Short reports

Archives of Disease in Childhood, 1975, **50**, 652.

Hyperbilirubinaemia and bacterial infection in the newborn

A prospective study

Bacterial infection and jaundice may be associated without severe constitutional upset and with few abnormal clinical signs or laboratory findings (Rooney, Hill, and Danks, 1971), and in this context the association of neonatal jaundice and urinary tract infection has been particularly emphasized (Seeler and Hahn, 1969; Seeler, 1973). In a retrospective study we found that jaundice was rarely the single, initial sign of infection in an asymptomatic neonate (Escobedo *et al.*, 1974). In this report we present the results of a prospective study of jaundiced infants evaluated for bacterial infection.

Materials and methods

A group of 69 term and preterm infants admitted to intensive care units at St. Louis Maternity Hospital and St. Louis Children's Hospital between April 1973 and May 1974 were studied (after parental permission and approval of the Human Experimentation Committee). The patients were selected from approximately 3250 deliveries at St. Louis Maternity Hospital and about 400 admissions to the neonatal intensive care unit, St. Louis Children's Hospital.

Hyperbilirubinaemia was defined as a serum bilirubin level above 5 mg/dl on day 1, 10 mg/dl on day 2, or 12 mg/dl on any day thereafter. These criteria agree with those of others for term infants but are lower than those usually presented for premature infants (A. K. Brown, personal communication, 1973; Maisels, 1972). Our criteria for prematures were adopted because the early widespread use of phototherapy in our nurseries did not permit bilirubin levels to rise to previously defined levels of hyperbilirubinaemia.

Bilirubin was determined by the Gambino modification of the Jendrassik and Grof colorimetric method (Gambino, 1965). All patients with a positive direct and indirect Coombs's test, any evidence of red blood cell haemolysis due to isoimmunization, large ecchymoses or cephalohaematoma, gastrointestinal obstruction, or evidence of liver disease were excluded. All eligible candidates were not included in the study, since some families refused permission, and some potential patients may not have been detected, but no bias of selection was apparent. 48 of the study infants were boys and 21 were girls.

The mean birthweight of the 69 patients was 2807 g

(SD 804 g). The smallest patient weighed 970 g and the largest 5150 g. 45 patients weighed >2500 g and 24 weighed <2500 g.

Sixty-seven of the patients developed hyperbilirubinaemia, as defined in this study, before day 7 of life. Only 2 patients entered the study after the first week—one at 11 days and the other at 15 days. 14 patients were studied on the first day of life because the bilirubin was >5 mg/dl. Only 5 babies in the study were breast fed.

Laboratory tests on these neonates included Hb, haematocrit, white blood cell count, reticulocyte count, blood type, and Coombs's test, blood cultures, and suprapubic aspiration of urine for culture. Bacterial cultures were obtained no later than 48 hours after the bilirubin reached the previously defined level. Clean-voided specimens of urine were obtained from 7 infants due to technical difficulty in obtaining suprapubic aspiration specimens. Other appropriate cultures were made if clinically indicated. 22 CSF specimens were cultured from this group.

Criteria for infection were any bacterial isolate from blood, suprapubic aspirated urine, or CSF, or >10⁵ organisms/mm³ from a clean-voided urine specimen.

Results

Since there were no significant differences between the data obtained from infants with birthweights less than and greater than 2500 g, the data for both groups were combined. The peak bilirubin levels and the day on which the peak occurred are summarized in the Table, together with information on phototherapy.

TABLE
Bilirubin data on 69 newborn infants

Peak bilirubin (d)	3.5 (± 1.07 SD)
Total bilirubin (mg/dl)	14.32 (± 3.32 SD)
Indirect bilirubin (mg/dl)	13.78 (± 3.19 SD)
% Direct/total bilirubin	3.8
Number receiving phototherapy	55
Day phototherapy began	2.69 (± 1.02 SD)
Duration of phototherapy (d)	3.41 (± 1.96 SD)

All patients who initially had signs and symptoms consistent with sepsis were treated with antibiotics until the results of the appropriate cultures were obtained. Phototherapy was usually begun early, day 2 or 3, and the duration of treatment averaged approximately 3 days. None of the patients studied had a bacteria isolated from blood or CSF.

None of the 14 neonates in whom the bilirubin was greater than 5 mg/dl on the first day of life had bacteria isolated from blood, urine, or CSF. Bacterial infection was noted in 2 patients.

Case 1 had peak total bilirubin of 18 mg/dl with 0.2 mg/dl direct bilirubin on day 3. A clean voided urine on day 3 yielded $>10^5$ colonies of *Esch. coli*/mm³ on bacterial culture. He was afebrile and had no pyuria at this time. He received a 10-day course of ampicillin (150 mg/kg) and kanamycin (15 mg/kg) therapy. Subsequent urinary tract infections with *Klebsiella* sp. at 3 weeks of age, and *Esch. coli* at 3 months of age were noted and treated. A normal intravenous pyelogram and cystogram were obtained at age 3 months.

Case 2 had a peak total bilirubin of 12.4 mg/dl on day 3 with a direct level of 0.4 mg/dl. Suprapubic urine aspirate performed at that time grew on culture $>5 \times 10^4$ /mm³ colonies of *Klebsiella* sp. The patient was afebrile and there was no pyuria. After a 10-day course of ampicillin (200 mg/kg) and kanamycin (15 mg/kg), urine obtained by suprapubic aspiration was sterile. The patient had a normal intravenous pyelogram and cystogram.

Discussion

Previous investigations have documented an association between jaundice and infection in the neonatal period. Bernstein and Brown (1962) described 9 infants, who had had a necropsy, with evidence of sepsis who developed jaundice after the first week of life. Hamilton and Sass-Kortsak (1963) reported a prospective series of 24 patients with proven bacterial infection who developed jaundice during the course of their illness. Only 8 of their patients developed jaundice within the first week of life. The range of total bilirubin reported was 3.1–27.3 mg/dl. Rooney *et al.* (1971) reported 22 cases of jaundice in newborns with bacterial infection. Jaundice was defined by either laboratory criteria (total bilirubin above 10 mg/dl in a term baby or 15 mg/dl in the preterm infant), or by clinically evident icterus beyond 7 days in a mature baby or 10 days in a preterm infant. Urinary tract infection was defined by a clean-voided specimen of urine containing $>10^5$ bacteria/mm³. 15 of the 22 neonates were asymptomatic. When jaundice appeared in the first week of life nearly all the bilirubin was indirect. However, when jaundice developed after the first week of life, the direct fraction was always greater than the indirect component.

Seeler and Hahn (1969) reported 11 patients from 8 to 56 days of age with jaundice and asymptomatic urinary tract infections. The total bilirubin

was above 15.4 mg/dl in 9 of the 11 patients. Only 2 infants in this study were less than 2 weeks of age. Seeler's recently expanded series (1973) (22 patients) contains no infants in the first week of life. *Esch. coli* was the predominant organism in 18 of the 22 cases.

The current prospective investigation was designed to determine how frequently unexplained hyperbilirubinaemia might be associated with neonatal bacterial infection especially in the first week of life. We found evidence for bacterial infection in only 3% (2/69) of our patients with hyperbilirubinaemia. None of the 69 blood or CSF cultures yielded a bacterial isolate. Two Gram-negative urinary tract infections were detected within the first 2 days of life. In neither case was the direct bilirubin greater than 0.4 mg/dl, being consistent with the findings of Rooney *et al.* (1971).

The evaluation of a hyperbilirubinaemic neonate poses a practical clinical problem. We conclude that bacterial infection is an infrequent cause of unexplained hyperbilirubinaemia in our patients. Our results indicate that urinary tract infections in the first week of life can be associated with jaundice, but the data are insufficient to document a cause-effect relation.

Summary

The incidence of bacterial infection associated with unexplained hyperbilirubinaemia was determined prospectively in 69 infants under 2 weeks of age. Blood and urine cultures were obtained from all patients, and 22 patients had their CSF cultured. Bacterial infection was documented in only 2 infants, who had asymptomatic Gram-negative urinary tract infections.

We thank Mead Johnson Laboratories for financial assistance; the house staff at St. Louis Children's Hospital for assistance in patient care; and Dr. Philip R. Dodge for review of the manuscript.

REFERENCES

- Bernstein, J., and Brown, A. K. (1962). Sepsis and jaundice in early infancy. *Pediatrics*, **29**, 873.
- Escobedo, M. B., Barton, L. L., Marshall, R. E., and Zarkowsky, H. (1974). The frequency of jaundice in neonatal bacterial infections. *Clinical Pediatrics*, **13**, 656.
- Gambino, S. R. (1965). Bilirubin. *Standard Methods of Clinical Chemistry*, Vol. 5, p. 55. Ed. by S. Meites. Academic Press, New York.
- Hamilton, J. R., and Sass-Kortsak, A. (1963). Jaundice associated with severe bacterial infection in young infants. *Journal of Pediatrics*, **63**, 121.
- Maisels, M. J. (1972). Bilirubin: on understanding and influencing its metabolism in the newborn infants. *Pediatric Clinics of North America*, **19**, 447.
- Rooney, J. G., Hill, D. J., and Danks, D. M. (1971). Jaundice associated with bacterial infection in the newborn. *American Journal of Diseases of Children*, **122**, 39.

Seeler, R. A. (1973). Urosepsis with jaundice due to hemolytic *Escherichia coli*. *American Journal of Diseases of Children*, 126, 414.

Seeler, R. A., and Hahn, K. (1969). Jaundice in urinary tract infection in infancy. *American Journal of Diseases of Children*, 118, 553.

P-O. CHAVALITDHAMRONG, M. B. ESCOBEDO, L. L. BARTON, H. ZARKOWSKY, and R. E. MARSHALL
Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, and the Divisions of Neonatology, Infectious Diseases, and Hematology, St. Louis Children's Hospital.

*Correspondence to Dr. R. E. Marshall, St. Louis Children's Hospital, 500 S. Kingshighway, St. Louis, Missouri 63110, U.S.A.

Fat absorption by small babies fed two filled milk formulae

In common with many others caring for small infants we employ artificial milk formulae when supplies of expressed breast milk run short and in 1972-73 used both Cow and Gate V (C&G V, Cow and Gate Ltd) and SMA Ready-to-feed (SMA, Wyeth Bros. Ltd.) formulae, since the manufacturers' literature suggested that each was a satisfactory breast milk substitute. The present study was prompted by the observation that the babies appeared to fare better on one of the two artificial formulae. A prospective study of fat balance showed that consistently more steatorrhoea occurred in infants fed C&G V formula. Some implications of these findings for postnatal development are discussed.

Patients and methods

Fat balance studies were performed on 8 infants, 4 of whom were fed SMA and then C&G V, and 4 fed in the reverse order. All the infants were of low birthweight (Table I) and were nursed for this reason in the Special Care Baby Unit. They were fed throughout their stay by gavage or bottle, with SMA or with C&G V supplied in prepacked liquid form. According to the manufacturers' specifications the total protein, fat, carbohydrate, and mineral contents of the two preparations are similar. After at least 3 days on the first milk, stools were collected between carmine markers over a 72-hour period. The infant was then changed to the other milk and after 3 or more days a further 72-hour stool collection was made. Faecal fat was measured by the method of van der Kamer, ten Bokkel Huinink, and Weijers (1949) using the modification described by Varley (1967) and excretion was expressed as a percentage of the fat ingested. Gas liquid chromatography was performed as described by Matthys, Christophe, and Verdonk (1972) on faecal fat extracts prepared for total fat analysis.

Results and discussion

The infants varied in gestational age from 30 to 37 weeks and in birthweight from 1.16 to 2.11 kg (Table I). The degree of steatorrhoea varied greatly but was greater when the infants were fed C&G V in 7 out of 8 cases. The mean ($\pm$ SEM) fat excretion expressed as a percentage of the intake on C&G V was 28.1 ± 3.9 and higher than the value of 10.5 ± 2.3 when the same infants were fed SMA ($P < 0.01$).

Gas-liquid chromatography was performed on three pairs of faecal extracts. The fatty acids detected were C14:0, C16:0, C18:0, and C18:1. The percentage of stool fat that each of these comprised is shown alongside the fatty acid composition of the two milks in Table II. No conclusions can be drawn from such limited observations other than that in 2 infants C16:0 formed a larger fraction of stool fat when they were fed C&G V. Despite a higher percentage of C18:1 excreted by these infants when fed SMA, the absolute amount of C18:1 lost in the stools on either milk did not differ.

Variation in fat absorption by infants fed different milks is well documented (Southgate *et al.*, 1969; Fomon *et al.*, 1970; Williams *et al.*, 1970), but the milks used in this study are described in the manufacturers' literature as substitutes for human breast milk and specifications are given which led us to anticipate that they should be interchangeable. For these reasons they were chosen as suitable alternatives to expressed breast milk for infants of low birthweight.

Steatorrhoea was more likely to be under- than overestimated because of the possibility of incomplete stool collection, but there is no reason to expect that this occurred more with one formula than the other. Likewise care was taken to stop the application of cream to sore buttocks during the period of stool collection as this could exaggerate the estimate of faecal fat content. When C&G V formula was given by gavage a tendency for the lipid to separate out and smear the bottle and tube was noted. This did not appear to occur with SMA and might have resulted in an underestimate of the degree of steatorrhoea in those infants fed C&G V. Though this study has not proven why infants fed C&G V have more steatorrhoea than those fed SMA, a suggestion can be made from knowledge of the fatty acid composition of the lipid in the two milks. Palmitic acid (C16:0) constitutes 31.7% of the fatty acid content of C&G V formula but only 14.8% of SMA. SMA has higher concentrations of shorter chain saturated fatty acids, linoleic (C18:2) and other unsaturated fatty acids (Table II).