# Life-Threatening Pneumopathy and *U urealyticum* in a STAT3-Deficient Hyper-IgE Syndrome Patient

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A deficiency in signal transducer and activator of transcription 3 (STAT3) is responsible for autosomal dominant hyperimmunoglobulin E syndrome, an immunodeficiency syndrome causing *Staphylococcus aureus*, *Streptococcus pneumonia*, *Haemophilus influenzae*, and, rarely, *Pseudomonas aeruginosa* and *Aspergillus sp* infections. Currently, intracellular pathogens are not targeted in the management of severe infections. The pathophysiologic mechanism of hyperimmunoglobulin E syndrome immunodeficiency has recently been linked to a disorder in the T helper 17 pathway and disruption of the interleukin -23/interleukin-17 axis. We report an unusual case of severe pleuropneumopathy by *Ureaplasma urealyticum* in a teenage girl with STAT3-deficient hyperimmunoglobulin E syndrome (STAT3 HIES). A previous case of severe lung infection by *Mycoplasma pneumoniae* has already been described in a STAT3-deficient patient, but *U urealyticum* has never been reported in patients with STAT3 HIES. After a review of the literature, it seems that the specific immunodeficiency pathway of STAT3 HIES exposes STAT3 HIES patients to *Ureaplasma* lung infections because the pathophysiology of STAT3 HIES and *Ureaplasma* is based on STAT3 and T helper 17 cells.

## CASE REPORT

A deficiency in signal transducer and activator of transcription 3 (STAT3) is responsible for autosomal dominant hyperimmunoglobulin E syndrome (AD-HIES), a rare and complex primary cellular immune disorder linked to a mutation (Online Mendelian Inheritance in Man No. 147060) in the gene encoding for the transduction signal STAT3. STAT3-deficient HIES (STAT3 HIES) patients are characterized by high serum immunoglobulin E levels and, typically, lung and skin infections.[1–3] The pathogens that cause lower respiratory tract infections are mostly *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, but *Aspergillus* and *Pseudomonas aeruginosa* are also involved in patients with damage from lung infections.[1,3,4] Lung infections might result in pneumatocele and are reported as the main risk factors for worsened outcome as well as the first cause of death.[4]

*Ureaplasma urealyticum* is known to cause lung damage in preterm newborns.[5] *U urealyticum* has been reported on rare occasions in immune-compromised or HIV-positive patients, but never in STAT3 HIES patients.[1,3,4] We report the case of a 17-year-old female referenced in the French national cohort of immune defects as having a molecularly proven STAT3 deficiency,[1] who experienced a life-threatening pleuropneumopathy caused by *U urealyticum*.

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Dr Deverrière drafted the initial manuscript; Drs Lemée and Boyer carried out infection analysis and reviewed and revised the manuscript; Dr Grangé performed medical intensive care, carried out analysis of medical data, and reviewed and revised the manuscript; Dr Picard carried out genetic analysis and reviewed and revised the manuscript; Dr Fischer carried out immunologic analysis, diagnosis, and treatment and reviewed and revised the manuscript; Dr Marguet performed pneumological and medical care, carried out analysis of immunology data, and reviewed and revised the manuscript; and all authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This work was presented in part at the French Paediatric Pulmonology and Allergology Society Congress; November 15, 2013; Paris, France.

**DOI:** 10.1542/peds.2016-0845

Accepted for publication Nov 30, 2016

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**To cite:** Deverrière G, Lemée L, Grangé S, et al. Life-Threatening Pneumopathy and in a STAT3-deficient Hyper-IgE Syndrome Patient. *Pediatrics.* 2017;139(6):e20160845

AD-HIES was suspected in our patient at age 5 years because she required surgery for a large nonmalformative bulla of the middle lobe. A review of her medical history found repeated lung infections, and periinfectious, noneczematic skin lesions, food polyallergy, total immunoglobulin E levels >1000 kUI/L, and moderate asthma with chronic reversible obstructive syndrome. A broad nasal bridge and rough facial skin characterized her facial morphology.[1] The diagnosis was confirmed at 9 years of age on finding a heterozygous missense mutation in the 22nd exon of STAT3 (T708N).[1,2] The treatment administered comprised inhaled corticosteroids and a long-acting β agonist for asthma, food avoidance and antihistaminic drugs for allergies, and several courses of oral antibiotics for lung infections. Additional recurrent severe acne occurred with β-lactamins and macrolides, and this adverse effect limited the use of those antibiotics. Prophylactic administration of cotrimoxazole, itraconazole, and weekly subcutaneous γ globulin injections allowed control of recurrent infections. Unfortunately, therapeutic adherence weakened at age 14 years leading to noncompliance and irregular follow-up.

At 17 years of age, the patient presented with an episodic fever and productive cough. At that time, compliance was poor and follow-up irregular. This condition lasted for 2 months, despite 2 courses of amoxicillin/clavulanate. Due to increasing fatigue, she subsequently presented to our tertiary care center. A chest radiograph displayed a middle lobe consolidation, and only a multisensitive form of *S pneumoniae* grew in the sputum analysis. Given the infectious epidemiology of STAT3-deficient patients and the lack of other pathogens in our patient, she was administered a 6-day course of intravenous (IV) ceftriaxone at home. She was hospitalized the day after her home treatment, due to persistent fever, marked fatigue, dyspnea, extension of the left upper lobe consolidation, and atelectasis of the left lower lobe. She improved with a 10-day course of IV aminoside and clindamycin and was discharged. The patient's fever relapsed 3 days later and she had severe fatigue, respiratory distress, and inflammatory syndrome (C-reactive protein: 190 mg/L). She was admitted to ICU and underwent noninvasive ventilation. Extended investigations were performed with bronchoscopy and bronchoalveolar lavage (BAL), microbial research by growth cultures, molecular biology and serology, and a broad immunity assessment. A computed tomography scan showed multiple atelectasis of the left lung and preexistent bronchiectasis. Based on STAT3 HIES and the lack of an identified pathogen, probabilistic treatments against other germs that may be found in patients with bronchiectasis, such as *S aureus, Pseudomonas*, and *Aspergillus*, were started. A pleural empyema occurred 1 month later in spite of several courses of antiinfectious treatments. Routine cultures and polymerase chain reaction (PCR) were negative for *Mycoplasma pneumoniae, Chlamydophila pneumoniae, and S pneumoniae*. The 16S ribosomal RNA sequencing from the BAL and pleural sample revealed the sole presence of *U urealyticum*. This was additionally confirmed by the pleural effusion culture with a positive growth of *U urealyticum* (> $10^4$ colony-forming unit/mL). Unfortunately, an antibiogram was not achieved. The patient's personal history confirmed an act of unprotected oral sexual intercourse a few weeks before the onset of symptoms. All other tests for sexually transmitted infections were negative. Our patient's outcome greatly improved early on in the 14-day course of spiramycin, and she was rapidly weaned from mechanical ventilation. Apyrexia was obtained and her C-reactive protein level rapidly decreased. However, since that time, our patient has undergone an alteration in maximal expiratory flows and has a remaining pneumatocele formation in the left upper lobe.

Screening for *U urealyticum* is challenging because culture and PCR are not routinely performed, and the ubiquity of this pathogen complicates the interpretation of serology tests.[6] Even though a recent study suggests that *U urealyticum* is underestimated in children with chronic respiratory disease, with a prevalence of 2.8% in 319 pediatric BAL samples, it has never been reported in STAT3 HIES cohorts.[1,4,5] Conversely, this pathogen causes lower respiratory tract infections in neonates, data that is in accordance with the fact that *U urealyticum* preferentially colonizes the distal urinary tract.[5,6] In our patient, the mode of contamination was finally explained by an act of unprotected oral intercourse.

*S pneumoniae* is well recognized as a causal infectious agent in up to 24% of lower respiratory tract infections in STAT3 HIES patients.[1] Indeed, because *S pneumoniae* was the only pathogen initially identified in our patient's sputum culture, we administered appropriate antibiotics and observed a transient improvement. Thereafter, an 16S ribosomal RNA test was performed that detected *U urealyticum* and confirmed the eradication of *S pneumoniae*. These test results argued for a coinfection involving both *U urealyticum* and *S pneumoniae*. Similar coinfections involving *M pneumoniae* have already been reported in the ICU.[7]

Our patient's delayed clinical attendance and subsequent delay in treatment might also have enhanced the severity of her infection. Such delay was closely linked to her psychological status and her reluctance to consult.

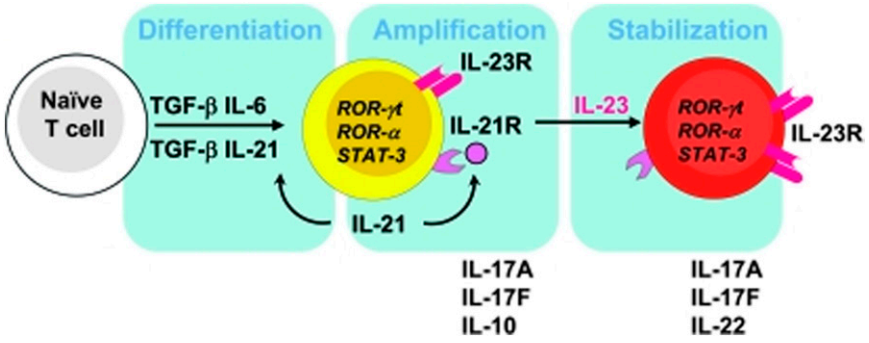


**FIGURE 1**

Generation of Th17 cells: Transforming growth factor β and IL-6 initiate Th17 differentiation. Th17 cells produce IL-21, which amplifies Th17 generation and induces expression of IL-23 receptor. IL-23 stabilizes the Th17 phenotype by secreting IL-17A, IL-17F, and IL-22 and helping Th17 cells to acquire effector functions. IL-6, IL-21, and IL-23 signal through STAT-3.[8] R, receptor.

Nevertheless, the uncommon severity of our patient's infection might be explained by her particular immunologic condition. The pathophysiologic mechanism of STAT3-deficiency has recently been linked to a disorder in the T helper (Th) 17 pathway.[1–3,9,10] Indeed, STAT3 mutation, through a disruption in the interleukin (IL)-23/IL-17 axis (Fig 1), provokes a circulating defect in Th17 cells and a resulting deficit in IL-17 production, which has already been described in STAT3-deficient patients.[1,3,8–10] This disruption alters epithelial immune responses and neutrophil recruitment in the lungs and skin, making patients highly vulnerable to lung and skin infections.[1,3] Interestingly, recent studies have shown that the IL-23/IL-17 axis pathway is involved in the host defense against the mycoplasma species, which *U urealyticum* belongs to.[11,12] Even though more data are still required, some works suggest the implication of Th17 cells in host defenses against intracellular pathogens.[8,13,14]

Although macrolides are easily recommended as the second-line treatment of acute pneumonia, our patient was not given them because she had previously developed severe acne with this class of antibiotics and because *M pneumoniae* and *C pneumoniae* PCR and serologies were repeatedly negative. Spiramycin was administered after taking into account the patient's history of reaction to macrolides and the need for IV administration due to her clinical condition.

Although we cannot entirely prove it, the specific immunodeficiency pathway of STAT3 seems to expose STAT3-deficient patients to *Ureaplasma* lung infections because the pathophysiology of AD-HIES and of *Ureaplasma* is based on STAT3 and Th17 cells. Coverage of atypical pathogens, such as *Mycoplasma* and *Ureaplasma*, should be considered empirical therapy when dealing with infections in individuals with HIES.


## ACKNOWLEDGMENT

We thank Nikki Sabourin-Gibbs (Rouen University Hospital) for editing the manuscript.


## ABBREVIATIONS

AD-HIES: autosomal dominant hyperimmunoglobulin E syndrome
BAL: bronchoalveolar lavage
IL: interleukin
IV: intravenous
PCR: polymerase chain reaction
STAT3: signal transducer and activator of transcription 3
STAT3 HIES: STAT3-deficient HIES
Th: T helper


PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).





**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** No external funding.

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.


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*Pediatrics* 2017;139;
DOI: 10.1542/peds.2016-0845 originally published online May 17, 2017;

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