

Primary immunodeficiency syndrome (PID)

Survey on the treatment and quality of life of patients

Results of the questionnaire survey



Blood Product Subcommittee, Biologics Committee
European Federation of Pharmaceutical Industries and Associations, Japan (EFPIA Japan)

With the Cooperation of Specified Nonprofit Corporation, PID Tsubasa No Kai

〈Introduction〉

● About European Federation of Pharmaceutical Manufacturers' Associations, Japan (EFPIA Japan)

Established in April 2002, EFPIA Japan is a leading organization of innovative European pharmaceutical companies operating in Japan and represents 25 R&D-oriented pharmaceutical companies. It aims to contribute to medical care and patients in Japan through the early introduction of innovative pharmaceuticals and vaccines. EFPIA Japan activities are carried out through six committees (Pricing & Economics Committee, Technical Committee, Corporate Ethics Committee, Intellectual Property and Legal Committee, Biologics Committee, and Public Relations Committee), which discuss and raise awareness of issues related to the pharmaceutical industry and make proposals to address them. (Home Page: <http://efpia.jp/>)

● About Blood Product Subcommittee

Blood Product Subcommittee, together with Vaccine Subcommittee and Biological Products Subcommittee, belongs to Biologics Committee. Blood Product Subcommittee aims to build a framework for the stable supply of human plasma-derived products (plasma fraction preparations), which are not replaceable by other pharmaceuticals and are medically indispensable, and blood-related recombinant products manufactured with world's cutting-edge technologies, to patients in Japan into the future.

Objectives and methods of the survey

This survey was conducted by the Blood Product Subcommittee in EFPIA Japan with the support of Specified Nonprofit Corporation, PID Tsukuba No Kai. In order to understand various conditions surrounding patients with primary immunodeficiency (PID), the survey was conducted in members of PID Tsubasa No Kai and volunteers from PID patients nationwide and asked questions related to hospital visits and patient quality of life (QoL). Responses were collected through a web-based survey form and a paper-based survey form. PID Tsubasa No Kai supported the distribution of the paper-based survey form to its members and PID specialists. Medical institutions involved in PID treatment across the country also supported the distribution of the paper-based survey form to PID patients. Without their support, it was difficult to collect a substantial number of responses. Member companies of Blood Products Subcommittee, EFPIA Japan also distributed a total of more than 3,000 copies of the survey form to medical institutions.

The questionnaire survey was conducted during the period from July 1, 2017 to January 31, 2017, and responses were collected from 165 patients or patient family members. The Blood Product Subcommittee hopes that the results of the survey would serve as a useful reference to patients, their families, healthcare professionals, and other stakeholders.

As an industry-wide organization, EFPIA Japan would like to utilize the results in supporting activities of patient groups and healthcare professionals.

Overview of the survey results

After confirming the attributes of the respondents, the survey asked them about the following six major items: "status of hospital visits, complications, and daily precautions", "treatment", "kindergarten and school life", "employment", "physical disability certification", and "patient needs for society". The results of the survey are summarized below.

1. Responses were received from 165 persons, including 69 patients, 93 patient families, and three others (Fig.1 and 2).
2. The respondents with diseases primarily based on humoral immunodeficiency (81 patients) and primary phagocytic dysfunction and deficiency (42 patients) accounted for approximately 75% of the entire respondents (Fig.3).
3. 47.9% of the patients were diagnosed as PID at age one or younger, including 31.5% who were diagnosed before the age of one, indicating that many of the patients were diagnosed during infancy. However, 16.4% received a definite diagnosis for the first time at the age of 16 to 60 years (Fig.4).
4. 62.4% of the patients visited a medical institution regularly at least once a month (Fig.5), and mostly visited a pediatric department (Fig.8). The patients saw a specialist, since PID is a rare intractable disease (Fig.9).
5. More than 43% of the patients spent at least one hour to visit a medical institution (Fig.6). 38.8% of the patients spent three to six hours in a medical institution and 9.1% spent six hours or more (Fig. 7). This suggested that many patients spared a day for a hospital visit. Considering the characteristics of PID, the long waiting time in a

medical institution increases the risk of infection and exhaustion. Improvement is therefore expected in the system for patient access to PID care to reduce the patient burden for hospital visits.

6. PID patients who are prone to infections frequently develop various symptoms, even when they receive appropriate treatment depending on the type of PID (Fig.11).
7. When asked about symptoms of the infectious diseases that the patients contracted in the past five years, it was revealed that they easily acquired opportunistic infections which healthy persons hardly develop, and tended to suffer from diseases that often leave aftereffects when repeatedly recurred. Besides, the incidence of respiratory infections, such as bronchitis and pneumonia, was high. In particular, when the patients developed pneumonia, the rate of hospitalization was as high as 68% (Fig.12).
These become chronic, making treatment difficult and having a major impact on daily life (Fig.13).
8. Many of the PID patients were in poor physical condition and lived a life with limits. It is expected that the survey results will help patients with PID improve their awareness of the need for infection prevention and gain understanding of the community (Fig.14 and 15).
9. 58.5% of the patients received immunoglobulin therapy to prevent infections (Fig.16), and as high as 74.2% of the patients were aware of their IgG trough levels (Fig.18), indicating improved informed consent and increased patient awareness about their disease status.
10. However, as mentioned above, the incidence of complications including infections and various symptoms associated with PID remained high, and it was considered that some patients receiving immunoglobulin replacement therapy may better consult their physician to see if the trough levels are optimal or if complicated symptoms can be reduced (Fig.19).
11. PID is designated as an intractable disease by the national government and public assistance is available to have support for the treatment costs for PID and associated complications. However, 31.4% of the patients had experience where they could not receive public assistance for the treatment costs for complications associated with PID (Fig.20). When PID patients visit a medical institution, they often need to be accompanied by their family member or caregiver, which also imposes a large financial burden, suggesting that these issues put pressure on their livelihood (Fig.21).
12. The survey investigated the impact of PID on school attendance. 64.3% to 70.4% of the patients were able to attend nursery school, kindergarten, elementary school, junior high school, or high school for 10 to 12 months in the year (Fig.22), indicating that many patients faced a severe environment in their school life, where they had to comply with instructions of their physician and live a life with limits to prevent infection (Fig.23 and 24).
13. 36.1% of the patients who attended high school answered that the disease negatively affected the school performance and 31.9% answered that they had to compromise on career options (Fig.25 and 26).
14. 59% of the patients aged 18 years and older were employed (Fig.27). This was lower than the 75.8% employment rate of healthy general people aged 15 to 64 years identified in the National Survey of the Ministry of Internal Affairs and Communications. These findings suggested that the PID patients faced a difficulty in employment. 41% of the patients were not employed (Fig.27), but many of them wanted to work (Fig.29).
15. Lack of understanding among colleagues about PID patients who need to visit a medical institution regularly and take measures to prevent infections impeded them from working. Overwork may worsen the patient condition and lead to retirement or absence from work. It was highlighted that it was difficult for PID patients to find a workplace with a good understanding.
16. Approximately 80% of the patients expected that physical disability certification would help reduce economic burdens of medical and traveling expenses and 80% expected that the disabled employment system would enable them to work in an appropriate environment (Fig.32). 51.5% of the patients expected much of patient group activities to achieve designation of the physical disability certification for PID (Fig.33).
17. The survey showed that because of the frequent occurrence of complications, not only medical expenses but also related costs for visiting a medical institution were pressing on their lives. Furthermore, the disease affected the school attendance and employment of the patients. Many patients wanted to work but were in a situation where they were not able to work. It is much expected that these issues would be shared with healthcare professionals and the Ministry of Health, Labour and Welfare in order to achieve designation of the physical disability certification for PID.



<Details of the survey results>

1. Attributes of the patients who responded

Fig.1 Respondents

165 respondents

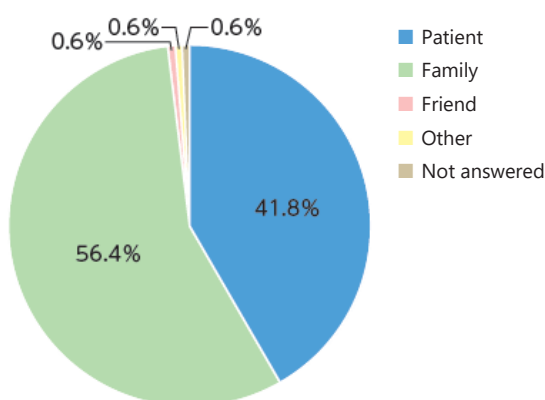
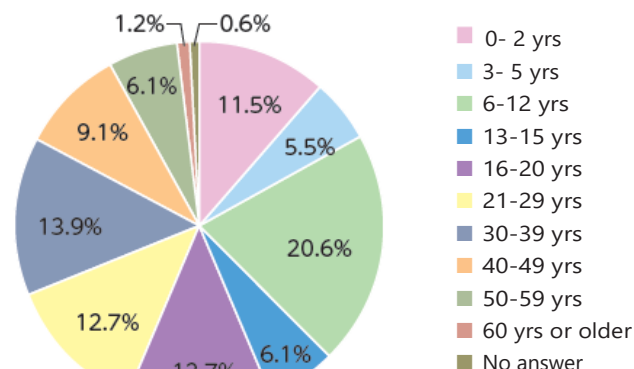


Fig.2 Age

165 respondents

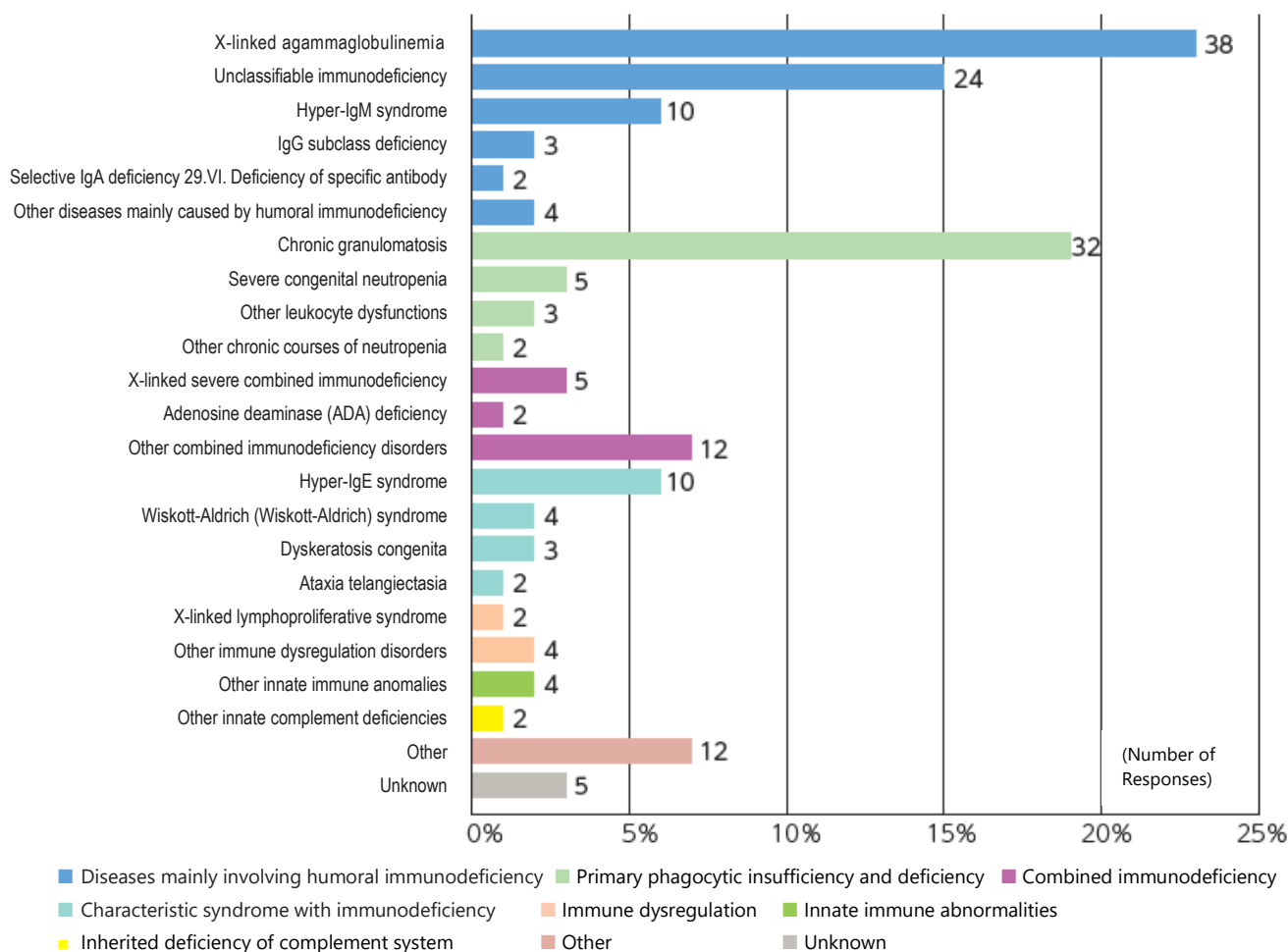


• A total of 165 patients responded; 69 (41.8%) were patients, 93 (56.4%) were patient family members, two (1.2%) were "other", and one (0.6%) did not answer.

• 93 (56.7%) were aged 0 to 20 years, and 71 (43.3%) were aged 20 years or older, excluding the one who did answer.

Fig.3 Disease type

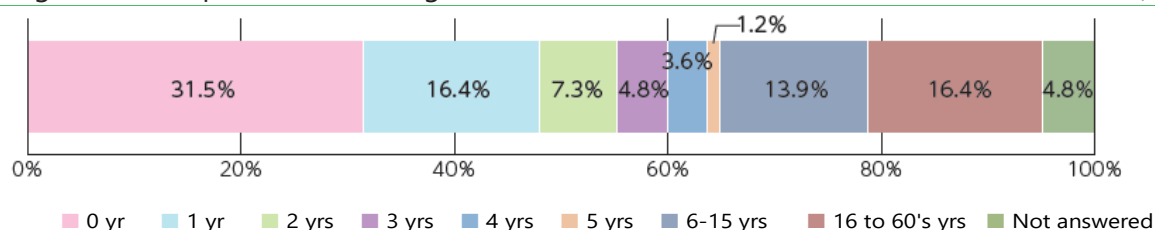
165 respondents (multiple choice n=190)



The disease types of the respondents were similar to those frequently reported in the national survey by the Ministry of Health, Labour and Welfare. 81 patients (49.1%) had diseases mainly due to humoral immunodeficiency and 42 patients (25.5%) had primary phagocytic insufficiency and deficiency. These two disease types accounted for 74.5% of the entire respondents.

Fig. 4 Age when the patients were diagnosed PID

165 respondents

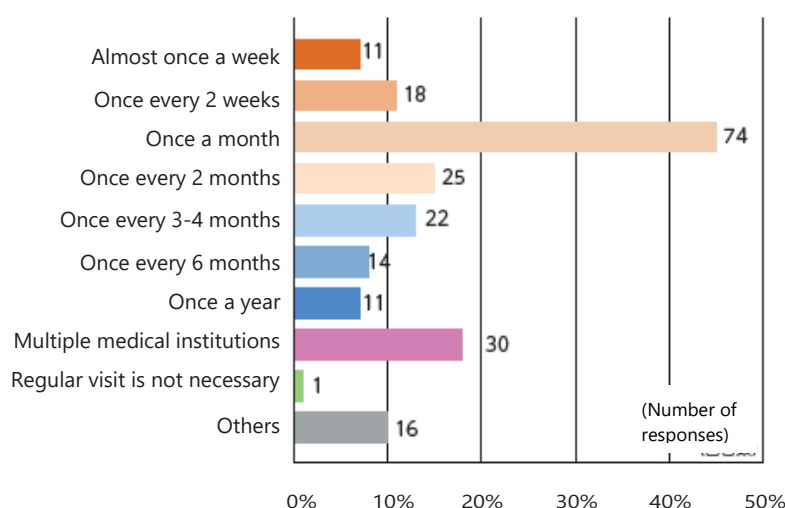


47.9% of the patients were diagnosed as PID at age one or younger, including 31.5% who were diagnosed before the age of one, indicating that early diagnosis was quite prevalent. However, 16.4% of the patients received a definite diagnosis for the first time at the age of aged 16 to 60 years. This may be because some PIDs do not cause severe symptoms in childhood or develop in adulthood.

2. Hospital visits and complications

Fig. 5 Frequency of hospital visits for PID treatment

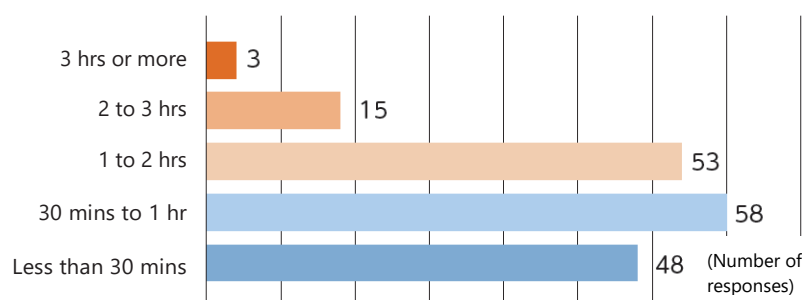
165 respondents (multiple choice n=222)



103 patients (62.4%) visited a medical institution once a month or more frequently. 29 patients (17.6%) answered once a week to once every two weeks. Such frequent visits were considered to be due to the treatment of complications. 30 patients (18.2%) regularly visited multiple medical institutions.

**Fig. 6** Travel time to visit a hospital (one-way)

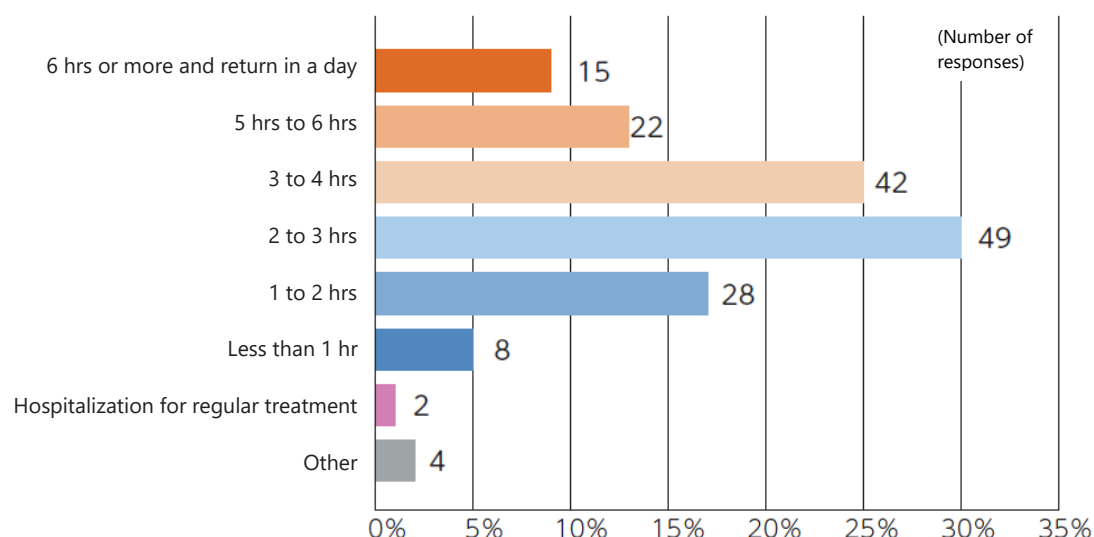
165 respondents (multiple choice n=177)



Many patients spent less than one hour to visit a medical institution. However, 43% of the patients took more than one hour to receive the treatment for PID, a rare intractable disease, and some spent more than three hours.

Fig.7 Time per visit spent in a hospital

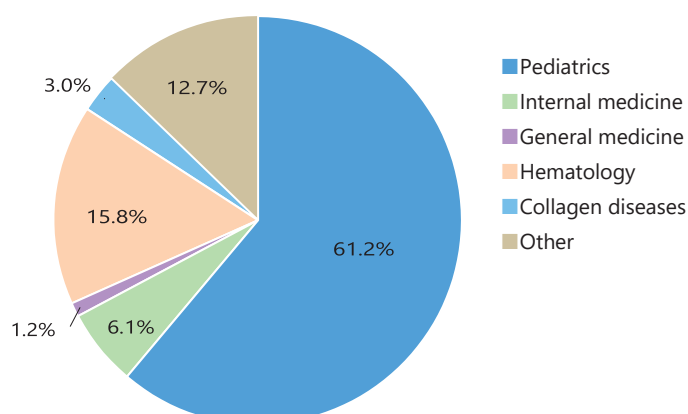
165 respondents (multiple choice n=170)



38.8% of the patients stayed in a medical institution for three to six hours, and 9.1% for six hours or more, indicating that many patients spared a day for a hospital visit.

Fig. 8 Department the patients consulted for the treatment of PID

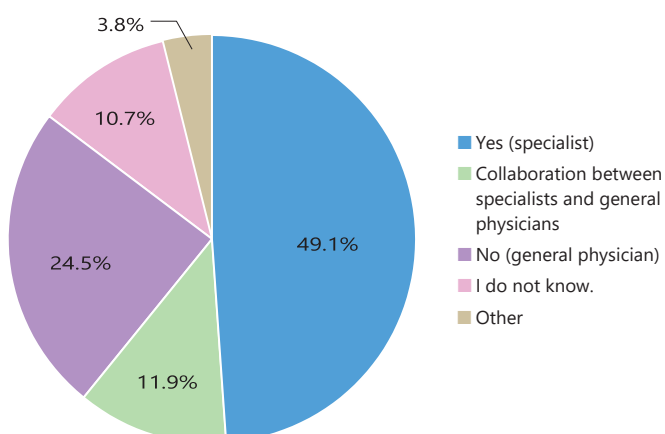
165 respondents



Of the total respondents in this survey, while 43.7% were patients 15 years of age or younger, as many as 61.2% visited pediatrics. It was considered that patients 15 years of age and older continue to visit pediatrics, and patients diagnosed with PID in and after adulthood often visit pediatrics where many specialists belong to.

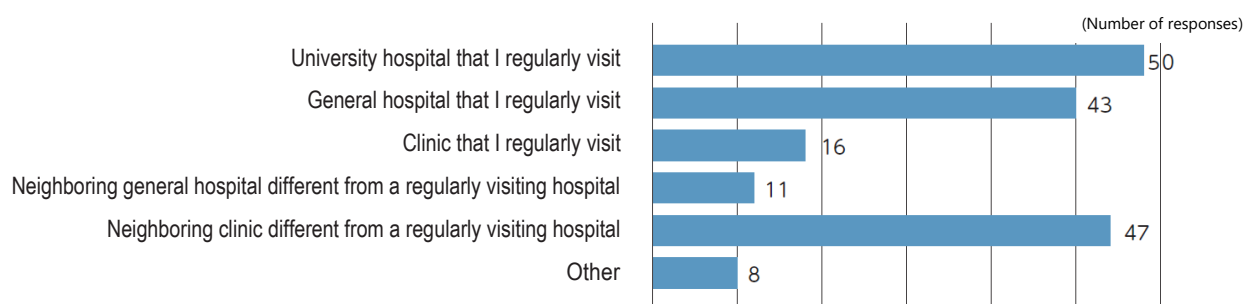
Fig. 9 Whether the patients consulted a PID specialist

159 respondents



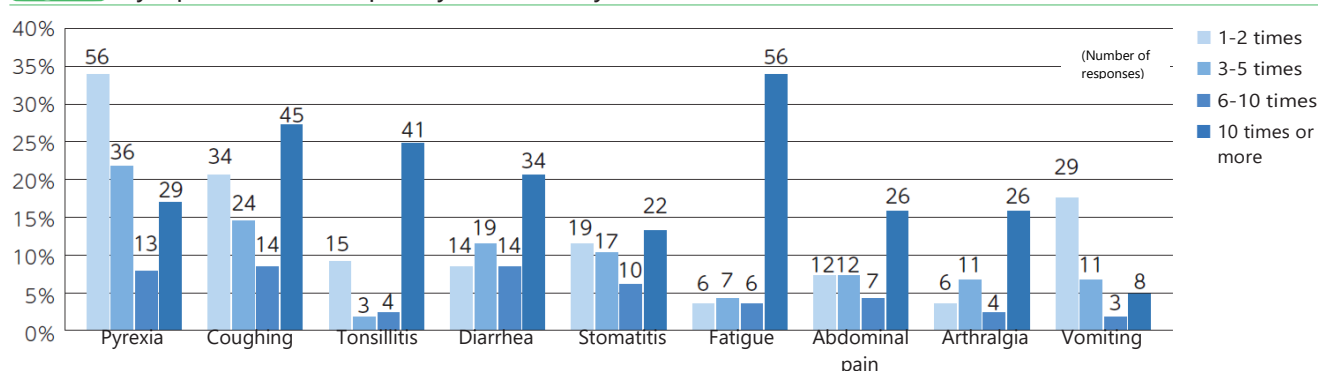
As PID is a rare intractable disease, the proportion of the patients who saw a specialist was very high. Nevertheless, for 11.9% of the patients, PID care was coordinated between specialists and general physicians. Such care coordination allows specialists in university hospitals and general hospitals (core hospitals) to share with physicians in the patient's neighborhood information about appropriate treatment for acute symptoms, which may reduce the various burdens on patients for hospital visits. Therefore, it is necessary to study and share cases where effective care coordination between PID specialists and general physicians is in place.

Fig.10 Type of the hospital the patients consulted for acute symptoms such as pyrexia 165 respondents (multiple choice n=175)



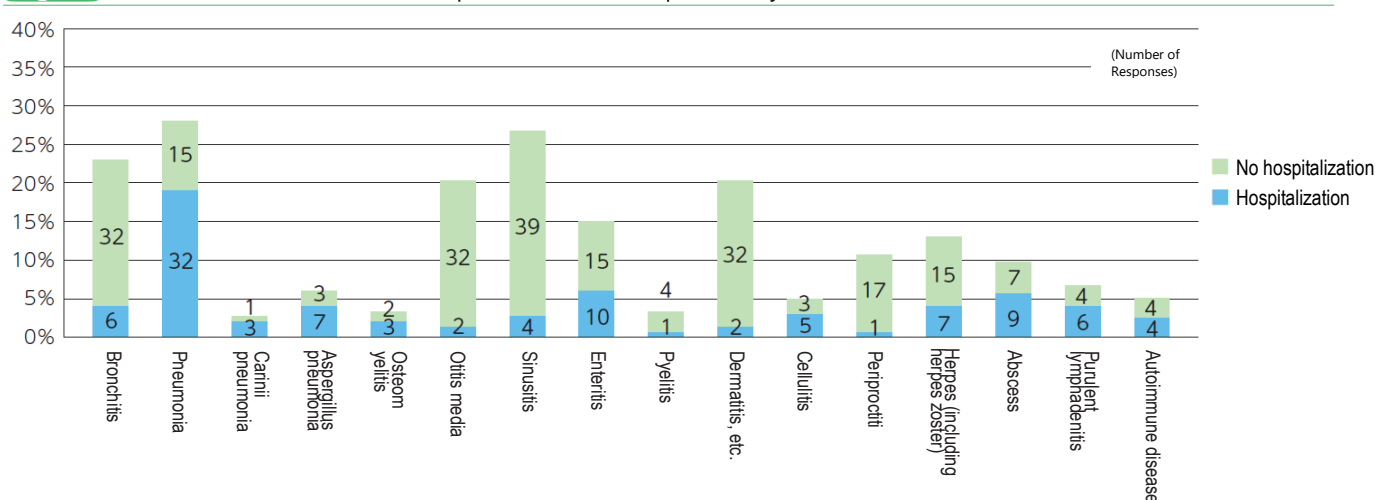
Many patients had to consult the university hospital or general hospital that they regularly visited and might spend many hours in the hospital for the treatment of acute symptoms of complications such as infectious diseases where they might be physically exhausted.

Fig.11 Symptoms and frequency in the last year 165 respondents



PID patients are susceptible to a variety of infections on a daily basis. Even they may limit activities to prevent infections, infections and various symptoms can interfere with their lives.

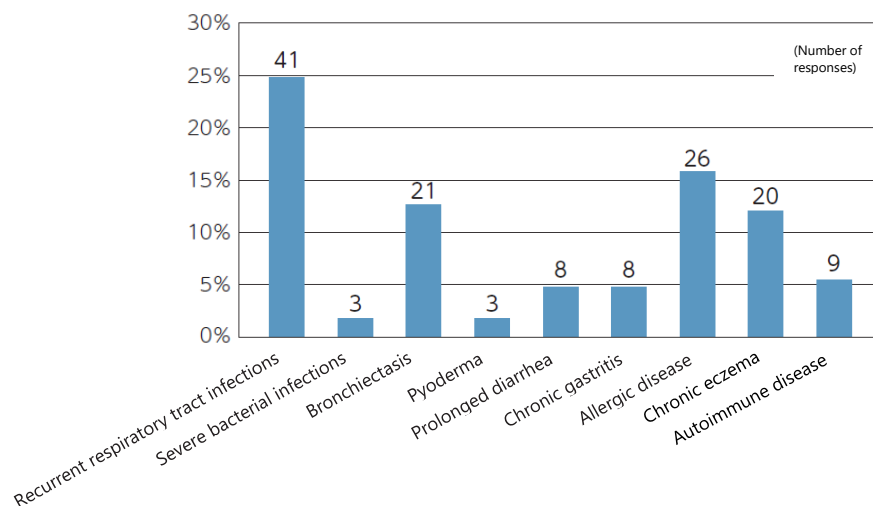
Fig.12 Number of infections and hospitalization in the past five years 165 respondents (multiple choice)



Complications that occurred in the past five years included diseases affecting various sites of the body, which healthy people do not usually develop and a high incidence of respiratory infections and enteritis, including upper respiratory tract infections. The rate of hospitalization (number of hospitalizations/incidence) was as high as 68% (32/47) in cases of pneumonia, and 40% (10/25) in cases of enteritis. Although the incidence was not high, the rate of hospitalization for skin disorders related to the underlying disease was high. This indicated that it is important for PID patients to take measures to prevent infections, receive appropriate treatment, and appropriately manage drug therapy. Complications should be treated early to prevent deterioration.

Fig.13 Chronic complications

165 respondents (multiple choice)

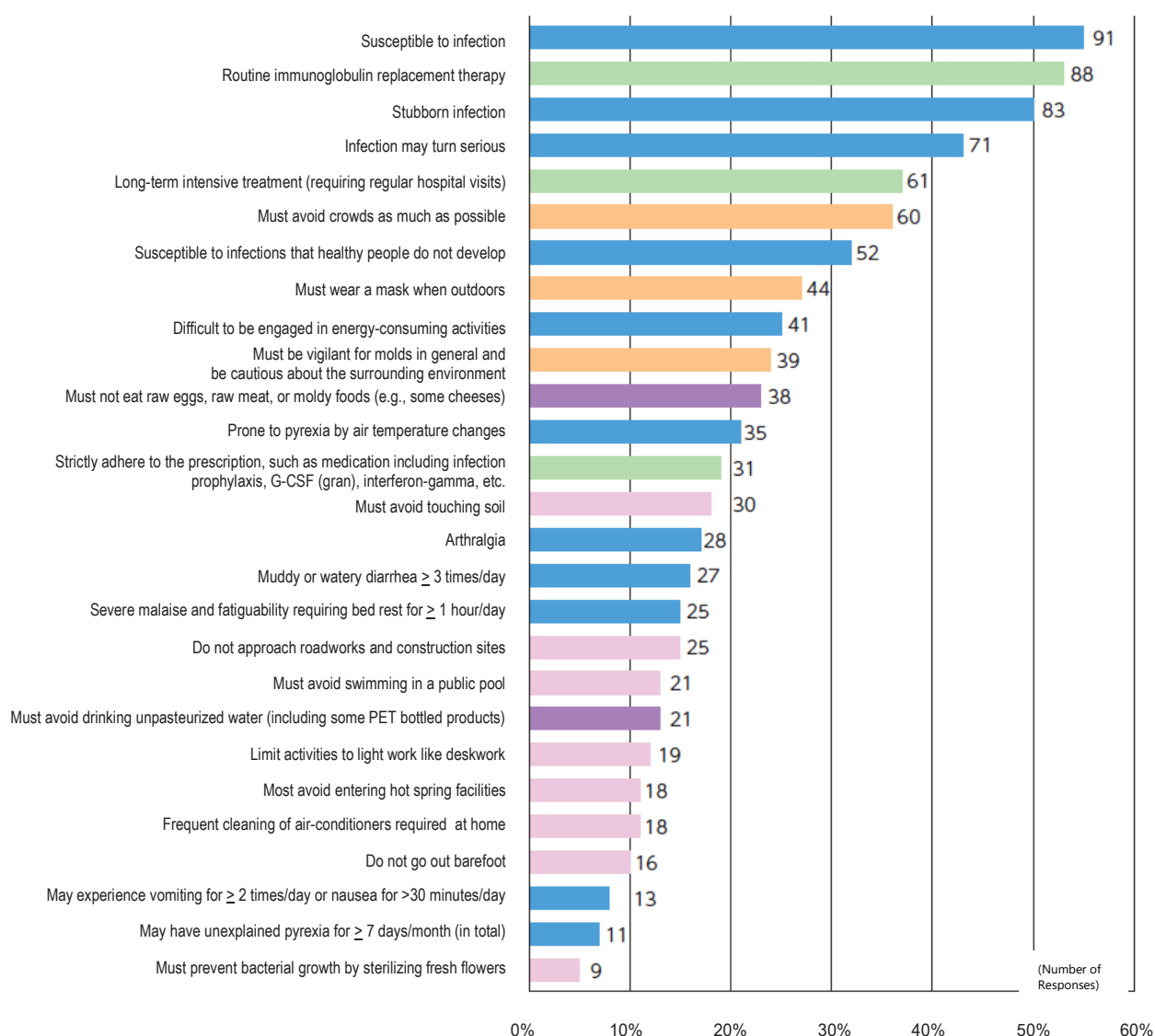


It was considered that complications with a high incidence may become serious or chronic, the treatment of which may be difficult, leading to a major impact on daily life.

*Major answers are shown.

Fig.14 Limitation in the patient lives and tendency of the symptoms

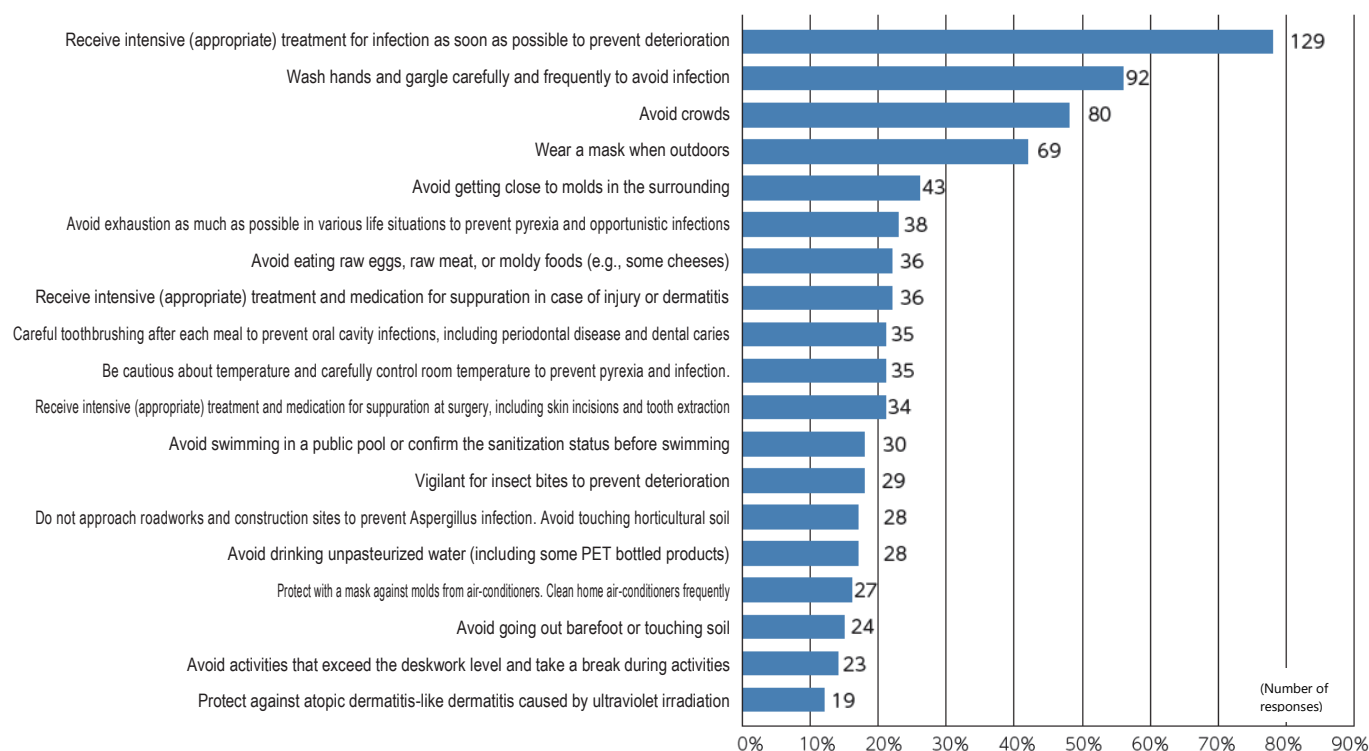
165 respondents (multiple choice n=1,015)



■ Symptoms associated with susceptibility to infection ■ Treatment compliance ■ Restrictions on outings (to prevent infection)
 ■ Dietary restrictions (to prevent infection) ■ Activity restrictions (to prevent infection)

Fig.15 Precautions that the patients took or should take routinely

165 respondents (multiple choice, n=835)

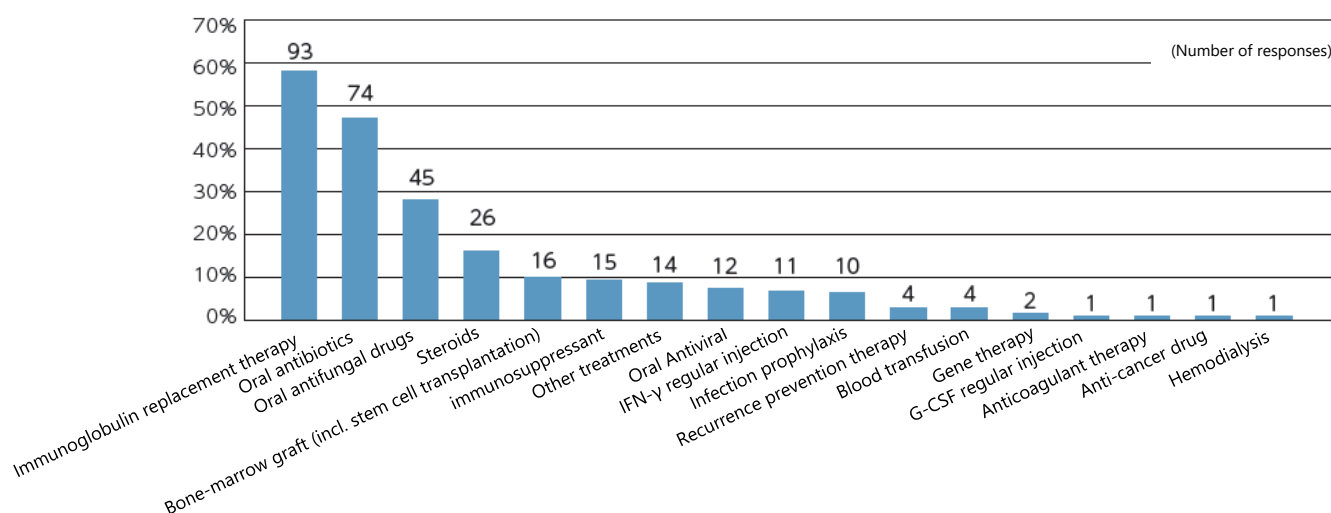


PID can be life-threatening without lifelong treatment for the underlying disease and care for immune dysfunction. In addition, PID patients live a life with limits depending on the type of PID. Understanding of the surroundings is critical for PID patients to participate in society.

3. Ongoing treatment

Fig.16 Treatments for PID

159 respondents (multiple choice n=330)



58.5% of the patients received routine immunoglobulin replacement therapy (injection) to prevent infection. Many patients received oral medications, such as antibiotics and antifungals. As the half-life of immunoglobulin products is three to four weeks, patients need to visit a medical institution regularly at least once a month.

Fig.17 Measurement of trough level of serum IgG
93 respondents

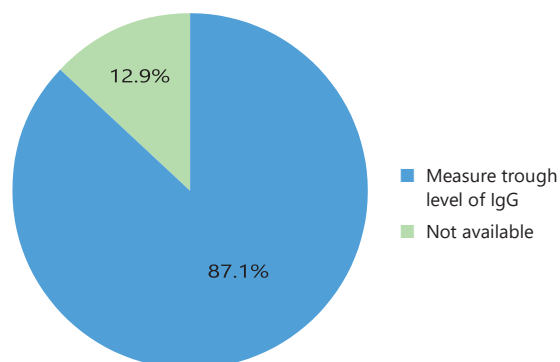
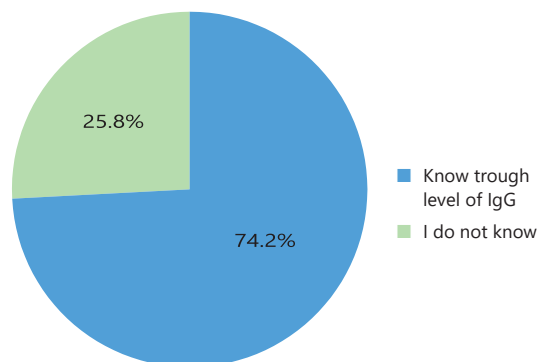
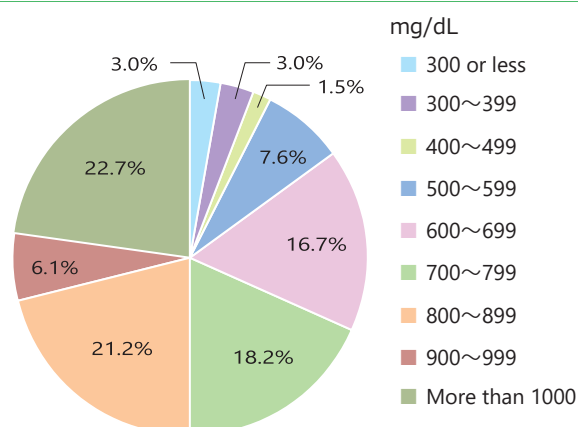


Fig.18 Awareness of trough level of serum IgG
93 respondents



74.2% of the patients receiving routine replacement therapy with immunoglobulin products (IgG) knew their trough levels of IgG, which suggested that physician's careful informed consent and patient's awareness of the disease were in place. On the other hand, 12.9% of the patients answered that trough level of IgG was not measured, and 25.8% did not know their trough level, which suggested that some patients did not know it even though it was measured.

Fig.19 Patients trough levels of serum IgG
66 respondents



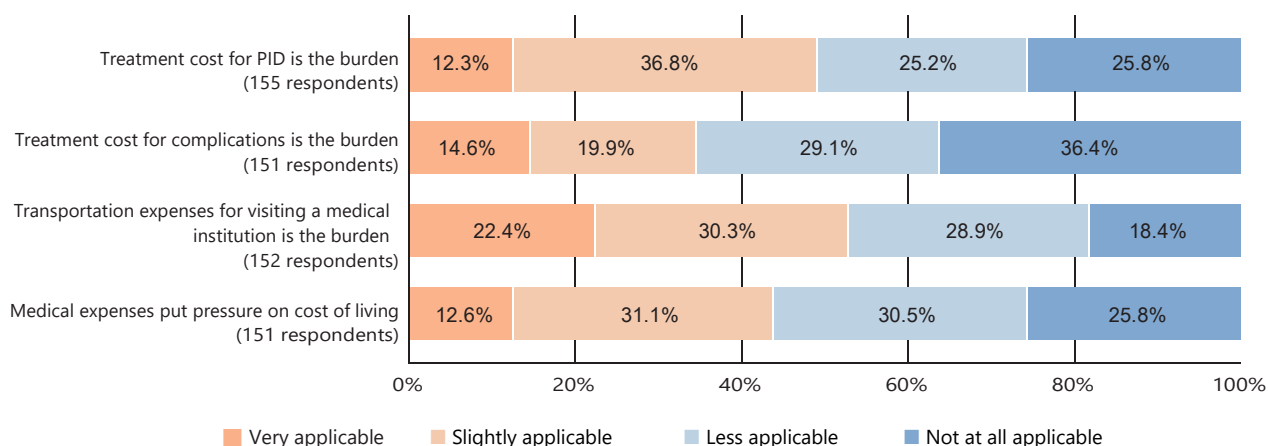
While the optimal trough level varies from patient to patient, it is reported (in package insert for IgG products) that the incidence of infections and length of stay were 1.04 times/year and 0.70 days/year, respectively in patients with trough level of 500 mg/dL or higher IgG. In 66 patients who answered the trough level, 7.5% had trough level of 500 mg/dL or lower and 22.7% had trough level of 1,000 mg/dL or higher. It seemed necessary to identify the optimal trough level depending on the patient's lifestyle changes while consulting with the doctor.

Fig.20 Public assistance of treatment costs
137 respondents



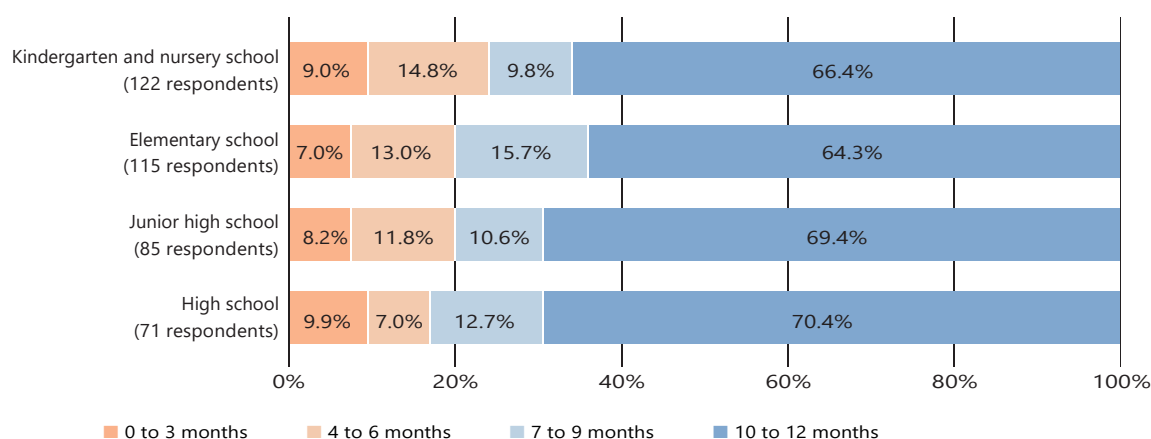
■ All expenses are subsidized (excluding those under the upper limit of out-of-pocket payments) ■ Part of medical expenses for complication are not subsidized

PID is designated as an intractable disease by the Japanese government and PID treatment costs, including those for associated complications are subsidized. The survey respondents were asked if the medical expenses for complications were subsidized or not, and it was found that 31.4% of the patients did not receive any subsidies. It was considered necessary to promote understanding about the public assistance program among medical institutions.

Fig.21 Economic burden of treatment

As mentioned above, there is a subsidy system for medical expenses for PID treatment, but patients need to bear the costs under the cap of out-of-pocket payments. Even with subsidies, 49.1% of the patients (the sum of "very applicable" and "slightly applicable") reported that the treatment cost was the burden. In addition, patients may be required to pay treatment costs for complications or acute symptoms outside the subsidy system, and 34.5% (the sum of "very applicable" and "slightly applicable") of the patients felt that such costs were the burden. Besides, because many patients need to travel a long distance to a general hospital for regular treatment and treatment of complications, these costs, including transportation expenses for the patient's family, seemed to be pressing on their living expenses.

4. Kindergarten and school life

Fig.22 How many months the patients attended school in a year

64.3% to 70.4% of the patients were able to attend kindergarten, nursery school, elementary school, junior high school, or high school for 10 to 12 months throughout the year. This may be because patients had to be absent from kindergarten or school due to the necessity of regular visiting to a medical institution or hospitalization for the treatment of PID and associated acute symptoms or complications. In high schools, it is generally said that absence of 1/3 leads to holdover or that presence of more than 2/5 of the actual number of school days is required. It was assumed that there were cases in which PID patients forced themselves to attend school and were suffering from this.

Fig.23 Compliance with instructions from physicians during school life

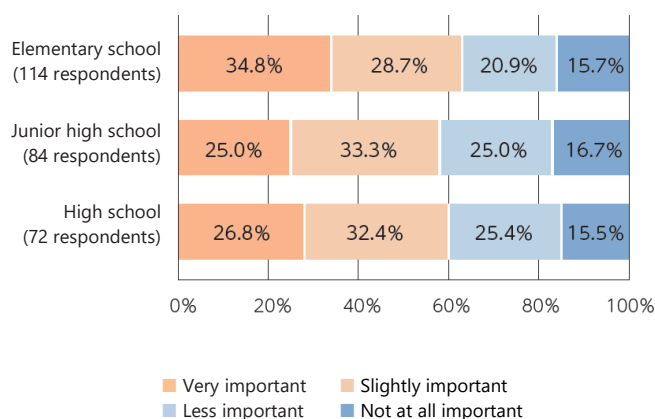
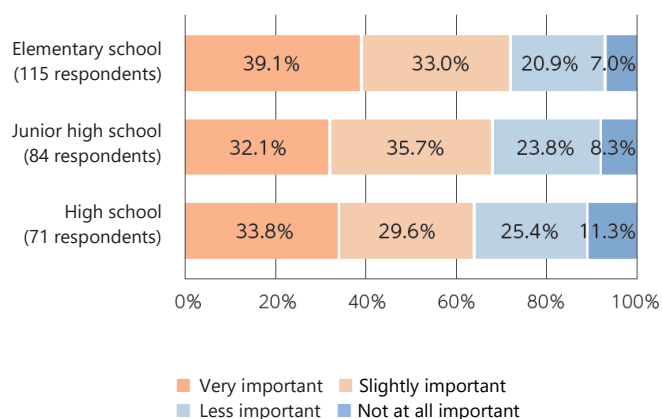


Fig.24 Efforts to prevent infection as much as possible during school life



The patients had a lot of limitations in their daily lives, and in school to comply with the instructions from a physician and try to prevent infections. It can be assumed that it is very hard for growing children, even with the support from their families. This is consistent with the afore mentioned influence on school days.

Fig.25 Absence from classes due to disease affected school performance

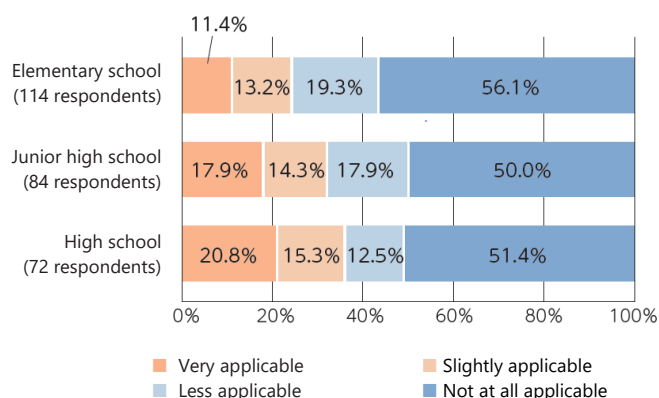
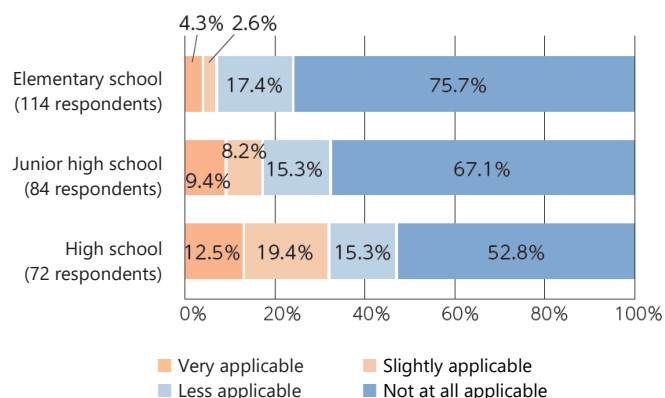


Fig.26 Compromise on career options because of the disease



The number of the respondents who answered that the disease affected school class and performance increased in upper grades and reached 36.1% in high school students (the sum of "very applicable" and "slightly applicable"), and the impact on career options increased in upper grades to 31.9% in high school students.

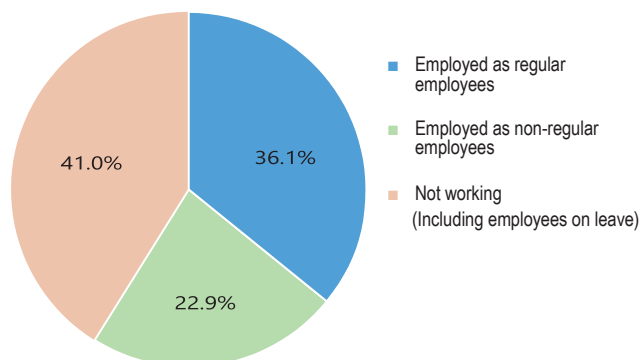
*Adult patients and patients who already graduated from kindergartens and schools also answered the questions based on the situation in their school age.



5. Employment (*in the respondents aged 18 years and older)

Fig.27 Current working conditions

83 respondents

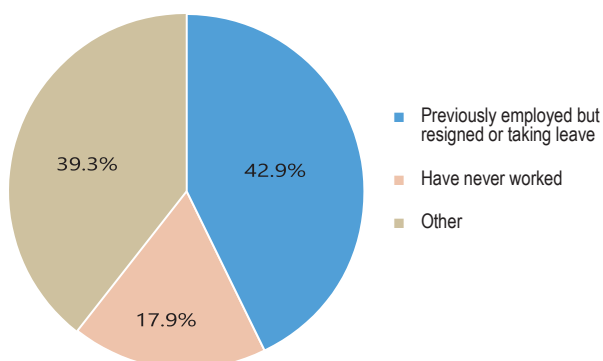


The employment rate of the patients aged 18 years and older was 59.0%. This was lower than the 75.8%* employment rate of healthy general people aged 15 to 64 years according to the National Survey of the Ministry of Internal Affairs and Communications. These findings suggested that the patients were in a difficult working environment.

*Calculated based on December 2017 data from the Labor Force Survey, Statistics Bureau, Ministry of Internal Affairs and Communications

Fig.28 Reasons for not working at present

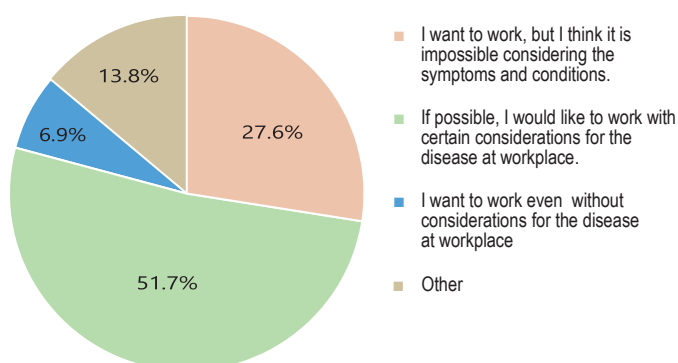
28 respondents



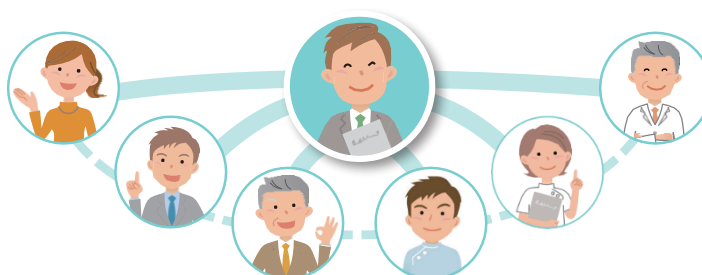
The reasons for not working were answered by 28 persons, and 42.9% of them answered that they had worked before but resigned or were taking leave due to some reasons. When asked about the reason, 75% answered "because the disease worsened."

Fig.29 Patient expectations about employment in the future

29 respondents



Twenty-five out of 29 (86.2%) of those who were not working had intention to work. It is much expected to have acceptance and understanding at workplace about the disease, including acute pyrexia and deterioration in physical condition, in order for PID patients to comply with restrictions and maintain their physical condition while working. If physical disability certificate is issued for PID, understanding and support of society would advance, and the number of PID patients in employment would increase



6. Physical disability certification

Fig.30 Patients with physical disability certification

165 respondents

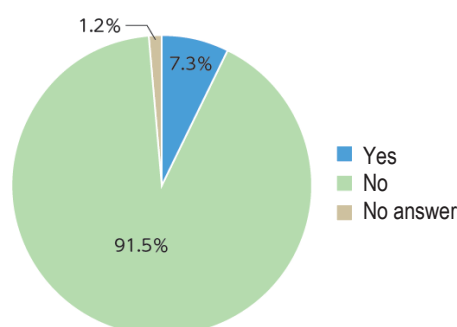
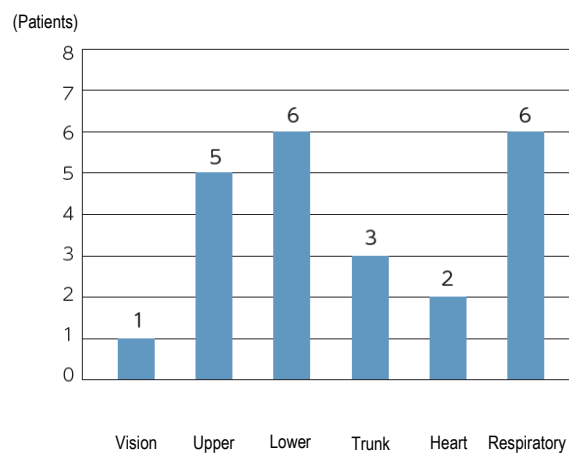


Fig.31 Dysfunction subject to physical disability certification

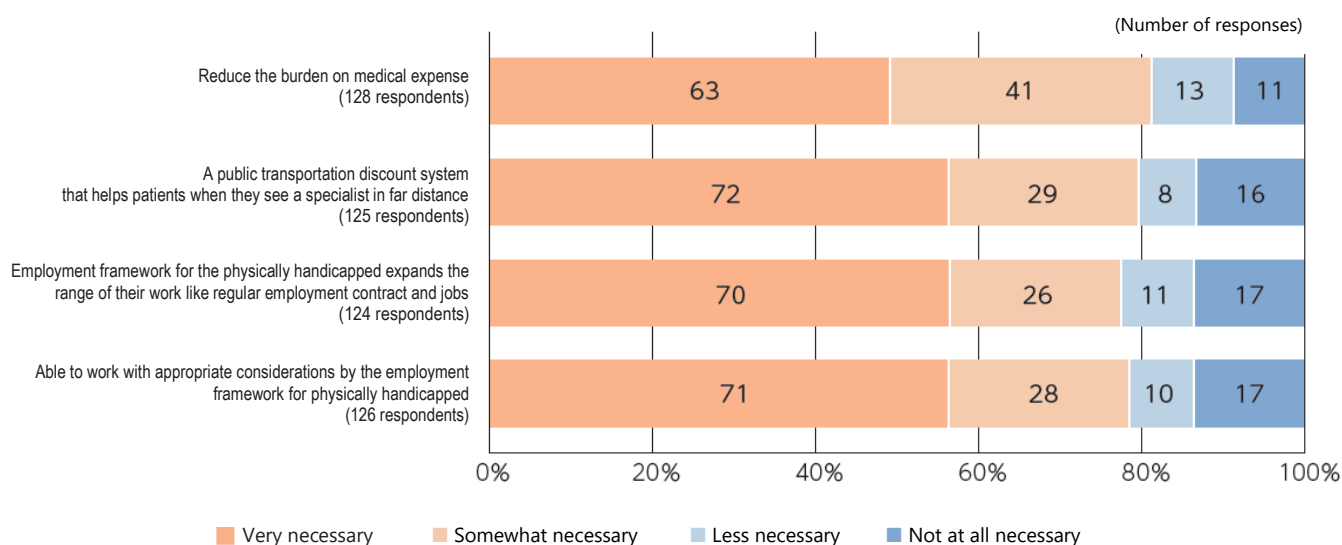
12 respondents (multiple choice)



Twelve of the respondents (7.3%) were certified as physically handicapped, but it was not certified as a result of PID-induced innate immune dysfunction.

*Fig.31 lists only major sites of dysfunction

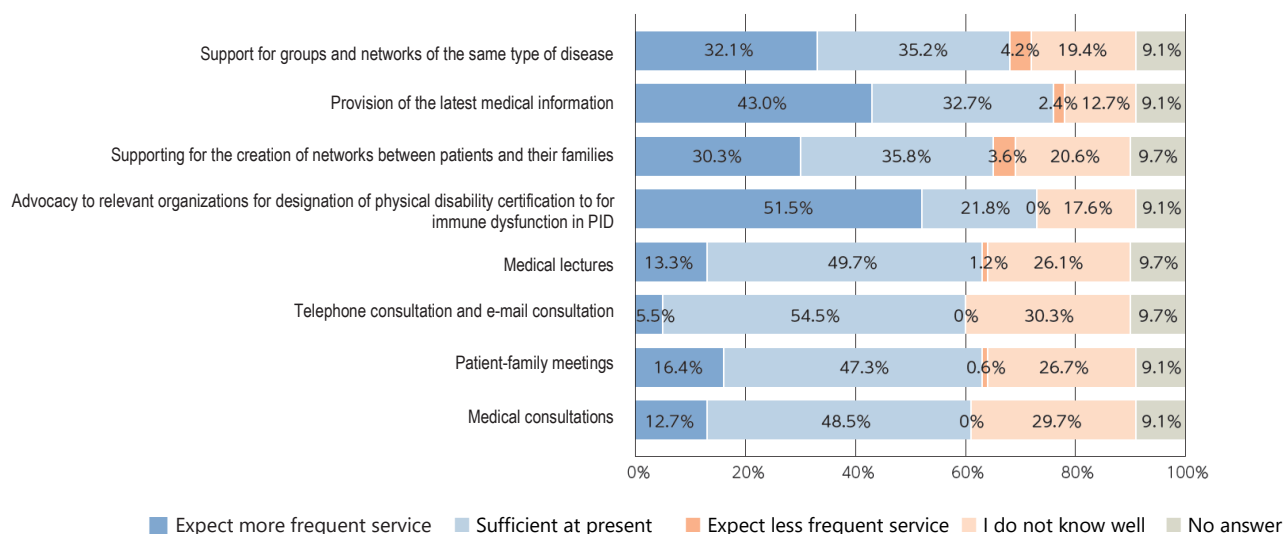
Fig.32 When the patients felt the need of physical disability certification



It was found that approximately 80% of the patients considered that physical disability certification would help reduce the economic burden of medical expenses and transportation expenses for the treatment of PID. About 80% of the patients expected that the certification would enable them to work in the employment framework for the physically handicapped. Many PID patients showed expectation towards designation of physical disability certification for immune dysfunction.

7. What the patients want for the society

Fig.33 Expectations to PID Tsubasa No Kai



The respondents expected various activities by Specified Nonprofit Corporation, PID Tsubasa No Kai, where they looked forward to efforts to encourage related organizations for designation of physical disability certification for PIDs, to the dissemination of the latest medical information, and to support the creation of networks among patients.



<Acknowledgement>

Blood Product Subcommittee of EFPIA, Japan extends deep gratitude to the patients and their families for their participation in the questionnaire survey.

The Subcommittee also extends appreciation to Specified Nonprofit Corporation, PID Tsubasa No Kai, Shire Japan K.K., Novo Nordisk Pharma K.K., and Bayer Yakuhin, Ltd. for their cooperation in the survey form distribution and data aggregation.

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