# Spectrum and Outcome Analysis of Marked Neonatal Hyperbilirubinemia with Blood Group Incompatibility

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**Background:** Blood group mismatch between a mother and newborn carries a substantial risk for neonatal hyperbilirubinemia and kernicterus. In the current study, we investigate the spectrum and outcome of marked neonatal hyperbilirubinemia with blood group incompatibility.

**Methods:** We retrospectively assessed a cohort of 413 neonates with peak total serum bilirubin (TSB) values ≥ 20 mg/dL between 1995 and 2007. Those with a gestational age < 34 weeks, birth weight < 2000 grams or G6PD deficiency were excluded. A total of 83 subjects with blood group incompatibility were enrolled. Neonates with unknown etiology of hyperbilirubinemia (except breast milk feeding) were selected as the controls (n = 168). Kernicterus referred to classic neurological signs after follow up for more than 1 year.

**Results:** The clinical symptoms of acute bilirubin encephalopathy included apnea (2.4%), tachypnea (6.0%), fever (1.2%), irritability (2.4%), lethargy (4.8%), seizures (1.2%) and poor feeding (19.3%). Hyperbilirubinemia was more severe among babies with Rh incompatibility than those with ABO incompatibility. After double-volume exchange transfusion, the TSB levels significantly decreased from 25.8 ±3.5 to 17.6 ±4.0 mg/dL. Using logistic regression analysis, we found neonates with blood group incompatibility more often had a reticulocyte count > 7%, a hemoglobin value < 13 g/dL and a peak TSB at age < 3 days old than the controls ($p < 0.01$). Furthermore, kernicterus was more common in neonates with blood group incompatibility (9.8%) than in the controls (0.0%) ($p < 0.01$).

**Conclusions:** This survey depicts the clinical profiles of babies with marked neonatal hyperbilirubinemia with blood group incompatibility. Neonates with blood group incompatibility often develop early-onset, hemolysis-mediated hyperbilirubinemia. Our findings show they are at great risk of kernicterus.

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**Key words: blood group incompatibility, exchange transfusion, kernicterus, neonatal hyperbilirubinemia**

Hyperbilirubinemia is a common disorder during the neonatal period. It is associated with a variety of physiologic and pathologic conditions.[1] Isoimmune hemolytic disease has been identified as

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a pathologic cause of neonatal hyperbilirubinemia attributed to blood group incompatibility.[2] Group A and group B newborns of group O mothers are defined as having ABO incompatibility.[3] ABO hemolytic disease is the major cause of neonatal hyperbilirubinemia in Taiwan.[4] Hemolysis owing to Rh incompatibility occurs when an Rh-positive infant is born to an Rh-negative mother with Rh antibodies. Isoimmunization to the Rh D antigen is the most common type of Rh incompatibility. The serum bilirubin level in isoimmune hemolytic disease can rise quickly in the first days of life, so intervention must be prompt to prevent bilirubin encephalopathy. Bilirubin encephalopathy has acute and chronic clinical manifestations. The chronic form, also known as kernicterus, is a type of severe and irreversible long-term neurological damage. Most infants with kernicterus display signs of acute bilirubin encephalopathy.

The purpose of this study is to evaluate the clinical features and outcome of marked neonatal hyperbilirubinemia with blood group incompatibility. Although this disorder has been widely investigated in Taiwan for several decades,[2-8] little has been mentioned about the outcome.[9-11] To our knowledge, this is the first survey in Taiwan to verify the spectrum and long-term neurological sequelae of severe hyperbilirubinemia among neonates with blood group incompatibility.

## METHODS

### Subjects and laboratory analyses

The medical records of neonates admitted to the neonatal intensive care units at Chang Gung Children's Hospital from 1995 to 2007 with peak total serum bilirubin (TSB) values ≥ 20 mg/dL were reviewed. The TSB levels were determined with a Unistat bilirubinometer (Cambridge Instruments, NY, U.S.A.). Blood group A or B newborns of group O mothers were defined as having ABO incompatibility. Rh-positive infants born to Rh-negative mothers were categorized as having Rh incompatibility. Infants with the following conditions which could confuse the clinical features and outcome were excluded: glucose-6-phosphate dehydrogenase (G6PD) deficiency, gestational age < 34 weeks, birth weight < 2000 grams, perinatal asphyxia, congenital infection, sepsis, meningitis, congenital anomaly, inborn error of metabolism, and disorders of the central nervous system. In order to distinguish the unique characteristics of blood group incompatibility, infants without known etiology of hyperbilirubinemia (except breast milk feeding) were enrolled as controls. The hemoglobin value, reticulocyte count and direct Coombs' test (direct antiglobulin test, DAT) were collected as indices of hemolysis. Clinical characteristics, including gender, delivery mode, birth weight, gestational age, treatment, and age at peak TSB level, were also analyzed.

A total of 413 neonates had a peak TSB value ≥ 20 mg/dL during the 13-year study period. Among them, 102 (24.7%) were categorized as having ABO incompatibility (n = 90) or Rh incompatibility (n = 12). From this group we excluded 3 neonates with a gestational age < 34 weeks, 1 with a birth weight < 2000 g and 15 who were G6PD-deficient, leaving 73 ABO- and 10 Rh-incompatible neonates to be enrolled. None had minor group incompatibility. In addition, 186 neonates with a peak TSB value ≥ 20 mg/dL with no leading cause of hyperbilirubinemia (except breast milk feeding) were enrolled as the control group.

Babies were diagnosed with kernicterus if they had two or more of the following signs after follow up for more than 1 year: (1) athetoid cerebral palsy confirmed by rehabilitation doctors and/or pediatric neurologists, (2) gaze impairment, especially of upward gaze confirmed by ophthalmologists, (3) delayed developmental milestones confirmed by pediatric psychiatrists and/or neurologists, and (4) auditory disturbances, diagnosed by either a brainstem auditory evoked potential test in the neurology department or an auditory brainstem response test in the ear, nose and throat department.

### Statistical analyses

Logistic regression analysis was used to examine relationships among variables. Significance was defined as $p < 0.05$. The statistical analysis was conducted using a commercially available program (SPSS 10.0, SPSS Inc., IL, U.S.A.).

## RESULTS

### The clinical profiles of neonates with blood group incompatibility

In this survey, clinical symptoms of acute biliru-

bin encephalopathy were not very common (Table 1). Except for icteric skin, approximately 80% of neonates did not present with any clinical symptoms. There was no case of hydrops fetalis. At admission, 5 neonates suffered from respiratory distress and 2 manifested apnea. Poor appetite was noted in 16 neonates. The other symptoms included fever, irritability, lethargy and seizures. Before discharge, the symptoms had resolved in all cases. The combined factors which could aggravate hyperbilirubinemia are also shown in Table 1. All neonates received intensive phototherapy and intravenous fluid supply. Two required nasal continuous positive airway pressure for respiratory support.

**Table 1.** Clinical Symptoms and Combined Factors in 83 Neonates with Blood Group Incompatibility at Peak Total Serum Bilirubin Level ≥ 20 mg/dL

| Clinical symptoms | % |
|---|---|
| tachypnea | 6.0 |
| apnea | 2.4 |
| fever | 1.2 |
| irritability | 2.4 |
| lethargy | 4.8 |
| poor feeding | 19.3 |
| seizure | 1.2 |
| **Combined factors** | **%** |
| exclusive breast milk feeding | 16.9 |
| urinary tract infection | 2.4 |
| cephalohematoma | 1.2 |

We further investigated the correlations within 12 clinical characteristics in neonates with blood group incompatibility by logistic regression analysis (Table 2).

***Gender***

Forty of the neonates with blood group incompatibility were male (48.2%). Male gender was more common in neonates with Rh incompatibility than in those with ABO incompatibility ($p < 0.01$).

***Birth place***

Most enrolled neonates were born outside our hospital (73.5%). Neonates born outside our hospital tended to have hemoglobin values < 13 g/dL ($p < 0.01$).

***Gestational age***

The gestational ages ranged from 34 to 41 weeks. Only 10.8% of neonates were late preterm (34 to 36 weeks). Premature neonates tended to have hemoglobin values < 13 g/dL ($p < 0.01$). Rh incompatibility was more common in premature infants

**Table 2.** Logistic Regression Analysis of Correlation within 12 Clinical Characteristics of 83 Neonates with Blood Group Incompatibility

| characteristics | A | B | C | D | E | F | G | H | I | J | K | L |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A gender | | NS | NS | * | NS | NS | NS | NS | NS | NS | NS | NS |
| B birth place | NS | | NS | NS | NS | NS | NS | NS | NS | * | NS | NS |
| C direct Coombs' test | NS | NS | | NS | * | NS | NS | NS | * | NS | * | * |
| D blood group | * | NS | NS | | * | * | NS | * | NS | NS | NS | * |
| E delivery mode | NS | NS | * | * | | NS | NS | NS | * | NS | NS | NS |
| F gestational age | NS | NS | NS | * | NS | | NS | NS | NS | * | NS | NS |
| G birth weight | NS | NS | NS | NS | NS | NS | | NS | NS | NS | NS | NS |
| H peak TSB level | NS | NS | NS | * | NS | NS | NS | | NS | * | NS | * |
| I age at peak TSB | NS | NS | * | NS | * | NS | NS | NS | | * | * | * |
| J hemoglobin value | NS | * | NS | NS | NS | * | NS | * | * | | * | * |
| K reticulocyte count | NS | NS | * | NS | NS | NS | NS | NS | * | * | | * |
| L exchange transfusion | NS | NS | * | * | NS | NS | NS | * | * | * | * | |

**Abbreviations:** NS: not significant; TSB: total serum bilirubin; *: $p < 0.01$.

than full term subjects.

***Birth weight***

Four neonates had birth weights ranging from 2000 to 2500 g (4.8%). There was no significant difference in birth weight < 2500 g between each category.

***Delivery mode***

The incidence of Cesarean section was 32.5%. Neonates delivered by Cesarean section tended to have a positive DAT ($p < 0.01$), Rh incompatibility ($p < 0.001$) and peak TSB at age < 3 d/o ($p < 0.01$).

***Blood group***

Six neonates had Rh D 2 had Rh E, and 2 had Rh E incompatibility. Neonates with Rh incompatibility were more likely to be male ($p < 0.01$), born by Cesarean section ($p < 0.001$), preterm ($p < 0.01$), have a peak TSB value > 25 mg/dL ($p < 0.01$), and have exchange transfusions (ET) ($p < 0.01$), than subjects with ABO incompatibility.

***Direct Coombs' test (direct antiglobulin test, DAT)***

Positive DATs were found in 36.1% of neonates with blood group incompatibility, 28.8% with ABO incompatibility and 90% with Rh incompatibility. Neonates with a positive DAT tended to be born by Cesarean section ($p < 0.01$), and have a peak TSB at age < 3 d/o ($p < 0.01$), a reticulocyte count > 7% ($p < 0.01$), and ET therapy ($p < 0.01$).

***Peak TSB level***

Approximately 30% of neonates had a peak TSB level > 25 mg/dL. These neonates were more likely to have a hemoglobin value < 13 mg/dL ($p < 0.01$) than those with lower peak TSB levels. Furthermore, Rh incompatibility was more common in these neonates ($p < 0.01$). These infants also more often required ET ($p < 0.001$).

***Hemoglobin value***

A total of 42.2% of neonates had a hemoglobin value < 13 g/dL. These neonates tended to have a reticulocyte count > 7% ($p < 0.01$), a peak TSB level > 25 mg/dL ($p < 0.01$), a peak TSB at age < 3 d/o ($p < 0.01$), preterm delivery ($p < 0.01$), and ET therapy ($p < 0.001$).

***Reticulocyte count***

Neonates with reticulocyte count > 7% more often had a positive DAT ($p < 0.01$), a hemoglobin level < 13 g/dL ($p < 0.01$), a peak TSB at age < 3 d/o ($p < 0.01$), and ET ($p < 0.001$) than those with lower reticulocyte counts.

***Age at peak TSB***

In addition to the correlation with 4 characteristics above (DAT, delivery mode, hemoglobin value and reticulocyte count), neonates with a peak TSB at age < 3 d/o more often required ET therapy than subjects with a peak TSB at a higher age ($p < 0.001$).

***Exchange transfusion (ET)***

Double-volume ET was performed in 31 neonates (37.4%). As mentioned above, ET was associated with 6 clinical characteristics. The ET procedure was done in 172 ± 64 min., and did not result in any mortality or morbidity. Laboratory changes after ET are summarized in Table 3. Thrombocytopenia was the most common laboratory abnormality. Two neonates had hyperglycemia with serum glucose levels of 354 and 517 mg/dL. Three developed hyponatremia with sodium levels ranging from 126 to 131 mM/L. Hypokalemia was noted in 2 neonates with potassium levels of 3.0 mM/L. Although calcium gluconate was routinely given dur-

**Table 3.** Laboratory Abnormalities and Total Serum Bilirubin (TSB) Level after Exchange Transfusion (ET) in 31 Neonates with Blood Group Incompatibility

| Abnormal laboratory data | % |
|---|---|
| Na < 135 mM/L | 9.7 |
| K < 4 mM/L | 6.5 |
| Ca < 8 mg/dL (< 7 for preterm) | 12.9 |
| Glucose > 200 mg/dL | 6.5 |
| Platelet < 100,000 | 71.0 |
| **TSB level** | **mg/dL** |
| before ET | 25.8 ± 3.54 |
| 1 h after ET | 17.6 ± 4.00 |
| 4 h after ET | 17.5 ± 3.59 |
| 12 h after ET | 17.3 ± 4.29 |

ing ET, hypocalcemia still occurred in 4 cases. No neonates had significant clinical symptoms related to these laboratory abnormalities. One hour after ET, the TSB level significantly decreased from 25.8 to 17.6 mg/dL. Thereafter at 4 and 12 hours, there were no significant alternations in the TSB level. Four neonates needed a second ET. Two received ET 4 times.

**The unique characteristics of blood group incompatibility**

The clinical data of the study and control babies were compared to verify the unique characteristics of blood group incompatibility (Table 4). There were significant differences in three characteristics, age at peak TSB, hemoglobin value, and reticulocyte count, between the two groups. Neonates with blood group incompatibility were more likely to have a peak TSB level at age < 3 d/o (odds ratio: 8.16; 95% CI: 1.98 – 33.7), hemoglobin value < 13 g/dL (odds ratio: 2.17; 95% CI: 1.05 – 4.50), and reticulocyte count > 7% (odds ratio: 5.23; 95% CI: 1.92 – 14.2) than the controls, demonstrating that these neonates more often develop early-onset, hemolysis-mediated hyperbilirubinemia.

**Outcome**

Forty-one infants with blood group incompatibility and 69 controls were followed-up for more than 12 months. Four babies had clinical manifestations of kernicterus (Table 5). Kernicterus was more common in neonates with blood group incompatibility (9.8%) than the controls (0.0%) ($p < 0.01$). We further incorporated 12 variables using univariate analysis to determine the risk factors for kernicterus in blood group incompatibility. Blood group, peak TSB level, age at peak TSB level and exchange transfusion were the significant or borderline-significant variables related to kernicterus. These four variables were then analyzed by a multivariate logistic regression model which showed that the peak TSB value was the significant risk factor associated with kernicterus (odds ratio: 1.41; 95% CI: 1.04 – 1.90).

## DISCUSSION

In Taiwan, there are no recent data on the long-term outcome of neonates with blood group incompatibility. Our study is the first to investigate the prognosis of marked hyperbilirubinemia with blood group incompatibility in Taiwan. In this study, we eliminated infants with G6PD deficiency to better understand the profiles of blood group incompatibility.[12,13] By using a comparison with the control group, we distinguished the unique characteristics of hyperbilirubinemia with blood group incompatibility. Our data demonstrated that neonatal hyperbilirubinemia with blood group incompatibility was often early-

**Table 4.** Data Analyses of Neonates with Blood Group Incompatibility and Controls

| Category (%) | Blood group incompatibility (n = 83) | Controls (n = 168) | *p* value | Odds ratio | 95% CI |
|---|---|---|---|---|---|
| Male | 48.2 | 57.1 | 0.08 | 1.76 | 0.93 – 3.34 |
| Inborn | 26.5 | 37.5 | 0.22 | 0.65 | 0.33 – 1.29 |
| Cesarean section | 32.5 | 17.3 | 0.15 | 1.75 | 0.82 – 3.72 |
| Gestational age 34 – 36 weeks | 10.8 | 15.5 | 0.93 | 0.96 | 0.36 – 2.52 |
| Birth weight 2000 – 2499 g | 4.8 | 5.9 | 0.93 | 1.06 | 0.25 – 4.51 |
| Peak TSB level > 25 mg/dL | 28.9 | 19.6 | 0.61 | 1.26 | 0.52 – 3.07 |
| Peak TSB at age < 3 d/o | 32.5 | 1.8 | < 0.05 | 8.16 | 1.98 – 33.7 |
| Hemoglobin < 13 g/dL | 42.2 | 17.3 | < 0.05 | 2.17 | 1.05 – 4.50 |
| Reticulocyte > 7% | 42.2 | 5.4 | < 0.05 | 5.23 | 1.92 – 14.2 |
| Exchange transfusion | 37.4 | 10.7 | 0.46 | 1.48 | 0.53 – 4.14 |

**Table 5.** Clinical Profiles of 4 Patients with Kernicterus

| Patient number | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Peak TSB (mg/dL) | 38.6 | 30.5 | 28.0 | 20.9 |
| Blood group incompatibility | ABO | Rh | Rh | ABO |
| Gender | female | male | male | male |
| Delivery mode | vaginal | C/S | vaginal | C/S |
| Inborn | no | no | yes | yes |
| Gestational age (w) | 40 | 38 | 39 | 35 |
| Birth weight (g) | 2500 | 3600 | 3750 | 2660 |
| Direct Coombs' test | negative | positive | positive | negative |
| Exchange transfusion | once | once | once | none |
| Age at peak TSB (d/o) | 7 | 2 | 1 | 5 |
| Hemoglobin (g/dL) | 12.2 | 8.9 | 11.1 | 15.0 |
| Reticulocytes (%) | 2.2 | 37.9 | 25.8 | 2.9 |
| Acute symptoms | hypotonia lethargy | hypotonia poor feeding | fever hypotonia poor feeding | hypotonia poor feeding |
| Chronic symptoms | athetoid cerebral palsy hearing impairment speech delay | development delay hearing impairment speech delay | hearing impairment gaze abnormalities speech delay | development delay gaze abnormalities |

**Abbreviations:** TSB: total serum bilirubin; C/S: Cesarean section.

onset and hemolysis-mediated. Furthermore, we showed that, at a peak TSB level ≥ 20 mg/dL, infants with blood group incompatibility were at higher risk of developing kernicterus than those without hemolysis. The mechanism of how babies with blood group incompatibility are susceptible to brain injury remains somewhat unclear. The products of hemolysis, such as heme, may be neurotoxic or potentiate bilirubin encephalopathy.

In our study, most neonates did not manifest the clinical symptoms of acute bilirubin encephalopathy. Occasionally, infants with kernicterus do not present with any antecedent signs of this condition.[14] Thus, laboratory assessment is of critical importance. Our analyses revealed that the peak TSB level was a risk factor of kernicterus among neonates with blood group incompatibility. Most physicians believe that neonates with a TSB value ≥ 20 mg/dL are vulnerable to kernicterus, but there is still no specific threshold to distinguish a safe TSB level from an unsafe one.[15] In addition, the albumin binding capacity and the intactness of the blood-brain barrier (BBB) are also crucial indices of kernicterus. Asphyxia, sepsis and dehydration could destroy the BBB and expose the brain to the toxicity of bilirubin. In our study, these conditions were excluded. Furthermore, preterm infants are also vulnerable to bilirubin toxicity since they have an immature BBB and a lower binding capacity of albumin. In our study, one premature infant with a peak TSB level of 20.9 mg/dL developed neurological impairment. However, we can not make any conclusions regarding the correlation of preterm birth with kernicterus because the case number was too small.

Our data disclosed that neonates with Rh incompatibility had more severe hyperbilirubinemia than those with ABO incompatibility. It is noteworthy that, in addition to Rh D incompatibility, incompatibility due to Rh E and minor groups should be considered as possible causes of neonatal hyperbilirubinemia.[16] Moreover, our results did not reveal a correlation of a positive DAT with severe hyperbilirubinemia. The DAT is used to identify neonates with a high risk of hyperbilirubinemia, but some

studies suggest that their relationship, while significant, is moderate.[17,18]

Phototherapy is the mainstay of treatment for neonatal hyperbilirubinemia, with ET held in reserve for severe cases. Our data demonstrated ET was an effective and safe means to lower the TSB level for neonates with blood group incompatibility. Formerly, kernicterus was so rare that most physicians had never seen a case, and conservative management had been recommended.[19] Unfortunately, in the last few years, kernicterus has been observed again.[20,21] In our series, ET was performed under liberal guidelines. With this approach, there were cases of kernicterus in neonates with blood group incompatibility. These data suggest that aggressive treatment is necessary to avoid the sequelae of neonatal hyperbilirubinemia with blood group incompatibility. Recently, intravenous immunoglobulin (IVIG) has been used as an additional therapy to reduce the TSB levels in blood group incompatibility.[22] The mechanism is unclear yet, and competition with antibodies to occupy the Fc receptors is hypothesized. Tin-protoporphyrin, a competitive inhibitor of heme oxygenase,[23,24] is also reported to decrease the TSB levels in neonates with ABO incompatibility.[25] In our study, neither IVIG nor tin-protoporphyrin was used as an adjunct treatment for neonatal hyperbilirubinemia.

One would question whether the analysis of the outcome data is in doubt, since only half of the infants were followed up for more than 12 months. Our findings showed that the clinical characteristics of the infants and controls who were followed up resembled those of the initially enrolled babies (data not shown). These data are reliable to conclude that neonates with blood group incompatibility are at higher risk of developing kernicterus than controls. In conclusion, we depict the spectrum and outcome of blood group incompatible infants with peak TSB levels ≥ 20 mg/dL. Blood group incompatibility is an important risk factor for kernicterus. Rh incompatibility is less common, but results in the development of more severe hyperbilirubinemia and hemolytic anemia than ABO incompatibility. Early detection and aggressive treatment may help reduce the complications of severe neonatal hyperbilirubinemia.

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# 嚴重新生兒高膽紅素血症合併血型不合之臨床表徵及預後分析

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**背 景：** 母子血型不合爲新生兒高膽紅素血症之主要病因之一，嚴重的高膽紅素血症會導致永久的神經學後遺症(核黃疸)。本研究之目的在探討嚴重新生兒高膽紅素血症合併血型不合者之臨床表徵及預後分析。

**方 法：** 我們整理 1995 年至 2007 年間血清膽紅素值大於或等於 20 mg/dL 共 413 位新生兒，排除出生週數小於 34 週、出生體重小於 2 公斤以及 G6PD 缺乏者，共有 83 位血型不合者。另外，我們選擇 168 位找不出特別原因(哺餵母乳除外)之高膽紅素血症新生兒做爲對照組。追蹤 1 年之後發現有神經學後遺症之醫療紀錄者被視爲核黃疸。

**結 果：** 急性膽紅素腦病變之臨床徵狀包括呼吸暫停 (2.4%)、呼吸急促 (6.0%)、發燒 (1.2%)、噪動不安 (2.4%)、嗜睡 (4.8%)、抽筋 (1.2%) 及餵食量減少 (19.3%)。Rh 血型不合者所產生的高膽紅素血症比 ABO 血型不合者嚴重。交換輸血可有效降低血清膽紅素值。我們採用邏輯式回歸分析，發現血型不合之新生兒比對照組容易有 (1) 網狀細胞數大於 7% (2) 血紅素小於 13 g/dL (3) 最高之血清膽紅素值發生在小於三天大時。血型不合者產生核黃疸之機會 (9.8%) 也明顯比對照組 (0.0%) 高 ($p < 0.01$)。

**結 論：** 本文分析嚴重高膽紅素血症合併血型不合之新生兒的臨床表現。我們發現母子血型不合者比較容易在出生初期就出現嚴重黃疸之症狀，且較會有溶血現象。本研究顯示高膽紅素血症合併血型不合者較容易產生核黃疸。

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**關鍵詞：** 血型不合，交換輸血，核黃疸，新生兒高膽紅素血症

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