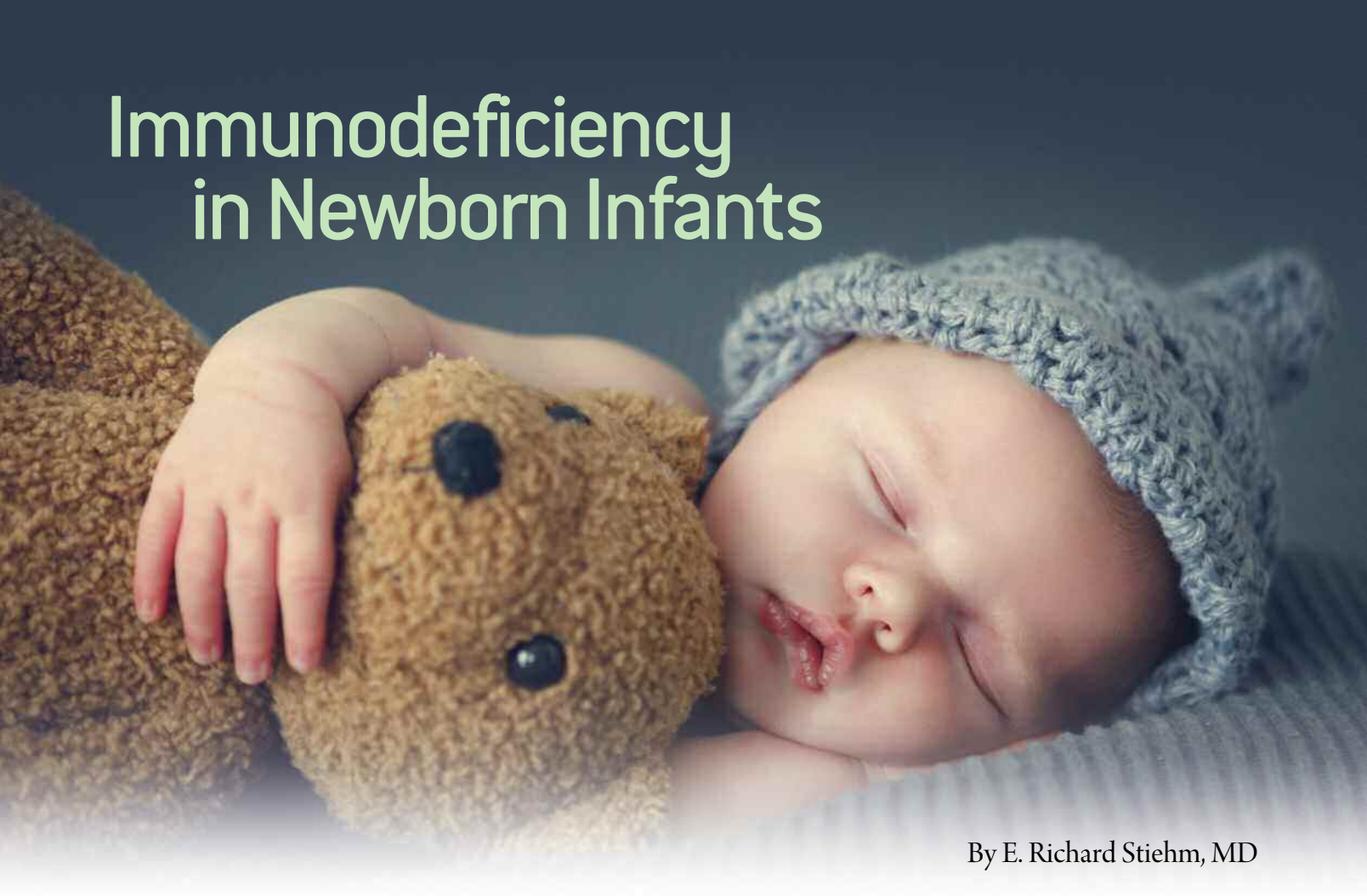
Immunodeficiency in Newborn Infants



By E. Richard Stiehm, MD

Four vignettes describe risk factors for immunodeficiency in newborns, as well as diagnoses and treatments.

THE NEWBORN EMERGES from the womb into an environment swarming with microbes, which quickly colonize the infant's upper airway, skin and gastrointestinal tract. Most newborns survive this invasion because of anatomic barriers, innate immunity and maternal transplacental antibodies. In addition, most U.S. newborns are cared for in clean environments, away from unwell persons and fed breast milk or sterile nutrition.

Newborns have an immune system that is anatomically intact, antigenically naïve and functionally compromised. Their B cells have a reduced capacity to make antibodies, their T cells are functionally weak and their phagocytic cells have poor mobility and a diminished marrow reserve. All of these weakened responses make infection a significant hazard.[1,2] But, if an infant has additional immune defects as a result of prematurity, maternal illness or medication, or heredity, the risk for infection is greatly enhanced. Thus, recognizing an immunodeficiency in newborns is crucial before infections ensue.

Factors that predispose newborns to an immunodeficiency are listed in Table 1. The most common risk factor is prematurity, in proportion to their degree of immaturity. Some of these are illustrated in the following vignettes.

Case 1: Tommy is a 32-week-old preemie with fever and poor feeding on day three

Tommy was born with a birth weight of 1,470 grams (3 pounds, 2 ounces) to a 35-year-old woman. Her fourth pregnancy was complicated by preeclampsia with hypertension and proteinuria (urine containing abnormal amount of protein), requiring antihypertensives during the last months of pregnancy. After a two-hour labor, Tommy was born vaginally with an Apgar score of 7. On the third day of life, he developed a fever and poor feeding. Physical exam showed tachypnea (rapid breathing) and abdominal distention.

Tommy's hemoglobin (Hb) was 14.7 g/dL, and white blood cell count (WBC) was 4,250/uL with 10 percent neutrophils, 80 percent lymphocytes, 6 percent monocytes and 4 percent eosinophils. His platelet count was 53,000/uL. Blood and urine cultures were positive for E. coli. Tommy was started on intravenous ampicillin and cefotaxime. He became afebrile after three days, but the neutropenia (low concentration of a kind of white blood cells) continued for a week with WBCs less than 1,000/uL. A bone marrow showed a maturation arrest. Genetic tests for congenital neutropenias were negative, as were tests for

neutrophil antibodies in the mother's and infant's serum.

Diagnosis: Neutropenia of infancy with sepsis secondary to maternal hypertension

Comment: Variable neutropenia occurs in 40 percent to 50 percent of babies born to hypertensive mothers.[3] Usually, the neutrophil count is less than 3,000 cells/uL but greater than 500 cells/uL. Neutropenia is more likely in low-birth weight infants and those with a fever or other evidence of infection. Most neutropenic infants remain well, and their neutrophil count normalizes in a few weeks. Antibiotic treatment is indicated if there is fever, chorioamnionitis (bacterial infection that occurs before or during labor) or prolonged rupture of membranes.

Other causes of neutropenia in infancy include drug reactions, isoimmune or autoimmune neutropenia, severe congenital neutropenia (Kostmann syndrome), viral infections, cyclic neutropenia and several primary immunodeficiencies, including reticular dysgenesis (rare and severe form of combined immunodeficiency) and the hyper IgM syndromes.[2,3]

Case 2: Sally is a 3-month-old infant with a heart murmur and cyanosis (bluish discoloration of the skin due to lack of oxygen)

Sally was the first child for an unrelated couple. The 29-year-old mother has diabetes and an alcohol problem. The infant weighed 3,500 grams (7 pounds, 7 ounces) after a 38-week pregnancy. The infant was slightly cyanotic and tachypneic with crying and feeding. A faint heart murmur was noted. A chest X-ray disclosed a boot-shaped heart, absent thymus and diminished lung markings. An echocardiogram disclosed Tetralogy of Fallot (congenital heart defect).

The Hb was 15.2 g/dL and WBC was 8,500/uL with 65 percent neutrophils, 15 percent lymphocytes, 15 percent monocytes and 5 percent eosinophils. Platelets were 26,000/uL, and electrolytes, calcium and phosphorus levels were normal.

An immunologic consultant noted tapered fingers, low-set ears and slight microcephaly (smaller than normal head). Flow cytometry showed CD3 total T cells of 820/uL, CD4 helper T cells of 620/uL, CD8 cytotoxic T cells of 130/uL, CD19 B cells of 250/uL and CD16/56 natural killer (NK) cells of 140/uL. A lymphoproliferative assay with the mitogen phytohemagglutinin (PHA) showed a stimulation index of 35 compared to a control of 80 (a low normal response). Chromosome fluorescent in situ hybridization analysis identified a 22q11 deletion in the patient but not in either parent.

Diagnosis: Partial DiGeorge syndrome with low but not absent T cells

Table 1. Prenatal Factors That Increase the Risk of Newborn Immunodeficiency

- Family history of immunodeficiency or early death
- Consanguinity (common blood ancestry)
- Ethnicity with a high incidence of primary immunodeficiency (e.g., severe combined immunodeficiency in Navajos, ataxia-telangiectasia in Amish and Bloom syndrome in Ashkenazi Jews)
- Maternal infection (chronic, acute, perinatal)
- Maternal hypertension
- Maternal autoimmune disease
- Maternal immunodeficiency
- Maternal immunosuppressive medications
- Maternal malnutrition or obesity
- Maternal use of alcohol, tobacco, opioids or street drugs

Comment: DiGeorge syndrome, sometimes called the CATCH-22 syndrome (Cardiac defects, Abnormal facies, Thymic aplasia, Cleft palate, Hypocalcemia/Hypoparathroidism and deletions of Chromosome 22[4]) is the second most common chromosome abnormality (after Down syndrome) with an incidence of one in 3,000 births. Diabetes and alcohol abuse during pregnancy may be risk factors.[3] Only a small percentage (5 percent) have a profound combined immunodeficiency — the complete DiGeorge syndrome. Sally was scheduled for corrective heart surgery after she had grown to 8 kg (17.6 pounds). Because of her low CD4 count, she was started on Bactrim prophylaxis, and given palizumab (Synagis) in the winter months. Serial immune studies were recommended after inactivated vaccines to measure her antibody function.

DiGeorge syndrome patients may develop autoimmunity, endocrinopathies, palatal and swallowing problems, and slow mental and physical development.[4] Selective IgA deficiency and specific antibody deficiency are not uncommon. All patients with cardiac outflow tract abnormalities should be studied for DiGeorge syndrome.

Case 3: Jorge is a 2-month-old ex-premature infant with fever and tachypnea

Jorge is a 2-month-old male born at 31 weeks with a birth weight of 1,460 grams (3.2 pounds). He was the first child for the 24-year-old mother who had two prior miscarriages associated with severe obesity and tobacco use. The infant

had moderate respiratory distress and was on a ventilator for two weeks with repeated monitoring of the blood gases. At 4 weeks old, he developed a fever and tachycardia (rapid heart rate).

Jorge's WBC was 18,000/uL with 72 percent neutrophils, 10 percent monocytes and 18 percent lymphocytes. Blood, throat and urine cultures were obtained. A chest X-ray showed a few streaky densities. IgG was 120 mg/dL (very low), IgM was 35 mg/dL, IgA was less than 5 mg/dL and ESR was 45 mm/hr. T and B subsets were low normal. The mother's IgG was 502 mg/dL (low normal), IgM was 102 mg/dL and IgA 30 was mg/dL. Complement activity (CH 50) was 75 units (normal for age).

Infants suspected of a primary immunodeficiency should be kept in protective isolation, or if at home, away from individuals (including siblings) who may transmit infection to them.

Because of the fever, low IgG and suggestive evidence of pneumonia, Jorge was started on antibiotics and intravenous immune globulin (IVIG) to maintain his IgG near 600 mg/dL. Bacterial and viral cultures were negative. He became afebrile after three days, and the chest X-ray infiltrates were resolving.

Diagnosis: Pneumonitis in a hypogammaglobulinemic premature

Comment: Jorge's low IgG was a result of four factors: 1) low maternal IgG with diminished transplacental IgG passage, 2) prematurity further reducing the IgG transplacental passage, 3) frequent blood draws and 4) presence of infection, which accelerates IgG catabolism. A primary antibody deficiency such as X-linked agammaglobulinemia was excluded by the presence of normal B cells. Prophylactic use of IVIG in prematures is not recommended unless the child is infected and/or profoundly neutropenic.

Case 4: Jason is a 3-month-old boy with sudden onset of diarrhea and vomiting

Jason was the first child of unrelated parents. He was born at term with a birth weight of 4,250 grams (9.37 pounds) and did well for the first months of life on breast feedings. He received all recommended vaccines starting at 2 months of age (hepatitis B, measles-mumps-rubella, Haemophilus influenzae, pneumococcal conjugate and oral rotavirus vaccines). Three weeks after these vaccines, he developed fever and diarrhea requiring hospitalization for dehydration. Physical exam disclosed oral thrush, dehydration and a distended abdomen.

Jason's hemoglobin was 14 g/dL and WBC was 9,300/uL with 72 percent granulocytes, 1 percent lymphocytes, 8 percent monocytes and 7 percent eosinophils. His platelet count was 152,000/uL, and his absolute lymphocyte count was 1,540/uL. Blood chemistries showed a mild acidosis. Jason's IgG was 205 mg/dL, IgM was 15 mg/dL and IgA was less than 3 mg/dL. Lymphocyte phenotyping showed CD3 T cells of 95/uL, CD4 of 52 /uL, CD8 of 32/uL, CD19 of 600/uL and CD 16/56 of 24/uL. Thus, he had a T-B+NK-severe combined immunodeficiency.[2,3] A stool culture was positive for rotavirus.

Jason was given intravenous fluids, IVIG therapy and Bactrim, and he improved after one week. The rotavirus was typed as a vaccine strain. He continued to shed virus in his stool until he underwent a successful stem cell transplant from unrelated human leukocyte antigen-matched cord blood.

Diagnosis: Rotavirus vaccine-induced diarrhea in severe combined immunodeficiency (SCID)

Comment: Jason was born in one of the few states that did not have newborn heel stick SCID screening. Thus, he received the live attenuated rotavirus vaccine. Because he could not develop an immune response to the vaccine, the virus proliferated in his gastrointestinal tract to cause diarrhea.[5]

Genetic analysis indicated that he had a new mutation of the IL-2 receptor gene on the X chromosome. This receptor is also termed the common gamma gene receptor since it is also the receptor for five other cytokines (IL-4, IL-7, IL-9, IL-15 and IL-21). The mother was not a carrier, so this was a new mutation. This is the most common mutation resulting in SCID.

One advantage of SCID testing and early diagnosis in infants is to avoid live virus and bacterial vaccines. There are several reports of post-vaccine diarrhea following rotavirus vaccine in SCID children but no fatalities.[5,6] Newborn screening also identifies severe lymphopenia in other disorders, including ataxia-telangiectasia, extreme prematurity, maternal immunosuppres-

sive therapy or in utero fluid extravasation into the chest or peritoneum.[7]

Discussion

Prebirth risk factors that increase the likelihood an infant will be immunodeficient are listed in Table 1. In the cases above, one woman had hypertension during pregnancy, another had diabetes and alcohol use and another had risk factors for premature delivery (smoking, obesity). One infant was at risk because he had a genetic defect and was born in a state where newborn SCID testing was not yet in place. These factors emphasize the importance of vigilance during pregnancy and good prenatal care.

Several clinical or laboratory features suggest immunodeficiency (Table 2). The most common is low birth weight and/or prematurity, particularly those with birth weight less than 1,500 grams (3.3 pounds). These infants have diminished opsonic activity (process by which bacteria are altered so that they are more readily and efficiently engulfed by phagocytes) due to low IgG and complement levels, and more compromised antibody and T cell immunity than term infants. Some of these infants have characteristic clinical features that warrant an immunologic evaluation. Others are recognized by newborn SCID screening or an abnormal routine laboratory test.

Initial laboratory studies begin with a complete blood count with differential. The presence of leukocytosis (a WBC less than 12,000 cells/uL) or leukopenia (a WBC less than 4,000 cells/uL) may be a primary or indicate infection or a hematologic illness. The absolute lymphocyte count (as determined by the differential and a WBC less than 2,500 cells/uL) suggests a T or B cell defect. Thrombocytopenia (platelets less than 100,000 cells/uL) occurs in certain immunodeficiencies (e.g., Wiskott-Aldrich syndrome) or viral infections. If lymphopenia is present, a chest X-ray should be done to look for the presence of a thymic gland; its absence suggests SCID or DiGeorge syndrome.

IgG determination is also recommended. A term infant's IgG level reflects the maternal IgG level, but the premature's IgG level is lower than that of the mother in proportion to the degree of immaturity. An elevated IgM (greater than 20 mg/dL) suggests congenital infection, and an elevated IgA suggests maternal-fetal bleed. A very low IgG level may result from extreme prematurity, IgG loss, maternal hypogammaglobulinemia or medication such as rituximab.

Additional screening tests may include a chemistry panel (electrolytes, blood urea nitrogen, creatinine, liver function, albumin, calcium and phosphorus), urinalysis and acute phase reactants (erythrocyte sedimentation rate and/or C-reactive protein). Infection evaluation includes imaging of suspected sites of infection, and cultures or polymerase chain reaction tests to identify an infectious agent.

Table 2. Clinical Features Suggestive of Newborn Immunodeficiency

- Infection at any site
- Failure to thrive
- Chronic diarrhea
- Heart or lung disease
- Mucosal abnormalities: thrush, mouth sores, ulcerations
- Rashes, pigmentary abnormalities, alopecia
- Petechiae, melena, bleeding
- Lymphadenopathy and/or hepatosplenomegaly
- Syndromic appearance (abnormal facies or habitus)
- Abdominal distention
- Neonatal surgery
- Delayed umbilical cord separation
- Infection following live vaccine

The first intermediate test recommended is lymphocyte subset enumeration by flow cytometry. This procedure measures the number of total T (CD3) cells, helper T (CD4) cells, cytotoxic T (CD8) cells, NK (CD8 /CD16) cells and B (CD19) cells, and will identify most patients with SCID or complete DiGeorge syndrome. If a T cell defect is suspected, their function is assessed by their ability to proliferate following activation by the mitogen PHA.

Infants suspected of a primary immunodeficiency should be kept in protective isolation, or if at home, away from individuals (including siblings) who may transmit infection to them. Advanced diagnostic tests should be done in conjunction with an immunologist.

If blood products are given, they should be irradiated, cytomegalovirus-negative and leukodepleted. Formulae should be sterile. Breast milk feedings are allowed unless there is a suspicion of maternal HIV infection. If IVIG infusions are planned, blood for IgG levels and antibody titers should be drawn prior to its administration.

If infants are suspected of immunodeficiency, live vaccines (e.g., rotavirus, BCG) should be avoided. Prophylactic antibiotics to prevent Pneumocystis are given to infants with severe T cell deficiency. In addition to IVIG therapy, palivizumab (Synagis) is given monthly in the winter to prevent respiratory

Table 3. Most Common Causes of Immunodeficiency Presenting at Birth or in Early Infancy[3]

Cause	Features
Humoral (antibody) deficiencies (IgG <400 mg/dL, severe <200 mg/dL)	
Prematurity	Severe infection in infants less than 1,500 grams
Physiologic hypogammaglobulinemia of infancy	Usually asymptomatic
Maternal hypogammaglobulinemia	Mother has untreated hypogammaglobulinemia or on immunosuppression causing low B cells
Immunoglobulin loss	Surgery, blood drawing, diarrhea, exudative skin lesions
Congenital agammaglobulinemias	Usually asymptomatic, IgG low after several months
Combined immunodeficiencies	Severe infection, IgG low after several months
Cellular (T cell) immunodeficiencies (CD3 T cells <500/microL, severe <200 cells/microL)	
Severe combined immunodeficiencies	Thrush, diarrhea, failure to thrive, Pneumocystis jirovecii pneumonia
DiGeorge syndrome	Outflow cardiac defects, typical facies, hypocalcemia, absent thymic shadow
Wiskott-Aldrich syndrome	Boys with thrombocytopenia, bleeding, eczema, respiratory infections
Hyperimmunoglobulin M syndromes	Respiratory infection (e.g., P. jirovecii pneumonia), neutropenia, elevated IgM hemolytic anemia
Mucocutaneous candidiasis	Early onset of thrush, esophagitis, skin infections, endocrinopathies
Neutropenia (granulocytes <500 cells/microL, severe <200 cells/L)	
Neutropenia due to maternal hypertension mild	Asymptomatic
Drug-induced neutropenia	Various drugs, usually reversible, asymptomatic
Benign neutropenia	Moderate, asymptomatic, normalizes with infection
Severe congenital neutropenia	Early onset of refractory infection
Cyclic neutropenia	Moderate or severe infections, often asymptomatic
Autoimmune or isoimmune neutropenia	Maternal neutropenia, neutrophil antibodies, familial
Neutropenia of infection	Develops during severe infection of the newborn, poor prognostic sign
Other phagocytic immunodeficiencies (T and B cell function normal, no neutropenia)	
Chronic granulomatous disease	Deep-seated infections, abscesses, pneumonia, moderate leukocytosis
Leukocyte adhesion deficiency	Marked leukocytosis, poor wound healing, delayed umbilical cord separation (>30 days)
Immunoregulatory disorders	
Mendelian susceptibility to mycobacterial diseases	Chronic Bacillus Calmette-Guérin (BCG) infection, environmental nontuberculous mycobacteria
Hemophagocytic lymphohistiocytosis (HLH)	Fever, vomiting, hepatosplenomegaly, seizures, liver failures
Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome	Boys with enteropathy/colitis, diabetes, dermatitis
Innate immune defects	
NF-kappa-B essential modulator (NEMO) defects	Severe infections, sparse hair
Toll-like receptor (TLR) defects	Severe bacterial infections (especially Staphylococcus and pneumococcus) with little or no fever or elevation of inflammatory markers
Congenital asplenia	Overwhelming sepsis, other abnormalities
Natural killer cell deficiencies	Severe herpes infections
Complement deficiencies	
Prematurity with opsonic defects	Neonatal sepsis in infants <1,500 grams
Regulatory protein deficiencies	Hemolytic-uremic syndrome, renal failure, thrombocytopenia

syncytial virus infections. Referral to a medical center for a definitive diagnosis, genetic testing and advanced therapy should be considered.

Some of the most common immunodeficiencies of the young infant are presented in Table 3.

Summary

The newborn immune system is anatomically intact, antigenically naïve and functionally deficient. Most newborns survive their entry into the external world thanks to innate immunity, passive maternal antibody, a clean environment and sterile feedings. Just a few infants have early onset of a primary or secondary immunodeficiency.

Factors predisposing immunodeficiency include maternal illness, infections and inherited factors. These infants may present with low birth weight, infection, hepatosplenomegaly (enlargement of both liver and spleen), skin abnormalities, failure to thrive or syndromic appearance. The most common causes of immunodeficiency are prematurity, neutropenia and DiGeorge syndrome. Less common disorders include variable T-cell defects, phagocytic disorders and innate immune defects.

Blood tests, cultures and genetic tests are available to pinpoint an exact diagnosis. Consultation with an immunologist for diagnosis and treatment is recommended. ■

E. RICHARD STIEHM, MD, is professor of pediatrics at the David Geffen School of Medicine at the University of California, Los Angeles.

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