

Impact of intravenous immunoglobulin (IVIG) treatment among patients with Primary Immunodeficiency diseases¹

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1. Background

Primary immunodeficiency diseases (PIDD) represent a class of disorders in which there is an intrinsic defect in the human immune system (rather than immune disorders that are secondary to infection, chemotherapy, or some other external agent). In some cases, the body fails to produce any or enough antibodies to fight infection. In other cases, the cellular defenses against infection fail to work properly. There are more than 150 different primary immunodeficiency diseases currently recognized by the World Health Organization [1].

Primary immunodeficiency diseases are often described as rare disorders, but the worldwide incidence and population prevalence of these diseases, either individually or in the aggregate, is not well established. There have been some estimates of the incidence and prevalence of some disorders based on primary immunodeficiency registries in various countries [2,3]. In 2005, a national telephone survey of 10,000 households by the Immune Deficiency Foundation (IDF) yielded an estimated population prevalence of diagnosed primary immunodeficiency diseases at 1 in 1,200 persons in the United States. When applied to the U.S. population of 297,386,000 persons, this suggests approximately 250,000 persons have a diagnosed primary immunodeficiency disease in the United States [4]. Unfortunately no similar study has been done in Europe.

The Immune Deficiency Foundation has commissioned a series of surveys over the past decade to try to estimate the characteristics and experiences of patients with primary immunodeficiency diseases in the United States. The First National Patient Survey was conducted by IDF in 1996–1997. Nearly 3,000 persons with a diagnosis of a primary immunodeficiency disease participated in this survey. Those patients

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from the first national patient survey who reported being treated with intravenous immunoglobulin were included in the First IDF Treatment Survey, which was conducted in 1997. A Second National Survey of Patients with Primary Immune Deficiency Diseases was conducted by IDF in the fall of 2002. A total of more than 1,500 patients with primary immunodeficiency diseases, who were not interviewed in the first national patient survey, completed the second national patient survey. Subsequently, IDF conducted a Survey of the Treatment Experiences and Preferences of Patients with Primary Immune Deficiency Diseases in the fall of 2002 with samples of the patients who participated in the first national patient survey and the second national patient survey.

This paper draws upon the findings of these four national surveys of patients (or parents of patients) with primary immunodeficiency diseases in the United States. It should be noted, however, that the IDF mailing lists provided the sampling frame for these surveys. Although the samples are large and distributed nationally, unlike the prevalence survey they are not true probability samples of the total population. Patients who are associated with patient organizations are likely to be more knowledgeable about their condition and treatment. Hence, their treatment experience may be closer aligned with professional standards of care than patients who are not as engaged with a patient organization.

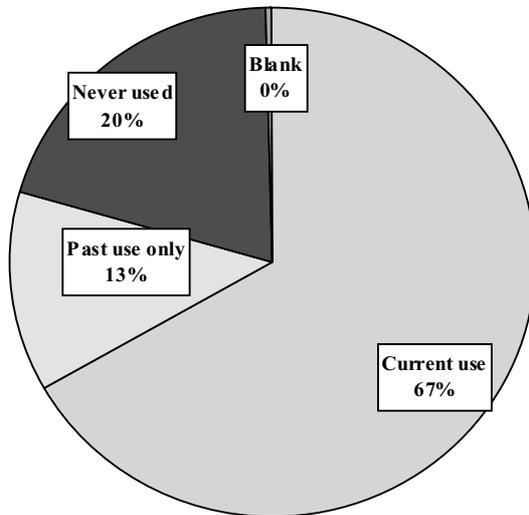
2. Diagnosis and treatment

The prevalence of specific diagnoses in the Second National Patient Survey in 2002 was similar to the distribution reported in a 1995 survey of medical specialist who had patients with PIDD. The most common diagnosis was Common Variable Immune Deficiency, which accounts for a majority (52%) of the patient sample. The next most common diagnoses were IgG Subclass Deficiency (12%) and IgA Subclass Deficiency (10%). X-linked agammaglobulinemia (XLA) was the fourth most common of the primary immunodeficiency diseases in the patient sample (8%). Smaller proportions of patients report Severe Combined Immune Deficiency (2%), Chronic Granulomatous Disease (2%), Hyper IgM (2%), DiGeorge Anomaly (1%), and Wiskott-Aldrich Syndrome (1%). Seven percent reported other diagnoses and 2% reported no specific diagnosis.

Four out of five patients with primary immunodeficiency disease in the Second National Patient Survey report that they have been treated with intravenous immunoglobulin (IVIG) for their disorder. Two thirds (67%) were currently being treated with IVIG. However, one in eight patients with a primary immunodeficiency disease (13%) had stopped taking IVIG (Fig. 1).

The discontinuing IVIG users were asked why they were no longer being treated with IVIG. Some discontinuing IVIG users reported that better health (12%) and/or normal to near normal immunoglobulin levels (12%) were the reasons that stopped the therapy. Others did so because their doctors didn't think it was necessary (10%),

Use of IGIV Status



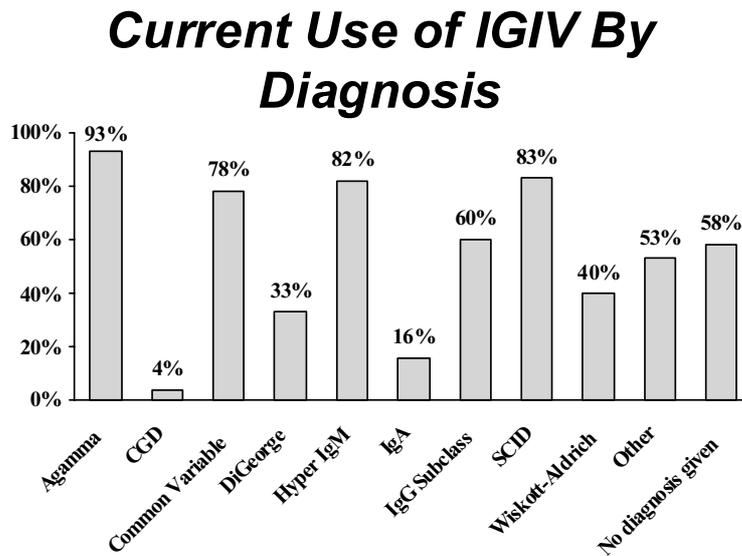
Q31. Has he/she ever been treated with intravenous gammaglobulin (IGIV) on a regular basis. Q33a. Is he/she currently being treated with intravenous gammaglobulin (IGIV) for his/her immune deficiency disease? (Base: N=1,526)

Source: IDF2003 Second National Patient Survey

Fig. 1.

they felt that there were no real benefits (9%) or they wanted to see how they did without IVIG treatment (8%). A small proportion had been cured by bone marrow transplantation (4%). Nonetheless, some patients diagnosed with primary immunodeficiency who had discontinued this treatment did so due to a lack of insurance coverage (14%), side effects or reactions to IVIG (12%), fear of contracting disease through the product (3%), costs or coverage of treatment (5%), or lack of product availability (3%). Nearly half of patients with primary immunodeficiency diseases who discontinued using IVIG had one of these non-medical reasons for not using IVIG.

Current IVIG use varies by diagnosis among primary immunodeficiency diseases. It is most common for X-linked Agammaglobulinemia (93%). It is also commonly reported by four out of five of those with Common Variable Immunodeficiency (78%), Hyper IgM (82%) and Severe Combined Immunodeficiency (83%). It is also reported by a majority of patients with IgG Subclass Deficiency (60%). It is least commonly used for DiGeorge Anomaly (33%), IgA deficiency (16%) and Chronic Granulomatous Disease (4%) (Fig. 2). In general, most, but not all of those patients with antibody deficiencies were currently being treated with IVIG.



Q33a. Is he/she currently being treated with intravenous gammaglobulin (IGIV) for his/her immune deficiency disease? (Base: N=1,526)

Source: IDF 2003 Second National Patient Survey

Fig. 2.

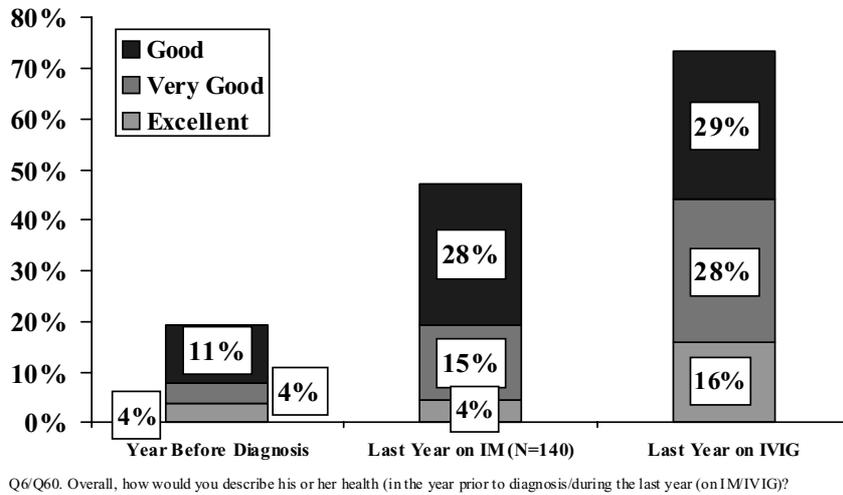
3. Impact of treatment on patient health and quality of life

In the 1997 IDF Treatment Survey, patients who had been treated with IVIG were asked about various aspects of their health status during the year prior to diagnosis and during the last year (or their last year on IVIG). A segment of the patient population had initially been treated for the primary immunodeficiency disease with intramuscular (IM) immunoglobulin before IVIG had been approved by the FDA. These patients were also asked about their health status during their last year on IM therapy.

Self-reported health status is the best global measure of individual health. Most patients with PIDD (or their parents) described their overall self-reported health status as only fair or poor during the year prior to diagnosis. Less than one in five said that they would describe their health in the year prior to diagnosis as excellent (4%), very good (4%), or good (11%). By contrast, patients report an improvement in their overall health status after diagnosis and treatment during the last year on intramuscular immunoglobulin with nearly half rating their health as excellent (4%), very good (15%) or good (28%) (Fig. 3).

According to patients with PIDD, treatment with IVIG has further improved their overall health status. Nearly three quarters of patients reported their overall health to be excellent (16%), very good (28%) or good (29%) during their last year (on IVIG).

Health Status: Before and After Treatment



Source: IDF 1997 First National Treatment Survey

Fig. 3.

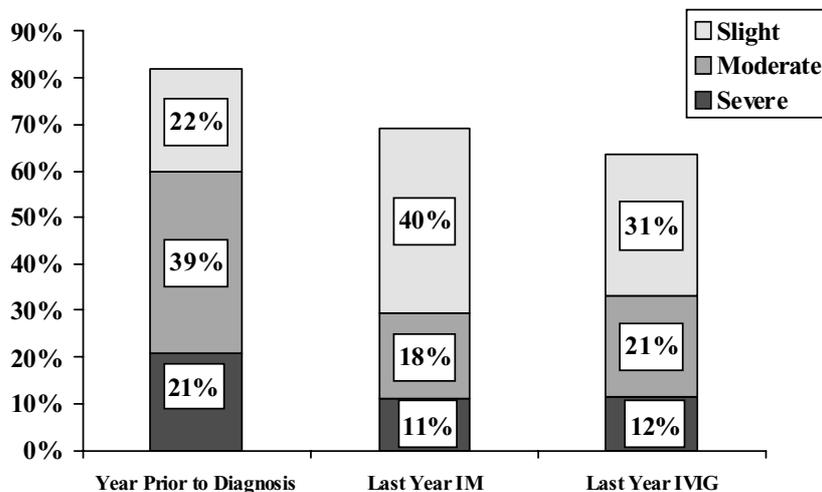
This is nearly four times as many patients who reported their current health as good or better compared to the year prior to diagnosis and treatment. It is also four times as many patients who reported their health on IVIG as excellent compared to the last year on IM (Fig. 3).

A second, more specific, measure of health status is activity limitation. Patients were asked what limitations on work, play or normal activities of living, if any, did they have as a result of illness in the year prior to diagnosis. Four out of five patients with PIDD reported at least slight limitations in activities as a result of their health in the year prior to diagnosis. Three out of five reported severe (21%) or moderate (39%) activity limitations due to health in the year prior to diagnosis (Fig. 4).

Treatment reduces the degree of activity limitation due to health in patients with PIDD, but not to the extent seen with self-reported health ratings. The proportion that reports any activity limitations due to health declines from 80% in the year prior to diagnosis to 64% in the last year (on IVIG). The proportion of patients that reports moderate or severe activity limitations due to PIDD declines from 60% in the year prior to diagnosis to 33% in the most recent year on IVIG (Fig. 4).

It is important to note in the evaluation of the efficacy of IVIG treatment for PIDD that nearly two out of five patients with PIDD (37%) in the second national patient survey report permanent functional impairment as a result of infections prior to their diagnosis. Nearly a quarter (23%) of patients reported they had suffered

Activity Limitation: Pre/Post Treatment



Q15/Q42/Q69 What limitations on work, play or normal activities of living, if any, did the patient have as a result of illness (in the year prior to diagnosis/during the last year (on IM/IVIG)?

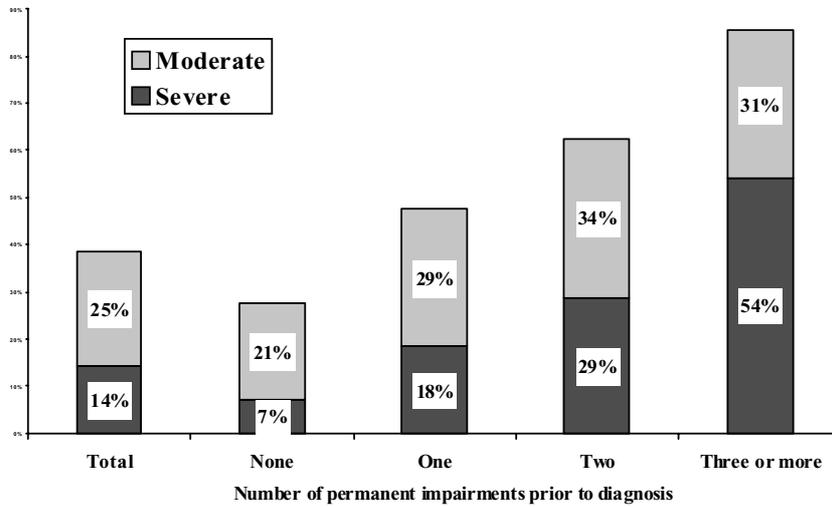
Source: IDF 1997 First National Treatment Survey

Fig. 4.

a permanent loss of lung function prior to diagnosis. About one in ten patients with PIDD reported a permanent loss of hearing (11%) or digestive function (9%) prior to diagnosis. Others reported permanent loss of mobility (7%), vision (2%), neurological functioning (2%) or other permanent loss (6%) prior to diagnosis. Some patients reported multiple functional impairments prior to diagnosis.

Current activity limitation is directly affected by functional impairment prior to diagnosis (Fig. 5). Only 28% of patients who had no permanent loss of function prior to their PIDD diagnosis reported severe (7%) or moderate (21%) activity limitation in the last year as a result of their health. By contrast, nearly half of those who had a permanent loss of one function prior to diagnosis had severe (18%) or moderate (29%) activity limitation in the last year. The proportion of patients with severe or moderate activity limitations increases to 63% of those with two functional impairments prior to diagnosis and 84% of those with three or more functional impairments prior to diagnosis (Fig. 5). Despite the effectiveness of IVIG in improving the patients' ability to avoid repeated, unusual and severe infections, IVIG cannot reverse the permanent organ damage done by such infections prior to diagnosis. Hence, early diagnosis needs to be coupled with effective treatment for a patient with PIDD to expect normal health status after treatment.

Current Activity Limitation by Number of Functional Impairments before Diagnosis



Q22. How much is he/she limited in work, play or normal physical activity as a result of his/her health? (Base: N=1,526)

Source: IDF 2003 Second National Patient Survey

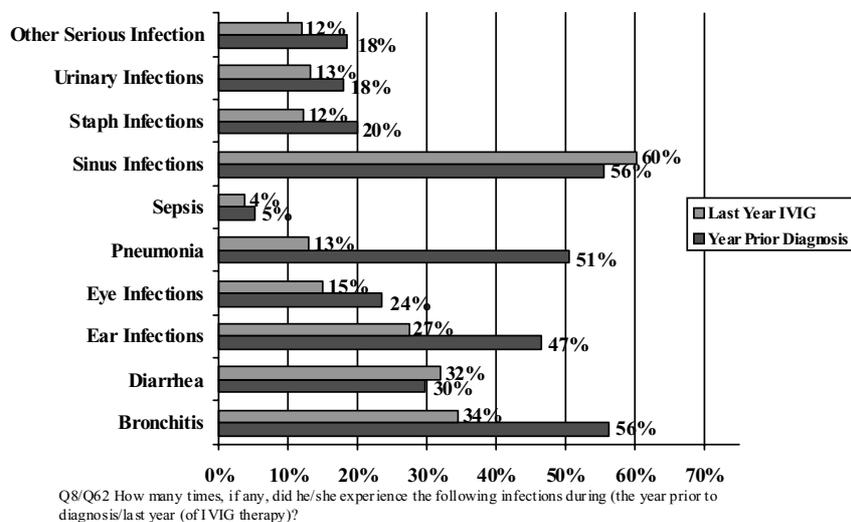
Fig. 5.

4. Impact of treatment on health care costs

Treatment of patients with primary immunodeficiency disease with IVIG is expensive. The average product and administrative cost per infusion in physicians' offices in the United States in 2005 was \$2,075. This includes a product cost of \$1,807 for 32 grams of IVIG and \$268 in administrative costs for a 3-hour infusion [5]. If we adjust this two-year old data to reflect consumer price index inflation we would expect the average infusion to cost approximately \$2,262 [6]. At one infusion every four weeks this represents an average annual cost of \$29,406 per patient.

However, failure to treat those who have antibody disorders with IVIG can also be expensive because IVIG reduces the frequency of infections in patients with primary immunodeficiency diseases. One of the hallmarks of PIDD is severe, persistent, recurrent and unusual infections such as pneumonias, bronchitis, staphylococcus and ear infections. When comparing the frequency of infections for patients during the year prior to being diagnosed with a PIDD to the frequency of infections for the patient's last year on IVIG therapy there is a dramatic reduction in the incidence and frequency of these acute conditions. The proportion of patients with PIDD who report pneumonias drops from 51% to 13%, bronchitis drops from 56% to 34% and the proportion with ear infections drops from 47% to 27%. There are also significant

Acute Conditions: Before and After IVIG



Source: IDF 1997 First National Treatment Survey

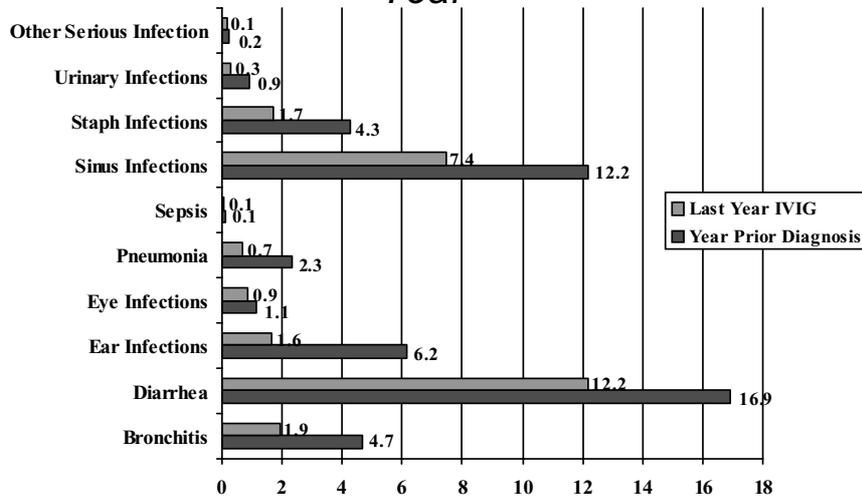
Fig. 6.

declines in the proportion of patients with eye infections (24%–15%), staph infections (20%–12%), urinary infections (18%–13%), and other serious infections (18%–12%) between the year prior to diagnosis and the patient’s last year on IVIG (Fig. 6).

Although there was little difference in the proportion of persons who reported diarrhea in the year prior to diagnosis (30%) and the last year on IVIG (32%), there was a significant drop in the average number of times with diarrhea before diagnosis (16.9) and after IVIG treatment (12.2). Similarly, there was little difference in the proportion of patients with sinus infections (56% to 60%). However, the average number of sinus episodes for patients dropped from 12.2 in the year prior to diagnosis to 7.4 in the last year on IVIG. There was also a four-fold decline in the number of ear infections between the year prior to diagnosis (6.2) and the last year (1.6) on IVIG (Fig. 7).

The reduced frequency of infections among patients with PIDD after treatment with IVIG translates into health care cost savings. The majority of patients with PIDD (57%) report being hospitalized during the year prior to diagnosis. By contrast, only a quarter (25%) report being hospitalized in the last year while on IVIG therapy (Fig. 8). In the year prior to being diagnosed with a primary immunodeficiency and receiving IVIG therapy, the average number of nights spent in an intensive care unit was just under one (0.9). During the last year on IVIG the average number of nights spent in an intensive care unit drops to 0.5 (Fig. 9). Assuming an average cost of

Mean Number of Episodes of Infection per Year



Q8/Q62 How many times, if any, did he/she experience the following infections during (the year prior to diagnosis/last year (of IVIG therapy)?)

Source: IDF 1997 First National Treatment Survey

Fig. 7.

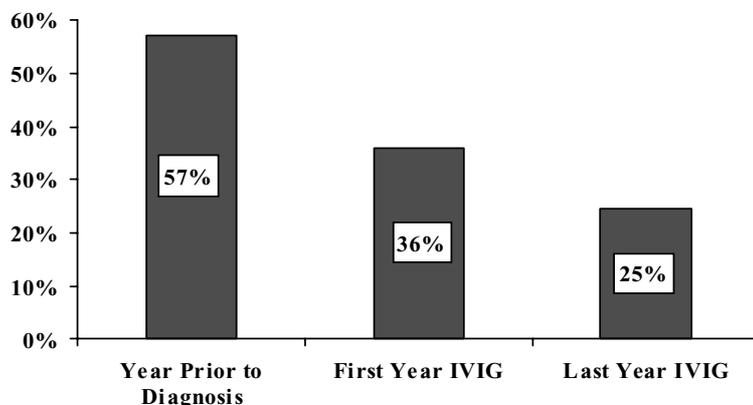
\$6,667 for one night in an intensive care unit, the 0.4 fewer nights per annum results in a \$2,667 savings per patient on IVIG [7].

In terms of nights in the hospital, the average number of hospital nights for patients with PIDD was 9.2 in the year prior to diagnosis (Fig. 9). During the last year, the average number of nights in the hospital for patients was 4.3. The average savings is 4.9 hospital nights per year after treatment. Assuming an average cost of \$3,000 per hospital night, the IVIG treatment saves the health care system over \$14,700 per annum in patient hospital costs alone [8].

In addition to hospital stays, patients with PIDD who are being treated with IVIG report fewer operations. The average number of in-patient operations for patients is less than half (0.2) in the last year, compared to (0.5) the year prior to diagnosis. The average number of out-patient operations (0.3) in the last year is also half the rate of out-patient operations (0.6) in year prior to diagnosis (Fig. 10). If the average cost for an in-patient operation is \$14,729, then treatment reduces the costs to the health care system by another \$4,419 per patient [9]. Assuming an average retail cost of \$2,423 for a hospital outpatient surgical procedure, the 0.3 fewer operations per annum after treatment represents another \$726 in treatment savings per patient on IVIG [10].

The difference in the rates of infections before and after treatment with IVIG also translates into differences in the number of sick days experienced by the patient

Percent Hospitalized: Pre/Post IVIG



Q9a. During the year prior to diagnosis as immune deficient, was the patient ever hospitalized overnight for any reason? Q63a. Was he/she hospitalized overnight or longer during the last year (on IVIG therapy)?

Source: IDF 1997 First National Treatment Survey

Fig. 8.

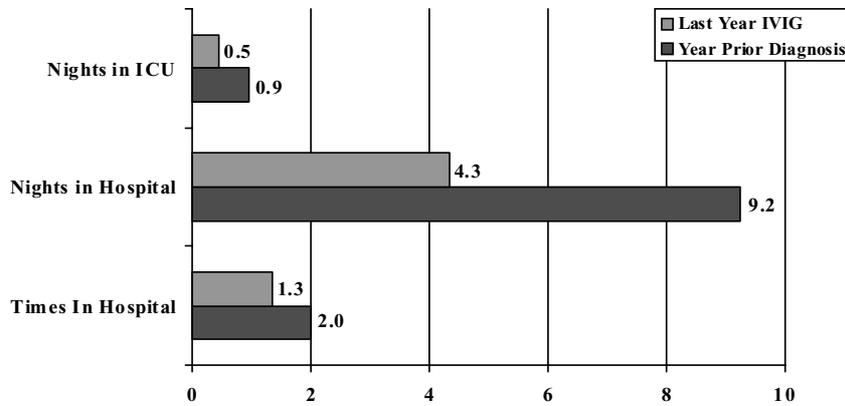
and the number of doctor visits outside of hospitalizations. The average number of doctor visits in the year prior to diagnosis was 12, or approximately one a month. The average number of doctor visits in the last year on IVIG was 6, or approximately one every two months (Fig. 11). A savings of six doctor visits a year at an average cost of \$100 per doctor visit represents another \$600 savings per patient on IVIG [11].

The difference in the average number of sick days for patients with PIDD after treatment is even more dramatic. During the year prior to diagnosis, the patient was too sick to go to work, school or perform normal activities on average 20 days. During the last year, the average patients had only 5 sick days on average (Fig. 11). At an average annual wage of \$38,651, the cost per sick day would be \$148.66 [12]. The cost of the difference in 15 sick days before and after treatment is approximately \$2,230.

In total, we believe that we can demonstrate a minimum estimate of approximately \$25,300 in health related savings per patient as a result of their IVIG treatment. It is important to note that this conservative estimate does not include the cost of medicine and other treatments in the year prior to treatment. This cost savings per patient for IVIG covers more than 85% of the average annual cost of IVIG therapy (\$29,406) for patients with PIDD.

The cost-benefit for IVIG treatment among patients with PIDD would be higher if these patients did not suffer permanent organ damage prior to initial diagnosis and treatment. Unfortunately, the average time between the onset of PIDD symptoms

Number Hospital Visits and Nights per Annum: Before and After IVIG



Q9b/Q63b Number of time he/she was hospitalized (in the year prior to being diagnosed/during the last year). Q9c/Q63c Number of nights hospitalized on ALL those occasions. Q9d/Q63d Number of nights, if any, in the Intensive Care Unit. Base=All Patients

Source: IDF 1997 First National Treatment Survey

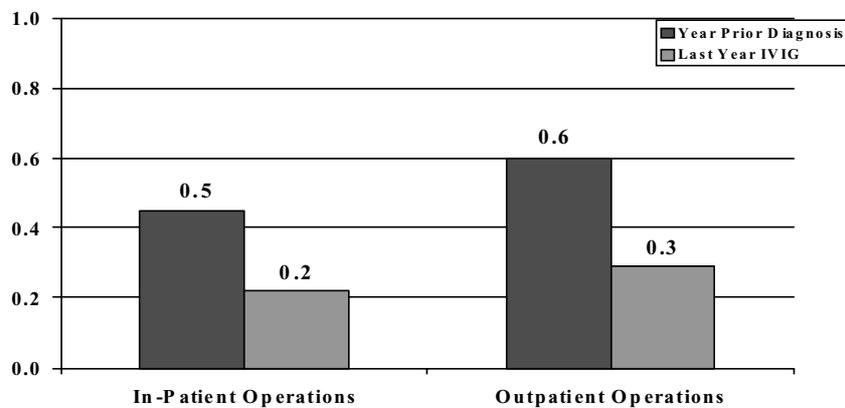
Fig. 9.

and an actual diagnosis of PIDD is just over nine years [13]. One of the reasons for such late diagnosis is the fact that the vast majority of patients have no family history of immunodeficiency disease. Nine out of ten patients report repeated serious or unusual infections prior to diagnosis. Indeed, most patients report that they were initially tested for immunodeficiency because of repeated infections, serious infections or unusual infections.

For the patient the cost of late diagnosis is a heavy burden of disease. Nearly two out of five (37%) immunodeficient patients report suffering permanent functional impairments prior to diagnosis. The likelihood of permanent impairment of lung function, mobility, digestive function, vision and hearing is related to the time between symptom onset and initial diagnosis of immunodeficiency. The relatively high proportion of patients with PIDD who have already experienced functional impairment prior to diagnosis tends to suppress the treatment effects of IVIG since their impairments and disabilities cause excessive health care utilization post-treatment.

Aside from suppressing the positive treatment benefits of IVIG, the permanent organ damage caused by untreated primary immunodeficiency diseases causes additional costs to the government for disability payments. Based on IDF survey data we would expect to find approximately 4,000 patients diagnosed with a PIDD who are under the age of sixty-five and receive Social Security Disability Insurance payments which is available to those workers who become disabled and are no longer capable of working. The average yearly Social Security payout for disabled workers under

Number of Operations per Annum: Before and After IVIG



Q10/Q64 Number of operations, if any, (in the twelve months before diagnosis/during the last year on IVIG therapy?) Base=All Patients

Source: IDF 1997 First National Treatment Survey

Fig. 10.

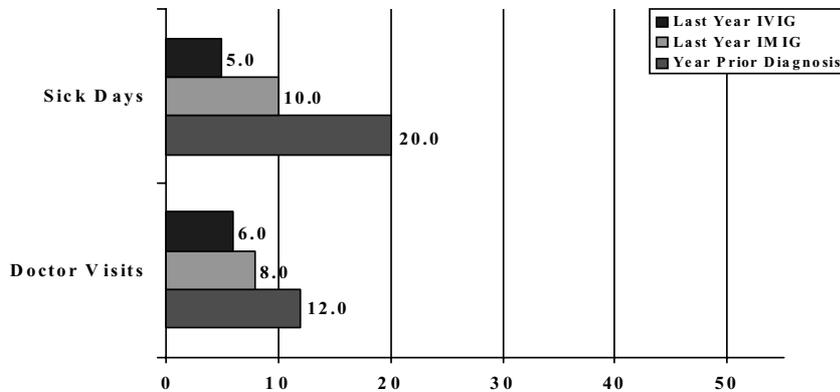
the age of sixty-five is \$11,748 [14]. In addition to these direct costs there are also the opportunity costs to consider as the taxes that would be generated by an otherwise healthy, working patient are no longer collected.

Using the average annual wage of \$38,651, the US government forgoes the collection of approximately \$5,000 in income taxes [15]. An additional \$4,792 is lost in Social Security taxes (6.2% employer contribution, 6.2% employee contribution) and \$1,120 (1.45% employer contribution, 1.45% employee contribution) lost in Medicare taxes [16]. For each disabled patient with PIDD the US Government forgoes collecting approximately \$10,900 per patient. Adding the cost of the benefits paid out to the amount of lost tax revenue we find an approximate cost to the US government of around \$22,600 per year for each disabled patient. If just 25% of the estimated 4,000 disabled patients with PIDD who fit this category could avoid long term disability through early diagnosis and treatment of their primary immunodeficiency, the potential five year savings for the government of the United States would be over \$110 million.

5. Conclusions

There is no doubt that IVIG replacement therapy has a significant and positive impact for the diagnosed primary immunodeficient patient. Once these patients

Median Number of Doctor Visits and Sick Days per Annum: Before and After IVIG



Q11 Not counting hospitalizations, about how many days was he/she too sick to go to work, school or perform his/her usual activities (in the twelve months before diagnosis/in the last year (on IVIG)? Q12a/Not including hospital stays (or IVIG infusions), how many doctor visits did the patient make (in the year prior to diagnosis/in the last year (on IVIG therapy)?

Source: IDF 1997 First National Treatment Survey

Fig. 11.

begin receiving IVIG on a regular basis their health status improves markedly, their activity limitations drop significantly and their quality of life improves dramatically.

The cost of IVIG infusions, which is medically indicated for improving the health of antibody deficient patients with primary immunodeficiency, is expensive - costing upwards of \$29,000 per year. We can, however, demonstrate significant cost savings that accompany treatment with IVIG. These savings in terms of hospital, healthcare and lost wages represents most, if not all, the costs of this therapy.

The key to a better prognosis for the patient is early diagnosis and treatment of their primary immunodeficiency. All too often patients are not diagnosed until well after the irreversible effects of repeated, crippling, infections have taken their toll. For many this results in life-long impairments and disabilities that could have been avoided with the early intervention of IVIG therapy. The additional cost for these permanently disabled individuals is much greater than any residual cost of the IVIG therapy itself.

While we cannot claim that all of the possible costs and benefits of IVIG treatment for primary immunodeficiencies have been measured, as a first and major step towards performing a cost-benefit analysis of this treatment a few things are abundantly clear. IVIG is a life-changing and life-saving therapy that creates healthier and more productive members of society. The early diagnosis of PIDD and subsequent treatment with IVIG therapy is critical if patients with PIDD are to avoid many of the long-term debilitating conditions that place an increased burden not only on the patients but on the US healthcare system as well.

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