Hemolytic Disease of the Newborn Caused by Anti-Wright (Anti-Wr\(^a\)):
Case Report and Review of the Literature

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Antibodies to red cell antigens that are found at low frequency in the general population are rare causes of hemolytic disease of the newborn. To understand how to detect these cases, we provide a basic review of routine antenatal maternal antibody testing and report a case of a neonate with severe HDN caused by anti-Wright (anti-Wr\(^a\)), successfully managed with transfusion, phototherapy, and high-dose intravenous immunoglobulin.

When hemolysis in a newborn is suspected in the absence of major blood group incompatibility or commonly detected maternal red cell antibodies, a direct antiglobulin test should be performed. A positive DAT should alert the clinician to the presence of maternal antibodies against low-incidence antigens. Antibodies to the Wr\(^a\) antigen are one such rare cause of HDN.

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A brief review of antenatal antibody/antigen testing and the more common blood groups routinely tested will help to describe how this particular antigen/antibody incompatibility (Wra) can easily be missed unless the clinician is astute, understands the limitations of routine antenatal testing for red cell antigens, and is aware of the significance of a family history suspicious for HDN.

ROUTINE ANTENATAL TESTING FOR RED CELL ANTIGENS

Routine antenatal testing includes an antibody screen on maternal blood for the presence of common red cell antibodies. A positive antibody screen means that the mother has developed an antibody to a common red cell antigen and identifies some pregnancies to be at risk for HDN. The antenatal history may also provide clues that suggest a higher risk of HDN such as previous pregnancies with HDN, previous infants with hyperbilirubinemia, abortions or any unexplained neonatal deaths in the family history. A mother who is RhD negative may have a positive antibody screen because of the development of an anti-D antibody or because of the previous Rh immunoglobulin (RhIg) administered to prevent the development of alloimmunization. For RhD negative mothers, it is important to clarify if RhIg was given during pregnancy and when and how much was given. To detect the presence of antibodies directed at the fetal red blood cell (RBC), there are two laboratory tests that can be performed either prenatally on the mother or postnatally on the fetus: the indirect antibody test (indirect Coombs test, Figure 1) or the direct antibody test (direct Coombs test, Figure 2).

INDIRECT ANTIGLOBULIN TEST (IAT OR INDIRECT COOMBS TEST)

The antibody screen is performed by using the indirect antiglobulin test (IAT) (also referred to as the indirect Coombs test) to screen maternal plasma for red cell alloimmunization, or the development of circulating antibodies against common RBC antigens. RBC alloimmunization occurs when the mother develops an antibody to RBC proteins not present on her RBCs but present on the fetal RBCs. These fetal RBC antigens are inherited from the infant’s father. In the IAT, the commercial RBCs provided for the antibody screen are blood group O and have a detailed listing of the presence or absence of the following most common clinically significant antigens including the following:

- Rh group (C, c, D, E, and e)
- Lewis and P blood group (LEa, LEb, and P1)
- MNSs blood group (M, N, S, and s)
- Kell blood group (K, k)
- Duffy blood group (Fya, Fyb)
- Kidd blood group (Jka, Jkb)

The commercial screening cells are derived from two blood donors with strong expression of antigens commonly implicated in hemolytic transfusion reactions and HDN. They do not carry all antigens implicated in HDN and thus a negative reaction does not exclude the potential for HDN.

After delivery, the IAT can also be performed on the neonate’s serum to detect red cell antibodies of maternal origin. If clinically significant circulating red cell antibodies are present, they may cause hemolysis of the neonate’s red cells. In these cases, the mother has produced an immunoglobulin G (IgG) antibody in reaction to a foreign red cell surface antigen, which has crossed the placenta. The strength of the antibody can be graded from 1+ (weak reaction) to 4+ (strong reaction). The presence of antibodies does not always predict hemolysis.

DIRECT ANTIGLOBULIN TEST (DAT OR DIRECT COOMBS TEST)

The direct antiglobulin test (DAT) is an important test to detect HDN (Figure 2). The DAT tests the neonate’s RBCs to determine if there is maternal IgG antibody that has crossed the placenta and attached to the surface of the neonatal RBCs. If the test is positive, then the neonate is at risk for hemolysis, although clinical hemolysis may not necessarily occur.

Because the DAT is performed on the neonatal RBCs, it may be possible to detect situations where the maternal antibody is directed against a rare red cell antigen, such as Wra on the surface of the neonate’s RBC. In this case, the routine maternal antibody screen using the IAT would be negative because the rare Wra antigen was not present on the commercial RBCs used in the antibody screen. Additional maternal antibody testing for rare antigens would not normally be
performed unless there was a suspicion of HDN such as a positive family history. In the case study presented, the mother was not aware that there was a history of previous HDN because of anti-Wra hemolysis in her husband’s family or that there was any significance to some of the issues she encountered in her previous pregnancies. If there had been a history of HDN, the antibody could have been detected by performing a cross-match between the mother’s plasma and the father’s RBCs. If the clinical team is suspicious of a higher than normal risk of HDN (e.g., a prior history of hyperbilirubinemia because of hemolysis in a previous infant in the setting of a negative maternal antibody screen), they should request compatibility testing be performed between the parents.

**REVIEW OF ABO INCOMPATIBILITY**

There are four ABO blood group types: O, A, B, and AB. Patients with group A blood have naturally occurring antibodies to the B antigen, and patients with group B blood have naturally occurring antibodies to the A antigen. Blood group AB has both A and B antigens, and consequently this group has no antibodies against both antigens. Patients with group O blood have no A or B antigens and naturally express antibodies to both A and B antigens. The blood group phenotype refers to the expression of RBC antigens on the surface of RBCs—O, A, B, and AB. The blood group genotype refers to what blood group genes are present and inherited from both parents: O is OO, A may be AA or AO, B is either BB or BO, and AB is AB or BA. Blood groups A and B are codominant whereas O is recessive. Occasionally, the phenotype does not correlate with the genotype when there is nonexpression of the gene because of small point mutations.

**ETIOLOGY OF ABO INCOMPATIBILITY IN HDN**

ABO incompatibility is the most common cause of HDN. Mothers with O blood group produce naturally occurring IgG antibodies against A and B blood group antigens that can cross the placenta. The antibodies may cause HDN if the neonate has blood group A, B, or AB. ABO incompatibility occurs in up to 40–50 percent of primigravidas, although few develop clinical HDN. Mothers with A or B blood groups predominantly produce immunoglobulin M (IgM) class antibodies rather than IgG antibodies. When incompatibilities occur in mothers with A or B blood groups, the risk of hemolysis is less severe because the IgM antibodies are too large to cross the placenta. The surface A and B antigen expression on fetal RBCs is also decreased compared with adult cells. Sensitization as evidenced by a positive DAT is seen in 3–4 percent of ABO incompatibility but the actual occurrence of symptomatic ABO HDN is only 1 percent.

When ABO incompatibility occurs, spherocytes may be observed in the neonate’s blood film. The DAT may be positive or negative. A positive DAT has a sensitivity of 86 percent and a positive predictive value of only 23 percent in predicting significant hemolysis and need for phototherapy in ABO incompatibility. Because of the low sensitivity, if the clinician is suspicious for ABO-mediated HDN, an eluate should be requested. An eluate (antibodies taken off
the neonate’s RBCs) is tested against A and B cells to detect if there is an antibody with anti-A or anti-B specificity.

**REVIEW OF RH INCOMPATIBILITY**

The Rh system consists of over 40 known red cell antigens. There are currently five antigens that have been described in the Rh group system, which are implicated in most cases of Rh-related HDN: D, C, c, and E, and e antigens. Eighty-five percent of the population are RhD positive. Approximately 15 percent of Caucasians are RhD negative, whereas the RhD negative phenotype is only present in 8 percent of the African American and 0 percent of the Asian populations.

If an RhD negative mother conceives with a partner who is RhD positive (heterozygous), there is a 50 percent chance that she will conceive a baby who is RhD positive. If an RhD negative mother conceives with a partner who is RhD positive (homozygous for the D antigen), there is a 100 percent chance that she will conceive a baby who is RhD positive. Rh incompatibility occurs when an RhD negative mother has an RhD positive baby. If the mother develops an antibody against the RhD antigen, the mother’s IgG antibodies can cross the placenta and coat the fetal RBCs, which are then destroyed by the fetal spleen. In this case, the mother’s IAT is positive. A DAT performed on the neonate’s RBCs will also be positive. Subsequent pregnancies exhibit more severe HDN as the antibody titers increase. There appears to be some protection when ABO blood group incompatibilities exist where the risk of RhD alloimmunization is reduced from 16 percent to 1–2 percent because of fetal cells that enter the maternal circulation are destroyed because of ABO incompatibility.

The first pregnancy with RhD incompatibility is usually unaffected with less than 1 percent risk of developing HDN. However, this risk may increase if there has been prior sensitization such as previous undetected spontaneous abortions (SAs) of an RhD positive fetus. Sensitization may also occur in any situations potentially causing fetomaternal hemorrhage such as breech presentation, maternal trauma, multiple births, ectopic pregnancy, external cephalic version, adherent placenta, placenta abruption, or placenta previa.

Prevention of the development of an anti-D antibody can be achieved by administration of RhIg. RhIg is a human derived blood product containing anti-D antibodies (IgG) and was developed in 1960s by Dr. Vincent Freda, a professor of obstetrics and gynecology at Columbia University. With the use of RhIg, the incidence of anti-D sensitization during pregnancy has decreased from 1 to 0.1 percent.

RhIg is given to the RhD negative mother during pregnancy at 26–28 weeks to prevent maternal antibody production that may occur secondary to incidental fetomaternal hemorrhage. This is documented to occur in 7 percent of Rh negative mothers in their first trimester, 16 percent in the second, and 29 percent in the third trimester. In the peripartum period, it may be as high as 50 percent. RhIg should also be given to Rh negative pregnant women during invasive procedures, such as chorionic villus sampling, amniocentesis, and cordocentesis.

Fetal therapy, such as intrauterine transfusion, is needed in 9 percent of HDN cases. If the mother is sensitized, close monitoring of the fetus is indicated with repeated ultrasound to detect fetal anemia by measurement of the velocity of blood in the middle cerebral artery of the fetus. If the ultrasound suggests fetal anemia, invasive measurements are required such as amniotic fluid analysis for bilirubin concentration or umbilical cord blood sampling for hemoglobin (Hb) measurement and possible intrauterine transfusion.

**DIEGO BLOOD GROUP SYSTEM AND WRIGHT ANTIGEN**

The Diego blood group system is located on the band 3 protein (Figure 3). Band 3 is an integral component of the RBC membrane, making up 25 percent of its protein content, it also acts as an anion exchanger that facilitates the exchange of HCO3– and Cl–, and thereby participates in CO2 transport. Mutations of the band 3 protein have been implicated in the pathogenesis of various structural and functional abnormalities of the erythrocytes and the kidney such as Southeast Asian ovalocytosis, hereditary spherocytosis, congenital acanthocytosis, and distal renal tubular acidosis (Figure 3).

**FIGURE 3** RBC membrane major proteins. The Wr* antigen is present on Band 3.
The Diego system consists of 21 blood group antigens. In addition to its structural and functional role, band 3 also confers blood group expression. There are two sets of antithetical blood group antigens located on the band 3 protein, collectively known as the Diego system. The most important are the Diego blood group antigen (low incidence Di\(^a\) and high incidence Di\(^b\)) and the Wright blood group antigen (low incidence Wr\(^a\) and high incidence Wr\(^b\)). The Wright blood group antigen was first described in a case of HDN in 1953. Anti-Wr\(^a\) has been associated with HDN and hemolytic transfusion reactions. Antibodies can develop on exposure to Wra and Wrb antigens. Anti-Wra antibodies are relatively more common, present in approximately 1 in 25–100 healthy volunteer blood donors. Anti-Wr\(^a\) immunoglobulins can be IgM or IgG. As such, anti-Wr\(^a\) antibodies may cause hemolytic transfusion reactions, although rarely do, and if an IgG component is present, may also be associated with HDN. Anti-Wr\(^b\) antibodies have been described in autoimmune hemolytic anemia. The incidence of anti-Wr\(^a\) is somewhat greater among hospitalized patients especially, Rh negative pregnant women who developed anti-D during pregnancy patients with hemolytic anemia, and patients who received allogeneic transfusions compared to healthy blood donors. The incidence of anti-Wr\(^a\) may increase when the immune system becomes more active, such as in pregnancy, or with RBC antigen stimulation, such as after RBC destruction caused by ABO and Rh mismatch.

**CASE REPORT**

A healthy 35-year-old G3P2 Caucasian woman with no previous history of blood transfusion or surgeries gave birth to a 36-week-gestation female neonate. She had two previous uneventful spontaneous vaginal deliveries. At 12 weeks, the mother's prenatal labs were blood group A RhD positive, IAT was positive for a nonspecific antibody, hepatitis B surface antigen (HBsAg) negative, rubella immune, VDRL nonreactive (NR), human immunodeficiency virus (HIV) negative and group B streptococcus (GBS) negative. The IAT was repeated at 24 and 26 weeks and was negative. The positive IAT at 12 weeks was presumed to be a false positive. Her pregnancy was complicated by kidney stones requiring admission and treatment for a urinary tract infection (UTI). The pregnancy was otherwise uneventful until two days prior to delivery (gestational age 35 weeks and 5 days) when she was admitted because of decreased fetal movement. Her ultrasound was reassuring with good placental blood flow and a biophysical profile (BPP) of eight out of eight. The nonstress test (NST) was reassuring, and she was discharged home.

After two days, the mother noticed decreased fetal movement and was readmitted for fetal monitoring. Late decelerations prompted an emergent cesarean section. The female infant emerged pale and floppy with poor respiratory effort. The neonate's Apgar scores were 6, 7, and 9 at one, five, and ten minutes respectively. She required resuscitation...
with positive pressure ventilation (PPV) and 100 percent oxygen for dyspnea, pallor, and central cyanosis. It was noted that her lips were orange in color and the amniotic fluid was yellow. She had poor respiratory effort and continued to require PPV for increased work of breathing and persistent cyanosis despite 100 percent FiO2. Her perfusion was poor, she had weak thready central pulses, and capillary refill was prolonged at four seconds. Thrombocytopenia was suspected because a ring of petechiae developed where the continuous positive airway pressure mask was applied. The presumed anemia could not be explained by an abruption, cord, or placental anomaly. Cord blood was sent for fetal hemoglobin (HbF) quantitation by flow cytometry to rule out fetomaternal hemorrhage, a complete blood count (CBC) to confirm anemia, IAT and DAT to rule out rare immune HDN, and a serum bilirubin because of underlying jaundice with suspected hemolysis. A TORCH screen was also performed to rule out viral illness, which could also potentially cause thrombocytopenia, anemia, and jaundice. Upon questioning, the parents stated that they were not aware of any history of anemia or neonatal deaths in their immediate family. However, it was later revealed that their second baby did require phototherapy on the first day of life (DOL) but was not further investigated. In the crisis, this information, which would have alerted the health care team to the possibility of HDN, was not provided.

The neonate was found to be asymmetrically small for gestational age (ASGA) with a birth weight of 2,140 g (3–10th percentile), head circumference of 31.5 cm (10–50th percentile), and length 45.5 cm (10–50th percentile). Her examination was significant for severe pallor, petechiae, and an audible continuous cardiac murmur over the left upper and lower sternal border, weak central and peripheral pulses, splenomegaly, and a palpable liver at 2 cm below the right costal margin, with no peripheral edema.

Umbilical arterial and venous catheters were inserted. She required initial fluid resuscitation with normal saline (10 mL/kg) for hypotension and tachycardia of more than 180 beats per minute. A four limb blood pressure (BP) to rule out congenital heart defect showed widened pulse pressures but no gradient between upper and lower limbs. The systolic BPs were in the 50s, diastolic BP in the low 20s and mean arterial BP in the 30s. A cord blood gas was not performed. Urgent RBC and platelet transfusions were ordered because we presumed severe anemia and thrombocytopenia. Although there were no risk factors for sepsis, a partial sepsis work up and TORCH screen were sent including a urine sample for cytomegalovirus (CMV). A lumbar puncture was not performed because we presumed she was thrombocytopenic. She was treated with meningitic doses of antibiotics as we considered congenital sepsis or viral infections as a possible cause for anemia and thrombocytopenia. The chest x-ray (CXR; Figure 5) was significant for cardiomegaly and mild bilateral pleural effusions.

**FIGURE 5** Post intubation X-ray at approximately 3½ hours of age.

![X-ray Images](https://example.com/xray.jpg)

*Note: Chest x-ray and abdominal x-ray were significant for cardiomegaly, very mild bilateral pleural effusion. No hydrops was noted. Presumed to be a more chronic low level hemolytic process that allows the heart to compensate and delays the development of congestive heart failure. ETT at T2. The tip of the UVC at T8 at the level of the diaphragm. A. Lateral view. B. Anteroposterior view.*
Cord blood analysis revealed a Hb of 4.2 g/dL (42 g/L) and a platelet count of 47 × 10^9/L. An urgent RBC transfusion (15 mL/kg) of O negative red cells was administered followed by a platelet transfusion (10 mL/kg). She was treated for hypoglycemia (glucose 1.8 mmol/L or 32.4 mg/dL) with a 2 mL/kg bolus of D10%W. At two and a half hours of age, she was intubated for respiratory distress requiring 100 percent oxygen with conventional ventilation assist control, volume guarantee (AC/VG: rate 40 pressures 20/6). Her heart rate (HR) decreased to 150 beats per minute and her BP increased to 74/37 (mean of 50) post RBC transfusion, platelet transfusion, and normal saline infusions. The arterial blood gas (ABG) at two hours was pH 7.25, CO2 45 mmHg, bicarbonate 19 mmol/L, base deficit of −8 mmol/L, and O2 saturation of 95 percent. A hyperoxic test was positive with an increase in arterial PaO2 greater than 150 mmHg, excluding a cyanotic heart defect. Cardiology and hematology consults were requested. With a suspicion of congenital heart disease, the fluids were restricted to 60 mL/kg/day.

After three hours, she became tachypneic, breathing of 56–106 per minute, with a blood gas showing: pH 7.38, CO2 45 mmHg, bicarbonate 19 mmol/L, base deficit of −6 mmol/L. Her ventilation was weaned to a rate of 30 with peak pressures of 20 over 6, and she was weaned to 21 percent FiO2 with O2 saturations of 95 percent. The post-transfusion Hb was 7.8 g/dL (78 g/L), and her post transfusion platelet count was 55 × 10^9/L. Many nucleated red blood cells (NRBC-412) were seen on the peripheral blood film, suggesting bone marrow stress. Elevated NRBC are associated with perinatal asphyxia, hypoxia, and chronic stress and are seen when extramedullary hematopoiesis (see sidebar) has been activated. Extramedullary hematopoiesis (red blood cell production outside the bone marrow) usually begins 5–6 weeks in liver, later in the spleen and becomes the primary site for RBC production from 6 to 22 weeks. Production in the spleen normally ends at 28 weeks. The bone marrow begins producing RBC at 8–19 weeks and becomes the primary site after 22 weeks gestational age.

The baby’s blood group was A RhD positive. The mother was also A RhD positive with a negative antibody screen. The hematologist requested a DAT to look for rare red cell antigens because there was a high suspicion of HDN. After her resuscitation at four hours of life, she was treated with triple phototherapy for a cord total serum bilirubin of 10 g/dL (171 umol/L); the direct component was not available. She was very pale with underlying jaundice with orange lips and yellow sclera. Liver function tests were significant for an elevated aspartate aminotransferase (AST) of 225 IU/L (normal 14–75 IU/L). Alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were within normal limits. Elevation in AST can be associated with hemolytic anemia.37 A follow-up CBC differential revealed a normal white blood cell count without evidence of sepsis. Another RBC transfusion was administered for a Hb of 7.8 g/dL (78 g/L), along with another platelet transfusion for platelets of 55 × 10^9/L. Furosemide was given posttransfusion (dose 1 mg/kg) because of the concern of congenital heart disease. The partial thrombin time (PTT) was within normal limits at 30.4 seconds, and the prothrombin time (PT) or international normalizing ratio (INR) was prolonged at 2.16 seconds. There was no bleeding, and she had been administered vitamin K 0.5 mg intramuscularly at birth. The peripheral blood film showed acanthocytes, spherocytes, and increased polychromasia and nucleated RBCs consistent with severe immune-mediated hemolysis (Figure 6). Polychromasia refers to an increase in the blue staining of erythrocytes often because of an increase in reticulocytes as a result of the brisk response to hemolysis. The DAT on the neonatal sample was strongly positive (3+ out of 4+ grading) for IgG antibody. A presumed diagnosis of HDN was made while awaiting further serologic investigations.

On DOL 2, triple phototherapy and IVIG was given at the recommended dose of 1 g/kg/day on Day 1 and 2 for a rising bilirubin of 11.7 g/dL (200 umol/L). IVIG is hypothesized to block the neonatal reticuloendothelial system and decrease RBC (antibody coated) hemolysis (see sidebar). It must be given over four hours to decrease the risk of anaphylaxis, tachycardia, and hypotension. It provides many antibodies to neutralize toxins and remove antibodies by opsonization. A Cochrane review in 2003, investigating the use of immunoglobulin to treat jaundice in cases of isoimmune hemolytic anemia, three studies met the inclusion criteria. Although the quality of studies were not high, in 189 term and preterm infants with Rh and ABO

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**Extramedullary Hematopoiesis**

Extramedullary hematopoiesis (red blood cell production outside the bone marrow) usually begins 5–6 weeks in liver, later in the spleen and becomes the primary site for RBC production from 6 to 22 weeks. Production in the spleen normally ends at 28 weeks. The bone marrow begins producing RBC at 8–19 weeks and becomes the primary site after 22 weeks gestational age.
HDN, IVIG decreased the need for exchange transfusion and the number of exchange transfusions needed per infant. IVIG is recommended for HDN with severe hyperbilirubinemia so as to reduce the risk of exchange transfusion.

An echocardiogram on DOL 2 was significant for an age-related patent ductus arteriosus (PDA) and tricuspid regurgitation (TR). She was weaned to 21 percent FiO2 and extubated on DOL 3 without respiratory distress. There was no evidence of the mild pleural effusions seen at birth on a follow-up CXR on DOL 3 (Figure 7).

After three transfusions of RBC (15 mL/kg/dose) and five platelet transfusion episodes (10 mL/kg/dose), the Hb level increased to 11.4 g/dL (114 g/L) on DOL 3, and the platelet count increased to 102,000/μL on DOL 5. The HbF quantitation for fetomaternal hemorrhage was negative.

The blood cultures, metabolic screening, glucose-6-phosphate dehydrogenase (G6PD) deficiency screening, and tests for TORCH infection were all negative. A cardiac evaluation was negative other than a hemodynamically insignificant PDA, that closed spontaneously. Phototherapy was discontinued on Day 5. A gastroenterology consult (GI) was also requested because there was an elevated direct serum bilirubin and elevated AST. All other liver functions were within normal limits. The abdominal ultrasound

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**FIGURE 7** Follow-up chest X-ray and abdominal X-ray at approximately 14 hours of age.

**Note:** Lungs are clear except minimal left retrocardiac opacities, nonspecific, and might represent early infiltrates or subsegmental atelectasis. Cardiothymic contour is unremarkable. No detectable pleural effusion or pneumothorax. ETT was a little too low 2 mm above carina and was pulled back. UVC at the level of the diaphragm. A. Lateral view. B. Anteroposterior view.
was significant only for splenomegaly. The direct bilirubin level DOL 8 was 7.25 g/dL (124 mcmol/L) and the GI team recommended ursodeoxycholic acid, which was discontinued after 11 days. G6PD deficiency can also cause significant neonatal hemolysis, and the test may be falsely negative because of RBC transfusions and hemolysis. The G6PD test was repeated at six weeks of age and was normal.

Maternal plasma was screened for low incidence red cell antibodies and found to react against Wrα. Infant and paternal RBCs were confirmed to be Wrα positive whereas the mother was Wrα negative.

The head ultrasounds were normal, there was no evidence of hypoxic–ischemic encephalopathy, and she had an appropriate neurologic physical examination for her gestational age.

FAMILY HISTORY

Further detailed questions revealed that the mother’s eldest child (first born) did not have neonatal jaundice, but the second child required phototherapy (no CBC or DAT was performed at the time). It is of note that testing of the paternal grandmother revealed that she was also Wrα positive (Figure 8). No other cases of HDN were reported by the parents. However, the paternal grandmother had lost two neonates who died of unknown causes, a paternal uncle had a baby who died of unknown cause, and the paternal aunts had babies who had been jaundiced on the first day of life.

PROGRESS

The infant was discharged home 25 days after birth with a total serum bilirubin of 6.4 g/dL (90 umol/L), direct bilirubin of 2.8 g/dL (48 umol/L), Hb 10.6 g/dL (106 g/L), and platelet count 386 × 109/L. Follow-up at eight weeks revealed a normal healthy infant with appropriate growth, a Hb level of 9.7 g/dL (97 g/L), platelet count of 411 × 109/L, total bilirubin of 1.3 g/dL (22 umol/L), and direct bilirubin of 0 g/dL (0 umol/L). Antibody screen and DAT were both negative using gel technology at eight weeks of age. The hematologist monitored her CBC postdischarge until the hemolytic process ceased, and the antibodies against Wrα were no longer present in her circulation. At eight weeks of age, there were no detectable IgG antibodies against the Wrα antigen.

IMPLICATIONS FOR THE FAMILY

The mother was given an antibody identification card for future transfusions8 and was counseled that if she became pregnant with the same partner, she would need close follow-up for HDN. The father was informed that he has a low incidence antigen, and that his brothers also required testing in advance of conception to determine if their offspring could potentially be at risk. If the brothers were Wrα positive, their wives would be at risk for developing an anti-Wrα that could cause HDN. The paternal grandmother was also given an antibody identification card for future transfusions so that she would receive Wrα negative blood.8,30

DISCUSSION

Our case describes HDN occurring in the absence of ABO or RH incompatibility and with a negative maternal antibody screen. Further investigation of an unexpected positive DAT revealed that the HDN was caused by an antibody against Wrα, a rare blood group antigen.

There have been only four reported cases of HDN since the Wright blood group antigen was first described (Table 1).25,26,32,40 We believe that more cases have likely occurred, but may not have been diagnosed or reported because hemolytic reactions because of anti-Wrα are likely to be mild and are not detected with standard screening.

In spite of the low level of Hb, which our infant had at birth, neither our case nor any of the reported cases have presented with fetal hydrops. Previous research suggests that elevated central venous pressure (CVP) plays a role in the pathogenesis of hydrops fetalis and that severe anemia is not enough to produce hydrops fetalis.17,41 The absence of hydrops could be explained if the Wrα antigen had low immunogenicity or if anti-Wrα antibodies were present at low titers during pregnancy resulting in a more chronic low level hemolytic process that allows the heart to compensate and delays the development of congestive heart failure. Our baby had mild bilateral pleural effusion and cardiomegaly that required intubation and a brief period on conventional ventilation. Within two days, the CXR had normalized, she was extubated to room air on the third DOL and breast feeding within a few days. The thought was that our case was caused by a chronic low level hemolytic process, and the decreased fetal movement indicated that she was not tolerating the low Hgb and hypoxia. It is presumed that she would have developed hydrops with pleural effusions if she had delivered at term.
The persistent thrombocytopenia presented in our case was not reported in any of the previous case reports. This could be explained by the marked increase in extramedullary erythropoiesis, which was accompanied by a down-modulation of the megakaryocytes and decreased platelet production, or by associated hypersplenism and increased peripheral destruction, or both.\(^{33}\)

We speculate that the second child in this family was Wr\(^a\) positive given the unexplained high level of bilirubin on the first DOL. The opportunity to detect the anti-Wr\(^a\) may have been missed because a Hb and DAT were not done at the time because of the mild elevation in the serum bilirubin. Potentially, this severe case of HDN may have been anticipated had more in-depth investigations been sent on the second child. It is important to obtain samples prior to transfusion that may be required for blood investigations such as DNA banking, newborn screening, and genetics. If possible, delay the emergency transfusion until the antibody screen and crossmatch are complete, so as to provide antigen-negative (this case Wr\(^a\) negative) blood to prevent further aggravation of hemolysis.\(^{30}\)

**IMPLICATIONS FOR PRACTICE**

The significance of anti-Wr\(^a\) causing HDN or hemolytic transfusion reaction is limited by the rarity of the Wr\(^a\) antigen. Accordingly, routine screening for Wr\(^a\) antigen or anti-Wr\(^a\) antibodies is neither necessary nor cost effective.\(^8\)

However, we recommend including a DAT to screen for antibodies against low-incidence antigens, such as Wr\(^a\), in cases of hyperbilirubinemia or hemolytic anemia that are not explained by known blood group incompatibility. If a low-incidence antibody is suspected antenatally, a crossmatch between the mother's plasma and the father's RBCs can be used to exclude this in the differential diagnosis.

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SUGGESTED READINGS


A Review of the Management of Intersex

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The gonads do not have any male or female morphologic characteristics until the seventh week of gestation. In the early embryo-fetal development, primordial gonadal tissue is bipotential—that is, it has the potential to become an ovary or testis. The sex of an embryo is determined by its genetic code. The gene that causes the indifferent gonad to differentiate into a testis has been identified as the SRY gene in humans. It is therefore this gene that directs the gonads toward the male phenotype, whereas the absence of these genetic factors is thought to direct the gonads toward the female phenotype.

Thus, fetal sexual development progresses down one of two paths to result in a male infant with an XY karyotype, scrotal testes, and male genitalia, or a female infant with an XX karyotype, ovaries and a uterus, and female external genitalia. However, sexual determination and differentiation may not follow these dual “standard” pathways. The birth of an individual with a blend of both male and female internal or external genitalia is known as an intersex condition. The incidence of genital anomalies is estimated to occur in 1 in 4,500 live births. Each intersex condition is determined by the external genital appearance, internal genital structures, and fertility potential. The main concept involved in the management of intersex is the establishment of an experienced multidisciplinary team. Management of intersex conditions is complex and involves a person’s gender identity, gender role behavior, sexual orientation, sexual functioning, and psychological adjustment. This review will outline the management of intersex in the light of the latest research. We focus on diagnosis, surgical techniques, and the psychological aspects encountered in the management of intersex.

Etiology

The determination of the etiology of ambiguous genitalia is of vital importance in order to ascertain the sex of the individual. Each intersex condition is determined by the external genital appearance, internal genital structures, and fertility potential. These are dependent on gonadal production of sex steroid hormones and anti-Müllerian hormone (AMH) together with the cellular response of these hormones. Testosterone is responsible for actively inducing differentiation of the Wolffian duct into the epididymis, vas deferens, and seminal vesicle via the androgen receptor (AR) in target tissues. In addition to testosterone, the Müllerian inhibitory substance (MIS), produced by Sertoli cells (which are present inside the testes), promotes regression of the Müllerian (paramesonephric) ducts, which continues to puberty, after which the levels of MIS decrease (Figures 1 and 2).

Disclosure

The author discloses no relevant financial interest or affiliations with any commercial interests.
the third month of pregnancy and its end, the testes become transferred from the lumbar area into the future scrotum. Until 28 weeks of gestation, the testes stay in the area of the inguinal canal so they can enter into it. Under the influence of the androgen hormone, they reach the scrotum at roughly the time of birth, by which time they become palpable.

The primary modality for the establishment of the presence or absence of genitalia is ultrasonography; a rapid procedure that requires no sedation and radiation. Although ultrasonography is used for the evaluation of internal reproductive organs, genitography is used to document the urethra, vagina, and any other fistulas or complex tracts.

A karyotype is usually the first step in the management of intersex together with an abdominopelvic ultrasound scan. However, until a karyotype is made available, a buccal smear is usually taken for the presence or absence of Barr bodies (Barr bodies represent the heterochromatin of the inactivated X chromosome, identified as a condensed chromosome inside the nucleus of somatic cells of females). Moreover, measurements of 17-hydroxyprogesterone, testosterone, gonadotropins, AMH, serum electrolytes, and urinalysis are requested.

**GENERAL CONCEPTS IN THE MANAGEMENT OF INTERSEX**

The main facet of the management of intersex is the establishment of an experienced multidisciplinary team that offers good communication; this is essential for the family and patient in order to make an informed decision and, ultimately, a gender assignment. A multidisciplinary team should include appropriately trained pediatric surgeons or pediatric urologists, neonatologists, and pediatric endocrinologists and their specialist nurses, support workers, geneticists, biochemists, psychologists, psychiatrists, and gynecologists in order to offer a holistic approach and optimal care to the patient and family. The patient would need early referral to a tertiary center, which offers such a service.

**Clinical Evaluation**

To establish an intersex condition, the following criteria as outlined by the consensus statement on management of intersex disorders must be assessed:

- Overt genital ambiguity such as cloacal exstrophy
- Apparent female genitalia with an enlarged clitoris, posterior labial fusion, or an inguinal/labial mass
- Apparent male genitalia with bilateral undescended testis, micropenis, isolated perineal hypospadias, or mild hypospadias with undescended testis
- A family history of intersex such as CAIS
- A discordance between genital appearance and a karyotype

On a physical examination, anthropometric measurements of external genitalia are carried out. In the male, stretched penile length, penile width, and mean testicular volume are
FIGURE 2  Schematic illustrations showing differentiation of the indifferent gonads of a 5-week embryo (top) into ovaries or testes.

The left side of the drawing shows the development of testes resulting from the effects of the testis-determining factor (TDF) located on the Y chromosome. Note that the gonadal cords become seminiferous cords, the primordia of the seminiferous tubules. The parts of the gonadal cords that enter medulla of the testis form the rete testis. In the section of the testis at the bottom left, observe that there are two kinds of cells, spermatogonia, derived from the primordial germ cells, and sustentacular or Sertoli cells, derived from mesenchyme. The right side shows the development of ovaries in the absence of TDF. Cortical cords have extended from the surface epithelium of the gonad and primordial germ cells have entered them. They are the primordia of the oogonia. Follicular cells are derived from the surface epithelium of the ovary.

Reprinted from: The Developing Human. 266. Moore KL, Persaud TVN. (Figure 12-31), Copyright Elsevier (2007).
measured, whereas in a female, clitoral length, clitoral width, and perineal length are measured.\(^5\)

Prader classification can be used to classify the degree of ambiguity in which the appearance of the external genitalia is described on a scale of Stages 0 to 5 (Table 1). In this classification, Stage 0 is the normal external genitalia of a girl, whereas Stage 5 is the normal external genitalia of a boy.\(^8,10\)

The external masculinization score (EMS) is also used to describe the degree of genital ambiguity of a boy.\(^11\)

It can be hard to clinically differentiate a virilized girl from an undervirilized boy. The baby is more likely to be a boy if one or both gonads are palpable; however, the absence of palpable gonads does not exclude the male gender. In fact, external genitalia that are asymmetric and with only one gonad being palpable could result in either a normal or dysgenetic gonad or an ovotestis. On the other hand, if both gonads are palpable, the most likely diagnosis would be that of dysgenesis of the gonads (partial gonadal dysgenesis or PGD). Symmetric and palpable gonads would most likely result in partial androgen insensitivity syndrome (PAIS) or an androgen biosynthetic defect.\(^8,12\)

Positive Barr bodies indicate a high suspicion that the child is karyotypically a girl. The most common cause of the ambiguous genitalia may be caused by CAH. In this case, the baby must be kept under observation for two weeks because salt loss is apparent after the first week of life.\(^8\) If upon transabdominal ultrasound scan the uterus and ovaries are visualized, then it can also be confirmed that the child is a girl.\(^8\)

**TABLE 1** Prader Classification\(^{10}\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Appearance of Genitalia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal female</td>
</tr>
<tr>
<td>1</td>
<td>Female external genitalia with clitoromegaly</td>
</tr>
<tr>
<td>2</td>
<td>Clitoromegaly with partial labial fusion forming a funnel-shaped urogenital sinus</td>
</tr>
<tr>
<td>3</td>
<td>Increased phallic size with complete labioscrotal fusion forming a urogenital sinus with a single opening</td>
</tr>
<tr>
<td>4</td>
<td>Complete scrotal fusion with the opening of the urogenital sinus at the base of the phallus</td>
</tr>
<tr>
<td>5</td>
<td>Normal male</td>
</tr>
</tbody>
</table>

Surgical reconstruction carried out during infancy often needs revision at the time of puberty.\(^14\) Surgical interventions such as vaginoplasty or clitoral reduction or recession are recommended to take place in those individuals that show a highly virile intersex condition because of poor outcomes of early surgery.\(^13\) Individuals with Prader classifications of 3, 4, and 5 are candidates for surgery together with repair of common urogenital sinus when required.\(^5\) Because orgasmic function and erectile sensation may be impaired, it is important for the surgical procedure to be anatomically based to preserve erectile function and innervation of the clitoris to the glans, corpora, and hood.\(^4\) Furthermore, it is the functional outcome that must be emphasized rather than aesthetic factor brought about by surgery.\(^5\)

Medical doctors have reported unsatisfactory or poor cosmetic results in 28–46 percent of patients that underwent vaginoplasty, where 36–100 percent of women reported vaginal stenosis resulting in repeated surgery.\(^15\) This therefore leads to the frequent need of several revision surgeries in adolescence, even if the original procedure had been planned as a one-stage process.\(^4\)

In a recent study, feminizing genital reconstruction using the Gonzalez method (using the preputial flap and total urogenital mobilization) was carried out on six patients with ambiguous genitalia and CAH.\(^16\) Out of the six patients, three had good results, whereas the other three had long-term complications that included urethral fistula, distal vaginal stenosis, and urethral stricture. Distal vaginal stenosis was easily dilatable under general anesthesia. Furthermore, both patients and their parents were satisfied with the external genital appearance. However, on assessing sexual function of these patients, five of them reported sexual difficulties that included infrequent intercourse and anorgasmia.\(^16\)

In the case of hypospadias, surgical repair involves chordee correction, urethral reconstruction, and testosterone supplementation. In successful neophalloplasty, an erectile prosthesis is sometimes inserted, even though this has a higher rate of morbidity. In order to prevent malignancy in adulthood, the testes in patients with CAIS and PAIS raised as females should be removed and estrogen replacement therapy initiated. This removal also ensures the reduction of associated hernias with the presence of testes.\(^17\)

An intersex patient that is raised male should undergo surgery to remove the streak gonad using either open or laparoscopic techniques.\(^18\) In those patients raised female and with androgen biosynthetic defects, gonadectomy should take place before puberty.\(^5\)

**MEDICAL MANAGEMENT**

The treatment of intersex conditions requires hormonal therapy.\(^19\) Once gonadectomy has been carried out, it is
recommended to initiate hormone replacement therapy because of the risk of becoming deficient in sex steroids at a young age. Because hormone replacement therapy must be taken for a long period and has both benefits and risks, it is important to discuss this issue with the patient and his or her family in order to ensure fully informed consent. The aim of administration of hormones is to attempt to bring about normal pubertal maturation in order to induce secondary sexual characteristics, a pubertal growth spurt, and optimal bone mineralization.¹⁹

Different intersex conditions require different treatment as shown in Table 2.

**PSYCHOSOCIAL MANAGEMENT**

Genital ambiguity affects an individual’s psychological well-being. In fact, it is often assumed that surgical correction of the genital anatomy should normalize psychological and sexual behavior. Psychologists do not seem to share the latter point of view.²⁰ Part of the multidisciplinary team should involve psychosocial care provided by mental health staff or psychologists specialized in intersex conditions. These professionals can aid in decision making regarding gender assignment, timing of surgery, and sex hormone replacement. Genetic counseling should also be offered to parents and patients from the time of diagnosis because intersex conditions have lifelong implications and thus need psychological follow-up.⁸

Gender identity is one of the main problems encountered in intersex patients. The development of gender identity begins before the age of three; however, the earliest age at which this can be assessed still remains unclear.⁵ Children with intersex conditions are more prone to demonstrate atypical gender role behavior than in the general population. Yet again, this must not be used as an indicator for gender reassignment.⁵ Problems with gender identity result from reduced social competence and poorer body image as well as a greater chance of not being able to cope with depressed feelings. In cases where children and adolescents show a significant degree of gender dysphoria, psychological evaluation must be carried out to explore feelings about gender. Patients’ decisions must be respected and supported in the case of persistence from the patient’s side to change gender. Moreover, the desire to change gender later in life might also be caused by a decision that had been made by the parents when the patient was still a child in order to normalize him or her. However, reports have shown that this does not relieve parental anxiety and the intersex child is raised in a family environment that is characterized by shame, confusion, lack of discussion, and private distress.²¹

It is also important to note that some patients might have fears of rejection and may avoid building a relationship with a partner. In this case, the focus of psychological intervention should not only be on sexual function and activity but also on building interpersonal relationships. Referral for sex therapy may be needed. Repeated intrusive examinations of the genitalia may have a negative impact because the patient might feel ashamed.²² Moreover, medical interventions and negative sexual experiences may also be traumatic to the individual requiring the help of a mental health professional. This can lead to many social, familial, educational, and emotional factors that all have an influential effect on gender development. Thus, addressing the psychological well-being of patients with intersex conditions is a crucial factor in the management of such conditions.⁴

Some intersex conditions are inherited. These are most likely to be X-linked or autosomal recessive. In these cases, genetic counseling is particularly important, especially because families usually request the recurrence risk of intersex conditions. Hormonal determinations and genetic analysis of family members may be beneficial because phenotypic heterogeneity occurs in some conditions (e.g., PAIS).²³

**THE ROLE OF THE NEONATAL NURSE**

When the diagnosis of a congenital abnormality such as intersex is made, be it prenatally or at birth, parents experience

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**TABLE 2 ■ Therapeutic Management in Different Intersex Conditions**²³

<table>
<thead>
<tr>
<th>Intersex Condition</th>
<th>Aetiology</th>
<th>Hormone Level</th>
<th>Therapeutic Treatment</th>
</tr>
</thead>
</table>
| Congenital adrenal hyperplasia (CAH)   | Lack of 3β-hydroxysteroid dehydrogenase, 21β-hydroxylase, 11β-hydroxylase | ↓ cortisol. ↓ aldosterone ↑ androgens | a) Glucocorticoids  
b) Fluorocortisone (because of its moderate glucocorticoid potency and greater mineralocorticoid effect)  
c) Antandrogens (cyproterone) |
| Congenital androgen insensitivity syndrome (CAIS) | Androgen receptor insensitivity because of mutation in gene for androgen receptor located at Xq 11–12 | ↑ testosterone Estradiol concentration lower than normal females but higher than in a normal male | In females, after gonadectomy, estrogen replacement is recommended before puberty.  
In males, phallus is measured and photographed and then 25 mg testosterone IM every 4 weeks for up to 3 injections. An adequate response is an increase in stretching penile length into normal range. |
| Partial androgen insensitivity syndrome (PAIS) | Partial insensitivity to androgens | Same as CAIS | Same as CAIS with additional supraphysiologic doses of testosterone for optimal effect |
feelings of bereavement, even more so if the anomaly is part of a syndrome that eventually leads to the baby’s death. The neonatal nurse needs to bear in mind that each individual parent will react differently, depending on previous experiences and whether the condition was known antenatally.

Commonly, the parents’ initial reaction when told that their baby is suffering from a congenital abnormality is one of shock. Soon after, the parents may pass through a period of denial in which they cannot accept what the health care professional has just told them. Feelings of rejection toward their newborn may follow; some parents may also feel guilty at having such thoughts. Common questions that show that the parents are experiencing a feeling of guilt for giving birth to a baby with intersex include “Why did this happen to us?” “Why did it happen to our baby?” “What did we do wrong?” “Could we have done something to prevent it?” Therefore, the nursing team looking after the parents must realize that each parent will react in different ways at different times and in a variable order. Parents may also become hostile toward the health care professional who gave them the news and the nurse who is caring for them and their baby.

Gradually, as the diagnosis is established, the parents’ reactions tend to change again, for some becoming less acute, whereas for others, new emotions may emerge. Ideally, the explanation of the baby’s condition should be given by a senior pediatrician as part of a multidisciplinary team. The role of the nurse is to fill in any missing gaps in understanding and act as an advocate for the parents and family of a baby with special needs. Giving the parents a truthful assessment of the situation is almost always the best thing to do in the long term.

Every nurse has his or her own skills in understanding and counseling parents in distress. Nonetheless, some attitudes are known to be helpful, whereas others can be destructive. The empathic health professional will be the most supportive caregiver because he or she will understand what the parents are feeling, thus helping them to accept their current emotions. If the parents find adequate support, they will eventually find the strength to cope. Therefore, the neonatal nurse should be aware of the different organizations available locally and internationally that may be of support to these parents so to help them come to terms with the situation. Conversely, a nurse who fails to understand these parents, who is hurried and offers rapid solutions rather than listening to what the parents need to share, or who, worst of all, gives the impression that the parents are acting irrationally, may be the cause of additional burdens. Neonatal nurses caring for a baby with a congenital anomaly need to be supported themselves because such a situation places additional demands and stress on health care professionals.

The neonatal nurse has a pivotal role in helping the parents understand the embryologic problems related to their baby’s condition. Also, neonatal nurses are central in coordinating care, especially in managing the baby and observing for signs and symptoms of, for example, an electrolyte imbalance in CAH.

CONCLUSION

This review has outlined the important aspects in the management of intersex. Intersex conditions are hard to treat because they comprise a person’s gender identity, gender role behavior, sexual orientation, sexual functioning, and psychological adjustment. Decisions made by health care professionals and parents regarding the sex of an infant may not always be correct. It is therefore critical that correct management of these patients must be set up and rigidly followed in order to put the needs of the patient first in the hope of a better outcome.19

The techniques involved as well as the surgical and psychological effects on the patient must be evaluated in order to improve clinical practice.3 In this way, management of intersex may evolve in such a way to highlight the importance of managing patients with intersex, making health care professionals aware of their responsibilities and roles in such conditions.

REFERENCES


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“How much does my baby weigh?” and “How long is my baby?” are two of the most frequently asked questions in the delivery room. From that point on, growth is followed closely by parents and primary care providers alike. Anthropomorphic measurements (height/length, weight, head circumference) are obtained routinely and are compared with standardized references to follow the growth pattern compared with the norm.

Two of the most common tools used to describe growth in the neonatal and pediatric populations are percentiles and z-scores. Although both use normalized curves, z-scores are more sensitive and standardized across populations. This column will discuss and describe what z-scores are, how they are determined, how their use compares to and complements that of standardized growth curves, and how they are used to assess growth in neonatal and pediatric patients.

GROWTH CURVES

Intrauterine and postnatal growth curves are used in the neonatal intensive care unit (NICU). Intrauterine curves such as Fenton, Babson and Benda, Olsen, and Lubchenko are based on cross-sectional measurements from infants of varying gestational ages at birth. These charts vary as to the size of the database, the years in which the data was collected, and the geographic location and ethnicity of the sample, and do not take into account the initial weight loss after birth. They are also limited as to the length of time they can be used after birth, with some available for use as little as 40 days and others out to 168 days. Postnatal curves such as Dancis, Hall/Shaffer, Shaffer/Wright, Wright, Lair and Kennedy, and Ehrenkranz are generally based on a large sample of infants from a broad geographic area and usually reflect the initial weight loss after birth. They are limited, though, in that they were likely influenced by the medical and nutritional practices at the time the data was collected and that they do not show growth relative to that of the fetus.

WHAT IS A Z-SCORE?

A z-score is a statistical measure that describes how much a point deviates from the mean; that is, it quantifies the distance of a data point—measured in standard deviations—away from the mean of the data set (see sidebar).

There are z-score charts and spreadsheets available for various growth curves so that these numbers do not have to be generated each time; two examples are the Fenton, and Centers for Disease Control and Prevention (CDC) curves. The z-scores are derived from the data sets used to generate the growth curves, so a z-score chart is applicable only to its particular curve. For example, the Fenton z-score spread sheet would not be appropriate to use with the CDC curves because they describe different populations and are based on different measured values.

In nutritional assessment, z-scores are not only used to compare a population but also to compare progress in a particular patient over time, with a more positive z-score typically indicating an improvement in status. The most commonly used cutoff to define malnutrition with z-scores is two standard deviations below the mean, regardless of the indicator used (weight, length, or head circumference).

USING Z-SCORES IN THE NICU

Z-scores, being numerical values, are more sensitive than percentiles and allow a more precise assessment of growth as well as allowing for a description of growth outside of the 3rd and 97th percentiles. Thus, z-scores can pick up subtle changes from week to week and give a better overall picture of growth than looking at daily weight changes, for example. Consequently, there can be a fall in the z-score for weight in spite of an average gain of 20–25 g/day. In the NICU at the time of discharge, many infants have a z-score for weight two standard deviations below their birth score; that is, birth z-score.

Determining a Z-Score

A z-score is determined by subtracting the mean of the population from the actual value of the individual and dividing by the standard deviation of the population.

\[ z = \frac{(a - b)}{c} \]

Where \( a \) is the actual measured value (e.g., weight); \( b \) is the mean of the population; and \( c \) is the standard deviation of the population.

A z-score is negative when the actual score is below the mean and positive when it is above the mean. Because it is impossible to measure every individual to determine the true population standard deviation, a random sample allows for an estimation of the deviation. Unless there is access to all the raw data used to determine the curve, the practitioner would be unable to derive these numbers.

Disclosure

The author discloses no relevant financial interest or affiliations with any commercial interests.
discharge $z$-score $\leq -2$; this is not a desirable outcome as it reflects growth failure.\textsuperscript{16} By monitoring $z$-scores throughout admission, nutrients delivered can be adjusted as needed to maintain growth closer to the birth score.

Decreased morbidity and mortality have been associated with normal birth weight $z$-scores and with catch-up to birth scores by two years of age.\textsuperscript{16,17} When using the $z$-score, the goal is to achieve and maintain growth at or above the birth $z$-score in almost every case. This does not mean that every infant can or should achieve the 50th percentile for growth. It does mean that with an infant born at the 10th percentile, the goal is to achieve and maintain growth along the 10th percentile. It is important to note that $z$-scores do not differentiate between the causes of weight change such as changes in fluid status, lean body mass, or adiposity. Therefore, continuing to analyze weight for length is important in identifying both malnutrition and overnutrition. As with any anthropomorphic measure, the information that can be derived is only as good as the information received; inaccurate measures will not provide accurate $z$-scores.

**PRACTICAL USE OF THE Z-SCORE**

An example of how the $z$-score can be a more sensitive indicator of growth velocity changes in a 24-week gestation male infant can be seen in Table 1 and Figures 1 and 2. Both Table 1 and Figure 1 in this example are based on the Fenton growth curve demonstrating weight measures at various weeks gestation compared with the $z$-score for that weight at that age and the percentile at which the weight would plot.

**TABLE 1** Data of a 24-Week Gestation, 690-Gram Infant

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Measure (Weight in Grams)</th>
<th>Z-Score</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>690</td>
<td>0.16</td>
<td>56</td>
</tr>
<tr>
<td>25</td>
<td>725</td>
<td>-0.30</td>
<td>38</td>
</tr>
<tr>
<td>27</td>
<td>940</td>
<td>-0.25</td>
<td>40</td>
</tr>
<tr>
<td>28</td>
<td>1,100</td>
<td>-0.11</td>
<td>46</td>
</tr>
<tr>
<td>29</td>
<td>1,200</td>
<td>-0.26</td>
<td>40</td>
</tr>
<tr>
<td>30</td>
<td>1,375</td>
<td>-0.21</td>
<td>42</td>
</tr>
<tr>
<td>31</td>
<td>1,520</td>
<td>-0.32</td>
<td>38</td>
</tr>
<tr>
<td>32</td>
<td>1,670</td>
<td>-0.45</td>
<td>33</td>
</tr>
<tr>
<td>33</td>
<td>1,750</td>
<td>-0.78</td>
<td>22</td>
</tr>
<tr>
<td>34</td>
<td>1,970</td>
<td>-0.79</td>
<td>22</td>
</tr>
<tr>
<td>35</td>
<td>2,360</td>
<td>-0.43</td>
<td>33</td>
</tr>
<tr>
<td>36</td>
<td>2,175</td>
<td>-1.37</td>
<td>9</td>
</tr>
<tr>
<td>37</td>
<td>2,370</td>
<td>-1.32</td>
<td>9</td>
</tr>
<tr>
<td>38</td>
<td>2,390</td>
<td>-1.64</td>
<td>5</td>
</tr>
<tr>
<td>42</td>
<td>3,590</td>
<td>-0.60</td>
<td>27</td>
</tr>
<tr>
<td>43</td>
<td>3,745</td>
<td>-0.61</td>
<td>27</td>
</tr>
<tr>
<td>44</td>
<td>3,890</td>
<td>-0.64</td>
<td>26</td>
</tr>
<tr>
<td>45</td>
<td>4,185</td>
<td>-0.44</td>
<td>33</td>
</tr>
</tbody>
</table>

*Note:* Data are based on the Fenton growth curve demonstrating weight measures at various weeks gestation compared with the $z$-score for that weight at that age and the percentile at which the weight would plot.

**FIGURE 1** A graph of the weights for the 24-week gestation male infant presented in Table 1 as plotted on the Fenton growth curve. Note that he received significant fluid on day of life 2 as reflected by a weight plot at the 90th percentile.
data and illustrate weight changes over time. The patient is a 24-week gestation male with a birth weight of 690 g. Data are available through 45-weeks gestational age, by which time he weighs 4,185 g. His birth data as shown in both the \( z \)-score chart and the Fenton weight curve place him at the 56th percentile. Note that he received significant fluid on day of life 2 as reflected by a weight plot at the 90th percentile. On the Fenton growth curve, for the time period through 31 weeks gestation, he appears to be growing at the 50th percentile, and most practitioners would say he is following his curve. The \( z \)-score chart, however, shows a decrease in the \( z \)-score over this same period from his birth value of 0.16 to a value of −0.32, which is almost one half of a standard deviation difference. By week 44, he has demonstrated some catch-up growth from his low point but is now almost a full standard deviation away from where he began. If \( z \)-scores were not being followed and nutrition wasn’t adjusted to maintain those \( z \)-scores, he would likely have continued to fall further behind in his growth.

**SUMMARY**

In conclusion, growth curves do not always visually capture the distance that an infant’s growth is from the birth percentile. \( Z \)-scores offer a more precise assessment of growth by assigning a numerical description and a value for the distance from the goal birth weight score and percentile. The \( z \)-score, therefore, in conjunction with the growth curve, is a valuable tool in the neonatal population in particular, where growth is associated with developmental and medical outcomes.

**REFERENCES**


**About the Author**

Rita A. Chrivia, RD, CSP, LD received her BS in Dietetics at the University of California, Davis and completed her qualifying experience for dietetic registration at Harborview Medical Center, Seattle, Washington. She is licensed as a dietitian in the state of Missouri and is a Board Certified Specialist in Pediatric Nutrition through the Academy of Nutrition and Dietetics (formerly the American Dietetic Association). Rita has practiced for the past 14 years as a neonatal dietitian in the Level III NICU at SSM Cardinal Glennon Children’s Medical Center, St. Louis, Missouri where she also serves as dietitian for the nursery follow up clinic. Rita has presented lectures throughout the Midwest to physicians, nurse practitioners, nurses, dietitians, and pharmacists on neonatal and infant nutrition.

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Antimicrobial treatment is a mainstay therapy in the neonatal intensive care unit (NICU). Given the lack of specificity for clinical symptoms of infection in the newborn and the overwhelming impact of infection with rapid multisystem dissemination, NICU providers tend to treat early while awaiting laboratory results. With the high vulnerability of our special population to a variety of potential infecting microbes, a combination of antibiotics is preferred for initial treatment. The selection of these antibiotics is based on the known or presumed environment of exposure. If the newborn is within a week of birth, we can reasonably expect the likely environment of exposure is the community or the mother. If the newborn is older or has undergone numerous procedures, we can presume the exposure is more likely to be hospital-based.

The community–environment exposure is less likely to have pathogens genetically altered to be resistant, whereas the hospital is more likely to harbor resistant pathogens. The selection of antibiotics is determined by epidemiologic surveillance profiles from historical microbe cultures, and we are usually successful in choosing an antibiotic that is an effective first-line treatment. Unfortunately, as antibiotic use has become more common, organisms in the hospital and even in the community are becoming resistant to antimicrobial treatments. The purpose of this article is to review the basis of antimicrobial resistance and its relevance in the NICU to thereby encourage appropriate limitations on the selection and course of antimicrobials in the treatment of neonates.

DEFINITION OF ANTIBIOTIC RESISTANCE

Antibiotic resistance occurs when microorganisms are able to survive exposure to an antibiotic or antimicrobial agent. Most antibiotic resistance occurs from genetic mutation or alteration in the microbe. The gene mutations can be transferred between bacteria by conjugation, transduction, or transformation. Genes for antibiotic resistance evolve as a product of natural selection. Many of these genes reside on plasmids within the bacterial cell, and plasmids can facilitate their transfer to neighboring bacteria. Bacteria with several resistance genes are multiresistant organisms. Resistance occurs as a result of duration of exposure to an antibiotic.

Historically, the first antibiotic used to treat infection in humans was penicillin, discovered serendipitously in 1929. It was approved for medical use in the 1940s to treat infections in soldiers during World War II. The first resistance to penicillin was reported in 1967 to Staphylococcus pneumoniae. By 1980, 3 to 5 percent of S. pneumoniae were penicillin-resistant, and by 1998, 34 percent were resistant.1 Kanamycin, one of the original first-line antibiotics in the NICU before early 1970s, has become clinically useless as a result of kanamycin-resistant bacteria prevalence. Therefore, the combination of penicillin and kanamycin has been replaced by ampicillin and gentamicin in the NICU.

Mechanisms of Antimicrobial Resistance in Bacteria

Antibiotics have different modes of action against different types of organisms. Therefore, the mechanism of resistance will differ depending on the target organism and the antibiotic characteristic mechanism of action. Several bacterial cell mechanisms have evolved that render the bacterium resistant to the antibiotic (Figure 1). These are outlined in Table 1.

The most common mechanism is enzymatic inactivation of the antibiotic, in which a cellular enzyme is genetically modified, rendering the cell unaffected by the antibiotic as occurs with deactivation of penicillin G with some penicillin-resistant bacteria by development of β-lactamases.5 Bacteria are capable of transferring their resistance to other bacteria by several mechanisms collectively referred to as horizontal gene transfer (HGT), including conjugation, transformation, and transduction.5 These mechanisms are illustrated in Figure 2.

Antimicrobial/Antibiotic Resistance in NICU

Although other intensive care areas have greater numbers of hospital acquired resistant organisms, the NICU is also susceptible and our fragile and immunocompromised patients are more vulnerable to fatal dissemination of pathogens.4 Early-onset infections in the NICU population are primarily caused by Group B streptococcus and Escherichia coli. Despite the potential consequences of intrapartum antibiotic exposure in the high-risk obstetric population, there is no confirming epidemiologic data indicating widespread resistance in these organisms.6 However, with regard to nosocomial, hospital-acquired infections, what emerges in other hospitalized populations may serve as a template of future infections in the NICU.4 In the NICU, the most common

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infecting organisms causing late-onset infections are *Staphylococcus epidermidis* and *Staphylococcus aureus*, which together are responsible for 60 to 70 percent of infections. Gram-negative organisms, namely bacilli, such as *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, and *Serratia marcescens*, cause about 15 to 20 percent of late-onset NICU infections, and *Candida* species cause approximately 10 percent of late onset NICU infections.4,7

Cases of antibiotic resistance have been reported in all of the hospital-acquired pathogens in the NICU. Epidemiologic references are lacking in the literature, but case reports and single-center reports describe outbreaks rather than endemic infections.8–10 Infants in the NICU are at risk of becoming colonized with antibiotic-resistant organisms (ARO); these infants may become infected or become the source or reservoir of colonization and infection in other NICU infants.11

The most widespread ARO in the NICU is *S. epidermidis*, a coagulase-negative staphylococcus (CONS). *S. epidermidis* is commonly resistant to oxacillin, but additional CONS species have become multidrug resistant to gentamicin, rifampin, erythromycin, and clindamycin, limiting the potential for treatment options for synergy using two antibiotics.12 Limited sensitivity to vancomycin with *Staphylococcus warneri*, found on washed hands of NICU nurses, has also been reported and has been attributed to increasing empiric use of vancomycin.13

The source reservoirs of hospital-acquired methicillin-resistant *S. aureus* (MRSA) in the NICU has expanded as community-acquired MRSA has been introduced into the hospital milieu from staff, family, visitors, and even maternal anovaginal colonization in pregnancy.10,14 Although many MRSA found in the NICU are becoming community acquired (CA MRSA) rather than exclusively hospital acquired (HA MRSA), the HA MRSA is more often multidrug resistant, but the susceptibility varies regionally. The gram-positive cocci that tends to be vancomycin-resistant is most often vancomycin-resistant and ampicillin-resistant enterococci, which is found infrequently in the NICU. Vancomycin-resistant *S. epidermidis* and *S. aureus* have yet to be reported in the NICU, but the use of vancomycin prophylaxis in the NICU increases the potential for *S. aureus* and *S. epidermidis* to develop intermediate sensitivity to vancomycin and ultimately vancomycin-resistant. This potential is especially of concern in the NICU where central line use is common and *S. epidermidis* infections are frequent.15

![Bacteria resistance mechanisms.](image)

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**TABLE 1** Mechanisms of Antibiotic Resistance

<table>
<thead>
<tr>
<th>Reference</th>
<th>Mechanics of Resistance</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opal &amp; Mendeiros3</td>
<td>Chemically modify the antibiotic</td>
<td>β-Lactamase and Chloramphenicol</td>
</tr>
<tr>
<td>Opal &amp; Mendeiros3</td>
<td>Inactivate antibiotic by physical removal preventing drug accumulation via efflux pump</td>
<td>Fluoroquinolones and tetracycline</td>
</tr>
<tr>
<td>Patel &amp; Saiman4, Opal &amp; Menderios3</td>
<td>Modify the porins (protein channels) or portals of cell entry preventing drug entrance into the bacterial cell</td>
<td>Cephalosporins, imipenem, and carbencillin</td>
</tr>
<tr>
<td>Patel &amp; Saiman4</td>
<td>Modify the target site of antibiotic attachment for entry into the cell so the cell is not recognized by the antibiotic</td>
<td>Methicillin resistant <em>Staphylococcus aureus</em> (MRSA)</td>
</tr>
</tbody>
</table>
Gram-negative bacilli (GNB) are also increasingly antibiotic resistant, including cases of multidrug resistance. The most common resistant GNB (such as *P. aeruginosa* and *Acinetobacter baumannii*) are resistant to piperacillin/tazobactam, cefazidime, and gentamicin. However, there is an increasing emergence of GNB, including *K. pneumoniae* and *E. coli* that are resistant to third-generation cephalosporins, including cefotaxime, ceftriaxone, and ceftazidime. These resistant organisms are referred to as extended-spectrum β-lactamase (ESBL)-producing pathogens because they hydrolyze extended-spectrum cephalosporins with oxyimino side chains, such as cefotaxime, ceftriaxone, and ceftazidime. The resistance conferred by ESBL-producing pathogens is caused by mutations that are plasmid encoded for transfer to other bacteria. In addition to the ESBL-producing pathogens, there are reports of *Klebsiella pneumoniae carbapenemases* (KPCs) that hydrolyze carbapenem agents, including imipenem and meropenem used as an alternative treatment for ESBL organisms. These organisms are rare and, like the GNB resistant to all first-line antibiotics, are seldom isolated from NICU patients.

Finally, the use of fluconazole prophylaxis has been promoted in the NICU to prevent the feared candidemia in very low birth weight premature infants. Fluconazole-resistant *Candida* species have yet to be confirmed in the NICU but have been reported in other populations indicating potential.

**Clinical Significance of Antimicrobial Resistant Pathogens in Critically Ill Neonates**

The public health burden of ARO, resulting in escalating morbidity and mortality, presents an increased challenge in the NICU. Sick and very low birth weight neonates have comorbidities that may mask infections, and yet they are opportunistic hosts for infection leading to overuse of unspecific antibiotics. Critically ill neonates have increased lengths of stay with long-term needs for central lines or other indwelling tubes and have impaired immune responses promoting empiric antimicrobial choices and delaying specific treatment. Identification of ARO infections are often difficult to detect in neonates and specific treatment may be newer, more costly, and unstudied or known toxic in newborns, limiting treatment options. For example, critical neonates developing multidrug resistant *A. baumannii*, which may cause ventilator associated pneumonia, will require extended treatment with nonspecific antibiotics, multiple cultures, and isolation and cohorting. This results in overall higher costs because of extended lengths of stay, increased staffing requirements, increased laboratory, respiratory department utilization, and often ineffective long-term antibiotic treatment that in the end may not prevent compromising morbidity or mortality.

**PREVENTION OF ANTIBIOTIC RESISTANCE**

Overuse of antibiotics is one of the obvious causes of antimicrobial resistance, but it is not the only one, and reducing antibiotic use is not the only solution. Although resistance underscores the need for new antibiotic development, fewer pharmaceutical companies are interested in pursuing antibiotic development. The attraction for most pharmaceuticals to invest in development is limited by cost and prolonged safety evaluation with likelihood for short-term use given the tendency for induced resistance.

Prevention requires the analysis of causes of infection, including breakdown in measures intended to minimize the spread of infecting pathogens. Failure in techniques such as effective hand washing of healthcare workers and breaks in isolation precautions increase transmission of infectious diseases among hospitalized patients. Reduced exposure to infectious diseases in the NICU patient will protect against hospital-acquired infections and minimize the overuse of antibiotics, encouraging the cloning of resistant organisms. Furthermore,
Judicious use of antibiotics is essential, especially in the NICU where nearly 50 percent of patients receive antibiotics. The extensive use of penicillin agents prenatally and postnataelly promotes the development of MRSA, and use of third-generation cephalosporin agents in the NICU is associated with ESBL Gram-negative bacilli and the potential for resistant invasive candidiasis. Antibiotic combinations are commonly used and effective in the prophylactic management of suspected sepsis in the neonate; however, selection of antibiotic combinations requires careful scrutiny and can be deleterious. This was evidenced by the reported risk of mortality with the empiric selection of two broad-spectrum antibiotics—ampicillin and cefotaxime—during the first three days of life as opposed to the empiric antibiotic treatment preference by selecting narrow-spectrum antibiotics or reducing broad-spectrum antibiotic use has been shown to reduce outbreaks of resistant nosocomial organisms.

According to the Infectious Disease Society of America, antibiotic stewardship is a means of reducing antibiotic resistance and thereby improving the quality of care. Programs of antibiotic stewardship have made their way into many adult programs but have not been common in pediatric settings. Nevertheless, the Centers for Disease Control and Prevention has developed principles for judicious antibiotic use that are reasonably applicable to the NICU. These principles consist of four concepts referred to as “Get Smart in Healthcare Settings: Know When Antibiotics Work.” The concepts include timely antibiotic management; appropriate selection, administration, and de-escalation of antibiotics; access to infectious disease expertise; and improved data monitoring and transparency. These concepts are relevant to the NICU. Examples of antibiotic stewardship have been developed by Patel and Saiman and are summarized in Table 2. Despite confirmed emergence of associated resistance, prevention of ARO in the NICU should include careful use of prophylactic antimicrobials. In the NICU, proposals to use prophylactic antimicrobials in an effort to prevent or reduce infections have been inadequate infection control techniques risk the potential exposure of resistant organisms from the healthcare provider to the susceptible patient. Community-acquired infections are readily spread in day care centers, long-term nursing care facilities, military bases, and prisons. In addition, the inappropriate use of antibiotics in animal husbandry to promote the growth of livestock or prevent or treat individual diseases has led to Gram-negative resistance in humans, including resistant Salmonella, Campylobacter, and E. coli 0157. For example, the distribution of fluoroquinolone enrofloxacin in the water or feed given to flocks of chickens and turkeys to treat respiratory infections and promote growth of the birds has led to human-acquired drug resistant Campylobacter, Salmonella, Enterococcus, and E. coli.

TABLE 2 ■ Centers for Disease Control and Prevention Principles for Judicious Antibiotic Use: Relevant NICU Examples

<table>
<thead>
<tr>
<th>“Get Smart” Principles</th>
<th>Examples for the NICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timely antibiotic management</td>
<td>Use biomarkers such as C-reactive protein (CRP) to guide initiation of therapy</td>
</tr>
<tr>
<td>Accurately identify patients who need antibiotic therapy</td>
<td>Obtain simultaneous central venous catheter (CVC) and peripheral blood cultures when possible or obtain two peripheral blood cultures</td>
</tr>
<tr>
<td>Obtain appropriate cultures before start of antibiotics</td>
<td>Obtain sufficient blood culture volumes, &gt; 0.5mL</td>
</tr>
<tr>
<td>Administer antibiotics promptly</td>
<td>Change vancomycin to oxacillin once infection with methicillin-sensitive S. aureus (MSSA) is determined</td>
</tr>
<tr>
<td>Appropriate selection, administration, and de-escalation of therapy</td>
<td>Aim for higher vancomycin troughs (15–20 mcg/mL) for suspected meningitis</td>
</tr>
<tr>
<td>Make empiric choices based on local antibiograms (laboratory confirmed sensitivity of bacteria to an antibiotic)</td>
<td>Discontinue postoperative prophylaxis after 48 hours</td>
</tr>
<tr>
<td>Do not give therapy with overlapping activity</td>
<td>Avoid redundant anaerobic spectrum coverage (e.g., metronidazole and piperacillin/tazobactam)</td>
</tr>
<tr>
<td>Give the right dose and at right interval</td>
<td>Appropriate addition of synergistic antibiotic to optimize effectiveness of treatment and minimize resistance</td>
</tr>
<tr>
<td>Stop therapy promptly if indicated by culture results</td>
<td>Develop an antimicrobial stewardship team incorporating neonatology, clinical pharmacy, hospital epidemiology infectious diseases, and nursing services</td>
</tr>
<tr>
<td>Review and adjust antibiotics at all transitions of care</td>
<td>Obtain infectious diseases consultations</td>
</tr>
<tr>
<td>Monitor for toxicity and adjust therapy accordingly</td>
<td>Provide NICU-specific antibiograms for common pathogens</td>
</tr>
<tr>
<td>Access to expertise at point of care</td>
<td>Measure and provide feedback data on antibiotic prescribing to neonotologists, nurse practitioners, and residents in training.</td>
</tr>
<tr>
<td>Develop and make available expertise in antibiotic use</td>
<td></td>
</tr>
<tr>
<td>Ensure that expertise is available to all physicians at the point of care</td>
<td></td>
</tr>
<tr>
<td>Improved data monitoring and transparency</td>
<td></td>
</tr>
<tr>
<td>Monitor and feedback data regarding antibiotic use and adverse events</td>
<td></td>
</tr>
<tr>
<td>Make data visible to interdisciplinary care team</td>
<td></td>
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</tbody>
</table>

Source: Modified from CDC; Patel & Saiman, p. 555.
made (e.g., prophylactic fluconazole in very low birth weight infants to prevent candidiasis, prophylactic low dose administration, and equipment impregnated or intermittent vancomycin to prevent central line infections). The supporting literature for fluconazole prophylaxis reports inconsistent treatment plans, and reviews recommend consideration of broad prophylaxis regimes be limited to centers and regions with demonstrated rates of disease. The use of vancomycin prophylaxis is less widely promoted, and caution must be considered as any widespread and extended use of an antibiotic increases the risk of resistance.4,20,37,38

Scrupulous attention to infection control guidelines is essential to prevent infections, both in health care institutions and vulnerable group settings such as schools, day cares, military bases, and prisons. Strict compliance to infection control guidelines is the backbone of infection prevention in the NICU and should be combined with multidisciplinary antibiotic stewardship for comprehensive prevention of antibiotic resistance.

REFERENCES


About the Author

Patricia J. Johnson, DNP, MPH, RN, NNP, is a practicing neonatal nurse practitioner in the Phoenix metropolitan area. She piloted the NNP role during her master’s program in nursing in the early 1970s and subsequently established NNP teams in the Midwest and Southwest. She also taught and coordinated one of the early NNP certificate programs in Arizona. She has been an active volunteer with neonatal nursing organizations and is a recognized expert in the delivery of neonatal care by the advanced practice nurse. She received a doctorate in nursing practice from Arizona State University in 2008.

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Magnesium Sulfate (MgSO₄) has been widely used in the perinatal arena for many decades. It has been used for tocolysis in the U.S. for more than 60 years. Estimations of MgSO₄ use for preterm labor (less than 34 weeks of gestation) run as high as 80 percent. Magnesium sulfate is a smooth, skeletal, and cardiac muscle depressant. It is used for preterm labor because of its potential to decrease muscle contractility by interfering with calcium uptake in the cells. Thousands of moms and babies have been exposed to this medication even though tocolysis remains an off-label use, the exact mechanism of action is not completely understood, and there are studies that show that it is ineffective for this indication, and no evidence that it improves perinatal outcomes. Additionally, it is a high alert medication because of its narrow therapeutic window and the risk of causing an immediate life-threatening condition (acute respiratory failure) if an error in administration occurs.

A second perinatal use for MgSO₄ is for treatment and prevention of eclampsia. Magnesium sulfate is commonly administered peripartum for seizure prophylaxis in pre-eclampsia. When administered parenterally in doses sufficient to produce hypermagnesemia (serum magnesium concentrations greater than 2.5 meq/dL), MgSO₄ reduces the seizure threshold by depressing central nervous system's irritability. Magnesium sulfate produces its anticonvulsant effects by slowing neuromuscular conduction, depressing the vasomotor center, and causing neuromuscular blockade of peripheral neuromuscular transmission.

Cerebral Palsy (CP) is the most common cause of severe motor disability in childhood, with an incidence of 1 in 323 children. Cerebral palsy is defined as permanent, nonprogressive abnormal gross and fine motor functioning that is attributed to disturbances that occurred in the developing fetal or infant brain. It is 80 times more common in premature infants born at less than 27 weeks of gestation. Preterm labor prediction and prevention still eludes us, but advances in neonatal care have increased the survival of very preterm infants; those at the greatest risk of CP.

CP extracts an enormous economic and emotional burden. The Centers for Disease Control and Prevention (CDC) estimates the lifetime costs including direct medical (physician visits, hospital stays, medications, assistive devices, long-term care), direct nonmedical (home and automobile modifications, special education), and indirect (productivity losses) for all people born with CP in 2000 to be $11.5 billion. The Role of Magnesium Sulfate in the Prevention of Cerebral Palsy

Patricia Scheans, MSN, NNP-BC

MAGNESIUM SULFATE AND CP: A REVIEW OF THE EVIDENCE

As with many practice changes, the process of developing a base of evidence for the use of MgSO₄ for neuroprotection in children was a lengthy one. Early observational reports in the 1990s described cohorts of children with and without CP born at very low birth weights (VLBWs). Those with CP were significantly less likely to have been exposed to MgSO₄ in utero during delivery than those without CP, suggesting MgSO₄ had a protective effect of some sort.

Subsequent observational studies both confirmed and refuted this finding. In all these studies, MgSO₄ was administered for either tocolysis or prevention of eclamptic seizures, not neuroprotection.

Over the next 10 years, researchers on several continents searched for the link between MgSO₄ and neuroprotection and reduction in CP. Several preterm, prenatal prophylactic MgSO₄ randomized controlled trials were conducted with favorable outcomes. Finally, the results of three meta-analyses show convincingly that MgSO₄ given prior to premature birth reduces the risk of CP by 30 percent without increasing the risk of infant death or significant perinatal morbidity. In 2007, a Cochrane review was completed and concluded antenatal MgSO₄ therapy as a neuroprotective agent for the preterm fetus could not be recommended based on the data available at the time. In the 2009 update of this review, with the weight of the new studies—including 6,145 babies of moms given MgSO₄ for preterm labor at less than 37 weeks—the authors conclude that the neuroprotective role of this drug had been established.

THEORIES ON THE MECHANISM OF ACTION

Although there is evidence that the use of MgSO₄ decreases the incidence and severity of CP, the mechanism of action is not entirely clear. Volpe describes several effects of magnesium including blocking of glutamate receptors and other excitatory neurotransmitters, decreasing cytokine production, antiplatelet properties, and antioxidant properties. These properties may decrease cell apoptosis. Volpe also describes increased uterine blood flow and a potential for improved cerebral blood flow in the neonate, which may help to prevent hypoxia and tissue damaging ischemia. It has also been postulated that MgSO₄ has an effect on...
<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Number of Mothers/Babies Inclusion Criteria</th>
<th>Type of Study/Treatment Regimen</th>
<th>Primary Outcomes or Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson &amp; Grether, 1995(^9)</td>
<td>155,636 children born 1983–1985</td>
<td>Retrospective case-control study</td>
<td>In utero exposure to MgSO(_4) was more frequent in controls than in children with CP, suggesting a protective effect of MgSO(_4) against CP in VLBW infants.</td>
</tr>
<tr>
<td>Paneth et al., 1997(^10)</td>
<td>1,105 infants &lt; 2,000 g Mothers received MgSO(_4) (no specific indication)</td>
<td>Retrospective chart review.</td>
<td>Reduction of neonatal brain lesions or CP in low birth not statistically supported in this study, although a modest reduction in risk of CP cannot be excluded; suggestion that magnesium may be associated with reduction in risk of CP in low birth weight infants who have late-onset brain lesions.</td>
</tr>
<tr>
<td>Grether et al., 2000(^11)</td>
<td>458 infants &lt; 1,500 g &amp; 1,500–1,999 g &lt; 33 weeks gestation 1988–1994 without preeclampsia, delivered &gt; 3 hours after admission</td>
<td>Retrospective case-control study</td>
<td>Magnesium exposure not associated with lower risk of cerebral palsy in infants born prematurely to women without preeclampsia.</td>
</tr>
<tr>
<td>Marret et al., 2008(^16)</td>
<td>573 women/688 fetuses &lt; 33 weeks expected to deliver within 24 hours</td>
<td>RCT 4 g loading dose only</td>
<td>Protective against “severe motor dysfunction or death” (OR 0.62, 95% CI 0.41–0.93).</td>
</tr>
<tr>
<td>Crowther et al., 2003(^13)</td>
<td>1,062 women; &lt; 30 weeks</td>
<td>RCT at 16 tertiary hospitals in Australia and New Zealand. 4 g loading dose/ 1 g/hr or placebo.</td>
<td>Magnesium group had lower rates of pediatric mortality (13.8% vs. 17.1%; RR: 0.83; 95% CI 0.64–1.09); CP (6.8% vs. 8.2%; RR: 0.83; 95% CI 0.54–1.27), combined outcome of death or CP (19.8% vs. 24.0%; RR: 0.83; 95% CI 0.66–1.03).</td>
</tr>
<tr>
<td>Rouse et al., 2008(^14)</td>
<td>2,241 mothers/2,444 fetuses; 24–31 weeks of gestation at risk for imminent delivery</td>
<td>Multicenter placebo controlled trial. 6 g loading dose/2 g/hr or placebo.</td>
<td>Moderate to severe CP significantly lower in the magnesium group (1.9% vs. 3.5%; “RR 0.55; 95% CI 0.32–0.95). Only &lt; 28 weeks of gestation showed a significant reduction in moderate or severe cerebral palsy.</td>
</tr>
<tr>
<td>Marret et al., 2007(^12)</td>
<td>Meta-analysis of 4 RCTs</td>
<td>Neuroprotective role not demonstrated</td>
<td></td>
</tr>
<tr>
<td>Doyle et al., 2009(^17)</td>
<td>6,145 fetuses MgSO(_4) for preterm labor under 37 weeks</td>
<td>Meta-analysis of 5 eligible RCTs</td>
<td>Neuroprotective role is now established. Neuroprotective against motor disorders in childhood for the preterm fetus.</td>
</tr>
<tr>
<td>Conde-Agudelo &amp; Romero, 2009(^18)</td>
<td>5,357 babies MgSO(_4) prior to 34 weeks</td>
<td>Meta-analysis</td>
<td>Significant reduction in risk of CP, moderate or severe CP and substantial gross motor dysfunction.</td>
</tr>
<tr>
<td>Costantline, Weiner; for Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, 2009(^15)</td>
<td>5,235 fetuses/infants</td>
<td>Meta-analysis of 5 RCTs</td>
<td>Significantly reduces risk of cerebral palsy without increasing risk of death.</td>
</tr>
</tbody>
</table>

Note: VLBW = very low birth weight; CP = cerebral palsy; MgSO\(_4\) = magnesium sulfate; RCT = randomized controlled trial.
the fetal inflammatory response syndrome (FIRS), which is a risk factor for perinatal mortality and morbidities such as bronchopulmonary dysplasia and brain injury.20

The same mechanism that alters cerebral blood flow may affect other body systems and perfusion. Side effects of magnesium exposure have been reported, which include an increase in patent ductus arteriosus and alterations in bowel blood flow. There were no significant differences between the exposed and unexposed groups in intestinal blood flow velocities, but trials that prospectively evaluate intestinal blood flow velocities are recommended to further study potential effects of antenatal MgSO4 on the gastrointestinal tract of preterm infants and resultant clinical outcomes such as necrotizing enterocolitis.21,22 Magnesium at levels of 8–12 mg/dL results in loss of deep tendon reflexes and muscle weakness—including the diaphragm and other respiratory muscles—leading to acute respiratory failure. Cardiac arrest may occur at levels of 20–35 mg/dL. Because fetal levels approximate maternal levels, fetal sedation and respiratory depression are potential side effects of therapy.2,5

Intravenous MgSO4 has an immediate onset and duration of 30 minutes. Nursing implications of this therapy include the monitoring of newborns for hypotension, hyporeflexia, and respiratory depression.23

In spite of the potential side effects of maternal MgSO4 therapy, Elliott et al. concluded in their review of the literature that there is no association of magnesium exposure in an appropriate dose with excess risk for neonatal death or morbidity.24

FURTHER STUDIES

Despite the current body of knowledge about MgSO4, questions remain. It is unclear which group of infants might benefit most from this therapy: patients 34 weeks and lower, 30 weeks and lower, or 28 weeks. The number needed to treat—the number of mothers that would need to be treated to prevent one child from developing CP—ranges from 15 (for infants at 22–27 weeks of gestation) to 333 (at 32–36 weeks).8 This would indicate that younger gestational ages derive more benefit from magnesium prophylaxis. Additional information is needed about strategies to reduce maternal side effects during administration of MgSO4 therapy, as well as the short- and long-term side effects in the neonate.

Further research is needed to delineate the most efficacious dose and timing of MgSO4 administration. The dosage of MgSO4 used in the trials ranged from loading doses of 4–6 g with maintenance infusion of 0–2 mg per hour. It may be possible to use a much smaller dose and therefore reduce side effects but this has not been investigated. Additional questions include whether maintenance dosing is needed or not and whether repeated treatment is indicated when preterm labor is arrested, but reoccurs at a later date. It appears that having the MgSO4 in the fetal blood stream at birth may be important, but more research is needed to determine how long it needs to be in the nervous system to accomplish the beneficial effect and the most effective levels to achieve. An additional question is whether in emergencies, or in order to spare side effects to the mother, MgSO4 could be administered directly to the baby at birth, as has been reported to be beneficial in term asphyxiated neonates.5,25

NEXT STEPS

In March 2011, the American College of Obstetrics and Gynecology (ACOG) issued a committee opinion on the use of MgSO4 for neonatal neuroprotection. The ACOG supports administration of a loading dose of MgSO4 followed by maintenance therapy when imminent delivery seems likely. Specific guidelines for dosing and gestational age are not specified; providers are encouraged to develop these based on the clinical trials. The committee report recommends MgSO4 to be given before an indicated preterm delivery or prior to a scheduled cesarean delivery. In order to decrease maternal exposure to the medication, the ACOG also recommends delaying administration until cervical ripening is achieved and delivery is expected within 24 hours. The ACOG does not support delaying emergent delivery for the administration of MgSO4. At this point, no retreatment is recommended. The MgSO4 is discontinued when the baby is delivered, unless it is indicated for a maternal condition such as preeclampsia. The dosing recommended by the ACOG is similar to those used for tocolysis and preeclampsia, but as discussed earlier, future studies may find other dosing regimens that are safer and more efficacious.26

INTERNATIONAL IMPLICATIONS

The potential benefits of MgSO4 extend worldwide. While we debate the perfect dose of MgSO4 to administer, nurses in other parts of the world may debate whether they can afford to administer it at all. Many of the trials were conducted in developed countries, but the pathophysiology of CP and its sequelae are universal to all countries. In developed countries, as well as in developing countries, resources for caring for children with disabilities may be limited and difficult to access and have consequences on resource allocation. It may be tempting to jump to the use of a panacea for a known problem, especially when it is easily accessible.

Magnesium sulfate itself is not expensive, but as a high-alert medication, it has a very narrow safe dosage range, and overdose can cause serious complications, including acute respiratory failure and cardiac arrest.4 It may be that in some under-resourced settings, there may not be people and equipment available to administer MgSO4 with the monitoring needed to prevent and manage the potential complications. In these situations, weighing the risks to the mother and benefits of neuroprotection of infants will have to occur, and resource allocation decisions made.27

SUMMARY

A commonly administered perinatal medication, MgSO4, has a new use that can affect families all over the world. Few effective strategies exist for prevention of preterm birth
and the associated complication of CP, so the emergence of MgSO₄ as an easily accessible, low-cost intervention is exciting. Questions remain about dosing, timing, side effects, and resource use, and research is needed to elucidate these points. The neonatal nurse needs to be abreast of practice changes in obstetrics that may affect her patients. The use of antenatal prophylactic MgSO₄ to reduce the emotional and economic burden of cerebral palsy is one of these practice changes.

REFERENCES


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