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# Hyperimmunoglobulin E Syndromes in Pediatrics

**Qian Zhang** and **Helen C. Su**
Human Immunological Diseases Unit, Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

## Abstract

**PURPOSE OF REVIEW—**The hyper-IgE syndromes (HIES) are primary immunodeficiencies (PID) characterized by eczema, sinopulmonary infections, and elevated serum IgE. This review discusses the clinical similarities and differences between the autosomal dominant (AD-HIES) and autosomal recessive (AR-HIES) forms of this disease, as well as their causative genetic and pathophysiological mechanisms.

**RECENT FINDINGS—**Over the past four years, three genetic defects have been identified in HIES. Mutations in *STAT3* are associated with AD-HIES, whereas mutations in *DOCK8*, or rarely *TYK2*, are associated with AR-HIES. Recent work has confirmed that measuring T helper 17 cell numbers can help predict *STAT3* mutations. In AR-HIES, loss of DOCK8 expression was found to impair T cell expansion and durable specific antibody production by B cells. These factors probably contribute to the viral skin and other infectious susceptibilities, severe allergies, and high risk of malignancies that define this disorder.

**SUMMARY—**Establishing the molecular diagnosis of HIES is important for optimal patient management. Infections in AD-HIES are usually well controlled by antibiotics. By contrast, the viral infections in AR-HIES are difficult to manage. Their higher mortality and progressive course emphasizes the need to identify AR-HIES patients early, for consideration of potentially curative hematopoietic cell transplantation.

### Keywords

hyper-IgE syndrome; STAT3; DOCK8; TYK2; cutaneous viral infection

## Introduction

In 1996, Job's syndrome was described in patients who, like the biblical figure for which they were named, suffered from severe cutaneous abscesses, in their case due to *Staphylococcus aureus* infection [1]. This disease was also named hyper-IgE syndrome (HIES) when similar patients were discovered to have high serum IgE [2]. Since these original descriptions, more than 200 cases of HIES have been reported worldwide [3**]. Most cases result from dominant-negative *STAT3* mutations, which cause an autosomal dominantly inherited or sporadic form of HIES (AD-HIES) [4–6]. An autosomal recessive form of HIES (AR-HIES) differing from AD-HIES also exists [7]. Although *TYK2* mutations might explain a few cases [8], most cases of AR-HIES appear to result from mutations in *DOCK8* [9, 10]. This recent discovery has helped to define AR-HIES as a distinct clinical entity, which is characterized by a broad infectious susceptibility profile, including viral infections of the skin, as well as severe allergies, various malignancies, and a

Correspondence to Helen C. Su, MD, PhD, Human Immunological Diseases Unit, Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rm. 5W-3940, Building 10CRC, Center Dr., MSC 1456, Bethesda, MD, USA, 20892-1456, Tel: +1 301-451-8783; Fax: 301-480-0983; hsu@niaid.nih.gov.

poorer clinical outcome than AD-HIES [7, 9, 10]. Here, we review the latest clinical, genetic, and pathophysiological advances in HIES.

## Overview

The features common to all forms of HIES are eczema, recurrent sinopulmonary infections, and elevated serum IgE [11**]. However, AD-HIES and AR-HIES differ in many aspects, which we discuss below and summarize in Table 1.

## AD-HIES (Job's syndrome)

Dominant-negative mutations in *STAT3* cause a multisystem disorder that is characterized by eczema, recurrent staphylococcal infections of the skin and lungs, pneumatocele formation, mucocutaneous candidiasis, eosinophilia, elevated serum IgE, and various non-immune manifestations [3**, 11**, 12*].

Most immunological manifestations of AD-HIES are driven by *Staphylococcus aureus* infections of the skin and lung. More than half of patients with AD-HIES present with a newborn rash – sometimes present at birth – consisting of eosinophilic pustules [3**, 11**]. Nearly all patients develop unusual *S. aureus* skin abscesses that lack the usual redness, warmth, or pain (termed "cold abscesses"). These infections also induce eczematoid dermatitis. *S. aureus* also causes the majority of sinopulmonary infections in AD-HIES, with *Streptococcus pneumoniae* and *Haemophilus* species responsible for most of the remainder. Lung infections can usually be controlled by antibiotics, but abnormal lung repair often results in the development of pneumatoceles and bronchiectasis. Lung cyst formation occurs in 75% of patients. Parenchymal damage predisposes to chronic and opportunistic infections, including *Aspergillus*, *Pseudomonas aeruginosa*, *Pneumocystis jirovecii*, and atypical *Mycobacteria*.

The pathophysiological mechanisms by which *STAT3* mutations contribute to *S. aureus* bacterial infections are beginning to be understood. STAT3 is a transcriptional factor that is activated in response to various cytokines and growth factors, including interleukin (IL-6), IL-10, IL-22, IL-23, and macrophage colony-stimulating factor. Mutant STAT3 interferes with the signaling pathway downstream of these cytokine receptors, resulting in a complex array of altered immune responses [4, 13, 14]. For example, STAT3-dependent transcription mediated by IL-6, IL-22, and IL-23 binding to their specific receptors are essential for the differentiation of T helper type 17 (Th17) cells, which normally promote protective myeloid responses against extracellular bacteria and fungi by secreting IL-17A and IL-17F. Interestingly, a recent study suggested that keratinocytes and bronchial epithelial cells respond synergistically to both IL-17 and classical proinflammatory cytokines, e.g., tumor necrosis factor-alpha, IL-1β, and interferon (IFN)-γ, whereas other cell types, such as leukocytes, can compensate by responding to classical proinflammatory cytokines alone. Because of the lack of Th17 cells in AD-HIES, keratinocytes and bronchial epithelial cells produce less neutrophil chemoattractants and antimicrobial peptides [13]. These observations could explain why infections are localized to skin and lung but do not occur systemically. Furthermore, neutrophils from AD-HIES patients have decreased expression of chemoattractant receptors [15], which could also explain why the sites of infection often show minimal inflammation.

In addition to problems with localized bacterial infections, 40% of the patients also have fungal infections, which include mucocutaneous candidiasis, Histoplasmosis, and *Cryptococcus neoformans* [11**, 12*]. This is explained by the defective production of Th17 cells, as mentioned above. Moreover, the IL-17 produced in mucosa normally induces the production of histatins in saliva, so its deficiency could explain the high frequency of

thrush in AD-HIES patients [16*]. Together, these observations support an important role for the lack of Th17 cells in the immunopathogenesis of AD-HIES.

AD-HIES features skeletal, dental and connective tissue abnormalities [11**, 17]. By the time they are teenagers, ~90% of patients develop a characteristic asymmetric facies with deep-set eyes, prominent forehead and chin, and bulbous nose. Half of patients have increased interalar distance, cathedral palate, and central depressions of the tongue. Failure to exfoliate primary teeth is also common. Some patients show hyperextensibility, bone fractures following minimal trauma, and scoliosis. Moreover, surprisingly high frequencies of coronary artery tortuosity or dilation (70%), aneurysms (37%), and hypertension (42%) have been reported [18*]. These non-immunological manifestations reflect the broad expression and function of STAT3 in many tissues, and help to distinguish AD-HIES from AR-HIES.

Additionally, several cases of malignancy have been reported in AD-HIES [11**, 19*–21*]. Among the patients who were confirmed as having *STAT3* mutations, non-Hodgkin's lymphoma and diffuse large B-cell lymphoma were the most common [19*–21*].

The autosomal dominant or sporadic cases of Job's syndrome are caused by heterozygous missense mutations in *STAT3* [4–6]. Loss-of function mutations have not been identified in patients, arguing against a haploinsufficiency mechanism of disease pathogenesis. In normal individuals, STAT3 forms dimers upon stimulation, which translocate into the nucleus and bind to DNA to promote gene expression. However, in patients who express mutant and wild-type STAT3 proteins, abnormal dimers form. These abnormal dimers lead to dominant negative effects, although the precise mechanisms for these effects remains unclear. Mutational hot-spots, which are predominantly located in the DNA binding or SH2 (src-homology 2) domains, as well as other mutations in the transactivation or coiled-coil domains, have been reported [3**]. However, available data do not currently support any genotype-phenotype correlations [22].

## DOCK8 immunodeficiency syndrome (DIDS)

DIDS, which is the predominant form of AR-HIES, is a combined immunodeficiency characterized by severe atopy, recurrent viral and other infections, and early-onset malignancy [9]. Newborn rash is absent, but atopic dermatitis, which is often the first symptom, develops in infancy in nearly all patients. Unlike AD-HIES, 50% to 80% of DIDS patients develop severe allergies, including anaphylaxis, to food and environmental antigens, as well as asthma. These findings are accompanied by elevated serum IgE and eosinophilia [23**].

Severe chronic cutaneous viral infections, which afflict ~90% of patients, are a distinctive feature of DIDS [23**]. The most common pathogens are herpes simplex virus (HSV), human papillomavirus (HPV), molluscum contagiosum virus (MCV), and varicella-zoster virus (VZV). The viral susceptibility probably results from a variety of immune defects, including a progressive lymphopenia that affects CD4 and CD8 T cells. In particular, CD8 T cells from DIDS patients not only are decreased in number but also fail to expand normally in vitro after stimulation, and produce less antiviral cytokines [9]. Interestingly, patients do not seem to have increased susceptibility to systemic viral infections, suggesting additional immune defects specific to the skin.

DIDS patients are also susceptible to recurrent sinopulmonary infections caused by a wide variety of pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pneumocystis jirovecii*, *Histoplasma capsulatum*, *Legionella pneumophila*, respiratory adenovirus, and respiratory syncytial virus. The frequency of sinopulmonary infections

decreases with IVIG treatment, which suggests that these patients have significant defects in humoral immunity [9, 24*]. In fact, most patients have decreased IgM and some also have decreased IgA in the serum. Furthermore, specific antibody production is often impaired, consistent with the defective long-lasting antibody responses observed in a mouse model of DIDS [25]. Thus, abnormalities in B- as well as T-lymphocyte function contribute to the broad infectious susceptibility of DIDS patients.

Additionally, roughly half of DIDS patients develop mucocutaneous candidiasis, which may reflect the partially decreased Th17 cell numbers found in some patients [12*, 23**, 26, 27]. A minority of DIDS patients has CNS abnormalities resulting from infections or vasculitis [10]. Autoimmune hemolytic anemia has also been rarely reported.

DIDS patients are also highly prone to malignancy, with 10% to 36% of patients developing cancers in late childhood to early adulthood [23**]. Squamous cell carcinomas, which are associated with chronic HPV infections, and lymphomas, including Burkitt lymphoma or EBV- diffuse large B cell lymphoma, predominate. Other malignancies that have been reported include cutaneous T-cell leukemia/lymphoma, microcystic adnexal carcinoma, and $EBV^+$ perigastric leiomyoma [28]. These malignancies suggest defective immune surveillance for tumors, although a tumor-suppressor role for DOCK8 is also possible [23**].

Since the discovery in 2009 that loss-of-function mutations in *DOCK8* underlie AR-HIES, an estimated >100 patients worldwide have been identified. DOCK8, which is highly expressed in the immune system, is a member of a poorly characterized family of atypical guanine nucleotide exchange factors for Rho family GTPases. Interestingly, approximately 70% of reported mutations in *DOCK8* involve large deletions, which suggests that this genetic locus is a recombination hotspot [23**]. These types of mutations can be picked up by comparative genomic hybridization (CGH) or single nucleotide polymorphism (SNP) arrays, which are newer genetic diagnostic techniques that are available commercially.

## TYK2 deficiency

Only two cases of *TYK2* mutations resulting in TYK2 deficiency in humans have been reported [8, 29*, 30]. The first patient was diagnosed with AR-HIES [8], whereas the second patient was discovered in the analysis of a cohort of patients with mycobacterial disease [29*, 30]. Both patients had recurrent sinopulmonary infections, disseminated infection with Bacille Calmette-Guerin (BCG), and cutaneous viral infections (i.e., HPV, MCV, or HSV). However, the second patient lacked the atopic dermatitis, skin abscesses, candidiasis, or hyper-IgE found in the first patient. Functional assays showed that the AR-HIES patient had defective responses to multiple cytokines, including IL-6, IL-10, IL-12, IL-23, and type I IFN [8]. This finding is consistent with the known role of TYK2 as a tyrosine kinase that mediates signal transduction between cytokine receptors and STATs. Furthermore, they explain why this patient's phenotype overlapped with the phenotypes of patients with *STAT3* or *STAT1* mutations. Nonetheless, sequencing of other AR-HIES cohorts has not revealed additional patients with *TYK2* mutations, suggesting that TYK2-deficient patients may only account for rare cases of atypical AR-HIES [31].

## Diagnostic considerations

In 1999, an HIES scoring system was established at the NIH as a research tool [32]. It was subsequently modified and adopted as a diagnostic tool based on 19 clinical and laboratory findings characteristic of AD-HIES. Scores of at least 40 points were considered to indicate high likelihood of HIES, whereas scores below 20 indicated low likelihood [33]. Recently, Woellner et al. proposed a set of simplified diagnostic guidelines: Criteria predictive of

*STAT3* mutations were recurrent pneumonia, newborn rash, pathologic bone fractures, characteristic face, high palate, and lack of Th17 cells, in the setting of high serum IgE [3**]. In another study, adding Th17 cell measurements to the NIH scoring criteria also helped to differentiate patients carrying *STAT3* mutations from patients having garden-variety atopic dermatitis (who can sometimes have high serum IgE) [12*].

Although the HIES scoring system has proven useful for AD-HIES, it is weighted towards clinical criteria unique to AD-HIES and has not yet been rigorously validated for diagnosing AR-HIES. Of note, high serum IgE can occur in other immunodeficiencies that are not classified as HIES [23**, 34, 35]. Examples include the Wiskott-Aldrich syndrome, severe combined immunodeficiency (SCID)/Omenn's syndrome (especially ADA deficiency), and atypical complete DiGeorge syndrome. These immunodeficiencies can further resemble DIDS by featuring dermatitis, T-cell lymphopenia, and increased susceptibility to viral or other infections. Interestingly, AIDS patients are also known to develop a hyper-IgE-like picture [36], which further supports the association of T-cell deficiency with elevated IgE. Moreover, DIDS can be confused with the WHIM (*W*arts, *H*ypogammaglobulinemia, *I*nfections, and *M*yelokathexis) syndrome or with epidermodysplasia verruciformis, which are also characterized by extensive HPV infections [23**].

In many cases, diagnosing AD-HIES or AR-HIES is straightforward. However, the diagnosis may not be obvious in very young children, who have not had enough time to develop many characteristic features of HIES. In these, or atypical cases where there is high suspicion, measurement of Th17 cells, lymphocyte counts, and mutational analysis can help establish a definitive diagnosis.

## Treatment

Making a definitive molecular diagnosis is important because patient management differs markedly for AD-HIES and AR-HIES [11**]. In general, patients with AD-HIES respond well to conservative therapies and most survive into mid to late adulthood. In contrast, patients with DIDS suffer from greater morbidity and mortality. They typically follow a progressive course and succumb to infectious or CNS complications, or die from cancer in late childhood to early adulthood.

For AD-HIES, the main causes of death are related to infectious complications. Thus, a major goal of treatment focuses on aggressive control of skin and sinopulmonary infections. Control of *S. aureus* often results in significant improvement of skin abscesses, respiratory infections, and eczema. Furthermore, control of respiratory infections also decreases the risk of parenchymal lung damage, which predisposes to opportunistic infections, and intravenous immunoglobulin therapy may be useful achieving such control in some patients. AD-HIES patients benefit from prophylactic antibiotics, which may include antifungal agents. Additionally, bathing in antiseptics or diluted bleach, or swimming in chlorinated pools, effectively diminishes colonization by *S. aureus*. Because the infections in AD-HIES are usually well controlled, hematopoietic stem cell transplantation (HCT) is not recommended unless hematopoietic malignancy occurs. Despite two reported cases of improved eczema after omalizumab treatment, its role remains uncertain, as current knowledge does not support a significant role for the high serum IgE in the disease pathogenesis of AD-HIES [37, 38]. Non-immune manifestations, such as skeletal fractures or aneurysms, have been conservatively managed, although whether such medical intervention results in positive outcomes in AD-HIES is still unknown [11**].

As with AD-HIES, bleach baths are also recommended for AR-HIES. Because many DIDS patients have antibody defects, intravenous immunoglobulin treatment can be effective in decreasing the frequency of respiratory infections. By contrast, the cutaneous viral infections

are extremely difficult to control. Patients with recurrent HSV infections are usually treated with prophylactic valacyclovir. However, for the treatment of MCV and HPV, topical therapies have not usually been helpful. IFN-α given subcutaneously has shown success in some patients, and intravenous cidofovir may also prove to be helpful in a pre-transplant setting [11**]. The difficulty in controlling viral infections likely contributes to the increased risk for squamous cell carcinomas in DIDS patients.

Currently, HCT is the only definitive treatment available for DIDS. Five successful outcomes have been reported using matched related or unrelated donor hemaopoietic cells and reduced-intensity conditioning [39*, 40, 41, 42]. Patients achieved complete and stable engraftment, and their lymphocyte counts and functions normalized. Importantly, their eczema and chronic viral skin infections completely disappeared, and they had no new infections, although whether HCT will prevent future malignancies is unknown. Despite these encouraging results, the risks for HCT must be weighed carefully, as the viral infections appear to worsen in the immediate aftermath of transplantation, before eventually resolving with engraftment. Whether these post-transplantation complications will be less severe in younger patients is unknown, but the progressive course of DIDS argues that HCT should be considered as early as possible.

## Conclusion

Over the last five years, the genetic bases for AD-HIES and AR-HIES have been discovered. The identification of *STAT3*, *DOCK8*, and *TYK2* mutations has already improved diagnosis and treatment for patients. Future discoveries will better define these distinct clinical entities by building upon our understanding of the underlying disease pathophysiology mechanisms.

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## Key points

1. AD-HIES is caused by heterozygous, dominant negative missense mutations in *STAT3*, whereas AR-HIES is caused by homozygous or compound heterozygous loss-of-function mutations in *DOCK8*.
2. The clinical manifestations of AD-HIES are mainly driven by *Staphylococcus aureus* infections in the skin and lungs, and may also reflect decreased numbers of Th17 cells, which can also contribute to susceptibility to mucocutaneous candidiasis.
3. DIDS presents with a chronic viral infections of the skin and other infections, severe allergies, and early-onset malignancies. These features reflect the important role of DOCK8 for normal lymphocyte functions.
4. AD-HIES patients respond well to conservative therapies, whereas DIDS patients have high morbidity and mortality without hematopoietic cell transplantation.

**Table 1**

Comparison between AD-HIES and DIDS

| | | AD-HIES | DIDS |
|---|---|---|---|
| Infections | | | |
| Sinopulmonary | Bacterial | +++ | +++ |
| | Viral | + | + |
| | Fungal | +++ | + |
| Cutaneous | Abcesses (*S. aureus*) | +++ | ++ |
| | Viral (HPV/HSV/MCV) | − | +++ |
| Candidiasis | | ++ | ++ |
| Atopic diseases | | | |
| Newborn rash | | +++ | − |
| Eczema | | +++ | +++ |
| Asthma | | − | ++ |
| Food/airborne allergies | | − | +++ |
| Malignancies | | | |
| Lymphoma | | + | ++ |
| Squamous cell carcinomas | | − | ++ |
| Non-immunological manifestations | | | |
| Characteristic facial appearances | | +++ | − |
| Retained primary teeth | | +++ | − |
| Skeletal abnormality | | +++ | − |
| Vascular abnormality | | +++ | − |
| Central nervous system abnormality | | +++ | + |
| Laboratory findings | | | |
| Hyper-IgE | | +++ | +++ |
| Hypo-IgM | | − | +++ |
| T cell lymphopenia | | − | +++ |
| Eosinophilia | | +++ | +++ |
| Low Th17 T cells | | +++ | ++ |

+++ with high frequency; ++ with intermediate frequency; + occasionally reported; − rarely reported.