Direct Bilirubin Measurements in Jaundiced Term Newborns

A Reevaluation

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• To investigate the usefulness of measuring direct bilirubin in jaundiced term newborns, we reviewed the outcome of 5255 such measurements on 2877 term (37 weeks' gestation) newborns in two hospitals. Direct bilirubin tests were ordered 15 times as often per infant at the University of California, San Francisco, as at Stanford (Calif) University, and the reported results were more than twice as high. In most of the 149 infants with high (>95th percentile) direct bilirubin levels, the high levels remained unexplained (52% of cases) or were due to apparent laboratory errors (21% of cases). Forty infants (27%) had conditions sometimes associated with high direct bilirubin levels. Elevation of direct bilirubin levels contributed to the diagnosis in only four of these infants. All had minor laboratory abnormalities that resolved spontaneously. Because of their low yield and poor specificity, direct bilirubin tests are seldom helpful in evaluating jaundice in term newborns.

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The evaluation of jaundice in newborns is one of the most common tasks in pediatrics. Many authorities recommend measuring the serum direct bilirubin in significantly jaundiced infants to distinguish between conjugated and unconjugated hyperbilirubinemia; algorithms for differential diagnosis of jaundice commonly begin with this step.[1-6] However, the "direct bilirubin" reported by many automated chemical analyzers may be a poor measure of the infant's actual conjugated bilirubin.[7-14]

Although the two terms are often used synonymously, *direct bilirubin* is not the same as *conjugated bilirubin*. Direct bilirubin refers to the bilirubin that reacts directly with diazotized sulfanilic acid (ie, without addition of an accelerating agent) in commonly used chemical assays. Conjugated bilirubin refers to bilirubin that has been made water soluble by binding with glucuronic acid in the liver. The amount of bilirubin that is called direct reacting depends on the concentration of conjugated bilirubin, but also on other factors, including the amount of time it is allowed to react, the concentration of various reagents, and the concentration of unconjugated bilirubin.[8] Unfortunately, in contrast to total bilirubin, for which interlaboratory standardization is available through the College of American Pathologists, there is no standardization of direct bilirubin measurements from laboratory to laboratory.

About 10% to 20% of term newborns develop significant jaundice,[15] but only about 0.04% develop pathologic conjugated hyperbilirubinemia.[16] Because direct bilirubin measurements tend to be least accurate in the presence of high unconjugated bilirubin levels, like those commonly found in newborns, measuring direct bilirubin in jaundiced infants could lead to many false-positive results.[17,18] The purposes of this study were to determine how commonly high direct bilirubin levels occur in infants who are and remain apparently well, to determine how commonly elevations of direct bilirubin are associated with previously unsuspected disease, and to develop guidelines for ordering and interpreting direct bilirubin measurements in jaundiced term newborns.

PATIENTS AND METHODS

Database

We used the Combined Patient Experience (COPE) database as the primary data source for this retrospective study. As has been described in previous reports,[19,20] the COPE database was created by merging computerized data from the clinical laboratory information systems, hospital census records, and hospital discharge abstracts at two hospitals: the University of California, San Francisco, Medical Center (UCSF), and the Stanford (Calif) University Medical Center. We supplemented the COPE database with data from the UCSF obstetrics department database and the Stanford Hospital Medical Information System (for length of stay, race, birth weight, and gestational age estimates). For infants born at UCSF in 1986 and 1987, the COPE database includes laboratory tests performed (at UCSF) after hospital discharge; for all other infants, outpatient data were available only by review of medical records.

Infants were included in the study if they were born and dis-

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Table 1.—Demographic Characteristics of Infants Born During the Study Period at Both Hospitals

	University of California, San Francisco		Stanford (Calif) University	
	10/80-9/82	1/86-12/87	1/86-6/87	Total
Total No. of births	2777	3001	5185	**10 963**
Term group				
No. of births at ≥ 37 weeks' gestation (% of all births)	2417 (87)	2614 (87)	4595 (89)	**9626** (88)
Mean ± SD birth weight, g	3427 ± 496	3435 ± 488	3486 ± 507	3457 ± 499
Length of stay, d				
Median	3	2	2	2
95th percentile	8	7	5	7
Race, No. (%) of infants				
White	1088 (45)	889 (34)	2343 (51)	4332 (45)
Asian	338 (14)	601 (23)	322 (7)	1251 (13)
Hispanic	242 (10)	183 (7)	597 (13)	1059 (11)
Black	193 (8)	157 (6)	368 (8)	674 (7)
Unknown/other	556 (23)	784 (30)	965 (21)	2310 (24)

charged during the periods covered by the COPE database: October 1, 1980, to September 30, 1982, and January 1, 1986, to December 31, 1987, at UCSF and January 1, 1986, to June 30, 1987, at Stanford. Premature infants (obstetrician's estimate at the time of maternal admission of less than 37 weeks' gestation) were excluded. Term infants who were small for gestational age and sick infants were not excluded. Based on reviews of medical records and nursery log books, we estimated that the UCSF database was close to 100% complete and the Stanford database was about 97% complete. The project was approved by the human subjects committees of both UCSF and Stanford.

Laboratory Methods

At UCSF, direct bilirubin was measured on either a DuPont Automated Chemical Analyzer (Dupont Instruments, Wilmington, Del) or a Coulter DACOS analyzer (Coulter Electronics, Hialeah, Fla). Both machines use a modification of the Jendrassik-Grof (diazotized sulfanilic acid) reaction; they were calibrated against each other daily. At Stanford, the Kodak Ektachem 700 (Eastman Kodak Co, Rochester, NY) was used. The Ektachem method measures conjugated (rather than direct) bilirubin using a multilayer slide technique. The conjugated bilirubin is assayed spectrophotometrically after it passes through a selective screening layer and complexes with a cationic polymer.[21]

Data Analysis

Our first task was to define what constitutes an abnormal direct bilirubin level. Textbook definitions generally range from 17 to 34 μmol/L.[5(p23),21-25] (To convert from micromoles per liter to milligrams per deciliter, divide the value by 17.10.) However, because the normal range depends on the analytic method used, we selected the maximum direct bilirubin level recorded for each infant, and arbitrarily defined as abnormal those values in the top 5% (of maximum recorded direct bilirubin levels) for their hospital of birth (≥39 μmol/L at UCSF; ≥17 μmol/L at Stanford). For all such infants, we reviewed the computerized laboratory data and medical records to determine the apparent reason (if any) for the elevation, using the following classifications:

Laboratory Error.—To classify an infant's high direct bilirubin level as due to laboratory error, we required that there be no diagnosis of hepatobiliary disease and that any aminotransferase levels measured be normal. Most of the apparent laboratory errors were isolated high values. To be so classified, there could be only a single abnormal value, and normal values at least 8.5 μmol/L less than the abnormal value had to have been obtained within 25 hours before and after the abnormal value. Other apparent laboratory errors were for miscellaneous reasons, including direct bilirubin levels exceeding the total bilirubin level (n=2), specimens noted by the laboratory to be hemolyzed (n=2), misplaced decimal points (n=2), and mislabeled specimen (n=1).

Associated Conditions.—This group included any infant not meeting the criteria for laboratory error, with either elevation of aminotransferase levels or a discharge diagnosis (confirmed by laboratory data or medical records review) of any significant hepatobiliary, gastrointestinal, renal, hematologic (except polycythemia), cardiovascular, metabolic (except infants of diabetic mothers), or infectious disease. The direct bilirubin was assumed to have potentially contributed to the diagnosis if its abnormality preceded the signs or diagnostic evaluation that led to the diagnosis, unless progress notes unambiguously indicated another reason for the evaluation.

Unexplained.—This group included all other infants. The high direct bilirubin level was considered to have resolved spontaneously if a return to well within the normal range (<90th percentile) was documented or if the infant was followed up in the outpatient clinic for at least 2 months without evidence of associated disease.

RESULTS

Demographic data on the 10 963 infants born at the two hospitals during the study periods are provided in Table 1. Both hospitals serve ethnically diverse populations, have high rates of preterm or low-birth-weight infants, and have short stays for term infants.

Ordering patterns and results for total and direct bilirubin levels are shown in Table 2 and Fig 1. Data for the two UCSF periods were similar and are combined in Table 2. There was a remarkable difference in the laboratory testing patterns of the two hospitals: infants born at UCSF were more than three times as likely to have total bilirubin measured at least once and more than 10 times as likely to have direct bilirubin measured at least once. The total number of direct bilirubin measurements per infant was 15 times higher at UCSF than at Stanford.

The mean, SD, and, in fact, the entire distributions of total bilirubin levels obtained at the two hospitals were practically identical. This surprising result suggests that the more selective total bilirubin testing at Stanford was based on factors other than the degree of jaundice.

In contrast, the median, 90th, and 95th percentiles for direct bilirubin at UCSF were more than twice as high as those at Stanford (for conjugated bilirubin), reflecting the

Table 2.—Measurements of Total and Direct Bilirubin in Term Infants at Two Hospitals*

	University of California, San Francisco (n=5031)	Stanford (Calif) University (n=4595)	Total (n=9626)
No. (%) of term infants with total bilirubin measured at least once	2786 (55)	753 (16)	**3539**
No. (%) of term infants with direct bilirubin measured at least once	2642 (53)	235 (5)	**2877** (30)
Total No. of direct bilirubin tests	4948	307	**5255**
Mean (SD) maximum total bilirubin, μmol/L†	174 (63)	172 (62)	. . .
Maximum direct bilirubin percentiles, μmol/L†			
50	19	7	. . .
75	24	10	. . .
90	32	14	. . .
95	39	17	. . .
99	63	77	. . .

*At Stanford (but not at the University of California, San Francisco) direct bilirubin actually refers to conjugated bilirubin.

†To convert from micromoles per liter to milligrams per deciliter, divide the value by 17.10.

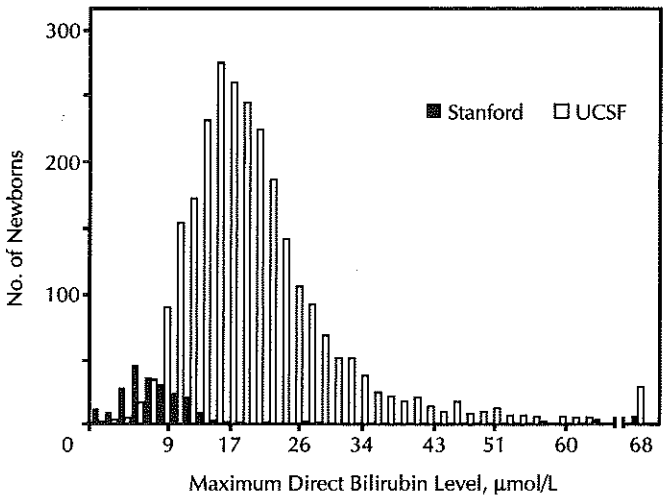

Fig 1.—*Maximum direct bilirubin levels for term infants born at Stanford (Calif) University (1986 to 1987) and at the University of California, San Francisco (UCSF) (1980 to 1982 and 1986 to 1987). To convert from micromoles per liter to milligrams per deciliter, divide values by 17.10.*

different measurement methods. The percentage of total bilirubin that was direct reacting at UCSF was similarly much higher than the percentage of conjugated bilirubin at Stanford.

Medical records were reviewed to determine possible reasons for direct bilirubin levels above the 95th percentile at each institution (Table 3). In most infants, the high direct bilirubin levels remained unexplained (52% of cases) or were due to an apparent laboratory error (21% of cases). Forty (27%) of the 149 infants with high direct

Table 3.—Reasons for Direct Bilirubin Levels Above the 95th Percentile Among Term Infants at University of California, San Francisco (n=140) and Stanford (n=9)*

Reason	No. (%) of Infants
Unexplained	
Resolved spontaneously, infant well	72 (48)
Well at discharge but no follow-up	6 (4)
Associated disease	
Direct bilirubin did not contribute to diagnosis†	
Isoimmunization	19 (13)
Sepsis or pneumonia	5 (3)
Congestive heart failure	5 (3)
Multiple anomalies	2 (1)
Pyloric stenosis	2 (1)
Extreme SGA, possible rubella‡	1 (1)
Hypothyroid (routine screening)	1 (1)
Choledochal cyst (prenatal sonography)	1 (1)
Direct bilirubin contributed to diagnosis	
Slightly high aminotransferase levels (<100 U/L)	3 (2)
Sludge in gallbladder	1 (1)
Laboratory error	
Isolated high value	24 (16)
Other	7 (5)

*At Stanford (but not at the University of California, San Francisco) direct bilirubin actually refers to conjugated bilirubin.

†Diagnosed from signs or symptoms, except as noted.

‡SGA indicates small for gestational age.

bilirubin levels had conditions that are at least occasionally associated with elevated conjugated bilirubin levels. However, the elevated direct bilirubin level did not lead to the diagnosis in any of these infants: most diagnoses were made before the direct bilirubin level was elevated, and most of the elevations were transient and of no apparent clinical significance. Four infants (3%) had findings identified apparently as a result of their direct hyperbilirubinemia. All had minor laboratory abnormalities that resolved spontaneously, including transient, slightly high (50 to 100 U/L) aminotransferase levels in three infants and "sludge" in the gallbladder in one infant.

Laboratory errors and unexplained elevations were frequent even at high levels of direct bilirubin (Fig 2). (The graph shows infants only at UCSF because seven of the nine infants at Stanford with maximum direct bilirubin values in the top 5% (for Stanford) had values less than 34 μmol/L) Use of a more restrictive cutoff resulted in little improvement in predictive value: of 30 infants with direct bilirubin values at or above the 99th percentile, only 11 (37%) had possibly associated conditions. Similarly, of 40 infants with direct or conjugated bilirubin levels exceeding the 95th percentile and comprising more than 30% of the total bilirubin, only 17 (42%) had possibly associated conditions. Thus, a more restrictive definition of direct hyperbilirubinemia was still associated with many apparently false-positive results.

We also investigated how often additional laboratory tests were ordered to evaluate direct hyperbilirubinemia. Only 23 (15%) of the 149 infants with high direct bilirubin levels had aminotransferase levels measured; levels were high in three well and 11 sick infants. Five infants received multiple serologic tests for congenital infection (no such infections were found), and three underwent serum protein electrophoresis, the results of which were normal. At least one infant underwent

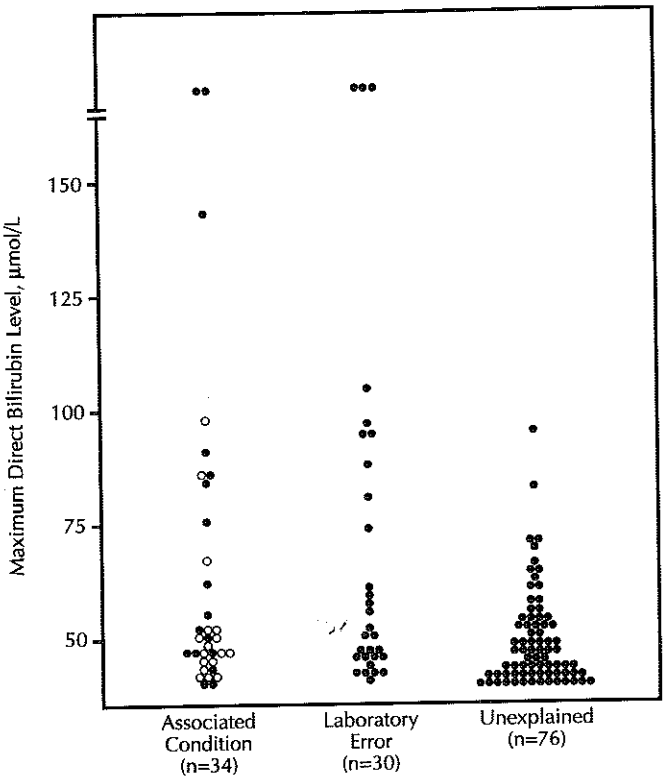

Fig 2.—*Distribution of the maximum direct bilirubin levels for infants born at the University of California, San Francisco (UCSF), with values in the top 5%, by apparent reason for the elevation. Open circles indicate infants in whom the elevation was attributed to isoimmunization; and solid circles, all other infants. To convert from micromoles per liter to milligrams per deciliter, divide values by 17.10.*

abdominal ultrasonography. Thus, additional tests were seldom performed; the usual response to high direct bilirubin levels was either to ignore them or to repeat them until they went down.

COMMENT

The COPE database allowed us to review results of more than 5000 determinations of direct bilirubin on 2877 infants at two hospitals. The striking findings were the marked variation in ordering patterns for this test at the two hospitals, the variation in the median and normal range for the different analytic methods, the high frequency of falsely positive results, and the absence of useful diagnostic information provided.

This study has some important limitations. Tests of direct bilirubin levels were ordered much more commonly at UCSF than at Stanford: the vast majority of infants (140 [94%] of 149) with documented high direct bilirubin levels were from UCSF. Since the analytic method at UCSF is particularly prone to errors, our results may not be generalizable to institutions using better methods. However, in a recent study, the DuPont ACA (used at UCSF) was the most popular machine, in use at 31% of the hospitals surveyed.[10] Clearly, clinicians interpreting results of direct bilirubin determinations need to be aware of the instrument used at their institution, as well as that instrument's accuracy and "normal range."

Our classification system for the high direct bilirubin values was necessarily arbitrary; we cannot say for sure that an isolated high direct bilirubin level was due to laboratory error, or that high values in infants with associated diseases were due to those diseases. However, in developing the classification scheme, we were very restrictive in the laboratory error and unexplained groups, and inclusive in the associated disease group.

This is illustrated by several diagnoses listed in Table 3. Pyloric stenosis, hypothyroidism, and even choledochal cysts are rarely associated with direct hyperbilirubinemia in the newborn period.[26-28] Thus, the elevations of direct bilirubin levels in infants in the associated condition category may have been largely coincidental. Among infants who had direct bilirubin measured, high values were only slightly more common in infants with a discharge diagnosis that would have qualified them for the associated condition category (97 [7.0%] of 1380 infants) than in infants with no such diagnosis (52 [3.5%] of 1497 infants). By including even questionable diagnoses in the associated disease category, we were giving the direct bilirubin measurement the benefit of the doubt in each case.

Similarly, in determining whether high direct bilirubin levels contributed to diagnoses, we required only that they could have contributed, not that they actually did. We were looking for instances in which direct bilirubin measurements led to diagnoses of unsuspected disease. Out of more than 5000 measurements of direct bilirubin, we found no such instances.

This study was limited to term infants, and most of those studied were well. It is likely that in a sicker population, a much greater proportion of the elevations of direct bilirubin would represent significant disease. For example, Wolf and Pohlandt,[29] in a recent case-control study of infants receiving parenteral nutrition, found that cholestasis (bilirubin levels >68 µmol/L with direct bilirubin levels >40% of the total) was strongly associated with sepsis. It apparently was not an early sign, however: the median time between onset of sepsis and cholestasis was about 7 days. Furthermore, although the method of measuring the direct bilirubin was not stated, the absence of elevated values in the control group suggests that it was measured more accurately than has been the case at UCSF.

Although this study included several thousand infants, it could still miss rare, treatable causes of direct hyperbilirubinemia. For example, it is not surprising that we did not find any cases of biliary atresia; its incidence is only about 1 in 10 000.[16] To be useful as a screening test for a disease that rare, however, the measurement of direct bilirubin would need to be much more specific. To have even a 10% positive predictive value would require a specificity of 99.9%, even if the test were 100% sensitive. Furthermore, because most cases of biliary atresia are not associated with cholestasis in the first few days of life,[16] direct bilirubin measurements would be insensitive as well as nonspecific. Finally, the prognosis for biliary atresia does not appear to worsen unless the diagnosis and surgery are delayed more than 2 months.[30,31] Thus, measurement of direct bilirubin in infants remaining jaundiced beyond the first week or two of life would be a more efficient strategy for detecting biliary atresia.

We do not know why tests of direct bilirubin were ordered so much less frequently at Stanford than at UCSF. While the charges for the test differed ($38 at Stanford vs $6 at UCSF), we doubt that the difference in frequency was due to the difference in charges. Rather, it is probably due to shorter stays at Stanford (leading to jaundice being noted in fewer infants), to differences in who

decides to order the test (almost exclusively nurses and house staff at UCSF, compared with private pediatricians in about half the cases at Stanford), and differences in nursery traditions at the two institutions. At UCSF (before this study), tests of total and direct bilirubin were almost always ordered together, because treatment decisions were often based on the level of serum indirect bilirubin (ie, the total bilirubin level minus the direct bilirubin level), a practice recommended in many textbooks.[5,25,32]

Is this practice justified? We think usually not. Although automated analyzers provide a value that can be subtracted from the total bilirubin, it is a number that may have little relation to the infant's actual level of conjugated bilirubin. (Interestingly, the Kodak Ektachem, used with admirable restraint at Stanford, is one of the few machines that actually provides a good estimate of conjugated bilirubin.[8,13]) Thus, unless the test used provides an accurate reflection of conjugated bilirubin, treatment decisions should be based on total bilirubin and other evidence of cholestasis (eg, light stools or bilirubin in the urine).

In sick, jaundiced infants, or in any infants in whom cholestasis is suspected, measurement of serum direct bilirubin may be useful. Even then, however, visual examination of the stool and use of a dipstick in the infant's urine[33] may be as good. The infant's kidney can fractionate bilirubin better than most automated chemical analyzers.

Measurement of direct bilirubin is a poor screening test. Clinically inapparent, treatable causes of direct hyperbilirubinemia are rare, and many current methods of measuring direct bilirubin are inaccurate, leading to a high frequency of false-positive results. The practice of ordering a direct bilirubin test to make treatment decisions based on the indirect bilirubin level also generally cannot be justified unless the measurement of direct bilirubin is known to reflect conjugated bilirubin accurately. Our results suggest that measurements of direct bilirubin to evaluate jaundice in term newborns could be drastically reduced with no adverse effect on health.

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