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Autosomal Dominant Hyper-IgE Syndrome in the USIDNET Registry

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Abstract

BACKGROUND—Autosomal dominant hyper-IgE syndrome (AD-HIES) is a rare condition.

OBJECTIVE—Data from the USIDNET Registry provide a resource to examine the characteristics of patients with rare immune deficiency diseases.

METHODS—A query was submitted to the USIDNET requesting deidentified data for patients with physician-diagnosed AD-HIES through July 2016.

RESULTS—Data on 85 patients diagnosed with AD-HIES (50 males; 35 females) born between 1950 and 2013, collected by 14 physicians from 25 states and Quebec, were entered into the USIDNET Registry by July 2016. Cumulative follow-up was 2157 years. Of these patients, 45.9% had a family history of HIES. The complications reported included skin abscesses (74.4%), eczema (57.7%), retained primary teeth (41.4%), fractures (39%), scoliosis (34.1%), and cancer (7%). Reported allergic diseases included food (37.8%), environmental (18%), and drugs (42.7%). The mean serum IgE level was 8383.7 kU/mL and was inversely correlated to the patient's age. A total of 49.4% had eosinophilia; 56% were known to be on trimethoprim-sulfamethoxazole, 26.6% on antifungal coverage, and 30.6% on immunoglobulin replacement therapy. Pneumonias were more commonly attributed to *Staphylococcus aureus* (55.3%) or *Aspergillus fumigatus* (22.4%); 19.5% had a history of lung abscess; these were most often associated with *Pseudomonas aeruginosa* (*P* Fisher's exact test = .029) or *A. fumigatus* (*P* Fisher's exact test = .016). Lung abscesses were significantly associated with drug reactions (*P* χ^2 = .01; odds ratio: 4.03 [1.2–12.97]), depression (*P* Fisher's exact test = .036), and lower Karnofsky index scores (*P* Mann-Whitney = .007).

DISCUSSION—Data from the USIDNET Registry summarize the currently reported clinical characteristics of a large cohort of subjects with AD-HIES.

Keywords

Buckley-Job syndrome; Chronic mucocutaneous candidiasis; Immunodeficiency; Pneumatocele; Quality of life

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Autosomal dominant hyper-IgE syndrome (AD-HIES) first described and named Job syndrome in 1966 is characterized by the triad of pulmonary infections, eczematoid dermatitis, and recurrent skin infections or localized abscesses. The "cold" abscesses initially described by Davis et al may occur, but inflammatory symptoms, such as tenderness and warmth, are more common. On aspiration, there is frank pus, and *Staphylococcus aureus* is usually cultured.[1] In 1972, Buckley et al recognized the multisystem nature of this

syndrome, and that elevated serum IgE was an integral part of the spectrum,[2] although IgE levels may decrease with age.[3] Patients often have characteristic facial features, including a wide nasal bridge, high palate, and/or wide or deep-set eyes and prominent forehead; other common features are mucocutaneous candidiasis, usually onychomycosis and thrush,[4] and fractures with minor trauma.[5] Bone abnormalities such as scoliosis and osteoporosis are common[5]; children may not shed primary teeth easily, requiring surgical extraction.[6] The prognosis of AD-HIES is largely determined by the degree of lung disease.[7] Recurrent pyogenic pneumonias commonly occur in childhood and lead to the formation of pneumatoceles, followed by fungal infections and other secondary infections, and the potential for hemoptysis, which are major causes of mortality and morbidity.[7,8] The extent of pulmonary infections may be out of proportion to the systemic signs of illness such as fever, leading to failure of early recognition of lung infections.

The multisystem involvement in AD-HIES may be accounted for by the widespread role played by the underlying genetic defect, heterogeneous mutations in signal transducer and activator of transcription 3 (STAT3).[7,9,10] STAT3 is a transcription factor that transmits signals to the nucleus after activation by a number of cytokines and growth factors, including IL-2, IL-6, IL-10, IL-12, IL-15, IL-21, IL-23, and IL-27.[11–14]

As AD-HIES is a rare disease (annual incidence is estimated at 1/1,000,000), physicians in Allergy/Immunology are likely to see only a few patients with this syndrome in their practice. In this report, we outline the immunologic and clinical aspects of 85 patients with AD-HIES as reported to the research consortium USIDNET Registry. As for the French National Survey of 60 patients,[15] the data from this registry provide a useful broad description of the clinical and immunologic features of this rare syndrome.

METHODS

The USIDNET Registry was formed in 1992 by the Immune Deficiency Foundation, and converted to an online electronic format in 2008 with standardized case report forms.[16] The online patient-consented Registry is funded by the National Institutes of Health (NIH), and maintains clinical, laboratory, molecular, treatment, and quality-of-life data for patients with a number of primary immune defects, including those with an unclear diagnosis. Data are entered from enrolling institutions in the North America as well as via a new link allowing patients to self-enroll and transfer medical records for entry into the Registry. Deidentified data available for research purposes were used for the current study, for which a query was submitted to the USIDNET requesting all data for patients with physician-diagnosed HIES through July 2016. The data fields surveyed included demographics, criteria used to render diagnosis, pedigree evaluation, clinical features, laboratory findings, treatment, and transplant records. The underlying genetic mutations for this cohort were not recorded. All statistical tests were 2-sided and computed using IBM SPSS Statistics 20.0 (IBM, New York, NY).

RESULTS

Demographics

As of July 2016, the USIDNET Registry contained data for 85 patients (50 males and 35 females) with HIES, entered by 14 physicians. The patients come from 25 different US states and Quebec, and the longest reported follow-up is 15 years (from 2001 to 2016). Considering the age of the patients at the last encounter, the total number of years of medical history encompassed totals 2157 years. For subjects with incomplete entries, the data available are included here. The median age at the onset of symptoms was 2 years (range: newborn to 18 years old); the mean age at diagnosis was 13.8 and at data entry 27.3 years (Table I). Of the total patients, 62.4% (53/85) were Caucasian, 11.8% (10/85) Hispanic, 11.8% African American, and 5.9% (5/85) Asian. Of the entered patients, 45.9% (39/85) had family histories of HIES: amongst the group were 8 affected mothers, 4 affected fathers, 1 affected sister, 3 affected brothers, 2 affected sons, and 1 affected daughter.

Laboratory data

The mean serum IgE for these patients was 8,383.7 kU/mL (range 3,600–53,399). As previously reported,[3] the levels of serum IgE were inversely correlated with the age of the patients (analysis of variance, N = 66; $P = .03$). Patients had normal levels of other serum immunoglobulins. Of the group, 54.9% (39/71) had peripheral blood eosinophilia (defined by a blood eosinophil percentage >5.0% and/or an absolute number $>1000 \times 10^3/\mu L$). A total of 41.2% (33/80) were found to be anemic; the range of hemoglobin levels was between 8.9 and 15.9 g/dL. The examination of 138 antibody responses was reported for 27 subjects; these showed absent or low titers to diphtheria (10/22 patients) and/or tetanus (8/16 patients), with a few subjects with poor or absent titers to measles (2/3 patients) or rubella (2/9 patients) after vaccinations.

Clinical complications, infections

Clinical data on the location of infections and the organisms identified were entered for 82 and 67 subjects, respectively. All 82 had encountered at least 1 infection; 185 specific infections were reported (Figure 1). The 2 most frequent infections were localized skin abscesses (74.4%), and pneumonias and infected pneumatoceles (together, 75.6%).[1] The majority of patients, 72% (59/82), had at least 1 pneumonia; these were due mostly to *S. aureus* (72.3%, 36/59) or *Aspergillus fumigatus* (27.4%, 14/59) (Figure 2). Infected pneumatoceles (16/82) were associated with *A. fumigatus* (57.1% *P* Fisher's exact test = .016) and *Pseudomonas aeruginosa* (35.7% *P* Fisher's exact test = .029). The majority of patients with infected pneumatoceles were women (62.5%, 10/16 patients). Not surprisingly, 12 of 16 (75%) subjects with infected pneumatoceles had thoracotomy procedures. Of the 82 patients, 74.4% (61/82) had a history of skin abscesses. Viral infections were rare; 7.4% (5/67) had a history of herpes infection, 1 patient was reported to have *Molluscum contagiosum*, and another patient had fever with an infection related to Epstein-Barr virus.

Allergic manifestations

Allergic manifestations of various sorts (118) were reported for 55 subjects with AD-HIES (65%). Of the group, 37% (31/82) of patients were reported to have food allergies; 21 patients reported an allergy to egg, and 30 additional subjects reported allergies to dust and to a number of other foods, including milk, soy, chocolate, nuts, amongst the more common. Fifteen patients (9 of them with concomitant food allergy) were reported as having environmental allergies (dust, animal, and dander pollens). Thirty-five had reported drug allergies, including antibiotics (trimethoprim-sulfamethoxazole, clindamycin, penicillin, antifungals, vancomycin) and also pain medications. Drug reactions were significantly more commonly in patients with infected pneumatoceles ($P\ \chi^2 = .01$; odds ratio: 4.03 [1.2–12.97]), perhaps because of the greater exposure to antibiotics. Allergies to latex or adhesive tape were noted for a few subjects (4 and 3 patients, respectively) and adverse reactions to pneumococcal vaccine were reported in 2 subjects, but the total number receiving pneumococcal vaccine is not known. Eight percent of patients (7) were reported to have had anaphylaxis, with causes listed as foods (6), drug reactions (4), or an environmental agent (1). Thirteen subjects also reported urticaria, and 9 other subjects reported angioedema or bronchospasm due to either foods or drugs.

Other clinical complications

The 2 most common noninfectious complications were eczema (57.3%, N = 47/82) and retained primary teeth (41.45%, N = 34/82) (Figure 3). As in other reports, 39% (32/ 82) of patients had bone fractures and 34.1% (28/82) were diagnosed with scoliosis (Figure 3). Of the total patients, 8.5% (10/85) had hyperextensive joints, 4.2% (5/85) had a cardiovascular arterial malformation, and 3.5% (3/85) had brain aneurysms. One patient had a benign tumor (tonsillar papilloma). Malignancy was diagnosed in 7% (6/82 patients): 3 patients had lymphoma (stage II non-Hodgkin lymphoma, stage IIa large B-cell lymphoma, Burkitt lymphoma); 1 patient had papillary thyroid carcinoma; 1 had a neoplasm of the brain; and 1 had a squamous cell carcinoma of the arm.

Treatments and procedures

For 69 patients, 258 courses of intermittent or continuous systemic antibiotic therapies were reported (Table II). These included 46 patients on trimethoprim-sulfamethoxazole and/or other antibiotics, 60 systemic antifungal therapies (given intermittently or as prophylaxis, topical antifungals [60 courses] and antiviral medications [6 courses]—valacyclovir, acyclovir). Of these patients, 30.6% (26/85) were also on immunoglobulin replacement therapy (Ig) (intravenous immunoglobulin [IVIG] in most cases or subcutaneously in 6 patients) (Table II). These patients were not in most cases subjects who had demonstrated low or absent antibody responses to one or more vaccine antigens as only 3 subjects in this category were treated with Ig. More than half of the patients on immune globulin had been followed at the NIH (57.7%, 15/26). A total of 19.5% of patients (16/82) had a history of lung abscess, and a significant percentage of these (9/16) were on Ig therapy (P Fisher's exact test = .033). Other therapies for this cohort included supplemental oxygen (11/19 total patient reported; other data were missing), intubation for longer than 2 days in 4 patients, and transient parenteral nutrition (7/19 patients reported).

Surgical procedures were reported for 55 patients: of those, 19 had limited lung resections, 2 of whom had pneumonectomies; 11 had sinus surgery; 10 had lymph node biopsies; 6 had splenectomies; and 6 had a spinal surgery (Table III). Collectively the patients also had a large number of other surgical procedures, including 17 gastrointestinal biopsies, 14 surgical tooth extractions, mastoidectomies, 13 drainages of skin and other abscesses, liver and lung biopsies, hemicolectomy, ileostomy, craniotomies, spinal fusions, and other procedures.

Three females and 1 male received hematopoietic stem cell transplantation (HSCT). One was transplanted for multiple reasons (autoimmune hemolytic anemia and persistent staphylococcus infections despite prophylaxis) and is alive and well off Ig and antibiotic prophylaxis.[17] Another patient, also alive, was transplanted for significant lung disease at a young age. One male patient did not return for his 6-month post-transplant follow-up. A fourth patient died of pulmonary failure.

One woman with severe mycobacteria-infected pneumatocele had bilateral lung transplantation, but died 3 years after transplant from massive pulmonary hemorrhage and sepsis.

Overall, 76 patients (91.5%, 76/83) were reported to be alive, 3 deceased (3.61%, 3/83), and 4 lost follow-up (4.8%, 4/83).

Quality of life

For 65 subjects, quality-of-life data were entered using the Lansky scale for children (N = 28) or the Karnofsky score for adults (N = 37). Sixteen (4 adult, 12 children) subjects were fully active with no signs of illness; 42 (30 adults and 12 children) had some mild impairment and the remaining 7 (3 adults and 4 children) reported significant impairment. A total of 23% (15/65) had respiratory insufficiency. Three patients (2 of them had a Karnofsky score of 70 and 90 and 1 patient had a Lansky score of 80) had cognitive impairment.

Depression (21.9%, 18/82) and fatigue (20.7%, 17/82) were noted in a significant number. Fatigue was more frequent in males (64%, 11/17 patients, $P(\chi^2)$ =.029) and in patients with a history of lung conditions (infected and noninfected pneumatoceles, P(Fisher) =.22), skin abscess (88.2%, 16/17 patients; P(Fisher) = .21), sinusitis (70%, 12/17 patients; $P(\chi^2)$ = .043), and *S. aureus* infections (85.7%, 12/14 patients; P(Fisher) = .32). Fatigue was not related to anemia ($P(\chi^2)$ = .43). A total of 88% (16/18) of the patients with depression had skin abscesses, mostly due to *S. aureus*. Infected pneumatoceles (16/82) were also associated with more depression (P Fisher's exact test = .038) and lower Karnofsky index scores (median [25th–75th percentiles]: 80 [70–90] vs 90 [80–100], P Mann-Whitney = .004).

DISCUSSION

Hyper-IgE syndrome is characterized clinically by a constellation of pulmonary infections, eczematoid dermatitis, recurrent skin infections, facial and bone abnormalities, and elevated serum IgE.[1,2] In this cohort, the majority were male and Caucasian. Overall, the reported

ethnicities reflect the US and Canadian ethnic distributions. Worldwide, STAT3 mutations have been found in multiple ethnic groups among Caucasians, Africans, and Asians.[18,19]

As found in other reports, the prognosis of this syndrome is related to the degree of lung disease. The majority of patients in this cohort (72%) experienced at least 1 pneumonia; 19% had lung abscesses. The relative lack of clinical symptoms with infections, along with poor tissue repair, may put patients with AD-HIES at higher risk for the development of pneumatoceles and bronchiectasis (found in 16 and 21 patients, respectively).[8] Possibly associated with more antibiotic exposures, drug allergies were reported more frequently in those with pneumatoceles. This was more commonly noted in females, in agreement with other reports that suggest that females are at higher risk for drug allergy in general.[20] In this cohort, as expected, pneumatoceles were associated with thoracic surgery, a procedure accompanied by significant risks of bronchopleural fistulae and possibly by respiratory failure in AD-HIES.[21] In addition, infected pneumatoceles were also associated with both depression and poor quality of life as reflected by the lower Karnofsky scores in these subjects.

As for other reports, this cohort of subjects had frequent skin and organ infections, as well as fractures, bone defects, and dental abnormalities. The frequency of fractures (39%) and scoliosis (34%) was similar to the French cohort (42% and 38%)[15] but lower than previously described in an NIH review.[22] Vascular lesions, such as coronary artery tortuosity or dilatation and remodeling, have been reported in AD-HIES.[23–25] Five patients were reported to have cardiac or pulmonary arterial malformations in our cohort. However, as most patients in this report would not have had these tests with no clinical symptoms, the true incidence is not clear.

We noted that a significant number of patients had reports of food, drug, and/or environmental allergies. Although the laboratory basis for these events was not available, this observation contrasts to the current literature, in which despite the elevated IgE, atopic disease in general and food allergy in particular are viewed as relatively uncommon in AD-HIES. Confirmation of food or drug allergy by specific challenges could be offered to these patients. Boos et al did not find significant increases in allergen-specific IgE to a large number of allergens, nor increased skin prick test positivity in patients with AD-HIES; this was in contrast to patients with AR-HIES due to mutations in DOCK8, who had IgE-mediated food allergies.[26,27] The diminished allergic diathesis in patients with AD-HIES has been attributed to potential impairment of mast cell and basophil degranulation in the context of dominant negative STAT3 mutations.[28]

Based on earlier reports, an increased risk of non-Hodgkin’s lymphoma in HIES has been suggested.[29] However, these earlier observations did not distinguish patients with HIES with biallelic mutations in DOCK8 from those with heterozygous mutations in STAT3. Similarly, based on reports published in 1998[27] and 2004,[28] it remains unclear if AD-HIES leads to an increased risk of cancer. However, as for other immune deficiency states, it is important to perform a lymph node biopsy (and generally not a fine needle aspiration) of an inflamed lymph node that did not respond appropriately to antibiotic therapy. It may not be easy, clinically, to distinguish a chronic lymph node infection from lymphoma. One of the patients

in the Registry developed a skin squamous cell carcinoma; he was not reported to be on voriconazole, which has been associated with both photosensitivity and an increased risk of skin malignancy.[30]

The mainstay of therapy in AD-HIES is continuous, full-dose daily trimethoprim-sulfamethoxazole or comparable antibiotic, and commonly, also antifungal coverage. In this cohort of patients with AD-HIES, 66% were on trimethoprim-sulfamethoxazole (separate courses or prophylaxis); a number of other antibacterial agents were also used. For antifungal coverage, itraconazole was the most prescribed, but other anti-fungal agents were used, both for prophylaxis and for the treatment of acute fungal infections.

Despite suboptimal responses to a number of vaccines and the possible efficacy of Ig in reducing the frequency of pneumonias,[15,31,32] guidelines on which patients with AD-HIES will benefit from Ig replacement therapy have not been established. STAT3 plays an important role for B-cell function, both intrinsically[33,34] and via follicular helper T cells,[35] providing a rationale for the use of Ig substitution. In this cohort, 30.6% were on Ig therapy (most commonly IVIG, at a dose of 400 and 600 mg/kg/every 4 weeks), but these were heavily weighted to 1 center and did not appear to be related to poor vaccine responses. Although earlier attempts at HSCT did not demonstrate long-term benefits in AD-HIES,[36,37] recent experiences have been more successful and are somewhat more encouraging.[17,38,39] This is the first study to report on quality of life in patients with AD-HIES revealing both depression and fatigue in a significant number, and associated with lung conditions. Because depression can lead to poor adherence to medical advice,[40] it would be important to screen patients for this and provide appropriate care.

Limitations of this study

This retrospective study is based on physician- and more recently, patient-reported, physician-verified data. Genetic data on the STAT3 mutation were not entered for these subjects, leading to the potential inclusion of a few subjects with DOCK8 deficiency or autosomal recessive phosphoglucomutase 3, more recently recognized immune defects. However, experienced physicians entered all patients with AD-HIES based on the combination of criteria used to render this diagnosis, including pedigree analysis, clinical features, and laboratory findings. In addition, viral infections were quite uncommon in this cohort, unlike DOCK8 deficiency. These data also reflect predominantly a single data entry summarizing data up until that time point; thus further longitudinal analyses will be important to better understand the predictors of outcomes and overall mortality. Such studies will also be needed to clarify if antibody titers are useful in guiding immune globulin replacement and the effect of this therapy on the incidence of lung infections. Given the rarity of AD-HIES, this Registry provides important clinical and immunologic features of a large cohort of subjects from a number of medical centers in North America.

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Abbreviations used

AD-HIES	Autosomal dominant hyper-IgE syndrome
HIES	Hyper-IgE syndrome
HSCT	Hematopoietic stem cell transplantation
Ig	Immunoglobulin
NIH	National Institutes of Health
STAT	Signal transducer and activator of transcription signal

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What is already known about this topic

Hyper-IgE syndrome (HIES) is a rare autosomal-dominant (AD) immune defect associated with lung, skin, and other infections, usually due to bacteria or selected fungi. Lung infections and hemoptysis are the major cause of mortality and morbidity.

What does this article add to our knowledge?

We report clinical, immunologic data as well as quality of life for a large cohort of patients with AD-HIES entered into the USIDNET Registry.

How does this study impact current management guideline?

Knowledge of the course and complications of a large group of patients provides critical information for providers caring for those affected with this rare condition. The use of immune globulin replacement on prevention of infections remains to be clarified.

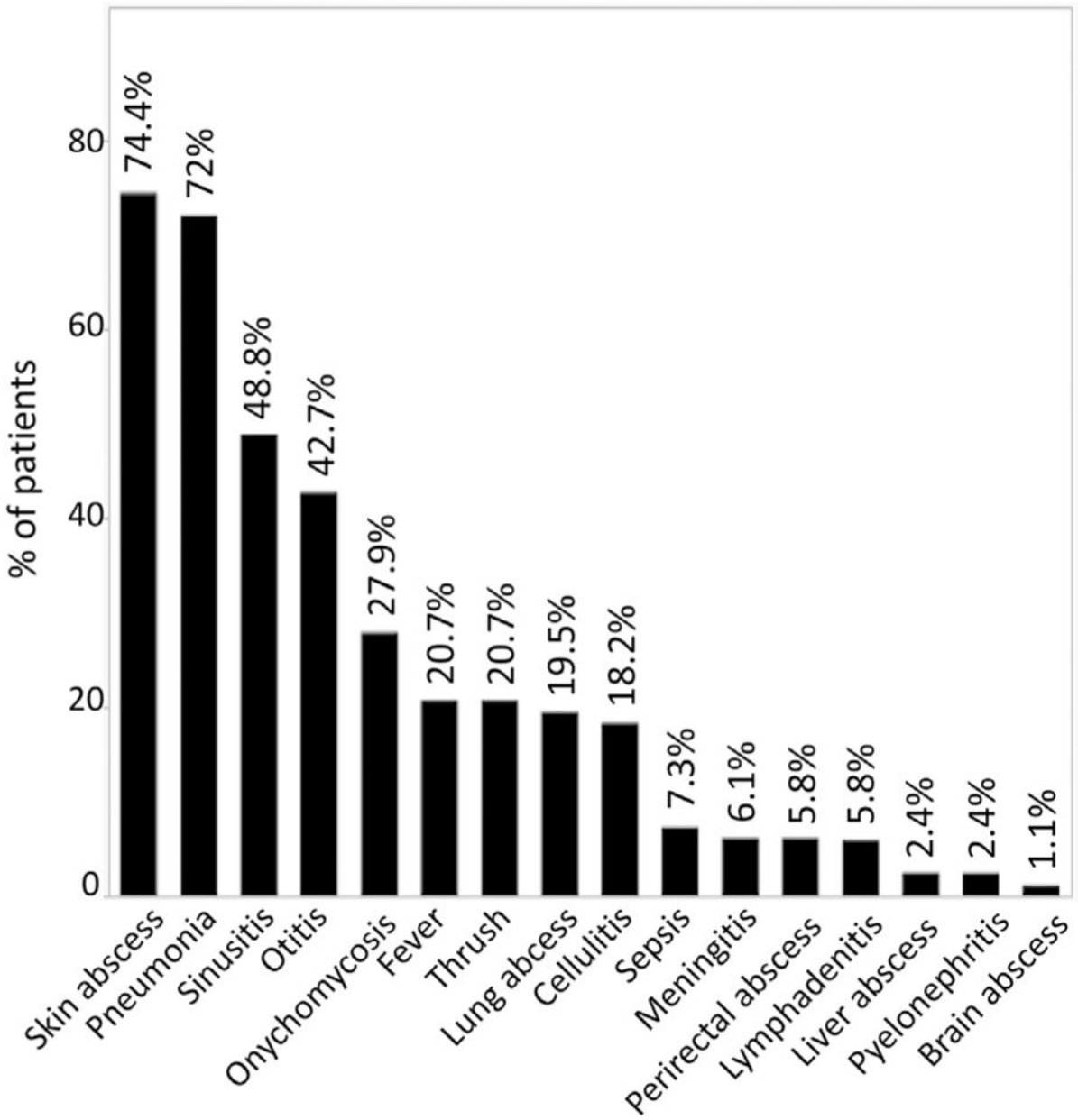

FIGURE 1.
Sites of infections.

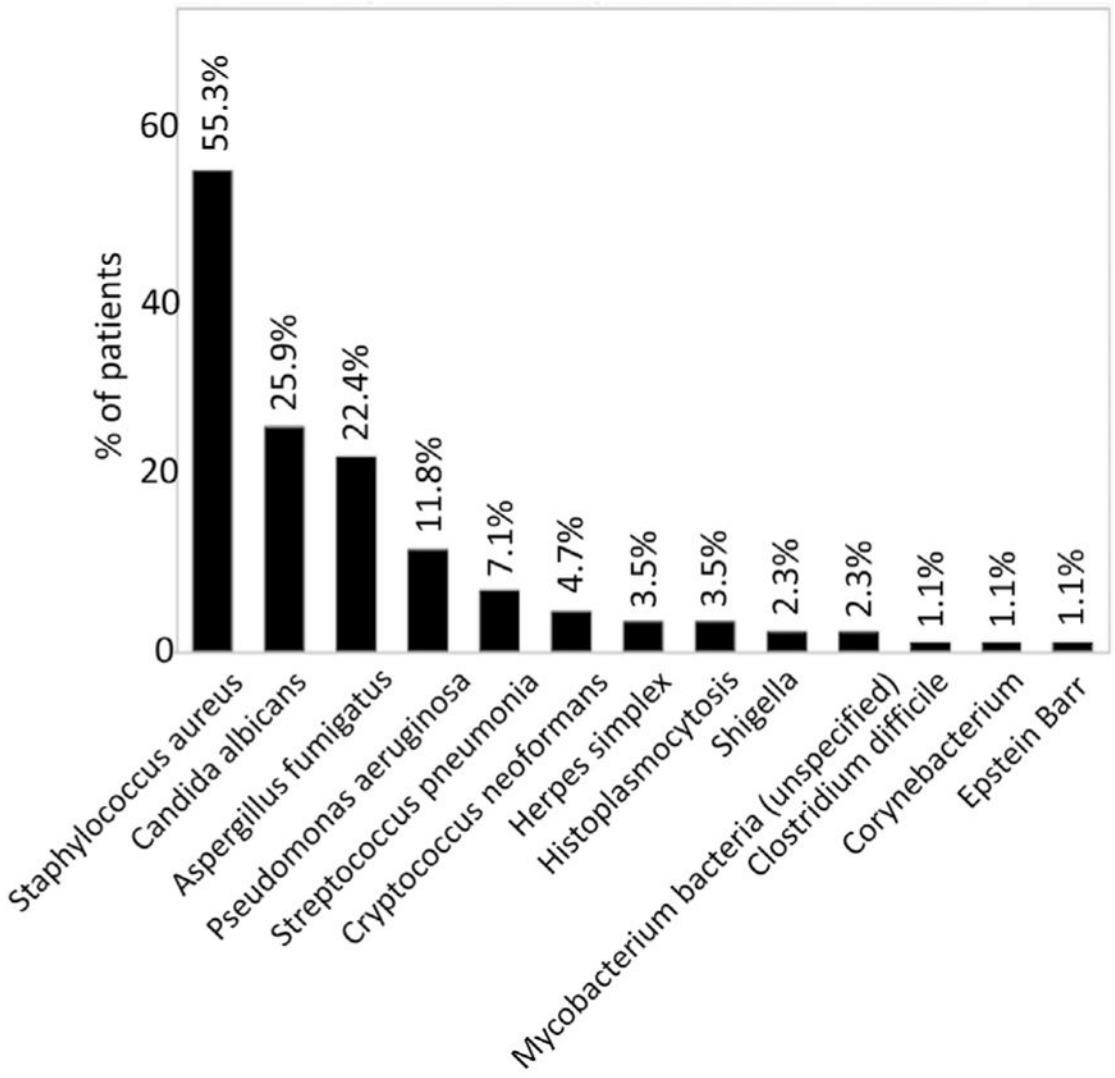

FIGURE 2.
Infectious organisms identified.

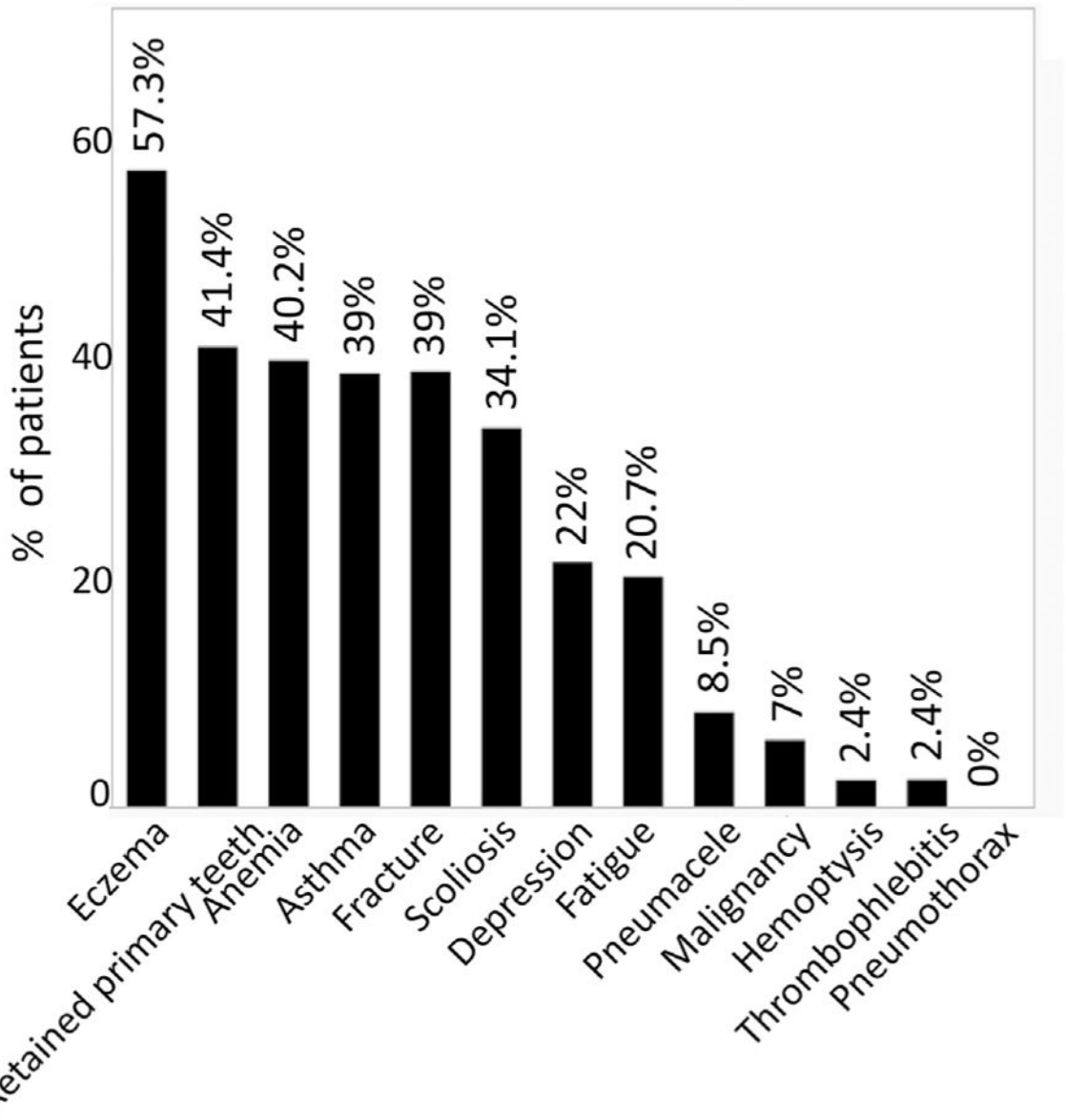

FIGURE 3.
Noninfectious complications.

TABLE I

Demographics of patients (N = 85)

Characteristic	No. of patients (%)
Male/female	50 M; 35 F
Age at onset of symptoms, median (range)	New born (0–18 yo)
Age at diagnosis, mean (range)	14 (0.2–61.6 yo)
Age at data entry, mean (range)	27.3 (3–66 yo)
Patient with known affected family members, n (%)	39 (45.9%)
Race/ethnicity, n (%)	
Caucasian	53 (62.4%)
African American	10 (11.8%)
Hispanic	10 (11.8%)
Asian	5 (5.9%)
Unknown	7 (8.2%)

F, Female; *M*, male; *yo*, year old.

TABLE II

Pharmacologic therapies (N = 69 except for immune globulin replacement, N = 85 patients)

Medications (treatment and/or prophylaxis)	No. of patients (%)
Trimethoprim-sulfamethoxazole	46/69 patients (66.6)
Other antibacterial agents (augmentin, azithromycin, ciprofloxacin, clindamycin, levofloxacin, moxifloxacin, doxycycline, linezolid, cephalexin, ceftriaxone, vancomycin were predominant)	187 courses/69 patients
Antifungal therapies: Itraconazole, fluconazole, posaconazole, caspofungin, isavuconazole, amphotericin B	65 courses/69 patients
Immune globulin replacement	26/85 patients (30.6)

TABLE III

Surgical procedures (N = 85)

Surgical procedures	No. of patients (%)
Lung biopsies/surgeries	28 (32.9)
Gastrointestinal biopsies/surgeries	21 (24.7)
Surgical tooth extraction (s)	14 (16.4)
Incision and drainage	13 (15.3)
Sinus surgery	11 (12.9)
Tonsillectomy	10 (11.7)
Lymph node biopsy	10 (11.7)
Appendectomy	8 (9.4)
Spine surgery	6 (7.0)
Splenectomy	6 (7.0)
Bone marrow transplantation	4 (4.7)