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Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies

A working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology

Pierre L. Yong [a,b], John Boyle [c], Mark Ballow [d], Marcia Boyle [c], Melvin Berger [e], Jack Bleesing [f], Franciso A. Bonilla [g,h], Javier Chinen [i], Charlotte Cunninghamm-Rundles [j], Ramsay Fuleihan [k], Lois Nelson [l], Richard L. Wasserman [m], Kathleen C. Williams [n], Jordan S. Orange [o,*]

[a] *Robert Wood Johnson Clinical Scholars Program, University of Pennsylvania, Philadelphia, PA, USA*
[b] *Division of Pulmonary, Allergy and Critical Care, University of Pennsylvania School of Medicine, Leonard Davis Institute of Economics, University of Pennsylvania, Philadelphia, PA, USA*
[c] *Immune Deficiency Foundation, Towson, MD, USA*
[d] *The Department of Pediatrics, State University of New York at Buffalo, School of Medicine and Biomedical Sciences, Women's and Children's Hospital of Buffalo, Buffalo, NY, USA*
[e] *Division of Allergy and Immunology, Rainbow, Babies and Children's Hospital, Case Western Reserve University, USA*
[f] *Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA*
[g] *Division of Immunology, Children's Hospital Boston, Boston, MA, USA*
[h] *Department of Pediatrics, Harvard Medical School, Boston, MA, USA*
[i] *Division of Allergy and Immunology, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA*
[j] *Department of Medicine and Clinical Immunology, Mount Sinai School of Medicine, New York, USA*
[k] *Division of Allergy & Immunology, Children's Memorial Hospital, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*
[l] *Division of Allergy and Immunology, Department of Pediatrics, University of Toledo College of Medicine, Toledo, OH, USA*
[m] *Dallas Allergy Immunology, Dallas TX, USA*
[n] *Department of Geography, University of Wisconsin-Milwaukee, Milwaukee, WI, USA*
[o] *Division of Immunology, Children's Hospital of Philadelphia, Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*

* Corresponding author. The Children's Hospital of Philadelphia, 3615 Civic Center Blvd. ARC 1016H, Philadelphia, PA 10104, USA.
E-mail address: Orange@mail.med.upenn.edu (J.S. Orange).

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KEYWORDS
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hygiene

Abstract There are an expanding number of primary immunodeficiency diseases (PIDDs), each associated with unique diagnostic and therapeutic complexities. Limited data, however, exist supporting specific therapeutic interventions. Thus, a survey of PIDD management was administered to allergists/immunologists in the United States to identify current perspectives and practices. Among 405 respondents, the majority of key management practices identified were consistent with existing data and guidelines, including the provision of immunoglobulin therapy, immunoglobulin dosing and selective avoidance of live viral vaccines. Practices for which there are little specific data or evidence-based guidance were also examined, including evaluation of IgG trough levels for patients receiving immunoglobulin, use of prophylactic antibiotics and recommendations for complementary/alternative medicine. Here, variability applied to PIDD patients was identified. Differences between practitioners clinically focused upon PIDD and general allergists/immunologists were also identified. Thus, a need for expanded clinical research in PIDD to optimize management and potentially improve outcomes was defined.

Introduction

Primary immunodeficiency diseases (PIDDs) represent more than 150 rare disorders, which impair immunological defenses resulting in increased susceptibility to infections. While many PIDDs result from mutations in genes required for specific elements of immunity [1], the diagnoses can be classified according to the impaired immunologic host defense mechanisms. This can be useful as particular groups of defects are associated with susceptibility to specific types of infections [2]. Such categorization of defects has been central to diagnosis and guides patient management.

Expanded understanding of the defective immunological mechanisms in, and genes responsible for PIDDs has led to improved diagnostic precision [3] as well as greater insight into human immunity [4]. Despite these advances, there has been a relative paucity of research in the practical management of PIDD. Furthermore, as the number of diagnoses increase, the potential for expanded and more specialized management strategies is likely to increase proportionally. This has led to a complex clinical discipline with numerous patient management options, some of which are only supported by expert opinion [5].

To better define management practices applied to PIDD patients in the United States, a survey of allergist/immunologists who were members of the American Academy of Allergy Asthma and Immunology (AAAAI) was performed. The objectives were: (1) to identify consistencies in the management of PIDD patients in order to suggest standards of care and (2) to identify areas in which there is more variability or inconsistency with published data in order to define important questions for future research. The results demonstrated areas of agreement in the care of PIDD patients provided by sub-specialists, but also identified some management practices that were more divergent. Thus, in order to optimize the quality and uniformity of PIDD clinical care, specific areas for clinical research studies should be promoted, prioritized, and merit enhanced funding support.

Methods

Survey design and data collection

A web-based survey regarding specialist perspectives on and therapy for PIDD was designed, validated, applied and data collected as described in the online supplemental material. A version of the survey optimized for print is also provided therein.

Data analysis

Using SPSS software version 15.0 (SPSS Inc. Chicago IL), descriptive statistics were calculated and stratified by focused immunologists (those devoting >10% of their clinical practice to PIDD) and general immunologists (those devoting <10% of their clinical practice to PIDD). Bivariate analysis, using the Fisher exact test, was used to examine the relationship between clinical focus and the dichotomous dependent variables, including the use of IVIG, prophylactic antibiotics, and the use of hygiene and complementary and alternative medicine (CAM) interventions. Additionally, a logistic regression model was used to calculate odds ratios controlling for demographics of the respondents including sex, age, year of graduation from medical school, training and practice type. Differences were considered statistically significant when $p<0.05$.

Results

Demographics of the respondents and clinical experience with PIDD

Three-thousand AAAAI members were invited to participate in the survey and 405 submitted responses (13.5%). Respondents were predominantly male physicians who graduated from medical school after 1974, trained in pediatrics, and who were engaged in private practice (Table 1). Forty-six of the 50 United States were represented; with California and New York having the greatest

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Table 1 Demographics of respondents.

Characteristics	General (n=336, 82.4%)	Focused (n=72, 17.6%)
Sex*		
Female	85 (25.4%)	29 (40.3%)
Male	251 (74.7%)	43 (59.7%)
Age (years)	51.8 (SD 9.5)	52.1 (SD 10.5)
Year of graduation		
1990 or later	83 (24.7%)	21 (29.2%)
1975–1989	151 (44.9%)	31 (43.1%)
1974 or earlier	102 (30.4%)	20 (27.7%)
Training*		
Pediatrics	172 (51.2%)	51 (70.8%)
Internal medicine	153 (45.5%)	19 (26.4%)
Both	11 (3.3%)	2 (2.8%)
Practice type*		
Private practice	268 (79.8%)	20 (27.8%)
Academic	68 (20.2%)	52 (72.2%)

* Statistically significant difference between subgroups at $p<0.05$.

number or responses (Supplementary Figure 1). General immunologists (n=334), classified as those who devoted <10% of their clinical practice to PIDD, composed 82.5%, while focused immunologists (n=71) accounted for the remainder. Focused immunologists were more likely to be female pediatricians practicing in academic settings.

Differences were identified in reported experience with specific PIDD diagnoses, both historical and current. The exposure of general immunologists to common variable immunodeficiency (CVID) (86.8%) and IgA deficiency (IgAD) (83.5%) approached that of focused immunologists (98.6% and 95.8%, respectively). Focused immunologists, however, had significantly broader clinical experience with PIDDs. While >60% of focused immunologists reported experience with rarer PIDDs, such as agammaglobulinemia, hyper-IgE syndrome (HIES) and Wiskott–Aldrich syndrome (WAS), <35% of general immunologists reported similar exposure ($p<0.05$).

Use of IVIG for PIDD

PIDD is one of the US Food and Drug Administration-approved indications for immunoglobulin therapy and represents a major use of IVIG in the United States [6]. On average, general immunologists reported caring for 14.0 patients (range 0–150) on IVIG, compared to 42.4 patients (range 0–200) for focused practitioners. Recommendations for IVIG varied considerably across PIDD diagnoses and by immunologist subgroup (Fig. 1). Almost 100% recommended IVIG for at least some patients with agammaglobulinemia and CVID, compared to less than 7.0% for patients with IgAD. Among the other diagnoses there were distinctions between general and focused immunologists. Focused immunologists recommended IVIG for ataxia–telangiectasia (AT), HIGM, SCID, WAS and XLP more frequently than generalists ($p<0.05$). Interestingly, 44.6% of general immunologists reported recommending IVIG in at least some patients with complement deficiencies compared to only 16.9% of focused immunologists ($p<0.05$).

98% of respondents calculated initial dosages of IVIG for patients with antibody deficiencies based upon patient body weight with 65% using a starting point of 400 mg/dL (Fig. 2A). However, 31.4%, and 14.8% of focused and general immunologists, respectively, reported using higher initial weight-based doses of IVIG. Eighty-seven percent of respondents provided their initial dosage every 4 weeks, and 11% every 3 weeks. Focused immunologists were no more likely initially to recommend more frequent initial IVIG dosing. While 8.3% of immunologists reported not considering trough IgG levels in their administration of therapy, almost 75% targeted an IgG trough of 500–750 mg/dL when treating patients with humoral defects. Focused immunologists were significantly more likely to aim for trough levels >750 mg/dL ($p=0.02$) (Fig. 2B).

79.6% of immunologists reported that at least some of their patients receive their IVIG infusions in a hospital outpatient setting, and 66.2% had patients treated at home facilitated by a home infusion service. 21.1% of practitioners had some patients who self-infused IVIG at home without additional medical supervision, although focused immunologists are more likely to engage in this practice ($p=0.02$).

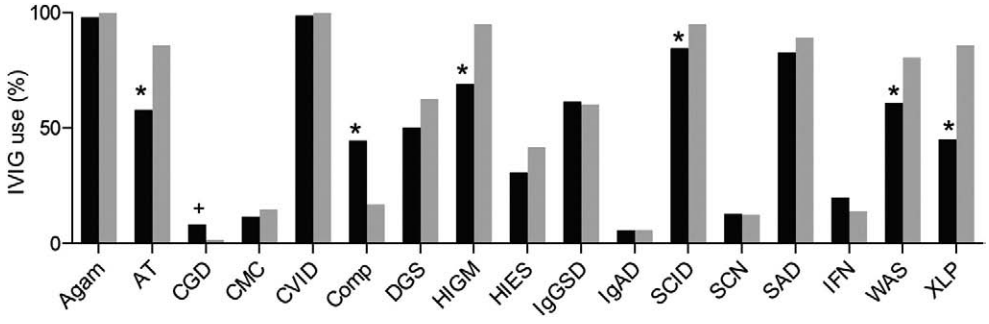

Figure 1 Percentage of general (black bars) and focused (gray bars) immunologists using IVIG for specific PIDD (in at least some patients with the listed diagnosis). N=408. *Significant difference ($p<0.05$). +Trend toward significant difference ($0.10<p<0.05$). Agam=agammaglobulinemia, AT=ataxia-telangiectasia, CGD=chronic granulomatous disease, CMC=chronic mucocutaneous candidiasis, CVID=common variable immunodeficiency, Comp=complement deficiency, DGS=DiGeorge syndrome, HIGM=hyper-IgM syndrome, HIES=hyper-IgE syndrome, IgGSCD=IgG subclass deficiency, IgAD=IgA deficiency, SCID=severe combined immunodeficiency, SCN=severe congenital neutropenia, SAD=specific antibody deficiency, IFN=inteferon-gamma receptor and type-I cytokine axis deficiency, WAS=Wiskott-Aldrich syndrome, XLP=X-linked lymphoproliferative syndrome.

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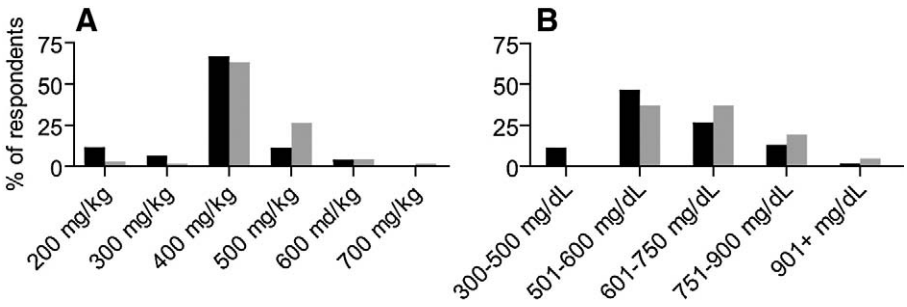

Figure 2 IVIG praxis of general (black bars) and focused (gray bars) immunologists for treatment of antibody disorders. $N=408$ (Note: *y*-axis scale is terminated at 75%). (A) Initial IVIG dosage. (B) Goal maintenance pre-IVIG infusion IgG trough.

A variety of medications were prescribed for use prior to IVIG infusion in order to reduce adverse events in at least some patients. These included acetaminophen (61.9%), antihistamines (83.8%), corticosteroids (32.9%), non-steroidal anti-inflammatory drugs (38.4%), and normal saline (31.6%). Focused practitioners were statistically more likely to prescribe antihistamines, corticosteroids, and non-steroidal anti-inflammatory agents as pre-medications. As administration of IVIG requires frequent intravenous access, 41.2% of general immunologists reported using implanted catheters in at least some of their patients to facilitate IVIG infusions compared to 69.6% of focused immunologists ($p<0.01$). Most commonly, however, this represented <5% of patients that a given immunologist was treating with IVIG.

When queried about pathogen safety, IVIG therapy was perceived by respondents as being associated with a risk of transmission of a variety of blood-borne infections. Over 80% of all respondents counseled patients on the risks of contracting prion disease through IVIG. Immunologists also counseled their patients on the risks of contracting Hepatitis C (76.4%), Hepatitis B (64.1%), human immunodeficiency virus (51.8%) and potentially undiscovered pathogens (96.6%).

Use of SCIG for PIDD

A limited number of questions were asked about the subcutaneous infusion of Ig for PIDDs associated with humoral immune defects. Importantly, FDA approval for a subcutaneous Ig was issued during the time-frame in which the survey was being conducted [7]. This said, 26.3% of immunologists believe that 25–50% of those patients who require immunoglobulin replacement would be better served by subcutaneous replacement, representing the most common opinion. 76% of respondents believed that subcutaneous immunoglobulin therapy was at least equal to IVIG for patients with antibody deficiencies with more focused

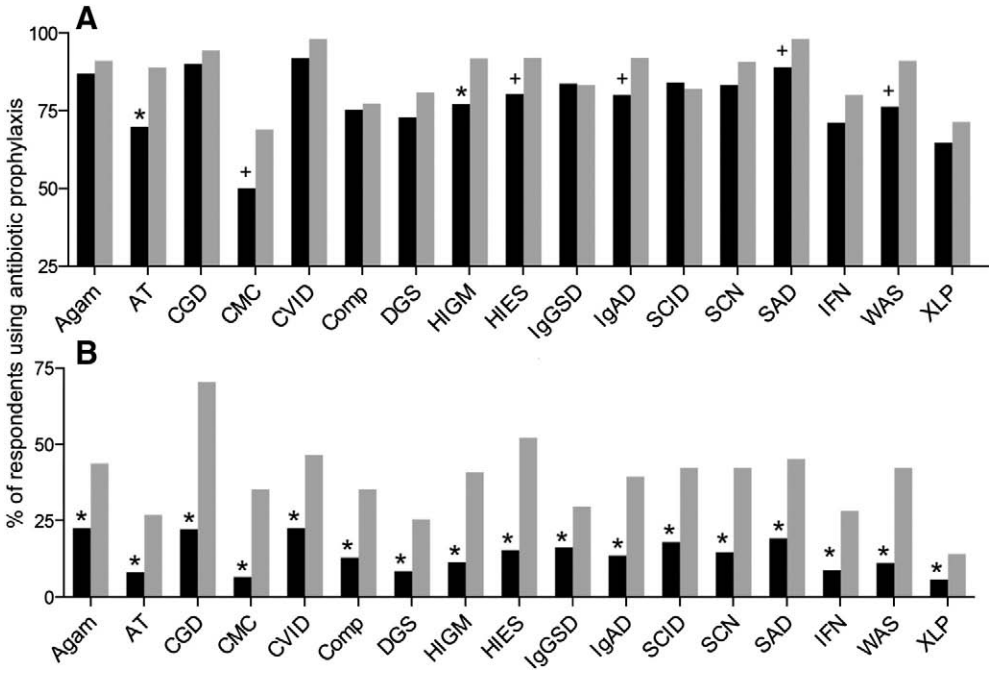

Figure 3 Antibiotic prophylaxis for PIDD. $N=408$. (A) Percentage of general (black bars) and focused (gray bars) immunologists using prophylactic antibiotics for at least some patients with specific PIDD. (B) Proportion of immunologists using prophylactic antibiotics who find prophylaxis moderately or extremely useful for specific PIDD. *Significant difference ($p<0.05$) (Note: *y*-axis scale in B is terminated at 75%). +Trend toward significant difference ($0.10<p<0.05$).

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Table 2 Most commonly prescribed prophylactic antibiotics (%).

For pediatric populations
Penicillin derivative/cephalosporins (22.2)
Amoxicillin (69.4)
Amoxicillin/clavulanic acid (13.5)
Trimethoprim/sulfamethoxazole (12.0)
Macrolides (1.5)
For adult populations
Penicillin derivative/cephalosporins (19.9)
Amoxicillin (62.8)
Amoxicillin/clavulanic acid (22.6)
Trimethoprim/sulfamethoxazole (14.0)
Macrolides (3.7)
Tetracyclines (1.7)
Fluoroquinolones (0.7)

immunologists (88.7%) having espoused this belief than general immunologists (68.6%) ($p<0.01$).

Prophylactic antibiotics

There is little evidence-based guidance regarding the use of antibiotic prophylaxis in PIDD patients and thus data were collected. 88.1% of focused and 47.7% of general immunologists reported utilizing prophylactic antibiotics to prevent infection in at least some of their PIDD patients (difference between groups was significant $p<0.05$). Over 75% of all respondents found prophylaxis clinically useful in at least some patients with all listed PIDD (except CMC —Fig. 3A). The greatest percentages (>90%) reported a perceived benefit for at least some CGD and CVID patients. Focused immunologists were more likely to have perceived a clinical utility of prophylactic antibiotics in patients with AT and HIGM than general immunologists. When examined further according to perceived degree of benefit, focused immunologists were more also likely than general immunologists to report finding prophylaxis moderately or extremely useful across all PIDDs (Fig. 3B). In addition, 75.7% of general, and 90.2% of focused immunologists used antibiotic prophylaxis as an adjunct to IVIG to prevent infection in at least some patients ($p=0.02$), with a minority (8.6%) having prescribed this for all or almost all patients receiving IVIG.

The most commonly prescribed antibiotic for prophylaxis in the PIDD patient population was amoxicillin. This was true for both pediatric and adult patients (Table 2) and was followed by trimethoprim-sulfamethoxazole. A few immunologists reported using macrolides in children and adults, but fluoroquinolones, only in adults. Fifty-two percent of immunologists rotated antibiotics when used for prophylaxis in antibody deficiencies, with 21.8% rotating on a monthly schedule.

Use of licensed vaccines

Sixty-four percent of respondents reported using licensed vaccines as a treatment of patients with PIDD outside the required pediatric immunization schedule and routine influenza vaccinations. Respondents also recommended avoidance of live viral vaccinations in selected PIDDs, most commonly SCID (71.4%), DiGeorge syndrome (52.6%) and agammaglobulinemia (51.6%). In the majority, they did not recommend live viral vaccine avoidance in other PIDD, including CGD, CVID, and XLP. Focused immunologists, however, were statistically more likely to avoid live viral vaccination of patients with HIGM, SCID and WAS (Fig. 4).

Complementary and alternative medicine (CAM) and hygiene

Because of the substantial use of CAM and hygiene interventions in general, specific questions targeted the perception of these practices in PIDD patients. A small but notable number of respondents believed CAM interventions, such as acupuncture, massage therapy and yoga, have a greater than placebo beneficial effect for enhancing immunity and preventing infections in patients with PIDD (Fig. 5). The most popular were aerobic exercise (24%), probiotics, vitamins, and nutritional supplements (each >9%).

With regards to hygiene measures, respondents believed that several offer good cost/benefit ratios for patients with PIDD (Fig. 6). Sixty-nine percent supported hand washing and 39% avoidance of daycare. While many immunologists favored alcohol-based hand gels for the patient (33.6%), family (27.9%) and classroom peers (22.0%), fewer believed that use of disinfectant cleaners and anti-bacterial soaps were justified. Less than 5% believed that HEPA filtration

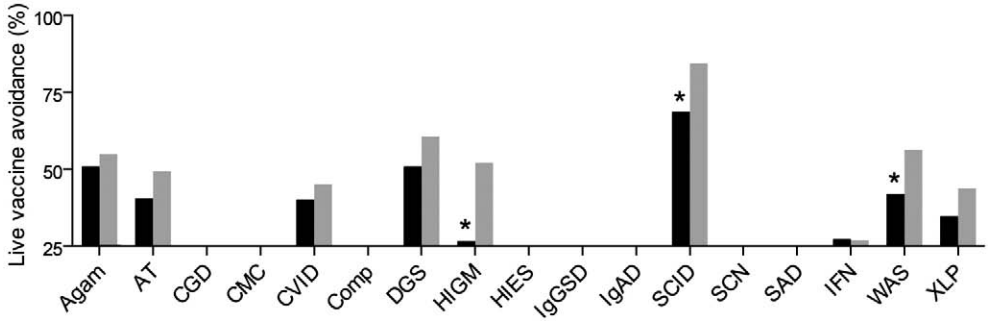

Figure 4 Percentage of general (black bars) and focused (gray bars) immunologists avoiding live viral vaccines for specific PIDD. $N=408$. *Significant difference ($p<0.05$). +Trend toward significant difference ($0.10<p<0.05$).

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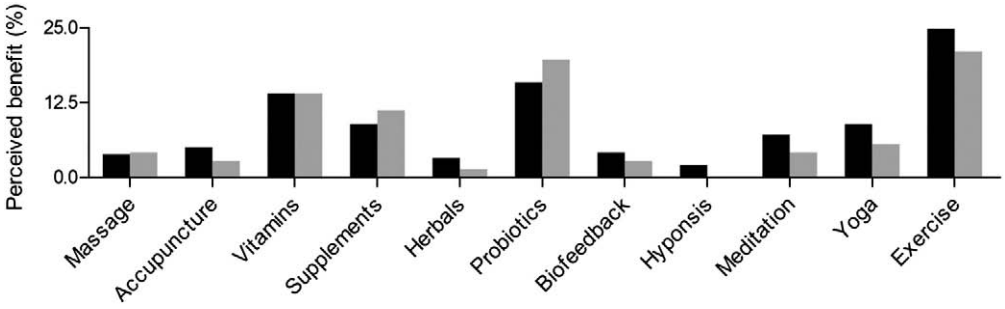

Figure 5 Percentage of general (black bars) and focused (gray bars) immunologists endorsing complementary and alternative medicine as beneficial for patients with PIDD. *N*=408 (Note: *y*-axis scale is terminated at 25%).

systems and dehumidifiers in the home environment benefited PIDD patients. There were no statistically significant differences in the opinions of general and focused immunologists regarding CAM or hygiene interventions. Data on the actual use of CAM or hygiene interventions by patients or recommendations made by immunologists were not collected as the focus was upon perceived benefit.

Multivariate logistic regression

As the survey respondents comprised a broad demographic range, multivariate logistic regression was performed to determine how demographic variables might have affected differences between focused and general immunologists. After controlling for demographic factors, focused immunologists remained more likely to recommend IVIG therapy for their patients with AT, HIGM and XLP. While significant differences were no longer found between the groups regarding perceived efficacy of subcutaneous immunoglobulin compared to IVIG, focused immunologists remained more likely to: (1) prescribe IVIG for their patients to be administered at home via self-infusion; (2) pre-medicate their patients receiving IVIG with antihistamines, steroids and non-steroidal anti-inflammatory agents; (3) recommend avoidance of live viral vaccines in HIGM (but the differences were no longer apparent for patients with SCID or WAS); and (4) view antibiotic prophylaxis as moderately or extremely useful across almost all PIDDs (excluding AT and HIGM) and were 17 times more likely than generalists to use prophylactic antibiotic therapy to prevent infections in PIDD patients.

Discussion

There are limited published primary data regarding clinical management of PIDD. Treatment decisions are likely based on case series, prior training or experience, expert opinions and/or data extrapolated from related studies and conditions. Placebo-controlled studies of interventions in PIDD are scarce and difficult to perform [8]. As a result, variations in care provided to PIDD patients are likely to increase as the numbers of patients diagnosed with PIDD in the United States increases [9]. The present work assessed specialist management practices and represents the largest scientifically conducted survey of the collective experience of practicing immunologists in the United States. There was a 13.5% response rate in this web-survey, which is comparable to general physician surveys conducted by telephone and mail. While many surveys of physicians offer financial incentives for participation this survey did not. Thus, given the extensive practice-related questions relating to PIDD in the survey, it is likely that any non-response bias was in the direction of AAAAI members with less interest in and experience with PIDD patients.

Importantly, the findings define certain routine standards of care, which are consistent with diagnostic and therapeutic

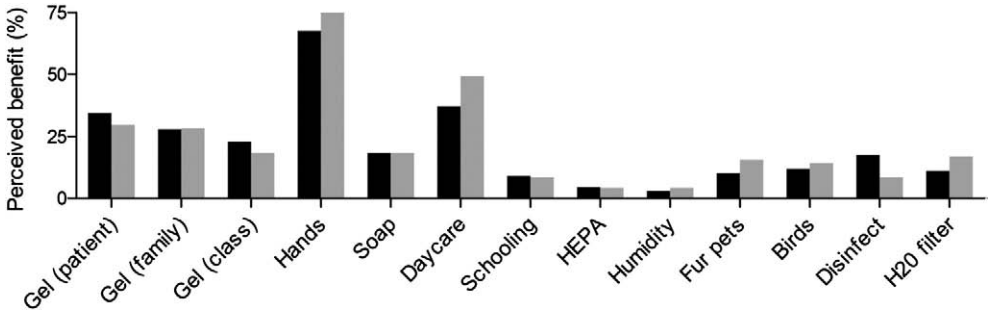

Figure 6 Percentage of general (black bars) and focused (gray bars) immunologists endorsing hygiene interventions as beneficial for patients with PIDD. *N*=408 (Note: *y*-axis scale is terminated at 75%). Gel, alcohol-based hand gel. Hands, hand washing. Soap, antibacterial soap. Daycare, daycare avoidance. Schooling, home schooling. HEPA, HEPA filter air purifiers. Fur pets, avoidance of furred pets. Birds, avoidance of feather pets. Disinfect, use of disinfectant cleaners. H_20 filter, use of water filtration.

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recommendations published by expert panels [5,10]. They also identify variability, especially in clinical situations where there is little quality data and guidelines are vague or non-existent. These results therefore identify areas in which additional research would be beneficial.

In general, important consistencies with existing guidelines include the use of IVIG in patients having diagnoses associated with absent B cells, or impaired IgG quality (Fig. 1) and not in PIDD diagnoses typically associated with intact B cell function [5,10]. Similarly the vast majority of immunologists prescribe IVIG consistent with product labeling at 400 mg/kg every 4 weeks. A substantial number, however, used higher initial doses of IVIG, a practice substantiated by studies demonstrating benefits to PIDD patients receiving higher maintenance doses [11-13]. Although 12% of immunologists reported administering IVIG more frequently than every 4 weeks there is scant data in this area. Most respondents reported checking trough IgG levels for PIDD receiving IVIG and the most frequently targeted level was 500 mg/dl - a level supported in studies of patients with PIDD [14-16]. The second most common practice was for maintaining trough levels even higher than 500 mg/dl, which is consistent with recent recommendations [10] as well as data from patients with agammaglobulinemia who had improved outcomes with these higher IgG troughs [15]. However, no prospective studies have evaluated specific IgG trough levels. Eight percent of immunologists reported not checking IgG through levels for patients receiving IVIG. While no reason for this practice was obtained, this may be more consistent with the concept of a "biological trough" in which a patient-specific dose regimen needs to be titrated to achieve an IgG trough level which is associated with clinical efficacy for that individual patient [17].

Immunologists appear to commonly use antibiotic prophylaxis in the care of PIDD patients. This practice was most consistently seen in CGD, likely because placebo-controlled studies showed remarkable improvements in clinical outcome in patients maintained on trimethoprim/sulfamethoxazole [18] and itraconazole [19]. The recommendations for using antibiotic prophylaxis in other diagnoses are less clear, and the data obtained in the survey were more variable. The most commonly used prophylactic antibiotic was amoxicillin in both pediatric and adult patients. Just over half of respondents claimed to rotate the prophylactic agent used, although there are no specific guidelines or data in PIDD regarding this practice. The avoidance of live viral vaccines was also common, but selectively applied to a majority of patients with SCID, DGS and agammaglobulinemia. This is substantiated by adverse outcomes of live viral vaccination previously reported in each of these patient populations [20,21], as well as in other PIDD patients [22-24]. Thus, more specific guidance or recommendations may be needed regarding the optimal use of vaccines in PIDD patients, even though in general live-viral vaccines are a contraindication in FDA-approved product licensing materials. It is noteworthy that there is no contraindication to the use of live virus Varicella vaccine in hypo- or agammaglobulinemic patients who have intact T cell function based on ACIP guidelines [25,26]. The optimized use of preventive vaccines and their efficacy versus safety risk is an area in need of further research. In addition, enhanced immunization of family members and caregivers to reduce infection risk to immunocompromised patients has been recommended and should be considered in PIDD (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm).

The survey noted common use of indwelling implanted catheters for venous access. This is contrary to existing guidelines [5,10]. Thrombotic events are potential adverse outcomes of IVIG therapy [27-29] and are listed as specific risks in IVIG licensing materials [30]. Given that indwelling venous access devices are associated with additional thrombogenic risks (with incidence as high as 50% [31]), and as the complication rate of indwelling devices in general approaches 31% [32], the two most recent AAAAI-associated PIDD guideline documents have specifically advised against the use of such devices [5,10]. Additional concerns exist regarding exposing immunodeficient patients to a foreign body, which could serve as a nidus for infection [33]. In rare circumstances, however, indwelling venous access devices offer a convenience to certain patients that may outweigh risks. This illustrates an opportunity for research, as prospective data on the actual incidence of complications of indwelling venous access devices in PIDD patients are not available. Given that subcutaneous immunoglobulin is now an option for PIDD patients the risk and benefit of this type of access needs to be reevaluated.

Numerous reports have documented the use of CAM and hygiene measures to either increase immune function or protect against infection in non-PIDD populations. Although there are essentially no data regarding CAM, or specific hygiene measures in patients with PIDD, their use and perceived benefit was common. Aerobic exercise, probiotics and vitamins were the most popular CAM, in that order. Evidence for each of these interventions in promoting immunity in non-PIDD populations exist [34-36] and in PIDD poor nutrition has been associated with lower immune indices [37]. Data on the use of specific dietary supplements/herbal medications in PIDD patients, however, are lacking. Hygiene measures were more widely perceived as useful and a majority perceive hand washing as beneficial. Only a minority, however, had the same opinion regarding the use of alcohol hand gels. Numerous studies demonstrate the equivalence (and even superiority) of alcohol hand gel to hand washing in reducing infection in the general population [38,39] and document the challenges of using proper hand washing technique [40]. Thus, a reevaluation of the perceived relative efficacy of hand washing is warranted. Since CAM and hygiene approaches are widely applied to PIDD patients, well-designed trials of these interventions as adjunct measures to improve outcome in PIDD are justified.

Although practices among immunologists were generally consistent, the survey also identified and evaluated differences between the 18% of responding immunologists who devote >10% of their clinical practices to the care of PIDD patients ("focused immunologists") as compared to the 82% of general immunologists. Examples included: (1) more frequent use of IVIG for certain PIDDs such as HIGM, WAS, XLP and SCID; (2) use of higher starting doses of IVIG and higher target trough IgG levels; (3) increased use of premedications to prevent and manage IVIG-associated adverse events; (4) more likely and uniform use of prophylactic antibiotics in PIDD; (5) greater likelihood of perceiving SCIG as therapeutically equivalent to IVIG; and (6)

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more frequent avoidance of live viral vaccinations in SCID, HIGM and WAS. Differences in the use of IVIG in specific indications, use of prophylactic antibiotics, and use of live viral vaccines withstood multivariate logistic regressions controlling for demographic factors. Therefore, these differences define variation among specialists, which correlate with the percentage of an individual physician's clinical effort devoted to caring for patients with PIDDs. Although case series and case reports may justify some of these practices, there have been no clinical trials substantiating many of the statistically different practices of the focused immunologists. Some of the differences however, likely arise because of the teaching of specific Allergy/Immunology training programs, the severity of cases presenting to academic medical centers, and geographical region of practice as they were no longer apparent after logistic regression. It is also possible that other differences may be due to more complex patients being referred to focused immunologists, necessitating certain differences in patient management. This illustrates the need for systematic tabulation and dissemination of the most current data to all immunologists who care for PIDD patients. The standardization of best practices is essential and suggests the ongoing need for clinical research, formulation of evidence-based practice guidelines and educational efforts aimed at both trainees and practitioners.

Conflict of interest statement

Consultancies or Medical/scientific advisory board membership for America's Health Insurance Plans (M. Berger), Baxter Biosciences (M. Ballow, M. Berger., J.B., C.C-R., R.F., R.L.W., J.S.O.), CSL Behring (M. Ballow, M. Berger., F.A.B., R.L.W., J.S.O.), IBT reference laboratories (J.S.O.), Rx Solutions (F.A.B.), Talecris Biosciences (M. Ballow, M. Berger., F.A.B., R.L.W., J.S.O.). Research support from Baxter Bioscience (M. Berger, C.C.-R., R.L.W.), CSL Behring (R.L.W.), FFF enterprises (R.L.W.), Genentech (L.N., R.L.W.), Novartis (L.N., R.L.W.), Omrix (R.L.W.), Talecris Biosciences (M. Ballow, M. Berger, R.L.W., F.A.B.). Speakers bureaus for Baxter Biosciences (R.L.W.), CSL Behring (M. Ballow , R.L.W.), Talecris Biosciences (R.L.W.). Medical advisory council and or visiting professorship program for the Immune Deficiency Foundation (F.A.B., C.C-R., R.F., J.S.O.). All authors except J.B., M. Boyle and K.C.W., are members of the AAAAI and some hold elected offices (M. Ballow, C.C-R., F.A.B, J.S.O.). From 2005-2007 KCW was a full-time employee of Executive Director, Inc an association management company responsible for the day-to-day operation of the AAAAI. M. Berger is presently a full-time employee of and stock holder in CSL-Behring. While the survey was designed and conducted, however, he was full-time faculty at Case Western Reserve University. M. Boyle is the President and Founder of the Immune Deficiency Foundation. J.B. is a member of the Board of Trustees of the Immune Deficiency Foundation and is a Principal of SRBI, a research organization specializing in public policy and opinion surveys. P.L.Y. and J.C. had no potential conflicts to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clim.2009.10.003.

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Supplementary Material for Yong, et. al.

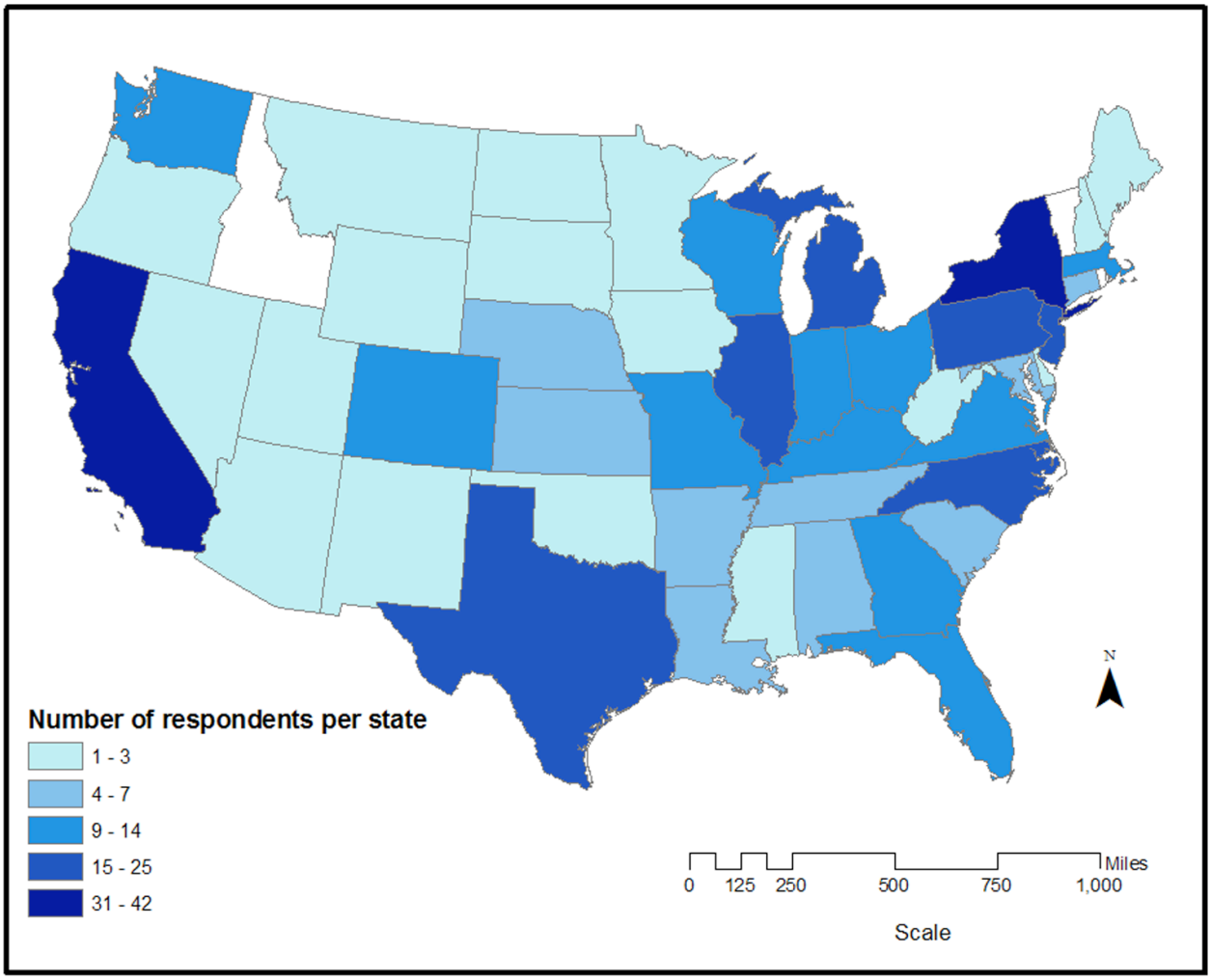
Supplementary Methods

Survey Design and Data Collection

A survey regarding specialist perspectives on and therapy for PIDD was designed jointly by the co-authors and reviewed by several members of the Primary Immunodeficiency Committee of the AAAAI. The survey instrument was then submitted to the Needs Assessment and Practice and Policy Committees of the AAAAI for further analysis and redesign. The final survey was coded for web acquisition of responses using drop down menus, response "buttons" and free form text fields by the AAAAI web services team. The web interface was then pilot tested by a subcommittee of the Primary Immunodeficiency Committee and data export as tab-limited text was validated. After functional validation, an e-mail inviting participation in a web-based survey was sent to all 3000 physician members of the AAAAI. Four subsequent reminder e-mails were sent prior to the close of the 4-month survey period. No financial incentives for participation were offered or provided. All replies were entered into an electronic database, which was used to generate tab-limited text reports that could be evaluated using Microsoft Excel and other software programs. Each physician was allowed to respond to the survey only once. Any duplicates were removed, and only the first survey response was used for analysis. A version of the survey optimized for printed pages, which verbatim recounts the specific questions asked of physicians, is provided on pages 4-7 of this supplement.

Suplementary Figure

Supplementary Figure 1: Number of survey respondents according to state of practice. Surveys were tabulated according to the state in which the respondent identified as that of their primary site of their clinical practice. Data were projected onto a map of the continental US using a color scale identified in the legend. There were no surveys submitted from Alaska or Hawaii and the greatest number from a single state was 42.



Survey Instrument: A version of the survey instrument optimized for viewing on a printed page is provided. The actual instrument was web based and consisted of response fields and drop down menus. The text provided in the provided version is identical to that used in the web-based version.

SPECIALIST PHYSICIAN PERSPECTIVES ON PRIMARY IMMUNODEFICIENCY DISEASES (PID) IN THE UNITED STATES: 2005

1. How much of your clinical practice is devoted to patients with PID or suspected of having PID?

- O <1%
- O 1-5%
- O 6-10%
- O 11-25%
- O 26-50%
- O 51-75%
- O >75%

2. In what type of ambulatory care setting do you spend MOST of your patient care time?

- O Solo practice
- O Single-specialty group practice
- O Multi-specialty group practice
- O HMO
- O Hospital outpatient
- O Other, please specify below

_____

3. In an average month, about how many patients do you see on an outpatient basis? (Your best estimate is fine.)

_____ patients per week

4. Have you ever treated patients with the following diagnoses?
MARK AS MANY AS APPLY

- O Agammaglobulinemia
- O Ataxia telangiectasia
- O Chronic granulomatous disease
- O Chronic mucocutanous candidiasis
- O Common variable immunodeficiency (CVID)
- O Complement deficiency
- O DiGeorge syndrome
- O Hyper IgM syndrome
- O Hyper IgE syndrome
- O IgG subclass deficiency
- O Selective IgA deficiency
- O Severe combined immunodeficiency (SCID)
- O Severe congenital neutropenia
- O Specific antibody deficiency
- O IFN-γ/IL-12 cytokine axis defect
- O Wiskott-Aldrich syndrome
- O X-linked lymphoproliferative syndrome (XLP)
- O None of these ever

IF NONE EVER, SKIP TO Q30a on Page 4

5. Do you currently follow any patients with the following diagnoses?
MARK AS MANY AS APPLY

- O Agammaglobulinemia
- O Ataxia telangiectasia
- O Chronic granulomatous disease
- O Chronic mucocutanous candidiasis
- O Common variable immunodeficiency (CVID)
- O Complement deficiency
- O DiGeorge syndrome
- O Hyper IgM syndrome
- O Hyper IgE syndrome
- O IgG subclass deficiency
- O Selective IgA deficiency
- O Severe combined immunodeficiency (SCID)
- O Severe congenital neutropenia
- O Specific antibody deficiency
- O Wiskott-Aldrich syndrome
- O X-linked lymphoproliferative syndrome (XLP)
- O None of these currently

6. In counseling a PID patient about to start IVIG therapy, how would you present their risk of contracting the following diseases as a result of treatment.

	NO RISK	⇩ LOW RISK	⇩ MODERATE RISK	⇩ HIGH RISK
HIV	O	O	O	O
Hepatitis B	O	O	O	O
Hepatitis C	O	O	O	O
Prion disease	O	O	O	O
Rotavirus	O	O	O	O
Yet to be discovered pathogens	O	O	O	O

7. Would you recommend intravenous immunoglobulin (IVIG) therapy for all, most, some, or few to no patients with…

	FEW TO NONE (<5%)	⇩ SOME (5-50%)	⇩ MOST (>50%)	⇩ ALL OR ALMOST ALL (>95%)
Agammaglobulinemia	O	O	O	O

Ataxia telangiectasia	○	○	○	○
Chronic granulomatous disease	○	○	○	○
Chronic mucocutanous candidia	○	○	○	○
CVID	○	○	○	○
Complement deficiency	○	○	○	○
DiGeorge syndrome	○	○	○	○
Hyper IgM syndrome	○	○	○	○
Hyper IgE syndrome	○	○	○	○
IgG subclass deficiency	○	○	○	○
Selective IgA deficiency	○	○	○	○
SCID	○	○	○	○
Severe congenital neutropenia	○	○	○	○
Specific antibody deficiency	○	○	○	○
IFN-γ/IL-12 cytokine axis defect	○	○	○	○
Wiskott-Aldrich syndrome	○	○	○	○
XLP	○	○	○	○

8. About how many PID patients do you follow who are maintained on IVIG to prevent infection?

_____ NUMBER

If zero skip to question 18

Questions 9 – 14 refer specifically to IVIG administered intravenously.

9. What percentage of your patients receives their IVIG at following sites?

	FEW TO NONE (<5%)	⇩	⇩	⇩
	SOME (5-50%)	⇩	⇩	⇩
	MOST (>50%)	⇩	⇩	⇩
	ALL OR ALMOST ALL (>95%)	⇩	⇩	⇩
Your office		○	○	○	○
Hospital outpatient infusion suite		○	○	○	○
Hospital inpatient		○	○	○	○
home with nurse		○	○	○	○
home via self infusion		○	○	○	○

10. What is the usual interval with which you recommend patients with antibody disorders receive their IVIG (on average)?

- ○ Every week
- ○ Every 2 weeks
- ○ Every 3 weeks
- ○ Every 4 weeks
- ○ Every 5 weeks
- ○ Every 6 or more weeks

11. What is the usual initial IVIG dosage per kilogram of body weight that you typically recommend for patients with antibody disorders (given at the interval in question 10)?

- ○ ≤200 mg/kg
- ○ 300 mg/kg
- ○ 400 mg/kg
- ○ 500 mg/kg
- ○ 600 mg/kg
- ○ >600 mg/kg
- ○ I do not consider mg/kg when dosing IVIG

12. What percentage of your patients receiving IVIG is pre-medicated with the following to facilitate infusions?

	FEW TO NONE (<5%)	⇩	⇩	⇩
	SOME (5-50%)	⇩	⇩	⇩
	MOST (>50%)	⇩	⇩	⇩
	ALL OR ALMOST ALL (>95%)	⇩	⇩	⇩
Acetaminophen		○	○	○	○
Antihistamine		○	○	○	○
Corticosteroid		○	○	○	○
Nonsteroidal anti-inflammatory		○	○	○	○
Saline IV		○	○	○	○

13. How many of your PID patients receiving IVIG have surgically implanted access devices to facilitate IVIG infusions?

- ○ >75%
- ○ 51-75%
- ○ 26-50%
- ○ 5-25%
- ○ <5%
- ○ None

14. What pre-infusion IgG trough do you try to achieve in your hypogammaglobulinemic patients?

- ○ 300-500mg/dl
- ○ 500-600mg/dl
- ○ 600-750mg/dl
- ○ 750-900mg/dl
- ○ >900mg/dl
- ○ I do not consider pre-infusion IgG levels.

15. How effective overall do you believe subcutaneous immunoglobulin therapy is compared to IVIG for patients with antibody deficiencies.

- ○ Much more effective
- ○ Somewhat more effective
- ○ Equally effective
- ○ Somewhat less effective
- ○ Much less effective
- ○ Not sure

16. What proportion of your patients who require immunoglobulin replacement therapy do you believe will ultimately be better served by

subcutaneous immunoglobulin?

- ○ >75%
- ○ 50-75%
- ○ 25-50%
- ○ 5-25%
- ○ <5%

17. How much risk do current reimbursement standards for IVIG pose to the health of PID patients?

- ○ Extreme risk
- ○ Serious risk
- ○ Moderate risk
- ○ Slight risk
- ○ No real risk

18. Approximately, what proportion of your patients with mild to moderate PID would you say are satisfied with the management of their disease? Would you say...

- ○ All (91-100%)
- ○ Most (51-90%)
- ○ Some (11-50%)
- ○ Few (1-10%)
- ○ None (0%)

19. On average, how often do you recommend that PID patients in otherwise good health be seen by an allergist/immunologist?

- ○ Every 3 months
- ○ Every 6 months
- ○ Every 12 months
- ○ Every 2 years
- ○ Only if levels or symptoms change

20. Do you use prophylactic antibiotic therapy for some of your patients with PID to prevent infection (excluding *Pneumocystis* prophylaxis)?

- ○ Yes
- ○ No - go to question 26

21. In which primary immunodeficiency diseases do you feel that prophylactic antibiotic therapy can be mildly, moderately or extremely clinically useful in preventing infection (excluding *Pneumocystis* prophylaxis).

	Extremely Useful	Moderately Useful	Mildly Useful	Not useful at all
Agammaglobulinemia	○	○	○	○
Ataxia telangiectasia	○	○	○	○
Chronic granulomatous disease	○	○	○	○
Chronic mucocutanous candidia	○	○	○	○
CVID	○	○	○	○
Complement deficiency	○	○	○	○
DiGeorge syndrome	○	○	○	○
Hyper IgM syndrome	○	○	○	○
Hyper IgE syndrome	○	○	○	○
IgG subclass deficiency	○	○	○	○
Selective IgA deficiency	○	○	○	○
SCID	○	○	○	○
Severe congenital neutropenia	○	○	○	○
Specific antibody deficiency	○	○	○	○
IFN-γ/IL-12 cytokine axis defect	○	○	○	○
Wiskott-Aldrich syndrome	○	○	○	○
XLP	○	○	○	○

22. What is the prophylactic antibiotic you use most commonly to prevent infection in children with antibody deficiencies?

_____

at a dose of _____mg/kg every _____ ○ hours ○ days

23. What is the prophylactic antibiotic you use most commonly to prevent infection adults with antibody deficiencies?

_____

at a dose of _____mg every _____ ○ hours ○ days

24. Do you rotate the antibiotic you use for prophylaxis in your patients with antibody deficiencies?

- ○ No, I do not rotate prophylactic antibiotics
- ○ Yes, I typically rotate antibiotics *monthly*
- ○ Yes, I typically rotate antibiotics *biannually*
- ○ Yes, I typically rotate antibiotics *annually*
- ○ Yes, I typically rotate prophylactic antibiotics but using some other regimen.

25. Do you use prophylactic antibiotic therapy as an adjunct to IVIG in order to prevent infection in patients with PID.

- ○ In all patients (91-100%)
- ○ In most patient (51-90%)
- ○ In some patients (11-50%)
- ○ In a few patients (1-10%)
- ○ I never use antibiotics this way (0%)

26. Do you believe there is a greater than placebo effect benefit to any of the following alternative therapies for enhancing immunity,

or preventing infection in patients with PID?
MARK AS MANY AS APPLY

- O Massage therapy
- O Acupuncture
- O Vitamins
- O Nutritional supplements
- O Herbal formulations
- O Probiotics
- O Biofeedback
- O Hypnotherapy
- O Meditation
- O Yoga
- O Aerobic exercise

27. Do you believe that any of the following hygiene related interventions offer a greater benefit than cost for patients with PID?
MARK AS MANY AS APPLY

- O Alcohol-based hand gels for patient
- O Alcohol-based hand gels for family
- O Alcohol-based hand gels for classroom
- O Regular soap and water handwashing
- O Use of anti-bacterial soaps
- O Avoidance of daycare
- O Home schooling
- O HEPA filter-based air purifiers in the home
- O Dehumidification systems in the home
- O Exclusion of furred pets from the home
- O Exclusion of feathered pets from the home
- O Use of disinfectant cleaners in the home
- O Use of water filtration systems in the home

28. Do you use licensed vaccines as a treatment for PID patients (not including allergy vaccines, influenza vaccination, or the required pediatric immunization schedule).

- O In all patients (91-100%)
- O In most patients (51-90%)
- O In some patients (11-50%)
- O In a few patients (1-10%)
- O I never use vaccines this way (0%)

29. For which PID patients do you recommend avoidance of live viral vaccination.
MARK AS MANY AS APPLY

- O Agammaglobulinemia
- O Ataxia telangiectasia
- O Chronic granulomatous disease
- O Chronic mucocutanous candidiasis
- O Common variable immunodeficiency (CVID)
- O Complement deficiency
- O DiGeorge syndrome
- O Hyper IgM syndrome
- O Hyper IgE syndrome
- O IgG subclass deficiency
- O Selective IgA deficiency
- O Severe combined immunodeficiency (SCID)
- O Severe congenital neutropenia
- O Specific antibody deficiency
- O IFN-γ/IL-12 cytokine axis defect
- O Wiskott-Aldrich syndrome
- O X-linked lymphoproliferative syndrome (XLP)

30a. Are you aware of any professional guidelines for the diagnosis and management of primary immunodeficiency diseases?

- O Yes
- O No **SKIP TO Q31**

30b. Who publishes those guidelines?

_____

31. Do you know that physicians in your community who may not get this survey are caring for PID patients?

- O Yes **ANSWER Q32**
- O No **SKIP TO Q33**

32. What are their specialties? (check all that apply)

- O Immunology
- O Pediatric Rheumatology
- O Adult Rheumatology
- O Pediatric Infectious Diseases
- O Adult Infectious Diseases
- O Hematology Oncology
- O Other_____

33. In what year did you graduate from medical school?

_____ YEAR

Please try to answer all questions to the best of your ability based upon your average approach to the "typical" patient with PID. If you have specific additional concerns or comments regarding a particular question you may list them below (or separately).

Question Concern

_____ _____
_____
_____

_____ _____
_____
_____

Your responses will be kept confidential.