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REVIEW PEDIATRICS

Primary immunodeficiency diseases in the newborn

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ABSTRACT

The normal neonate's immune system is anatomically completed but antigenically inexperienced and shows somewhat decreased role of a number of immunological pathways. Aside from anatomic characteristics (e.g., thin skin and mucosal barriers) of newborn, weakened pro-inflammatory and T-helper cell type 1 cytokine release and lessened cell-mediated immunity predispose the neonate more susceptible to all types of infections. Furthermore, many types of primary immunodeficiency diseases (PIDs) that present in neonatal period are potentially life threatening. However, most of the newborns stand this period without sickness due to complete innate immunity with other adaptive immune system mechanisms and transferred maternal immunoglobulin G. Besides unique immunity of the preterm and normal newborns; risk factors, clinical features, and laboratory evaluation of most common PIDs in newborn are told in this article. The range of PIDs is growing, and the diagnosis and management of these disorders continues to increase in complexity. The most common PID types of the newborn including antibody deficiencies, cellular/combined immunodeficiencies, phagocytic diseases, complement deficiencies, and innate immune system and other disorders are briefly mentioned here as well.

Keywords: Immunoglobulin; newborn; primary immunodeficiency disease.

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The premature and normal newborns are known to have a unique immunity. The innate and adaptive immune systems of neonates adapt as they become older. Many elements of the human immune system in healthy newborns are distinct since it is planned to make the evolution possible from intrauterine to exterior world [1]. Many types of primary immunodeficiency diseases (PIDs) appear in the neonatal period, but recognizing and managing PIDs in the newborns are challenging. The complexity is chiefly because of primitive neonatal immune system masking immune deficits and/or complicated analysis of clinical findings and laboratory assays. The early diagnosis of PIDs is vital for best possible therapy and better results before unwanted infections and succeeding tissue damages develop [2, 3].

The aim of this review is first to outline the differences and features of the neonatal immune system and discuss initial laboratory evaluation of most common types of PIDs seen as well as their management including hematopoietic stem cell transplantation (HSCT).

Unique Immunity of the Human Term and Preterm Newborns

The term neonate's immune system is anatomically complete, but antigenically inexperienced. It also shows somewhat decreased role of a number of immunological pathways, for example, pro-inflammatory/T-helper cell type 1 (Th1) cytokine release and cell-mediated immunity, aside from anatomic characteristics (e.g., thin mucosal barriers) [1].

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Premature newborns have immune defects, consistent with their degree of immaturity. Preterm newborn additionally demonstrates fragile skin, moderate-to-severe hypogammaglobulinemia, lower lymphocyte counts, plasma complement, and antimicrobial peptide levels [4–6].

These defects might make preterm and/or term neonates more susceptible to infections.[1] Thus, it can be hard to differentiate a premature infant with PID from an infant who is just premature, unless there is a positive family history of PID.

The neonatal innate immune system basically relies on antigen-presenting cells such as macrophages, granulocytes (chiefly neutrophils), natural killer (NK) cells, and complement system [7].

However, most newborn overcome this period without any illness because of their intact innate immunity, other adaptive immune defense mechanisms, and passive immunity through maternally transferred immunoglobulin G (IgG).

Physiologic Hypogammaglobulinemia of Infancy (PHI)

Maternal transferred IgG is existent at birth and disappears over several months, with a steady maturation of B cells to plasma cells able to synthesize immunoglobulins in the newborn. This may lead to PHI, with serum IgG levels <400 mg/dL, and lasts from roughly 3–6 months of age. In premature newborns, PHI occurs earlier, more intense and it persists longer [5, 8].

RISK FACTORS AND CLINICAL FEATURES OF PIDS IN NEWBORN

Some newborns inherit a genetic immune defect manifesting as PID at birth or early infancy. In the literature, more than 400 PIDs have been described so far. In a group, PIDs are relatively common, its prevalence, except for selective IgA deficiency, is ranging from 1/1.000 to 1/10.000 individuals worldwide [9]. During infancy, PIDs are more commonly seen in males than females (5:1). In adolescences, prevalence ratio of males/females (1:1) is equal [10, 11].

Risk Factors for Having PIDs

Factors mostly increasing risk of PID development in a neonate include: The most prognostic factor for a PID is a family history of immunodeficiency, confirmed or suspected, leading to early death or recurrent/chronic illness in one of more family members. Certain ethnic groups with founder mutations (e.g., severe combined immunodeficiency [SCID] in Navajos, ataxia-telangiectasia [AT] in Amish, and Bloom syndrome in Ashkenazi Jews) or nations/populations where there is a high incidence of consanguinity (Amish, Arab countries, etc.) have an increased incidence of PIDs [12].

Highlight key points

- Screening laboratory tests and preliminary evaluation should be done if one or more of the risk factors and/or clinical features for PIDs are available.
- Screening laboratory tests begin with DBS testing in neonates and preliminary evaluation starts evaluating CBC with differential.
- Lymphopenia is described as an absolute lymphocyte count <2.500 (3.000) cells/μL in infants.
- Most common PIDs of newborn are antibody deficiencies.
- HSCT is essential as much as early diagnosis.

Clinical Features in Newborns Suggestive of PIDs

A newborn at birth or during the 1st months of life might exhibit signs and symptoms, indicative of immunodeficiency, as mentioned below. These signs and symptoms are following: Syndromic look (abnormal facies); infection at any location; infection after live vaccines (e.g., rotavirus, Bacille Calmette-Guerin [BCG], oral polio, etc.); failure to thrive; chronic diarrhea; abdominal distention; lymphadenopathy and/or hepatosplenomegaly; lung or cardiac problems; mucosal diseases, for example, thrush, mouth sores, and ulcerations; skin rashes, pigmentary disorders, or alopecia; bleeding, petechiae, melena; and late separation of umbilical cord [13]. Warning signs of PIDs in the neonatal period are well-defined in a recent article [14].

INITIAL LABORATORY EVALUATION FOR PRIMARY IMMUNODEFICIENCIES OF NEWBORN

Screening laboratory tests and preliminary evaluation should be done if one or more of the risk factors and/or clinical features for PIDs are available. Screening laboratory tests begin with dried blood spot (DBS) testing in neonates and preliminary evaluation starts evaluating complete blood count (CBC) with differential and goes on more detailed tests.

Newborn Screening

T-cells are released from the neonatal thymus in a large amount, hence accounting for the high numbers of circulating lymphocytes in the neonatal blood. T-cells constitute nearly 50% of the lymphocytes in CBC of the 1st year of life. Circulating T-cells in the neonate's blood including heel stick blood can be predicted by determining T-cell receptor excision circles (TREC), a derivative of thymic production of freshly made T-cells [15].

TREC

Neonates with very low TREC should prompt evaluation of PIDs, but it may also result from a secondary cause of T-cell loss including egress of T-cells into third spaces, such as gastrointestinal disease, thymic removal following cardiac surgery, and neonatal leukemia. More than 35 diseases have been shown to be associated with low TREC counts [16]. A predictive value for T-cell lymphopenia of approximately 50% and it has sensitivity of nearly 100% for diagnosis of SCID and leaky SCID [17].

Preliminary Evaluation for Primary Immunodeficiencies in the Newborn

It starts with checking a CBC with differential. Leukopenia is described as a leukocyte count is <4.000 cells/μL. In mild neutropenia, neutrophil count is between 1.000 and 1.500 cells/μL; moderate neutropenia between 500 and 1.000 cells; and severe neutropenia comprises <500 cells. Neutropenia as deeper as 100 cells/μL could be life threatening. Neutropenia in the neonate can also be triggered by sepsis, necrotizing enterocolitis, maternal autoimmune disorders or medications, or primary phagocyte disorders [18].

Thrombocytopenia may be due to PID (e.g., in Wiskott-Aldrich syndrome [WAS]) or related with infections, for example, fungus or cytomegalovirus. Eosinophilia could be due to allergy, hyper-IgE syndrome, or immunodysregulation [10, 11].

Lymphopenia is described as an absolute lymphocyte count <2.500 (3.000) cells/μL in infants and suggests a T- and/or B-cell defect. T-, B-, and NK-cell identification by flow cytometry is requested if lymphopenia is observed on a CBC with differential, or if SCID is assumed even in the case of a normal lymphocyte count. Flow cytometric procedure enumerates CD3+ cells (T lymphocytes), CD3+CD4+ cells (T helper cells), CD3+CD8+ cells (T cytotoxic cells), CD19+ or CD20+ cells (B lymphocytes), and CD3-CD16+/56+ cells (NK cells). This test will discover most infants with SCID or complete DiGeorge syndrome and may give guidance as to the character of the T-cell-related defect [19, 20]. If a T-cell defect is thought, the preliminary test for T-cell function is a lymphocyte proliferation assay. Neonates normally demonstrate lymphoproliferation to non-specific stimuli, such as the mitogen phytohemagglutinin (PHA) or anti-CD3, but not to most other antigens [21].

Initial evaluation in the newborn also includes serum Ig levels. However, measuring quantitative Ig levels (IgG, IgA, IgM, and IgE) are less useful in neonate, because neonates produce only small amount of Igs and most of the IgG in early infancy is transferred IgG from the mothers [8, 10, 11, 22, 23].

MOST COMMON TYPES OF PIDS IN NEWBORN

Primary immunodeficiency disorders from almost all 10 subgroups, according to the last 2019 IUIS classification, could be seen in neonates [24]. Most common PIDs of newborn are also antibody deficiencies. When an immunodeficiency disorder is doubted, the next phase is to define whether the immunodeficiency is likely to be the physiologic abnormality of a newborn and/or heightened by additional factors causing a secondary/acquired causes (e.g., prematurity, blood loss due to phlebotomy, or surgery) or a PID due to an underlying genetic defect changing the immune system function.

Antibody Deficiencies

Antibody deficiency typically causes to frequent, often severe, upper and lower airway infections with encapsulated bacteria (e.g., *Streptococcus pneumoniae* and *Haemophilus influenzae*). Children usually are brought with recurrent otitis media, sinusitis, and pneumonia. Frequent accompanying findings in children include poor growth, failure to thrive, recurrent fevers, and chronic diarrhea [10, 25].

A neonate with hypogammaglobulinemia (serum IgG: <400 mg/dL, severe: <200 mg/dL) is infrequent, even regardless of low or absent B cells (Table 1). The most common reason is prematurity with exaggerated physiologic hypogammaglobulinemia. Another explanation may be a low maternal IgG level with lessened transplacental IgG passage [11, 25].

Table 1. Humoral (antibody) deficiencies in newborn (IgG: <400 mg/dL, severe: <200 mg/dL) [22]

Disorders	Clinical features
Prematurity	Severe infection in infants <1500 g (VLBW)
Physiologic hypogammaglobulinemia of infancy	Usually asymptomatic
Maternal hypogammaglobulinemia	Mother having hypogammaglobulinemia or immunosuppressive agent causing low B cells
Immunoglobulin loss	Blood sampling, diarrhea, surgery, exudative skin lesions
Congenital agammaglobulinemia	Usually asymptomatic, decreased IgG after several months
Combined immunodeficiencies	Severe infection, decreased IgG after several months

Infants including neonates with congenital agammaglobulinemia usually have low B cells and absent or very low IgM and IgA and do not become hypogammaglobulinemic until after the 3rd month of life, because of the existence of transplacental maternal IgG.

However, the prenatal diagnosis can be made in families with a history of agammaglobulinemia by genetic testing or assaying B cells on a fetal blood sample. The presence of a female fetus on ultrasound or chromosome analysis on prenatal blood makes X-linked agammaglobulinemia very unlikely. Routine kappa-deleting recombination excision circles testing at the time of birth is a planned screening/postnatal diagnostic method [26].

Agammaglobulinemia can be confirmed by an absence of B cells on flow cytometry. Documentation of a mutated Bruton's tyrosine kinase (BTK) gene confirms the most commonly seen X-linked agammaglobulinemia. If an infant is a girl or the BTK gene is normal, autosomal recessive (AR) agammaglobulinemia should be considered [19, 27].

Cellular/Combined Immunodeficiencies (with Syndromic Appearance or Dysmorphic Facial Features)

Infants with cellular immunodeficiency have deficiencies of both T-cell immunity and humoral (antibody) immunity (combined immunodeficiency: CID). They characteristically manifest in early infancy due to the defect in cellular immunity, especially those with a severe defect. They are caused by many diverse genetic defects and can be separated into severe and less severe CID groups.

Severe combined immunodeficiencies (SCIDs)

SCIDs are defined by profound, life-threatening severe defects in both cellular and antibody deficiency. These are deadly disorders that preventable with early detection and treatment. Their prevalence is 1 in 58,000 live births in the USA. More than 20 exclusive genes described thus far [28].

Most affected infants seem to be normal at birth, but develop severe infections with pathogens that include viruses, bacteria, and fungi within the first few months of life. Stark complications may happen after routine immunization with live virus vaccines. Related findings include chronic diarrhea and failure to thrive. Other motives to think SCID are lymphopenia on a routine CBC or a chest radiograph demonstrating no thymic shadow. A few infants are noticeable with graft-versus-host disease (GVHD) as a result of transplacental passage of alloreactive maternal T cells or unintentional delivery of viable lymphocytes from a blood transfusion. Manifestations of acute GVHD include maculopapular rash, vomiting, and diarrhea [29].

Inheritance of SCID is X-linked or AR. A family history of the disease is often negative because new (spontaneous) mutations are common. Early diagnosis can be made by prenatal tests of fetal blood, by neonatal TREC screening, or by recognition of early manifestations and confirmation by immunologic and genetic testing. Laboratory features of typical SCIDs on initial screening studies include profound lymphopenia with low T cells (<1.500 cells/μL) and absent antibody responses to vaccine antigens. Fewer than 300 T cells/ μL, <10% of normal PHA response, and/or maternal T-cell engraftment strongly suggest SCID [30]. Immunoglobulin synthesis is absent or minimal. Referral to a tertiary medical center for genetic analysis, HLA typing and HSCT are mandatory when SCID suspected.

Other (less severe) combined immunodeficiencies

The most common CIDs that present in the newborn period, or are identified by newborn screening, and their identifying features are as follows:

DiGeorge syndrome

The immunodeficiency spectrum can range from recurrent sinopulmonary infections to a SCID phenotype (complete DiGeorge). Associated features include conotruncal cardiac anomalies, hypoplastic thymus, hypocalcemia, and craniofacial abnormalities. It occurs rarely in individuals (<1.5%) with 22q11.2 deletion syndrome [31].

WAS

It is an X-linked disorder distinguished by thrombocytopenia, small platelets, early onset of eczema, and a CID. The patients manifest with petechiae, melena, bruising, bleeding after circumcision, or different infectious complications such as pneumocystis infection, meningitis, viral infections, or thrush [32].

X-linked hyperimmunoglobulin M syndrome (HIGM)

X-linked HIGM often manifests in the first few months of life with increased susceptibility to recurrent sinopulmonary infections, opportunistic infections, chronic diarrhea, and/or failure to thrive. CD40L deficiency accounts for 70% of X-linked HIGM [33].

Chronic mucocutaneous candidiasis

The patients typically present in the preschool years with chronic non-invasive Candida infections of the skin, nails, and mucous membranes, but a few patients manifest in the 1st months of life, especially those with familial candidiasis [34].

AT

Most patients are asymptomatic for the first several years, but a few patients have been detected on TREC screening, in spite of the existence of some T cells [35].

Immunoregulatory Disorders

Hemophagocytic lymphohistiocytosis (HLH) and immunodysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome are being come across in clinics during neonatal period.

HLH may manifest fever, vomiting, hepatosplenomegaly, seizures, and liver failure in clinic [36]. Genetic defects influencing the cytotoxic pathway of T and NK cells are positive in 45% of cases who present in neonatal period. There has also been mounting case reports associated with in utero onset leading to hydrops fetalis. Hepatic damage in neonatal HLH, including very early liver failure, is a commonly reported feature [37].

In boys with enteropathy/colitis, diabetes, dermatitis should make us think IPEX syndrome [38].

Phagocyte Defects

Infection spectrum of phagocytic disorders ranges from mild, recurrent skin infections to overwhelming, fatal, systemic infection. These patients are mostly vulnerable to bacterial (e.g., *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Nocardia asteroides*, and *Salmonella typhi*) and fungal (e.g., *Candida* and *Aspergillus species*) infections. Immune response to non-tuberculous mycobacteria (NTM) may also be atypical, especially in chronic granulomatous disease (CGD). Phagocytic diseases may manifest tissue and organ abscesses, abnormal wound healing, dermatitis/eczema, and stomatitis [39].

Congenital neutropenia(s)

They start roughly birth due to genetic defects causing primary bone marrow failure. Congenital neutropenic disorders include severe congenital neutropenia (<200 cells/μL; Kostmann syndrome), cyclic neutropenia, and Shwachman-Diamond syndrome. These individuals present with oropharyngeal problems, otitis media, respiratory infections, cellulitis, and staphylococcal and streptococcal skin infections. It could also be together with oculocutaneous hypopigmentation, pancreatic/bone marrow insufficiency, metabolic disease, as well as with other syndromic features (Table 2) [40].

Other non-neutropenic phagocytic immunodeficiencies (normal T-/B-cell function):

CGD

The X-linked type of CGD can present in infancy. It is a genetically heterogeneous disease known by life-threatening infection with specific bacteria and fungi causing to the formation of granulomata over the body. Deep-seated infections, abscesses, pneumonia, and moderate leukocytosis could be observed in clinic [41].

Leukocyte adhesion deficiency (LAD)

The LADs are a set of disorders described by recurrent bacterial infections and poor wound healing due to defects of neutrophil adhesion and movement.

- Begin at birth
- A typical characteristic is late separation of the umbilical cord (>30 days)
- Neutrophilia, often >100,000 cells/mL during infection (marked leukocytosis)
- Severe infections of the skin, respiratory tract, bowel, and perirectal area, with lack of pus formation at the site of infection
- If delayed separation of the umbilical cord is associated with normal leukocyte counts, it is very improbable to have LAD-1 for a neonate [42].

Table 2. Neutropenic disorders in newborn (neutrophils <500 cells/μL, severe: <200 cells/μL) [22]

Disorders	Clinical features
Neutropenia due to maternal mild hypertension	Asymptomatic
Drug-induced neutropenia	Different drugs, usually reversible, asymptomatic
Benign neutropenia	Moderate, asymptomatic, normalizes during infection
Severe congenital neutropenia	Refractory infection with early onset
Cyclic neutropenia	Asymptomatic moderate-severe infections
Autoimmune or isoimmune neutropenia	Familial, maternal neutropenia, neutrophil antibodies
Neutropenia due to infection	Develops during severe neonatal infection

Table 3. Innate immune defects in newborn [22]

Disorders	Clinical features
NF-kappa-B essential modulator defects	Severe infections, sparse hair, other anomalies
Toll-like receptor defects (MyD88 and IRAK4 deficiencies)	Severe bacterial infections (especially *Staphylococcus* and *Pneumococcus*) with little or no fever or increased inflammation markers
Congenital asplenia	Devastating sepsis, other abnormalities
Natural killer cell deficiencies	Severe herpes virus infections
Mendelian susceptibility to mycobacterial diseases	Chronic BCG infection, non-tuberculous mycobacteria

Other Defects in the Innate/Intrinsic Immune System

These contain NK cell deficiency syndromes and defects in cytokines and pro-inflammatory mediators released by innate immune cells, for example, Mendelian susceptibility to mycobacteria disease (MSMD) (Table 3).

Toll-like receptor defects (MyD88 and IRAK4 deficiencies, etc.)

Although these defects affect newborns, infants, and young children; invasive infections after the teenage years are not seen. Severe bacterial (especially *Staphylococcus* and *Pneumococcus*) infections occur with little or no fever or increase of inflammatory markers [25].

MSMD

It comprises defects in the interferon gamma-interleukin (IL)-12 and/or secondary pathways. It is characterized by early onset of potentially overwhelming infection with BCG as well as other NTM. BCG infections appear after weeks or months of BCG immunization. Infections with other intracellular pathogens (non-typhoid Salmonella) or viruses also could be occurred. Remarkable cutaneous lesions, abdominal tenderness, and hepatosplenomegaly are other manifestations for this defect [43].

Autoinflammatory Disorders

Neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular (CINCA) is an autoinflammatory syndrome that signifies the most severe type of the cryopyrin-associated periodic syndromes. It is related with a gain-of-function mutation in the NLRP3 (CIAS1) gene. It is the sensor molecule for the NLRP3 inflammasome, on which activated by infectious process or tissue damage, yields inflammation through the IL-1β and IL-18 secretion. Clinical features are seen very early in life. Although there are reports of the NOMID/CINCA manifesting at birth, diagnosis during neonatal period is uncommon. Symptoms of systemic inflammation comprise fever, urticarial eruption attributable to a neutrophilic infiltrate, inflammatory eye disease, chronic leptomeningitis, increased intracranial pressure, cochleitis, and bony overgrowth. Diagnosis is made through NLRP3 gene testing. Anakinra, an IL-1 receptor antagonist, is utilized lifelong as a therapy even though NLRP3 inhibitors are tried in murine experiments [44].

Deficiency of IL-1 receptor antagonist (DIRA) syndrome is due to AR mutations in the IL1RN gene pro-

gramming the IL-1 receptor antagonist that suppresses the pro-inflammatory cytokines such as IL-1α/-β. Uninhibited IL-1 signaling causes to excess of pro-inflammatory cytokine and chemokines. Cases having DIRA manifest postnatally in a couple of weeks and even it might happen in utero leading to fetal death. Manifestations of the DIRA consist of fetal distress, pustulosis rash, oral mucosal lesions, joint swelling, multifocal osteomyelitis, and periostitis characteristically involving the distal ribs and long bones. Gene testing for IL1RN helps to make the diagnosis. If untreated, DIRA cases may have a severe disease course resulting in death. Lifelong Anakinra therapy causes to quick improvement of symptoms and clinical remission [45].

Complement Deficiencies

Their prevalence is about 0.03% in population. Novel inherited complement deficiencies are infrequently defined in neonates without a family history of a complement deficiency. Screening for a complement defect is necessary in neonates with a positive family history and severe encapsulated bacterial infections, for example, streptococci, meningococci, or *H. influenzae* type B (43) [46].

- Classical pathway (C1q, C4, and C3) and alternative pathway (properdin, factor B) components are reduced in neonates. C3, C4, and total hemolytic complement (CH50) do not reach adult thresholds until 12–18 months of life.
- MBL stimulates the complement pathway in an antibody-dependent C1-independent manner. The serum levels of MBL, ficolins, and MBL-associated serum proteases are much lower in newborns and positively associated with gestational age and birthweight (44) [47].

Complement deficiencies cause decreased ability to lyse bacteria, defective chemotaxis, and lesser enrollment of leukocytes to infection sites and poorer phagocytic (opsonizing) capacity. Prematurity with opsonic defects may lead to neonatal sepsis in infants <1.500 g [47]. Certain regulatory complement protein deficiencies might result in hemolytic-uremic syndrome, renal failure, and thrombocytopenia [7, 48].

Bone Marrow Failures

Fanconi anemia and myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy syndrome present with anemia and intrauterine growth retardation during postnatal period [24].

Phenocopies of PIDs

Phenocopies are associated with somatic mutations such as cryopyrinopathy (CINCA/NOMID-like syndrome) and hypereosinophilic syndrome due to somatic mutations in STAT5b may be observed with urticaria-like rash and atopic dermatitis in neonates [24].

MANAGEMENT

HSCT is essential as much as early diagnosis. SCID cases undergoing HSCT before 3.5 months of age or infections contracted have a considerably better survival than those transplanted later or infectious complications gathered. Two-year survival of HSCT in infants is with no infections: 95%, with infections: 81% and after 3 months of age: 70% [49, 50].

Conclusion

The normal neonate's immune system is anatomically complete, but antigenically naive and functionally distinct, with lower inflammatory and Th1 responses, potentially making the newborn more susceptible to infection. Furthermore, many PIDs that present in neonatal period are potentially life threatening. The range of PIDs is growing, and the diagnosis and management of these disorders continues to increase in complexity. Early consultation with a pediatric immunologist is highly recommended.

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