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Recommendations for prevention of SARS-CoV-2 infection in immunocompromised patients

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Introduction

The appearance of the new SARS-CoV-2 coronavirus at the end of 2019 changed the reality and created a serious health threat on a global scale. The COVID-19 pandemic has killed more than 6 million people, and officially registered infections amount to 600 million. In Poland, 117 000 people have died, and the number of registered infections has exceeded 6 million; however, these numbers certainly do not reflect the actual values. In the last 2 years, risk factors for severe COVID-19 have been identified. In addition to cardiovascular diseases and metabolic diseases (diabetes, obesity), they include conditions associated with impaired immune system functions, either due to the disease process itself or as a result of treatment. These factors have double significance at present. In addition to the risk of a severe course of the disease, they also bring the risk of an inadequate response to COVID-19 vaccination, often implying the lack of any specific immunity.

In this article, we present the position of experts in oncology, hematology, transplantation (representing the Polish Oncological Society, the Polish Society of Hematologists and Transfusionists, and the Polish Society of Transplantation), and infectious diseases on COVID-19 prevention in the immunocompetent population. This population includes patients with solid tumors, hematological malignancies, and patients after hematopoietic cell/solid organs transplantation. To find relevant scientific evidence, a non-systematic search of clinical practice guidelines and medical information databases was performed. The legitimacy of using all currently available forms of prophylaxis does not raise any doubts, and numerous clinical observations, including Polish ones, confirm the importance of proper management, especially in this group of patients. The availability of vaccines against COVID-19 and the evolution of the virus (the emergence of new subtypes of the Omicron variant) gives hope for a gradual reduction in mortality. However, the discussed group of patients is still at risk of a severe course of disease due to the ineffectiveness of commonly accepted management strategies. Moreover, any delays in the treatment of underlying diseases resulting from SARS-CoV-2 infection carry a risk of poor prognosis.

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The course of SARS-CoV-2 infection in patients with solid organs malignancies (SOMs)

Effect of tumor type

Solid tumors *per se* have a smaller adverse effect on the course of SARS-CoV-2 infection compared to hematological malignancies; however, a worse ECOG performance status (PS) and a higher cancer stage in patients with solid tumors are associated with a higher risk of death due to COVID-19 [1]. The risk of having to be admitted to the intensive care unit (ICU) and the risk of death in this group increase by about 50–66%. Of course, this may be partly due to the specific age structure of cancer patients (older compared to the general population). Regardless of this, however, it is believed that diagnosis of SOMs is an independent risk factor for death and hospitalization in ICU due to SARS-CoV-2 infection.

The coexistence of COVID-19 with bilateral lung involvement and simultaneous lung cancer, both primary lung cancer and metastatic lesion, is a particularly life-threatening combination, increasing the risk of death [2]. This was also confirmed by the Polish report under the National Oncological Strategy "Impact of the COVID-19 pandemic on the cancer care system". The 30-day mortality rate among patients with lung and thoracic cancers exceeded 23%, with an expected mortality of 10.9% [standardized mortality ratio (SMR) = 2.27]. The worse course of COVID-19 may also be associated with tobacco-dependent neoplasms [3]. Moreover, the negative consequences of previous COVID-19 infection affect approximately 15% of cancer patients and have a negative impact on oncological treatment outcomes due to the need to interrupt/delay cancer therapy [4].

Effect of anticancer treatment type

Active systemic treatment of patients with solid tumors, especially cytotoxic chemotherapy, is associated with the risk of a more severe course of SARS-CoV-2 infection and an increased risk of hospitalization and death [1, 5–7]. The results of the meta-analysis did not show such a relationship in the case of molecularly targeted therapy, immunotherapy, or radiotherapy. In turn, many studies, including meta-analyses, have confirmed the negative impact of active SARS-CoV-2 infection during the postoperative period in cancer patients treated with surgery [8, 9].

The course of SARS-CoV-2 infection in patients with hematological malignancies

Effect of malignancy type

Analyzes of the correlation between malignancy type and the course of COVID-19 demonstrated conflicting results, but in most studies, acute myeloid leukemia (AML) was associated with a higher risk of death, exceeding even 40% [10]. In other analyzes, higher mortality was observed in patients with non-Hodgkin lymphomas (NHL), plasma cell neoplasms [11], or myelodysplastic syndrome (MDS) [12]. In a multicenter retrospective study, a severe course of COVID-19 (defined as hospitalization with the need for oxygen therapy or ICU admission) was observed in 65.6% of patients with chronic lymphocytic leukemia (CLL). The mortality rate was 27.3% (38.4% in patients with severe COVID-19) [13]. In the Polish analysis of 192 patients with CLL, the mortality rate was also high, amounting to 30% [14]. Relatively consistent data concern the milder course of COVID-19 in patients with chronic hematological malignancies, with the mortality rate in patients with chronic myeloid leukemia (CML) of 5.5% compared to 2.97% in the general population [15, 16]. Similarly, the diagnosis of a Ph-negative myeloproliferative neoplasm is associated with lower mortality compared to other neoplasms [17].

Effect of anticancer treatment type

Studies on the impact of specific anticancer treatments on the COVID-19 course did not report unequivocal results. In a meta-analysis of 34 studies, the type of treatment used was not associated with the severity of COVID-19 course or increased risk of death [18]. Smaller studies have shown that treatment with monoclonal antibodies, especially anti-CD20, was associated with higher mortality, longer hospitalization time, and a higher risk of death [17].

The use of chemotherapy is generally not associated with a worse prognosis [19] although one study reported a four-fold higher risk of death in patients undergoing intensive treatment, for example, high-dose methotrexate, DHAP (cisplatin, cytarabine, dexamethasone), escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), intensive chemotherapy in the treatment of patients with acute leukemia, as well as autologous and allogeneic hematopoietic stem cell transplantation (auto-, alloHSCT) [20, 21]. In a multi-center prospective analysis, the mortality rate due to COVID-19 in patients after HSCT was 28.4%, with no difference in survival between patients after alloSCT and autoSCT [22]. Chimeric antigen receptor-T cell (CAR-T) immunotherapy is associated with an even higher risk of death due to COVID-19, amounting to 41% [23].

Currently, no data suggest that drugs used in the treatment of patients with chronic myeloproliferative neoplasms (MPN), such as tyrosine kinase inhibitors, hydroxyurea, interferon alpha, anagrelide, or ruxolitinib increase the risk of SARS-CoV-2 infection or a severe course of the disease.

The course of SARS-CoV-2 infection in patients after transplantation

Patients after organ transplantation are at increased risk of infection and severe course of SARS-CoV-2 infection not only due to the weakened immune response caused by immunosuppressive treatment but also due to frequent comorbidities, such as diabetes, hypertension, or ischemic heart disease. The course of COVID-19 in transplant recipients is associated with increased morbidity and mortality. Published data show that mortality in transplant recipients in the first year of the pandemic was about 20%, while in the second year (2021), it decreased to several percent due to the introduction of vaccinations and more effective drugs. However, mortality in transplant patients was still higher than in the general population [24, 25].

Both the humoral and cellular responses to SARS-CoV-2 infection are weaker and disappear faster than in immunocompetent individuals. Similarly, the response to vaccination is poorer and of short duration, hence the fourth dose of vaccine is currently recommended.

The optimal regimen of immunosuppression in SARS-CoV-2 infected transplant recipients has not been established, therefore, the reduction of immunosuppression is dependent on the clinical course. In mild and moderate cases, it is recommended to discontinue the antiproliferative drug (mycophenolate mofetil). In severe cases, it is recommended to temporarily discontinue immunosuppressants and administer intravenous glucocorticosteroids. After 14 days, immunosuppression should be slowly increased. In patients without infection, the immunosuppressive treatment should not be modified [26, 27].

Additional therapies for SARS-CoV-2 infection may be used in transplant recipients taking into account their side effects, drug-drug interactions, and renal function [28, 29]. The response to vaccination and treatment may change with the emergence of new viral mutations [30, 31].

Effectiveness of vaccinations against COVID-19 in cancer patients

Patients with solid organs malignancies

Vaccination against COVID-19 is the basic method of reducing the risk of infection and the severe course of COVID-19 also in the group of patients with solid tumors [32]. The safety profile of vaccines based on mRNA technology is very good in this group of patients [33]. International guidelines currently recommend mRNA vaccines in cancer patients, with supplementary and booster doses [34]. A complete course of vaccination significantly reduces the risk of death in these patients. Most patients develop antibodies to SARS-CoV-2 [34, 35], but the production of antibodies (serological response) occurs after a longer period or at a lower titer than in the general population [36, 37]. This is particularly evident during active chemotherapy [38, 39]. In cancer patients, antibodies titer and the level of cellular response indicators decrease faster, which translates into lower protective effectiveness of vaccinations. In addition, the current dominance of the Omicron variant reduces the effectiveness of vaccination due to the antigenic differences between the vaccine and the current virus variant [40].

Patients with hematological malignancies

The same immunodeficiency mechanisms accompanying proliferative neoplasms of the lymphatic and hematopoietic systems that are associated with an unfavorable course of infection, including COVID-19, also contribute to a suboptimal response to vaccination against COVID-19. Compared to healthy subjects, lower antibody titers, shorter persistence of the post-vaccination response, and impaired antibody function are observed [41]. A large part of published data is based on the analysis of post-vaccination antibody production, ignoring cell-mediated immunity, which limits the full clinical conclusion on vaccine efficacy.

A Polish analysis [42] compared the effectiveness of vaccinations in the groups of two immune system cancers with significant immunodeficiency: multiple myeloma (MM) and CLL. A statistically significant increase in antibody titers was observed in patients with MM after the second dose of the primary vaccination, significantly greater than in patients with CLL. The antibody response rate in the CLL cohort was 41% after the second dose and increased to 71% at 12 weeks after the second dose of the vaccine. The rate of seroconversion in the CLL cohort did not correlate with age, disease stage, or sex. The results of recent studies have also shown significantly lower antibody titers in patients receiving anti-cancer therapy, especially those undergoing CAR-T and bone marrow transplant procedures. In patients with MM treated with targeted anti-CD38 or BCMA (B-cell maturation antigen) therapy and patients with lymphomas and CLL treated with anti-CD20 immunochemotherapy or Bruton tyrosine kinase (BTK) inhibitors, a poorer vaccine response has been observed. Stampfer et al. [43] reported lower antibody titers in patients receiving steroids, but this was not observed in Polish patients.

Vaccines against COVD-19 are effective in inducing the production of antibodies and increasing the titer of anti-RBD (receptor-binding domain) antibodies, which persist for at least 3 months after the second dose. Vaccination effectiveness is increased by 30% by a booster dose, and the persistence of antibodies is prolonged.

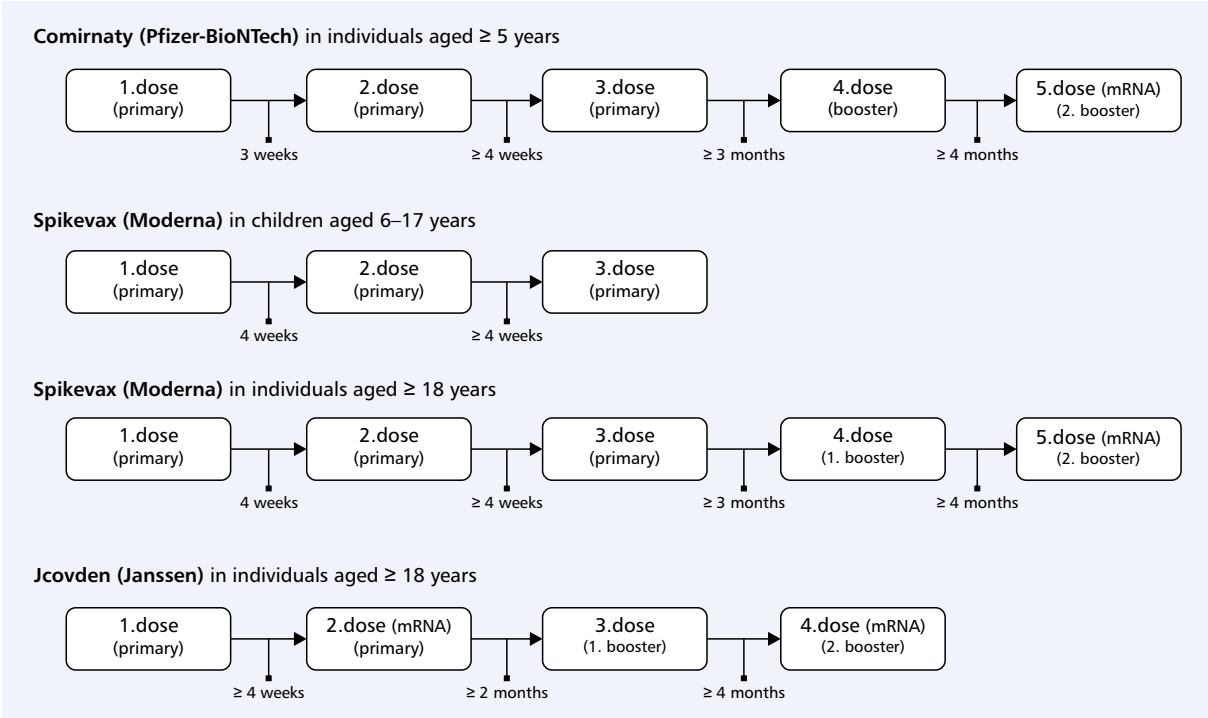

Figure 1. Recommendations for the time of administration of subsequent doses of vaccines against COVID-19 in people with severe or moderate immunodeficiency (based on: mp.pl — szczepienia and https://www.cdc.gov/vaccines/covid-19/clinicalconsiderations/interim-considerations-us.html]

Patients after organ transplant

In dialysis patients, a slightly delayed but good response to vaccination was observed [44, 45]. Patients after kidney transplantation responded to vaccination much worse. Only about 50% of patients achieved seroconversion after a two-dose mRNA vaccination, and the antibody titer was frequently lower than in the general population [46, 47]. In addition to patients' older age, factors adversely influencing the humoral response included immunosuppressive treatment, in particular intensive one and with use of polyclonal antibodies in induction therapy, as well as the use of antiproliferative drugs from the mycophenolate group in maintenance therapy [48, 49]. Due to the above data on the response to vaccination with the two-dose vaccination regimen in the population of patients treated with renal replacement therapies, including patients after transplantation, it is recommended to administer three doses of primary vaccination and treat the third dose as supplementary to the primary vaccination course. A primary cycle of 3 doses and a fourth booster dose after 5–6 months is now recommended.

In patients after transplantation, the clinical effectiveness of vaccinations is worse, which results from impaired immune response to vaccination (54% after the second dose, 67% after the third dose) [50].

Recommendations for the use of COVID-19 vaccines in non-immunocompetent individuals with severe or moderate immunodeficiency

The World Health Organization (WHO) has already issued a recommendation for an extended series of primary immunizations (i.e. third dose) and booster doses (i.e. fourth dose) in immunocompromised individuals for all COVID-19 vaccines. It is allowed to use booster doses in the form of homologous (the same vaccine platform) and heterologous (different vaccine platform) vaccines [51, 52].

Figure 1 shows the recommended COVID-19 immunization schedule for people with severe to moderate immunodeficiency.

Individuals 12 years of age and older should receive a booster dose (fourth) at least 5 months after the supplementary dose (third).

If possible, doses of COVID-19 vaccine should be administered at least 2 weeks before starting or resuming immunosuppressive therapy. The timing of vaccination against COVID-19 should consider current or planned immunosuppressive therapy, as well as optimization of both the patient's clinical state and response to the vaccine.

Currently, it is not recommended to perform serology or cellular response tests to assess response to vaccination against COVID-19.

The same preparation (i.e. from the same manufacturer) should be used for the primary vaccination, including the administration of a supplementary dose. In exceptional circumstances, where it is not possible to determine which mRNA vaccine was administered as the first dose of the baseline regimen, or if this preparation is not available, any other available mRNA vaccine may be administered to complete an already initiated regimen, with an interval of at least 28 days between doses. In people aged 18 years and above, in exceptional situations, when the patient received the first dose of mRNA vaccine, but it is not possible to complete the schedule with the same preparation or another mRNA vaccine (e.g. due to contraindications), administration of 1 dose of Janssen/Johnson & Johnson (J/J&J) vaccine may be considered at least 28 days apart to complete the schedule. Patients who receive the J/J&J vaccine after a dose of mRNA vaccine to complete the schedule that has been initiated should be considered vaccinated with a 1-dose J/J&J preparation.

Any age-appropriate mRNA preparation may be used as a booster (following a heterologous pattern). Jcovden (J/J&J) should not be used for the second booster vaccination.

Vaccination against COVID-19 is recommended for all people, regardless of previous SARS-CoV-2 infection (symptomatic or asymptomatic), and this applies to both basic vaccination, including administration of the supplementary dose, and booster vaccination. This recommendation applies to people infected with SARS-CoV-2 before vaccination against COVID-19 or between subsequent vaccination doses.

Additional booster doses for immunocompromised people

Additional booster doses in addition to the first supplementary dose are currently offered in some countries (i.e. fourth dose for the elderly and fifth dose for immunocompromised people). Data on the effectiveness of these additional boosters are sparse and do not predict the duration of continued protection. Data on additional booster doses are available only for mRNA vaccines [53].

Recommendations for passive immunoprophylaxis in non-immunocompetent individuals

On March 25, 2022, the European Medicines Agency (EMA) registered the Evusheld® preparation containing a combination of two antibodies (tixagevimab and cilgavimab) with prolonged action, for COVID-19 pre-exposure prophylaxis [54]. The preparation can be used in adults and adolescents aged 12 years and older who weigh at least 40 kg. The prerequisite for eligibility is the lack of a current SARS-CoV-2 infection, defined as exposure to a person infected with SARS-CoV-2 and the presence of moderate or severe immunodeficiency. The latter parameter, in accordance with the data cited earlier, may cause an insufficient immune response to vaccination against COVID-19. In addition, the preparation is intended for people who cannot receive any available COVID-19 vaccine. Administration of Evusheld® should be considered especially in people who are at particular risk of severe course of COVID-19.

The drug is administered by intramuscular injection and exhibits neutralizing activity against the Omicron SARS-CoV-2 variant, which is unique among currently available monoclonal antibodies. The drug does not replace the COVID-19 vaccine and should not be used in people without contraindications to vaccination, who are expected to respond adequately to the vaccine. Patients who have been vaccinated against SARS-CoV-2 may receive Evusheld® 2 weeks after the last dose of the vaccine at the earliest. However, vaccination can be performed regardless of when Evusheld® was administered.

Current registered drug dosage in Europe is 150 mg tixagevimab and 150 mg cilgavimab administered as two consecutive intramuscular injections.

Evusheld® has been registered based on the results of the PROVENT clinical trial. In this phase III, randomized, double-blind, placebo-controlled trial, the use of tixagevimab/cilgavimab for pre-exposure prophylaxis in a group of 5197 subjects was investigated. There was a 77% reduction in the risk of symptomatic COVID-19 confirmed by a positive SARS-CoV-2 RT-PCR (real-time polymerase chain reaction) test in the TIXA/CILGA arm compared to placebo after 3 months and 83% after 6.5 months of follow-up [55].

Evusheld® is the optimal form of prophylaxis in non-immunocompetent patients whose response to vaccination is unsatisfactory, short-term, or absent. The protective effect of antibodies lasts for at least 6 months [56].

The use of other monoclonal antibodies, such as bamlanivimab/etesevimab or casirivimab/imdevimab for pre-exposure prophylaxis, is currently not justified due to the dominance of the Omicron SARS-CoV-2 variant, which is not neutralized by these antibodies.

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