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Protocols of Standard of Care for Adult Patients with Primary Antibody Deficiencies Will Improve Timing of Diagnosis, Survival, and Quality of Life

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ABSTRACT

The majority of primary immunodeficiencies (PIDs) are antibody deficiencies (PADs), and not all of them are rare diseases; As an example, Caucasian individuals suffer from selective IgA deficiency at a frequency of 1:500.

In addition to infections, symptomatic patients with PAD are more likely to develop neoplastic, autoimmune, and allergic diseases. In the event that PAD is neglected or delayed for more than ten years, complications develop, eventually resulting in death. No studies have been conducted to devise and report detailed ready-to-use protocols for managing PAD to date.

This study aimed to propose protocols and guidelines for the adult PAD patients' standard care. Preparing the protocol, we considered the frequency and type of laboratory tests, imaging, endoscopic examinations, specialist consultations, and standardized recommendations for further care in the place of residence.

As a result of the proposed monitoring scheme, patients can be provided with complete care in terms of their underlying conditions and comorbidities, as well as early detection of complications. This protocol will serve as a guide for physicians dealing with these patients and enable comparisons of patient groups across a variety of treatment centers, even far away from each other.

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A national consultant in the field of clinical immunology verified the protocol mainly developed by Polish experts from reference immunology centres for adults.

Keywords: Adult; Clinical protocol; Guideline adherence; Primary immunodeficiency diseases; Standard of care

INTRODUCTION

Predominantly antibody deficiency (PAD) is the most common primary immunodeficiency (PID), and it accounts for more than 50% of the total PID cases and up to 78% as reported in some studies.[1-6] Symptomatic patients with these disorders are at a high risk of acquiring other infections and selected neoplastic diseases, autoimmune diseases, and allergies.[7-10] Lack of correct and timely diagnosis in most patients is a notable problem. It is speculated that 70%–80% of PID patients remain undiagnosed and are not registered in patient registries, and the rate of missed diagnosis in adults is higher than that in children.[11-13] This is due, inter alia, to the different clinical phenotypes of a given immunodeficiency in children and adults.[14,15] The delay in making the diagnosis is up to 10 years, and the consequence of this delay is the occurrence of numerous complications, which may result in death.[16] Another limitation is the lack of knowledge of non-immunologists regarding the health problems of patients with immunodeficiency. This results in making wrong decisions or shifting the responsibility to reference centers for looking after them, which, in many countries, including Poland, are too few. These patients should visit an immunologist only for follow-up appointments or in the case of specific situations, such as deterioration of the basic disease, or additional, atypical, and/or severe complications.

To provide patients with the best care, which includes the prevention of the development of complications, increase in overall survival time, and promotion of better quality of life, it is necessary to develop standardized protocols for patient observation and treatment.[17] Because the number of PID cases remains underestimated, currently available standards focus mainly on the best and earliest correct diagnosis, rather than long-term care and prophylaxis.[18-22]

Diagnostic delay and inadequate treatment (or the lack of treatment) are factors contributing to the occurrence of irreversible complications and increased mortality. Early diagnosis and appropriate treatment can improve the patient's quality of life. Studies conducted by Mokhtari et al, and Resnic et al, have shown that, in patients with common variable immunodeficiency (CVID), the occurrence of clinical non-infectious complications is associated with a higher mortality rate.[23]

This study presents a proposal for a standard of care for adult patients with PAD, with a particular focus on follow-up examinations and consultations, as well as their frequency. Because patients with PAD have an increased risk of respiratory and gastrointestinal infections, cytopenia, lymphomas, enteropathy, and allergies, the present study included studies that allow for the early detection of these complications. Unified recommendations for follow-up care at home have also been developed. This proposal allows for detailed care of patients about the underlying disease and comorbidities as well as the detection of complications. It is intended to help not only doctors who treat these patients daily (family doctors and specialists dealing with the complications of PAD patients) but also clinical immunologists who will be able to pass the protocols (in the original or modified version) to the aforementioned specialists. It also enables a comparison of the population of patients among various reference centers regionally and nationally. The standards that have been available thus far apply to selected groups of patients and examinations (e.g., frequency of imaging examinations in the case of complications from the lower respiratory tract).The introduction of a unified protocol of care will help to better characterize the population of patients with PAD and determine the frequency and severity of complications, and its analysis will verify whether there is a need to intensify or reduce the frequency of specific tests in this population. It will also allow us to estimate the cost of caring for patients with PAD.

The guidelines were created by a team of experts from leading adult immunology centers in Poland and verified by a national consultant in clinical immunology. The opinions of patients on the protocols introduced and of physicians of selected specialties including hematologists, oncologists, rheumatologists, pulmonologists, gastroenterologists, and allergists were also considered.

In different countries, there are large discrepancies in the standard of care for patients with PAD and different diagnostic and therapeutic possibilities of health care systems; therefore, we aimed to introduce the most universal recommendations and, at the same time, propose protocols that can be modified depending on the needs and characteristics of care in a given country.

For convenience, a practical clinical classification of patients with primary humoral immunodeficiencies is presented in Table 1.

Table 1. Clinical distribution of patients with primary antibody deficiencies

Group 1. Patients not requiring IgG replacement therapy
Group 2. Patients requiring IgG replacement therapy
Group 2A. Patients requiring substitution in hospital
Group 2B. Patients receiving substitution at home

Basic Patient Information

Basic patient information will be helpful both for the doctors who provide care and for the patients themselves. Required basic information is presented below in Supplementary Table-1 (Card A) When visiting every new doctor, particularly during consultations at the emergency room or during hospitalization, should show this information.

The time of diagnosis of deficiency and the occurrence of the first symptoms are very important elements of the interview, as they allow for estimating the time of the delay in the diagnosis and the associated increased risk of complications.[16] Information about the medical history of allergic reactions is useful, especially in cases of drug hypersensitivity. It is particularly important during infections, for example, in the case of disorders of consciousness in the course of fever, in patients with mental retardation, or in the elderly. Information such as telephone numbers of the treatment center is very important. In clinical practice, this information is important not only for patients but also for doctors providing care to patients at home, especially in terms of home therapy with immunoglobulin preparations and possible complications during their use.

Data concerning the use of stimulants are expected to draw special attention to the occurrence of related diseases and the possibility of the earlier appearance of other complications. The patients should be made aware of the fact that this information is not intended to stigmatize but to allow for the best comprehensive care.

Information about nutritional status is also very important, as malnutrition additionally leads to secondary immunodeficiency, which worsens the course of the underlying disease.[24-27] The effect of malnutrition is discussed later in this study, while excess body weight is associated with a greater risk of developing cardiovascular diseases, diabetes, neoplasms, obstructive sleep apnea, and respiratory problems as well as degenerative changes in the musculoskeletal system. It is also associated with an increase in all-cause mortality.[28-31]

Initial Examinations and Consultations

Initial examinations and consultations described in this study are not the same as qualifying examinations, which are a requirement for the diagnosis of a particular illness. The described tests and consultations are aimed at assessing the patient's disease status while establishing the diagnosis, or at the latest, in the first year after the diagnosis of PAD, with a particular emphasis on the damage to systems and organs, and the evaluation of factors whose modification may affect the patient's further functioning and the development of new diseases (the concentration of vitamin D3, lipid profile). The required basic examinations and preliminary consultations are presented in Supplementary Table-2 (Card B).

Laboratory Tests

The authors also emphasize that the final decision-making regarding the scope of the tests performed depends on the clinical condition of the patient and the specificity of health care in a given country and belongs to the doctor. The latter information has been included in the legend for both initial and follow-up examinations and consultations to make it visible to patients.

The determination of protein concentration, the concentration of folic acid, vitamin B12, and ferritin allows the exclusion of secondary immunodeficiencies. Lactate dehydrogenase is a cytoplasmic enzyme present in all cells, which is not only an indicator of their breakdown but, together with the concentration of uric acid, β2-microglobulin, and erythrocyte sedimentation rate can be an indicator of an active proliferative process. An elevated erythrocyte sedimentation rate is particularly useful for the simultaneous determination of CRP when the values of the latter are low.[32-37] Additionally, chronic hyperuricemia is a risk factor for hypertension, metabolic syndrome, chronic kidney disease, and cardiovascular diseases, similar to hyperlipidemia.[38-42]

Determination of tumor markers may be disputable. First, none of the markers has the desired 100% sensitivity and specificity. In addition, the concentration of almost all markers may be elevated in other disorders (including inflammation). Unfortunately, the levels of most markers are not elevated in the early stages of malignancy. Their concentrations do not correlate with the neoplasm stage and vary depending on some factors, for example, accompanying chronic renal failure and the method of its treatment. For example, hemodialysis, peritoneal dialysis, and kidney transplantation may affect the concentration of tumor markers. Taking the above aspects into consideration, each decision about the determination of the markers should be made individually.[43-46]

Imaging and Endoscopic Examination

Because complications from the respiratory and digestive systems are one of the most common problems in patients with primary humoral immunodeficiency, imaging, and endoscopic examinations are very important. Therefore, it is necessary not only to rule out secondary deficiencies but also to initially evaluate the damage to particular organs. This is particularly concerning to the lungs; therefore, in addition to spirometry and routine radiography, computed tomography (CT) or magnetic resonance imaging (NMR) of selected organs should be performed in the first year. Ultrasound examination of the lung may be considered in the case of radiosensitivity or a standardized method where available. Performing a fecal occult blood test can help to evaluate the urgency of gastroscopy and colonoscopy, especially if the patient does not consent to endoscopy. In the latter case, capsule endoscopy or virtual colonoscopy may be considered.[47-54]

Psychological and Psychiatric Evaluation

Unfortunately, the initial psychological and psychiatric evaluation, with particular emphasis on the history of affective disorders, continues to be underestimated. Published studies have more often reported this problem in children or adults infected with human immunodeficiency virus (HIV). In clinical practice, this problem is highly neglected in adults and it affects the patient's understanding of the underlying disease and its course, doctor-patient cooperation, treatment effectiveness, patient functioning in the family and the society, and self-perception. Research conducted among children with PID has shown a higher risk of significant anxiety and depressive symptoms, higher rates of mental disorders, especially emotional ones, and difficulties in relationships with peers compared to the control group, which included healthy children. The quality of life of children with PID was worse than that of healthy children from the control group and worse than that of children diagnosed with diabetes. Studies have shown that humoral immunodeficiency significantly affects the quality of life and mental well-being. It is also suggested that this effect differs depending on the severity of the underlying disease.[55-59] Studies involving the parents of children with primary immunodeficiency disorders have revealed that the most important stressors for them were fear of the long duration of the child’s illness, fear of incurable diseases of their child, and fear of side effects and complications of treatment.[60] The aforementioned studies are important, in particular, because most children will be referred to adult centers where the attention is focused more on the underlying disease and comorbidities and, to a lesser extent, on the psychological problems of the patients, especially if the patients themselves do not report them. Studies including adults have shown that immunodeficiency affects many aspects of the lives of patients and their families. Patients who are isolated have depressive-anxiety disorders, and either their family functioning is disturbed or their diagnosis is significantly delayed; they are most likely to develop psychosocial dysfunction such as excessive stress, high incidence of emotional and social problems, or poor quality of life. Young women experience stress because

of the possibility of passing on the deficiency to their offspring. Lung diseases, chronic diarrhea, chronic pain, and alopecia (in women) have been particularly strong negative predictors of quality of life. The perceived quality of life was also affected by the treatment intensity defined here as the number of antibiotic treatments, hospitalizations, and daily medications. The long duration of the disease must show a correlation with a low psychological quality of life, which highlights the need for psychological support not only after establishing a new diagnosis but also after years of the duration of the disease. The number of comorbidities, complications of the underlying disease, and the support of loved ones are not without significance. The aforementioned studies show that mental problems remarkably affect the functioning of patients, and therefore, the need for an initial psychological and/or psychiatric consultation is highly justified. This is all the more so because, during the follow-up appointments to the reference center, the attention of doctors is rather focused on the underlying disease, while psychologists and psychiatrists have the knowledge and tools to diagnose the most effective disorders related to their area of activity. When the patients have not consented to such consultations, their psychoemotional condition is worth assessing using appropriate scales, for example, Beck, Hamilton, and QLQ.[61-68]

Follow-up Examinations and Consultations

Çalişkaner et al, developed follow-up protocols for adult patients with CVID in a recently established immunology clinic for adults in Central Anatolia in Turkey, where a clinical immunology center for adults was not previously available.[17] However, the publication does not present ready-protocol templates but rather their description. However, Bethune et al, have developed a very useful consensus for this patient group concerning the management of non-infectious complications.[69] According to these recommendations, early diagnosis of some complications and/or comorbidities as well as the necessary interventions on time. This confirms that their introduction to a wider group of patients is highly recommended, especially because even mild hypogammaglobulinemia can be severely complicated and even take the form of an illness that could directly pose a threat to the patient's life.[70]

Some tests, such as the determination of tumor markers, have been discussed in the description of the initial examinations. As in the case of preliminary examinations, the final decision regarding the scope of the follow-up examinations depends on the clinical condition of the patient and the specificity of healthcare in a given country and belonging to the physician. This information has also been placed in the legend of Supplementary Table-3 (Card C) (follow-up examination and consultation card) to be visible to patients.

Laboratory Tests

The control determination of vitamin B12 and folic acid levels requires clarification. The authors' observations have shown that performing these tests in patients with a previously established diagnosis of PAD (e.g., in childhood) revealed a deficiency of these compounds in some patients without accompanying anemia, and their supplementation prevented its development. Moreover, vitamin B12 deficiency has shown a good response to oral substitution, and the data available in theliterature confirm these observations and explain them, among others, as connected with changes in eating habits, high food processing, or the abuse of certain drugs (e.g., proton pump inhibitors).[71,72] A similar relationship has been observed in the case of ferritin determination, especially in women; however, an increased concentration of vitamin B12 is an alarming signal to observe patients with accompanying lymphoproliferative disorders. Proteinography is recommended to exclude protein loss, which allows for the early diagnosis of some medical conditions and minimizes secondary antibody deficiency, making it possible to suspect a disease involving the production of a monoclonal protein. Proteinuria detected by general urine examination and elevated creatinine levels may additionally be markers of secondary amyloidosis. These determinations, along with serum amyloid A, have been included in the examination and consultation charts. These studies, along with serum amyloid A, have been included in the cards of examinations and consultations.

The examination and follow-up consultation card also included the monitoring of IgG concentration depending on the route of administration. It is worth remembering that in the case of an increase in the frequency of infection, it is worth determining the IgG subclasses, because the correct concentrations of individual subclasses in a given immunoglobulin preparation may not be reflected in the concentration of

the given subclasses in the patient, which requires modification of the immunoglobulin dose.

Imaging Examinations

Given the natural course of humoral immunodeficiencies, that is pulmonary complications and the increased risk of neoplasms, the development of a protocol for follow-up radiological and endoscopic examinations is particularly needed, and according to the available literature, chest radiography should be performed once or twice a year. Chest CT (preferably HRCT) is recommended every 2-4 years (at least once every 5 years) in patients with documented and potentially progressive abnormalities in the lungs and less frequently in patients with normal lung imaging. If more frequent examinations are necessary and/or in the case of accompanying radiosensitivity, the NMR test is the method of choice. Lung ultrasound examination can also be performed in cases of radiosensitivity or if a standardized method is available.[73,74] It is worth remembering about tests that may indicate pathological changes in the lungs and that do not increase patients' exposure to radiation. These include, in addition to the above-mentioned ultrasound, spirometry, DLCO, and body plethysmography.

There are no guidelines in the literature for imaging examinations in patients with immunodeficiencies. Therefore, their frequency was estimated after considering the frequency of particular complications, the presence of comorbidities, or familial predispositions. The lack of recommendations confirms the urgent need for standardized guidelines. The frequency of a follow-up CT scan of the sinuses depends on the initial results. In the case of routine examination, it is recommended to be performed at least once every 5 years. Abdominal ultrasound examination should be performed annually, which additionally helps to detect prostate enlargement in men. Despite this, urological consultation with ultrasound evaluation of the testicles is recommended at least once every 3 years.[75] Follow-up ultrasound examination of the lymph nodes is recommended once every 2-4 years. The frequency of thyroid ultrasound depends on the results of the initial examination. In the case of the presence of unsuspected thyroid nodules, an examination should be performed every 2 years, preferably once a year.[76,77]

It seems that the frequency of prophylactic examinations for the early detection of neoplasms of the reproductive system can be the same as that for the population of healthy women. The prospective analysis will allow for a more precise assessment and will enable its possible modification. A transvaginal ultrasound examination should be performed at least once every 2 years. In women, after the age of 20 years, it is additionally recommended to perform a self-breast examination at least once a month (always after menstruation) and an ultrasound scan at least once every two years. After the age of 30 years, an ultrasound examination should be performed optimally at least once a year, and after the age of 40 years, once every six months, and mammography once every two years.[78]

Echocardiography is an often-ignored test; however, because of the increased risk of infections (including the cardiac muscle), cardiovascular diseases, and autoimmune diseases with heart involvement (e.g., systemic lupus erythematosus), the periodic performance of this examination seems to be highly reasonable.[79] The frequency of the examinations depends on the results of the initial examination, the diagnosis of immunodeficiency, and the coexistence of complications, but unfortunately, no guidelines are available in this field. It seems that in the case of a normal, initial result, the examination should be performed at least once every 5 years, and in the case of mild cardiovascular diseases, every 2-to 4 years. Prospective analysis of the population of patients with PAD allows for determining the optimal frequency of this examination.

Endoscopic Examinations

Bronchoscopy and bronchoalveolar lavage analysis is recommended to collect a diagnostic specimen, for example, in an atypical lower respiratory tract infection and the case of suspected interstitial lung disease and malignancy, and after the diagnosis, follow-up examinations are performed if necessary.[75]

By analyzing the data available in the literature, the optimal frequency of routine gastroscopy (with *Helicobacter pylori* test) and colonoscopy is at least once every 3 years. Performing these examinations in the first year after diagnosis enables the initial evaluation of the condition of the digestive system and determination of the exact frequency of follow-up examinations, which depends, among other factors, on the presence of intestinal metaplasia, polyps, family history of neoplasms, or presence of inflammatory bowel disease.

In the case of Barret's esophagus and the presence of low-grade dysplasia, gastroscopy should be performed every 6-12 months, and in the case of high-grade dysplasia, endoscopic therapy is recommended; it should be remembered that in the case of the initial colonoscopy with polypectomy and the removal of adenomas in fragments of size>10 mm, a follow-up examination should be performed within 6 months, and only on this basis, the total risk should be evaluated. If colon cancer is diagnosed, a full colonoscopy should be performed within the first year (usually approximately~6 months after the surgery) to inspect for synchronous lesions. In the case of left-sided or extensive ulcerative colitis and a high risk of developing malignancy, colonoscopy should be performed annually.[80-83]

It should be remembered that each of the aforementioned examinations should be performed additionally in the case of a justified clinical situation and suspicion of the involvement of an organ with a disease process.

Nutritional Assessment

Systematic control of the nutritional status plays a very important role. As mentioned before, excess body weight is connected with a higher risk of developing cardiovascular disease, diabetes, neoplasms, obstructive sleep apnea, and respiratory problems as well as degenerative changes in the musculoskeletal system. It is also connected with an increase in all-cause mortality.[28-31] Malnutrition weakens immune functions and prevents the host from obtaining an adequate protective response to infectious agents. Infections affecting nutritional status may, in turn, lead to deficiency changes. Therefore, malnutrition and infection often act synergistically, thereby increasing morbidity and mortality. Malnutrition can influence almost all types of immunity, but the non-specific immune response and cellular immunity are affected more than the humoral response. It should be remembered that, in the elderly, we additionally deal with a disturbance of immune functions caused by the aging process. It is mainly concerning the abnormalities of T lymphocytes, such as decreased proliferation, and impaired response to immunization with T-dependent antigen. Delayed-type hypersensitivity reactions and interleukin-2 production are also impaired, while concentrations of anti-inflammatory cytokines are increased, suggesting the switch from a pro-inflammatory Th1 cell response to an anti-inflammatory Th2 response along with the aging process. Aging accompanied by nutritional deficiencies has a cumulative effect on the immune response. Maintaining optimal nutritional status is therefore of key importance for a good aging process, especially in the group of patients with PAD.[84]

Specialist Consultations

The role of systematic specialist consultations remains underestimated. Particular attention should be paid to regular appointments with the dentist, which should take place twice a year to check and remove plaque or, if necessary, even more frequently. Patients should also undergo regular examinations of skin lesions-a minimum once a year. Otolaryngological consultations should be aimed at the best possible control of upper respiratory tract infections, but they also involve screening that allows for the early detection of PAD complications. A check-up at the rehabilitation clinic is particularly noteworthy, among other factors, which aimsat learning and controlling pulmonary rehabilitation in patients with respiratory tract involvement.

Other Preventive Examinations

It is very important to monitor patients in terms of infectious agents. Not only bacterial infections are important, but also viral (especially EBV and CMV infections) and parasitic (e.g. Giardia spp. infection). These factors were also included in the care protocol.

In women, prevention and early detection of cervical cancer are important. It seems that similar to gynecologic ultrasound, breast ultrasound, and mammography, the frequency of cytology may be the same as that in the case of healthy women. A prospective analysis of the population of women with PAD that evaluates the results of this examination will allow for a more accurate assessment and possible modification of the recommendations. Preventive examinations of cervical cancer (cytology) should start after the age of 25 years but not later than at the age of 30 years, and since then, it should be performed systematically; in the case of early initiation of sexual intercourse, cytology should be performed no later than 3 years after sexual initiation. In women aged≥30 years and who have no lesions and their three consecutive cytology results are normal, as well as in women after the removal of the uterus and cervix due to benign lesions, screening

cytology can be performed every 3 years. Women infected with HIV, human papillomavirus, especially a type of high oncogenic risk, who take immunosuppressive drugs and were treated in the past for intraepithelial neoplasia (CIN2, CIN3) or cervical cancer, should be examined at least once a year. A cytological examination should be performed earlier than after 12 months in women who had no cells from the transformation zone or endocervix in the previous smears, and in the case of poor readability of previous smears due to inflammation or admixture of mucus or blood.[85,86]

Recommendations

Recommendations for patients should be unified. Currently, each center has its own intuitively developed guidelines for patients.

The developed recommendations should be useful to doctors of all specialties who may provide care to the patient. Information about the recommended blood derivatives is very important to avoid additional complications of transfusion and additional immunization of the patient. Moreover, not without significance is the information about regular physical activity, which is undoubtedly beneficial for physical and mental well-being. People who are more physically active can achieve a better quality of life under different medical conditions, especially because the available studies involving patients with primary immunodeficiencies have shown that most of these people can perform low or moderate physical activity.[87]

It is extremely important to be aware of the research methods using antibodies in patients, introducing this information to the patient's documentation allowed for the reduction of costs caused by performing examinations that are non-diagnostic in this group of patients; first, it resulted in better diagnosis of diseases by other specialists, either by selecting an appropriate diagnostic method or by creating awareness that the presence of pathological antibodies in the IgG class is the result of the presence of antibodies of the immunoglobulin donors.

Standardized recommendations for patients with humoral immunodeficiencies, considering specific situations such as traveling, pregnancy, and radiosensitivity, are presented in Table 2.

Table 2. Standardized recommendations for patients with humoral immunodeficiency

Recommendations for all patients
● A balanced diet that is in line with the principles of good nutrition
● Regular physical activity suitable for the patient's age, condition, and health condition
● Performing follow-up examinations and consultations following the attached scheme (Card C)
● In the case of deterioration of health, the occurrence of alarm symptoms (Appendix 1), increased infection frequency, and contact with a GP and, if necessary, a clinical immunologist
● Avoiding crowds
● Recommended vaccination against the influenza virus every year (as known, only if there are no contraindications) – the patient and people from the immediate surroundings
● If there is a need to transfuse blood derivatives, irradiated, leukocyte-depleted preparations should be used
● Vitamin D substitution following the recommendations
● It is not advisable to delay the start of antibiotic therapy in the case of prolonged infection. (When doubtful, it is recommended to perform a complete blood count with manual differential as soon as possible, CRP, and possibly culture)
● It is not recommended to travel to places of high sanitary and epidemiologic risk
● Please inform your family doctor and other specialists (in particular the clinical immunologist) about each new diagnosis and change of medications)
Additional recommendations for patients from Group 1
● Follow-up appointment in Immunology Clinic at least once a year
● IN THE PATIENT, TEST METHODS USING DETERMINATION OF ANTIBODIES IN THE CLASS... CAN BE NONDIAGNOSTIC.THE PATIENT SUFFERS FROM A DISORDER OF ANTIBODY PRODUCTION IN THIS CLASS.

Additional recommendations for patients from Group 2A

- Periodic control at Immunology Clinic (frequency of visits determined individually)
- In the case of delayed local or generalized adverse reactions, a doctor should be contacted immediately. In the case of a systemic reaction (urticaria, dyspnea), 40 mg of prednisone and 2 tablets of an anti-histamine drug must be taken orally, and the patient should visit a doctor urgently or call an emergency.
- Please note all adverse reactions and infection episodes in the treatment record.
- In the event of tooth extraction, respiratory tract infection, and fever, antibiotic treatment is necessary.
- Please come for the next immunoglobulin transfusion on….
- IN THE PATIENT, TEST METHODS THAT INVOLVE THE DETERMINATION OF ANTIBODIES CAN BE NONDIAGNOSTIC.THE PATIENT EXPERIENCES A DISORDER OF ANTIBODY PRODUCTION, AND ANTIBODIES IN IgG CLASS CAN BE THE RESULT OF THE PRESENCE OF ANTIBODIES OF THE IMMUNOGLOBULIN DONORS.

Additional recommendations for patients from Group 2B

- Check-up at Immunology Clinic every 3-6 months.
- Subcutaneous immunoglobulin replacement at home in the dose of ... g per ... weeks.
- In the case of local or generalized adverse reactions, the doctor should be contacted immediately. In the case of a systemic reaction (urticaria, dyspnea), please discontinue drug administration, take 40 mg of prednisone and 2 tablets of an anti-histamine drug, and visit a doctor urgently or call an emergency.
- Please note all adverse reactions and infection episodes in the treatment record.
- In the event of tooth extraction, respiratory tract infection, and fever, antibiotic treatment is necessary.
- Disposal of the medical waste following the instructions.
- In the case of a long-term journey, the patient can have an immunoglobulin preparation for 3 months, i.e., (name of the preparation: ……, number of vials ……..., total dose…).The drug must be stored at the temperature of.....
- IN THE PATIENT, TEST METHODS THAT INVOLVE THE DETERMINATION OF ANTIBODIES CAN BE NONDIAGNOSTIC.THE PATIENT EXPERIENCES A DISORDER OF ANTIBODY PRODUCTION, AND ANTIBODIES IN IgG CLASS CAN BE THE RESULT OF THE PRESENCE OF ANTIBODIES OF THE IMMUNOGLOBULIN DONORS.

Additional recommendations in specific situations

Pregnancy

- In the third trimester of pregnancy, it is recommended to increase the dose of immunoglobulins in the range of 10% to 50%

Radiosensitivity

- Radiological examinations (radiography and CT) are contraindicated, except in the case wherein a patient has a direct life-threatening condition. It is recommended to perform an ultrasound and NMR

Vaccination against COVID-19

- Vaccination against COVID-19 is advisable, preferably with a vector-free vaccine. If this type of vaccine is not available, it is advisable to use the currently available preparation.
- It is recommended to implement vaccination against COVID-19 as soon as possible in the patient and people from the immediate vicinity (cocoon vaccinations).
- In the case of immunoglobulin substitution, it is advisable to maintain a 2-week interval between vaccination and administration of immunoglobulins. If this is not possible, the vaccination should be vaccinated at a predetermined date.

DISCUSSION

Patients with primary humoral immunodeficiencies constitute a heterogeneous group. Although the diagnosis of primary immunodeficiencies is improving, and consequently, the time between the occurrence of the first symptoms and the diagnosis is shortened,[88] there is still a lack of a standardized prophylactic scheme available to patients, which would allow for an increase in the early detection of complications and make it possible to compare patients among many different centers. PIDs are a rapidly developing area of basic and clinical research.[89]

The proposal was designed to improve the quality of care given to patients with humoral immunodeficiencies, which will directly translate into the functioning of the patient in the family and the society, and into their self-perception. The introduction of high-dose IVIG therapy in the late 1990s remarkably improved the survival of patients with CVID. After 20 years of diagnosis, the survival rates were 64% for men and 67% for women, compared with the expected 92% and 94% survival rates of the population, respectively. Since 2000, as the standard IgG replacement dose is still increasing and an increasing number of patients maintain normal IgG antibody concentration for most of their lives, the expected overall survival time 45 years after diagnosis is 58%.[90]

Providing this group of patients with comprehensive specialist care is very important not only to delay the occurrence of complications and prolong their survival but also to ensure the best quality of life, including the possibility of choosing a school, work, or hobby, and to limit the isolation of these patients as much as possible.

Because there are large discrepancies in the care of patients with PAD in different countries, we tried to introduce the most universal recommendations based on the current literature and standards available to date.

We hope that the presented proposal of the standard of care for patients with PAD will facilitate and improve the quality of care for patients with PAD and will allow the estimation of the real costs associated with it.

At the same time, we emphasize that the work intends to present protocols that can be modified depending on the needs and characteristics of care in a given country.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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In memory of TŚ, RP, MD, PW, JPW patients who passed away too early.

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