improve management of breastfeeding in an attempt to prevent or manage hyperbilirubinemia include more intensive breastfeeding protocols (5, -22), temporary interruption of breastfeeding when serum bilirubin concentrations reach a predetermined level (+6, +14,), increased frequency of breastfeeding (+8, +20, -23), keeping infants with mothers during phototherapy (17), use of casein hydrolysate infant formula (+22, +29), and supplementation of breastfeeding with infant formula (+28).

Supplementation of breastfed babies with water was shown not to prevent or alter hyperbilirubinemia (7), or may increase serum bilirubin concentrations in the first week of life (9, 10).

Breastfed infants have a reduced response to phototherapy (28).

Increased serum bilirubin concentrations in otherwise healthy infants can produce kernicterus, particularly in premature infants (25).

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