

# Treatment of selective antibody deficiency with IVIG resulting in decreased frequency of streptococcal infection and improvement of guttate psoriasis

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## Abstract

The association between guttate psoriasis and infection with group A Streptococcus (GAS) has been well established in the medical literature. However, responses to treatments aimed at GAS eradication such as systemic antibiotics or tonsillectomy are inconsistent. Further complicating treatment recommendations for a disease with a suspected microbial trigger, the standard therapy for severe psoriasis is with systemic immunosuppressant medications. This case report illustrates the role of GAS as a trigger for acute onset severe psoriasis in a child whose skin disease initially worsened with a trial of methotrexate. An immune evaluation confirmed a co-existing selective antibody deficiency. Subsequent treatment with intravenous immune globulin dramatically improved his underlying immune function and decreased GAS infections. This improvement in overall immune function and decrease in GAS infections cleared his skin disease. An interval change in formulation to subcutaneous immune globulin was not as effective.

*Keywords: guttate psoriasis*

## Introduction

Guttate psoriasis is a unique form of psoriasis that primarily occurs in the pediatric and young adult populations [1]. This phenotype can clear spontaneously or be the first sign of chronic psoriasis. Approximately one third to two thirds (68%) of patients with guttate psoriasis eventually develop chronic plaque psoriasis [2, 3]. An association

between guttate psoriasis and acute pharyngitis has been recognized since the pre-antibiotic era [1, 4-6]. In the past 50 years, a correlation with group A *Streptococcus* (GAS) infection has been documented using a variety of parameters. A 1992 British study included 111 patients with psoriasis (median age 18 years, range 2-75 years), [5]. Evidence of streptococcal infection was most often detected in patients with guttate psoriasis, with 19 of 33 (58%) showing acute disease, and 7 of 27 (26%) exhibiting a guttate exacerbation of chronic psoriasis who had one or more of the three antibodies: anti-streptolysin O, anti-deoxyribonuclease B, and anti-hyaluronidase [6]. Positive cultures were documented in 9 of 34 (26%) with acute guttate psoriasis, 4 of 30 (13%) with guttate exacerbations of chronic psoriasis, and 5 of 37 (14%) with chronic psoriasis compared with 7 of 101 (7%) control patients seen for warts. In 2010, ribosomal streptococcal DNA was detected in the blood of 6 of 7 adults with guttate disease, and in 2 of 13 patients with chronic plaques using polymerase chain reaction (PCR) molecular techniques [6].

Only uncontrolled studies have been able to document the benefits of treatment with oral antibiotics. Of 198 publications on the subject identified by a Cochrane database review between 1966 and 1999, only one was randomized [7]. It compared the use of two oral antibiotic regimens, penicillin V plus erythromycin, with or without additional rifampin [8]. There were only 3 children (ages 12-15) among 20 subjects, all had evidence of GAS colonization, and 19 had guttate type psoriasis [8]. A subsequent randomized trial followed adult males with guttate psoriasis treated with either phenoxymethylpenicillin (N=14),

erythromycin (N=14) or no treatment (N=15), [7]. There was no significant statistically significant improvement in any the groups [7-9].

In the past decade, major advances in psoriasis therapy have focused on treating primary cutaneous immune dysregulation, prompting development of several systemic immunosuppressant agents. Traditionally, systemic immunosuppressant therapy has been used for moderate to severe psoriasis. Options include methotrexate, cyclosporine, and biologic agents that block CD2, tumor necrosis factor (TNF), or interleukin (IL)-12/IL-23 [10]. However, immunosuppressive medications have also been reported to cause acute psoriasis flares in adults and children treated with infliximab for inflammatory bowel disease or rheumatoid arthritis [11]. Other microorganisms have also been associated to trigger guttate psoriasis, including *Staphylococcus aureus*, *Malassezia*, *Candida*, human papillomavirus (HPV), retroviruses, and human endogenous retroviruses (HERVs) [12]. This may be partly the reason why immunosuppressive drugs may trigger guttate psoriasis. Children prone to chronic GAS carriage and recurrent infection may be another subset who are not suitable candidates for immunosuppressive therapy. In our case, however, the extent and severity of the boy's psoriasis warranted systemic immunosuppressive medication. Unfortunately, the treatment was not effective.

### Case Synopsis

A 9-year-old boy was referred to the Pediatric Dermatology service for further evaluation of a one year history of psoriasis, acutely worsening in the previous month following tonsillectomy and adenoidectomy. Past medical history was significant for recurrent infections beginning at 2-3 years of age. He had recurrent sinusitis 4-5x/year, otitis media 4-5x/year, and Streptococcal pharyngitis 8x/year. He had tonsillectomy and adenoidectomy at 8 years that did decrease the frequency of otitis media. In the previous year, his psoriasis was treated with topical triamcinolone and tacrolimus ointments, without benefit. The psoriasis involved 5% of his body surface area, including scalp, groin, and skin folds. Throat culture was positive for group A Streptococcus as well as clindamycin and erythromycin resistant *Staphylococcus aureus*. He subsequently developed

the usual constellation of findings that characterized his past acute infections with GAS: fever, abdominal pain, rhinorrhea, elevated transaminase levels, and positive throat culture. Treatment with oral amoxicillin improved his constitutional symptoms, but not his skin disease. Computerized tomography (CT) imaging of sinuses was normal. His 25-hydroxy-vitamin D level was low, at 19 ng/mL (normal 30-74 ng/mL).

Topical treatment was initiated with calcipotriol/betamethasone (Taclonex<sup>®</sup>) ointment for the body and compounded 2% salicylic acid, 2% coal tar extract, and 0.2% fluocinonide gel for the scalp, in addition to bland skin care with bleach baths, mild cleansing products, and frequent emollients. He was given supplemental ergocalciferol, 50,000 IU per week for 4 weeks, followed by 2,000 IU cholecalciferol daily. An 8 week follow-up vitamin D level was 27 ng/mL. After 2 months of treatment, his skin disease worsened to involve 20% of his body surface area and he was unable to tolerate topical medications or baths owing to skin burning. His sleep was significantly impaired, marked by several night awakenings, persistent scratching, and blood stained sheets. Oral methotrexate was initiated at 15 mg per week, along with additional immunologic evaluation. After 8 weeks of treatment, his skin worsened (**Figure 1**).



**Figure 1.** The patient's affected body surface area increased from 20% to >25% after 2 months on methotrexate.

**Table 1.** Immunologic Studies

Study	Patient	Normal for Age
IgG, mg/dl	742	503-1346
IgA, mg/dl	152	40-249
IgM, mg/dl	154	43-174
IgG1, mg/dl	449	350-900
IgG2, mg/dl	193	70-450
IgG3, mg/dl	59	20-90
IgG4, mg/dl	82	3-90
IgE, IU/ml	68	13-161
Anti-diphtheria toxoid, mcg/ml	0.6	≥0.05
Anti-tetanus toxoid, mcg/ml	0.4	≥0.5
Anti-HiB, mcg/ml	5.4	≥1.0
Anti- <i>S. pneumoniae</i>	Pre 3 of 23 (13%) Post 10 of 23 (43%)	≥1.3 mcg/ml in ≥70% of serotypes
ALC, cells/mm <sup>3</sup>	2535	1900-3700
CD3%	61	60-76
CD4, %	40	31-47
CD8, %	21	18-35
CD19, %	10	13-27
CD56, %	16	4-17
CD19+CD27+, %	0	25-40
CD19+CD27+IgD-, %	0	≥6

**Abbreviations:** HiB, *Hemophilus influenzae* type b; ALC, absolute lymphocyte count.

Immunologic evaluation included normal serum IgG, IgA, IgM, and IgG subclass levels and normal protective titers of anti-diphtheria toxoid, anti-tetanus toxoid, and anti-*Hemophilus influenzae* type B (HiB) antibodies. However, *Streptococcus pneumoniae* (Spn) antibody titers were decreased (23% protective pre- Pneumovax® immunization and 43% post-immunization measured 4 weeks after immunization; Normal Range is ≥1.3 mcg/ml in ≥70% of serotypes). Lymphocyte immunophenotyping demonstrated normal CD3+, CD4+ and CD8+ T cells, normal CD19+ B cells, and normal CD56+ natural killer cells (**Table 1**). However, there were no detectable classical CD19+CD27+ memory B cells and CD19+CD27+IgD-switch B cells. This immunologic profile reflects a diagnosis of selective or specific antibody deficiency

(SAD), [13, 14].

Intravenous immunoglobulin (IVIG) 500 mg/kg/month was initiated. Recurrent infections abated and psoriasis improved over 1-2 months and totally cleared over 3-4 months (**Figure 2**). Methotrexate was discontinued within 4 months and the psoriasis did not relapse during the next 9 months of IVIG infusions. However, within 6 months after initiating a formulation change to subcutaneous gammaglobulin (SCGG) at 125 mg/kg/week, the patient's psoriasis gradually relapsed, affecting primarily his scalp, with a total body surface area involvement of 13% and worsening plaques on the scalp, underarms, and groin area. He remained free of infections, including ear, sinus, strep, cold sores, or skin infections.



**Figure 2.** The patient's psoriasis significantly improved within 3 weeks after IVIG initiation and remained clear after 6 monthly infusions.

The patient was restarted on methotrexate at 10 mg every 7 days at his latest dermatology visit. IVIG was also reinstated at a subsequent visit by his immunologist to help with his psoriasis. His psoriasis improved slightly over the next 2 months. However, since then patient's family relocated to another state and has not followed up at our clinic.

## Case Discussion

Immunologic mechanisms have long been suspected in the pathogenesis of GAS-associated guttate psoriasis and recent studies have identified specific mechanisms. The strongest genetic susceptibility locus linked to psoriasis is HLA-Cw6\*0602 (PSORS1), [14-18]. HLA-C interacts with killer-immunoglobulin-like receptors (KIR) on natural killer cells (NK) or natural killer T (NKT) cells. The risk of psoriasis is increased up to 100 fold in individuals who carry other genetic mutations, including *CARD14*, encoding a nuclear factor of kappa light chain enhancer in B cells (NF- $\kappa$ B) in skin [19, 20]. Streptococcal antigens may be another factor complicating the regulation of this interaction [11]. Streptococcal components

have been reported to cross-react antigenically with epitopes in normal epidermis [21], and histologic findings from early-onset psoriatic skin lesions include infiltration of activated T cells and macrophages [22]. In addition, Group A streptococcal antigen-specific T cells and pro-inflammatory cytokines, such as interferon-gamma (IFN- $\gamma$ ) and interleukin 12 (IL-12), have also been isolated from psoriatic skin lesions. Streptococcal antigens may induce T cells via super-antigens that stimulate shared T cell receptor beta variable chain (TCR-V $\beta$ ) sequences, including Streptococcal pyogenic exotoxins (e.g. SPE, types A, B, and C, a 22-kd pepsin fragment of M type-5 protein, a *S. pyogenes*-derived cytoplasmic membrane-associated protein, and a secretion-type CAP). These super-antigens have been shown to induce CD4+ and CD8+ T cell actions via stimulation of TCR-V $\beta$ 2+ T cells in both the epidermis and dermis of guttate psoriatic lesions [23].

A variety of cutaneous disorders have been described in patients with common variable immunodeficiency (CVID), including atopic dermatitis, granulomatous skin diseases, chronic urticaria, vitiligo, alopecia, and psoriasis [24]. Our patient was diagnosed with SAD, characterized by normal serum IgG, IgA, and IgM levels and normal antibody responses to protein antigens but decreased antibody responses to bacterial polysaccharide antigens, such as *Streptococcus pneumoniae* [25, 26]. A review of infections occurring in 120 children with SAD included 91% with recurrent otitis media, 97% with sinusitis, 13% with pharyngitis, 57% with pneumonia, 6% with cutaneous infections, 5% with sepsis, and 2% with meningitis [27]. SAD improves or resolves in the majority of children presenting before age 6 [23], but the phenotype may evolve into CVID [28]. Reduced classical CD27+ memory B cells and CD27+IgD- switched B cells in patients with SAD and CVID have been associated with increased risk of bronchiectasis [30]. Our patient's lymphocyte immunophenotype analysis was without detectable classical memory CD27+B cells, supporting an increased risk of pulmonary complications.

IVIG is indicated at replacement doses in the treatment of primary immunodeficiency, but has been used in higher doses as an immune modulator in a variety of autoimmune disorders. The implicated

mechanisms of immune modulation include Fc-epsilon R blockade (ITP), antibody inhibition (myasthenia gravis), inhibition of immune activation (Kawasaki syndrome), complement inhibition (dermatomyositis), super-antigen inhibitor (toxic shock syndrome), and modulation of T cell activation (graft versus host disease), [26]. Replacement doses of IVIG were indicated for our patient because his age predicted a low likelihood that SAD would spontaneously resolve [29, 30]. There are a few case reports supporting the efficacy of low and higher-dose IVIG for psoriasis and psoriatic arthritis in adults [31-34].

Our patient's incidence of infections dramatically decreased and the severe psoriasis that had flared during 8 weeks on methotrexate significantly improved using a lower-dose infusion regimen. However, although his infections did not recur, our patient's psoriasis gradually worsened following a change from intravenous to subcutaneous gammaglobulin and again improved following re-initiation of IV administration. The pharmacokinetics of IVIG and SCGG differ dramatically. Peak blood IgG occurs 15 minutes following intravenous infusions, followed by a 1-2 day redistribution phase from blood to tissue, and a slower catabolic phase over 3 to 4 weeks [35]. In contrast, SCGG is administered weekly, at higher cumulative monthly doses, but absorption from subcutaneous tissue to blood occurs gradually over 2-3 days [35, 36]. Higher peak blood or tissue gammaglobulin may be more important in modulating inflammatory disease, as supported by our patient's response to treatment.

## Conclusion

Our case demonstrates that co-existing immune deficiency should be explored in guttate psoriasis patients who are streptococcal carriers because acutely treating streptococcal infection with antibiotics alone may not suffice, as seen in our patient. In addition, immune modulators like methotrexate may actually worsen psoriasis because of infectious triggers in such patients. Intravenous gammaglobulins can be helpful in such cases. But, intravenous and subcutaneous gammaglobulins have different pharmacokinetics and hence different effects on patients with guttate psoriasis.

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