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Special report

Vaccination of stem cell transplant recipients: recommendations of the Infectious Diseases Working Party of the EBMT

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Summary:

Over the last 25 years, the numbers of hematopoietic stem cell transplant (SCT) patients have increased rapidly. Infections have been major obstacles for successful transplantation. Thus, infection prevention is very important in transplant recipients. As the results of transplantation have improved, the number of long-term survivors has increased. Vaccination is a potentially important strategy for reducing the risk for vaccine-preventable infections after SCT. The EBMT produced recommendations for vaccination of SCT recipients published in Bone Marrow Transplantation in 1995. This paper updates the previous recommendations based on current knowledge.
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Over the last 25 years, the numbers of hematopoietic stem cell transplant (SCT) patients have increased rapidly. Infections have been major obstacles for successful transplantation. Thus, infection prevention is very important in transplant recipients. As the results of transplantation have improved, the number of long-term survivors has increased. Many patients remain immunosuppressed for a long time due to the interaction between the graft and the host, that is, GVHD. Immunizations, which have for various reasons not been used consistently at many transplant centers, are important for two main reasons. Obviously, the most important is the need to protect the transplant recipient against serious vaccine-preventable infections that may occur during the early or late post transplant period. However, another reason is the public health consideration point of view, namely, that it is essential not to have an increasing number of individuals vulnerable to important infectious agents.

The EBMT produced recommendations for vaccination of SCT recipients in 1995, which were updated in 1999. The United States Center for Disease Control (CDC) published recommendations in 2000. The aim of this paper is to update our previous recommendations. These are graded according to CDC guidelines[1] as described in Table 1 and summarized in Table 2.

General aspects

During the last two decades, several studies have been published regarding the loss of pretransplant immunity, which occurs after SCT, and the response to different vaccines. The loss of immunity seems to depend on the strength of existing pretransplant immunity in the patient and, to some extent, the immune status of the donor. For example, previously vaccinated patients are more likely to lose immunity to measles than patients who have experienced natural measles infection.[2,3] Chronic GVHD is important for loss of immunity to some pathogens, particularly to pneumococci. Most of the existing data relate to myeloablative conditioning regimens, and whether the risk of loss of immunity will be similar after reduced intensity conditioning regimens is still unknown.

Allogeneic and autologous SCT recipients are clearly different in the characteristics of their immune reconstitution. After an allogeneic SCT, the immune system of the recipient is replaced by that of the donor. Immune deficiency is caused by a combination of the preparative regimen given before SCT, GVHD, and immunosuppressive therapy given afterwards. Many studies have shown that immunity to some infectious agents can be transferred by the graft and be detectable in the patient early after the SCT. Persisting immune deficiency is common, in particular, in patients with chronic GVHD and influences the risk for late infections. In autologous SCT recipients, the immune system is depressed by high doses of chemo- and radiotherapy, but there is no immunological disparity between the graft and the host. The immune regeneration is, in most patients, quicker than after allogeneic SCT and even more so after peripheral blood stem cell transplantation, and there is little indication of persistent immune deficiency. Despite these differences, the risks of losing

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Table 1 Evidence-based system used to determine strength of recommendations

Strength of recommendations[1]		
A	Strong evidence for efficacy and substantial clinical benefit	Strongly recommended
B	Strong or moderate evidence for efficacy, but only limited clinical benefit	Generally recommended
C	Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (eg drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches	Optional
D	Moderate evidence against efficacy or adverse outcome	Generally not recommended
E	Strong evidence against efficacy or adverse outcome	Never recommended
Quality of evidence supporting recommendation		
I	Evidence from at least one well-executed randomized trial	
II	Evidence from at least one well-designed clinical trial without randomization; cohort- or case-controlled analytic studies (preferably from more than one center; multiple time-series studies; or dramatic results from uncontrolled experiments	
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees	

Efficacy is defined as development of protective antibody response after vaccination.

immunity to several infectious agents are similar after allogeneic and autologous SCT. The results of vaccination studies are also rather similar,[4–9] although there are a few reports showing that the type of transplant makes a difference to the results.[10] We have, however, chosen not to give different sets of recommendations for the different types of transplants, since using similar vaccination schedules for all transplant recipients is of practical importance for the work of transplant centers.

Which vaccines should be considered in SCT recipients? This question can be looked at from various aspects. First, it can be addressed from the point of view of the risk and severity of the infections against which the vaccines are directed. This can be subdivided into:

(a) Infections, including those due to pneumococci, *Haemophilus influenzae* type B (HIB), varicella-zoster virus (VZV), and influenza virus, which are more frequent and/or severe in SCT patients than in the general population.
(b) Infectious diseases, including tetanus, diphtheria, polio, and hepatitis B, which are not more frequent in SCT patients but for which vaccination recommendations exist to protect the general population.
(c) Infections to be considered in special situations such as in patients residing in certain endemic areas or for travellers.

A second aspect is the risk of side effects. Vaccines containing inactivated organisms, antigens, or subunits have been shown to be safe with no more side effects than in healthy individuals. Vaccines containing live organisms have the potential to cause significant disease in the immunocompromised patient and should either not be used at all (eg BCG, live polio) or only in certain circumstances (eg measles, varicella, rubella).

The vaccination response is usually poor during the first 6 months after SCT. However, an improved response to such early vaccination has been shown if donors have also been immunized in the case of hepatitis B, tetanus, HIB, and conjugated pneumococcal vaccines but not for pneumococcal polysaccharide vaccine.[11–14] A strategy of also immunizing the donor can therefore be contemplated, although practical and ethical issues have to be addressed. Efficacy in all these studies means development of an antibody response following vaccination, since data regarding protection against infection are not available.

One important question is whether to vaccinate patients with ongoing GVHD or ongoing immunosuppressive treatment. These patients should not be given live vaccines, but there is no evidence suggesting that the use of inactivated vaccines exacerbates chronic GVHD. However, the data are mixed regarding the effect of chronic GVHD on the response to immunization.[4,8,10,15]

Another way to possibly reduce the risk for disease in the SCT recipient is to reduce the likelihood of exposure. This can be achieved by vaccinating, for example, family members and hospital staff against influenza. In some countries such as the United Kingdom, there are also recommendations to immunize seronegative health-care workers with the varicella vaccine. Although varicella vaccine may be contagious and therefore transmitted to susceptible close contacts, transmitted vaccine-induced infections can be treated by acyclovir and therefore the benefit of immunizing seronegative family members with varicella vaccine is likely to be higher than its risk. However, the live poliovirus vaccine should not be used in family members or health-care workers caring for SCT patients.

Vaccines against bacteria

Pneumococcal vaccine

Pneumococcal infections are significant causes of morbidity and mortality after allogeneic SCT. Fatal infections can occur both early and late after transplantation as shown in an EBMT study.[16] The incidence of invasive pneumococcal infections was 8.23/1000 transplants. It was increased in patients with chronic GVHD where the incidence was 20.8/1000 transplants. Although autologous SCT patients are less prone than allogeneic patients to develop severe infections with pneumococci, the incidence was still much higher than in an immune-competent population with an incidence of 3.8/1000 transplants.

Table 2 Summary of the EBMT vaccination recommendations

	Available forms	*Available data in SCT patients*	*Recommended after SCT*	*Strength of recommendation*	*No. of doses*	*Time after SCT (months)*	*Improved by donor vaccination*
Bacterial vaccines							
S. pneumoniae	Polysaccharide (PS)	Yes	Yes	BII	1	12	No
	Conjugate PS	Yes	Yes (subgroups)	CII	3	Unclear	Yes
H. influenzae type B	Conjugate PS	Yes	Yes	BII	3	6	Yes
Neisseria meningitidis types A and C	PS	Yes	Individual assessment	CII	1	6–12	Unknown
N. meningitidis type C	Conjugate PS	No		CIII	1	6	Unknown
BCG	Live	No	Contra-indicated	EII	NA	NA	Unknown
Tetanus	Toxoid	Yes	Yes	BII	3	6–12	Yes
Diphtheria	Toxoid	Yes	Yes	BII	3	6–12	Likely
Bordetella pertussis[a]	Acellular, toxoid +/− other antigens	Yes	See text	CIII	3	6–12	Unknown
Viral vaccines							
Influenza	Inactivated	Yes	Yes, yearly	AII	1	4–6	Unknown
Inactivated polio	Inactivated	Yes	Yes	BII	3	6–12	Unknown
Hepatitis B	Inactivated plasma or recombinant DNA derived	Yes	See text	BII	3	6–12	Yes
Hepatitis A virus	Inactivated	No	In endemic areas and in travellers	CIII	3	6–12	Unknown
Measles[b]	Live	Yes	Individual assessment	BII		24[c]	Unknown
Rubella[b]	Live	Yes	Individual assessment	BIII	1	24[c]	Unknown
Mumps[b]	Live	Yes	Individual assessment	CIII	1	24[c]	Unknown
Varicella	Live	Limited	Individual assessment	CIII	Unclear	Before SCT or at 24[c]	Unknown
Yellow fever	Live	Limited	Individual assessment, travelers	CIII	1	24[c]	Unknown

[a]Combination vaccines including also tetanus, diphtheria, and pertussis with or without HIB and poliovirus components are available.
[b]Usually combined in an MMR vaccine.
[c]Not in patients with chronic GVHD or ongoing immunosuppression.

Immunity against pneumococci is mediated by antibodies directed against polysaccharides from the bacterial capsule. However, to determine immunity to pneumococci by serological testing is difficult. Antibody levels might not represent protective immunity well as these are usually measured only against a few of the large number of pneumococcal serotypes. Therefore, the results must be used with caution and a dialogue with the local laboratory is needed.

There are today two available vaccine types, that is, polysaccharide-based pneumococcal vaccines and conjugate vaccines. The polysaccharide vaccines elicit a T-cell-independent immune response and do not induce immunological memory. Therefore, these vaccines work poorly in young children and booster doses do not induce stronger responses. The current polysaccharide vaccines include 23 serotypes that cover most of the circulating common pneumococcal strains. On the other hand, the conjugate vaccines (pneumococcal polysaccharide conjugated with a protein) give a better immune response and development of T-cell memory can be achieved, but the construction of the conjugates makes it difficult to include a large number of serotypes. Therefore, protection against invasive pneumococcal disease from the conjugate vaccines will depend on the circulating serotypes in the community since only seven are included in the current vaccine. The selection of the serotypes was based on epidemiological data concerning invasive pneumococcal infections in children in the USA, but different serotypes circulate in other parts of the world.

Studies of the polysaccharide-based vaccines have shown that they can elicit antibody responses 6–12 months after allogeneic SCT in patients without GVHD but not in patients with chronic GVHD.[5,17–20] In particular, the specific IgG2 responses have been poor.[20,21] The immune response was not significantly improved by two doses of pneumococcal vaccine as compared to one dose.[5] Children given pneumococcal polysaccharide vaccines had short-lived responses of low avidity[22] in contrast to adults in

whom the avidity was high.[23] There is no advantage in vaccinating the donor. In autologous SCT recipients, the response to a single dose of pneumococcal polysaccharide vaccine is poor regardless of the stem cell source[5,9] and remains decreased for several years after transplantation for lymphoma as compared to controls.[24] There is no advantage in vaccinating autologous SCT patients before stem cell harvest with pneumococcal polysaccharide-based vaccine.[25] Thus, vaccination responses to the polysaccharide vaccines are suboptimal in many autologous SCT recipients, especially lymphoma patients.

Less information is available for the pneumococcal conjugate vaccine. Molrine *et al*[13] performed a randomized study with the conjugated vaccine comparing pretransplant vaccination of the patients and their donors with no vaccination pretransplant. All patients thereafter received three doses of the vaccine at 3, 6, and 12 months after transplantation. The majority of patients (72–100% for different serotypes) developed protective antibodies at 12 months after SCT.[13] There was an improved response (67 *vs* 36%) to the first dose post-SCT and a better immune response if the donor was also vaccinated. Similarly, preliminary results of a small pilot study show improvement of antibody responses also in patients with chronic GVHD (Hammarström and Ljungman, unpublished data). An EBMT randomized study comparing early and late start of vaccination is ongoing. There have been a few reports in other groups of patients that a dose of the polysaccharide vaccine given after the conjugate vaccine can improve the response.[26,27] This hypothesis is as yet untested in SCT recipients but a study is ongoing in the EBMT.

- Despite the poor responses to vaccination in some patients, the current recommendation is to vaccinate all SCT patients with one dose of pneumococcal polysaccharide vaccine at 12 months after SCT (BII).
- Despite the known variation in pneumococcal serotypes in some countries and hence the potential lack of protection provided by the heptavalent pneumococcal conjugate vaccine, it seems logical today to vaccinate small children and patients with chronic GVHD with three doses of this vaccine starting at 6–12 months after SCT (CII).
- In patients vaccinated with the conjugate vaccine, a subsequent dose of the polysaccharide vaccine can be considered (CIII).
- Prophylaxis against pneumococcal infections is indicated in patients with chronic GVHD. The choice of antibiotic depends on the local pattern of pneumococcal resistance (AII).
- Testing of pneumococcal immunity is recommended every 2–3 years in patients with chronic GVHD (BIII). Revaccination may be considered in patients lacking immunity to pneumococci (CIII).

HIB conjugate vaccine

HIB is also an important cause of infection in SCT recipients, although severe/fatal infections seem to be rare. Vaccination with conjugated HIB vaccine can elicit protective immunity after allogeneic SCT.[5,17,19] However, timing after SCT is important since it was reported that early immunization with HIB vaccine gave poorer responses in transplanted children.[28] Donor vaccination improved the response when patients were immunized at 3 months after SCT.[12]

Immunization with two doses of the conjugated HIB vaccine induced a protective immune response in 80% of SCT recipients,[5] but this might be improved by immunizing the patient before stem cell harvest. Immunization with a conjugated HIB vaccine before the harvest followed by immunization at 3, 6, 12, and 24 months after autologous SCT resulted in higher antibody titers after the dose given at 3 months:[25]

- Immunization with three doses of the HIB conjugate vaccine is indicated for all SCT recipients starting at 6 months after SCT (BII).
- Subsequent doses can be given 1–3 months apart (BIII).

Meningococcal vaccine

Meningococci cause occasional severe infections after SCT. Vaccination with a tetravalent meningococcal polysaccharide vaccine can elicit good responses in SCT recipients both against serogroup A and C.[29] A conjugated vaccine against serogroup C exists but no data are available in SCT recipients:

- Meningococcal vaccination is not routinely recommended after SCT but should be considered in situations where the risk of meningococcal disease is increased (CII).

Tetanus toxoid vaccine

Tetanus is a rare but life-threatening disease preventable by immunization. Most allogeneic SCT patients and a large proportion of autologous SCT patients will lose immunity to tetanus toxoid during extended follow-up.[30,31] The side effects from the toxoid vaccine are usually mild. Thus, there are good medical reasons for having an immunization strategy against tetanus in SCT recipients.

Several studies of immunization with tetanus toxoid have been published.[6,10,15,30,32] A primary schedule with repeated doses of these vaccines is needed to obtain stable protective immunity.[6,10,30] In most of the published studies, the immunization programs were initiated approximately 1 year after SCT.[6,10,30] However, it was shown recently that good and lasting immune responses can be obtained when immunizations are started at 6 months after SCT.[15,32] Therefore, vaccination should be started at 12 months after SCT, but it is possible, if indicated, to start at 6 months. Donor immunization with tetanus toxoid before the donation, combined with early post transplant vaccination, improves the immune response:[11]

- All SCT patients should be vaccinated against tetanus with three doses of tetanus toxoid (BII).
- The vaccination schedule should start at 6–12 months after SCT with subsequent doses given 1–3 months apart (BII).

Diphtheria toxoid vaccine

Diphtheria is a serious disease preventable by vaccination. Large epidemics of diphtheria have occurred in Russia recently and sporadic cases occur in many countries. Most allogeneic SCT patients and a large proportion of autologous SCT patients will lose immunity to diphtheria during extended follow-up. Thus, there are good medical reasons for having an immunization strategy against diphtheria in SCT recipients.

Similar to tetanus, a primary schedule with repeated doses of these vaccines is needed to obtain stable protective immunity. In most of the published studies, the immunization programs were initiated approximately 1 year after SCT:

- All SCT patients should be vaccinated against diphtheria with three doses of diphtheria toxoid (BII).
- The vaccination schedule should start at 6–12 months after SCT with subsequent doses given 1–3 months apart (BII).

Pertussis vaccine

There is no report of severe pertussis infection after SCT and no data regarding vaccine efficacy. In the general population, pertussis vaccination is recommended for infants and children younger than 7 years. There is no reason to believe that the side effects from the vaccine would be more severe in SCT patients than in healthy children.

- Routine vaccination against pertussis is not recommended (CIII).
- It could be considered after SCT in children younger than 7 years in epidemiological situations where the risk for pertussis is high (CIII).

BCG vaccine

Tuberculosis is a potentially very severe infection after transplantation.[33] However, the existing vaccine is poorly efficacious and has been reported to cause significant side effects in immunocompromised patients, in particular, those with defects in their T-cell immune function.

- BCG vaccine is contraindicated in SCT recipients (EII).

Other vaccines against bacterial infections

There are both live (oral) and inactivated (parenteral) vaccines against *Salmonella typhi*, but use of the live vaccine should be avoided. Regarding other live bacterial vaccines, the risk/benefit ratio must be carefully assessed.

- Live vaccines against bacterial infections should not be routinely used (DIII).
- In particular, in situations such as giving advice to travelers, a very careful assessment of potential risks and benefits must be performed (CIII).

Vaccines against viruses

Influenza vaccine

Influenza A and B infections can be severe and life threatening in SCT recipients.[34–37] Severe and even fatal infections can occur several years after SCT. The impact of the recently introduced antiviral neuraminidase inhibitors on severity and outcome of influenza in SCT patients is not yet clear.

The health authorities in several countries recommend a yearly influenza vaccination for immunocompromised patients. Immunization with two doses of influenza vaccine can elicit an immune response but in a study by Engelhard *et al*,[4] the timing after SCT was shown to be important. No patient responded when immunizations were given before 6 months after SCT, approximately 25% of the patients responded when immunizations were given between 6 months and 2 years after SCT, while more than 60% of the patients responded when immunizations were given more than 2 years after SCT. The addition of a second dose of influenza vaccine had only a marginal effect. In a randomized study of the usefulness of GM-CSF as a potential immune stimulant, only 30% of allogeneic and autologous SCT patients vaccinated between 4 and 12 months after SCT responded to the vaccination.[8]

The possibility that vaccinated patients might develop a milder influenza disease despite a less than optimal antibody response cannot be either supported or excluded by currently available data. Owing to the poor response to vaccination early after SCT, it would be logical to decrease the exposure to influenza by vaccinating family contacts and hospital staff. However, the impact of such a policy has not been formally studied.

It should be remembered that the influenza season is reversed in the Southern Hemisphere when giving travel advice to patients. The vaccines used in the two hemispheres may therefore differ slightly in their composition because of the addition of newly detected influenza strains, and the protection from recently given immunization might be suboptimal when traveling to the other hemisphere:

- Influenza vaccination with one dose of inactivated vaccine is recommended for all SCT patients (AII).
- Vaccination should be given before the influenza season starting no earlier than 4–6 months after SCT and continued yearly in allogeneic SCT patients at least as long as the patient has GVHD or ongoing immunosuppression (BII).
- The duration of yearly influenza vaccination in autologous SCT patients has to be assessed individually (BIII).
- Vaccination of family members before the first influenza season after SCT is recommended (BIII)
- Yearly vaccination of staff in transplant units is recommended (BIII).

Poliovaccine

Although the efforts to eradicate polio have been successful in many parts of the world, small outbreaks of poliomyelitis still occur in nonimmune populations. Thus, there are

good medical reasons for having an immunization strategy against polio in SCT recipients.

Two vaccines exist: one live and attenuated (oral) and one inactivated (parenteral). Only the inactivated polio vaccine should be used to avoid the possibility of a vaccine-induced paralytic disease. It is also important that the inactivated vaccine is used in family members, SCT patients and in hospital staff caring for these patients, since transfer of the live vaccine virus from an immune-competent individual to an immunosuppressed individual has been reported.[38] Several studies of immunization with inactivated polio vaccine have been published.[6,10,15,30,32] A primary schedule with repeated doses of this vaccine is needed to obtain stable protective immunity.[6,10,30] In most of the published studies, the immunization programs were initiated approximately 1 year after SCT.[6,10,30] However, it was recently shown that good and lasting immune responses can be obtained when immunizations are started at 6 months after SCT:[15,32]

- All SCT patients should be vaccinated with three doses of the inactivated poliovaccine (BII).
- The live, attenuated vaccine should not be used in SCT patients (EIII).
- The vaccination schedule should start at 6–12 months after SCT with subsequent doses 1–3 months apart (BII).
- Family members of SCT patients and hospital staff caring for these patients should only be given the inactivated poliovirus vaccine (BIII).

Hepatitis B vaccine (HBV)

HBV infection is a major cause of morbidity in many parts of the world. Three major situations are relevant for planning a vaccination program for SCT recipients. The first is in previously immunized patients who might lose immunity to hepatitis B through the transplant procedure as is seen for tetanus, diphtheria, and poliovirus. The second situation is in patients not vaccinated before SCT, but where an indication for HBV vaccination after SCT exists. The third and more important situation occurs when a seronegative SCT patient is scheduled to receive an HBsAg positive marrow graft, since these patients might develop severe primary HBV infections after the SCT.[39]

The first and second situations are similar, since immunization with HBV vaccine early after SCT is likely to be ineffective unless the donor is immunized. Immunization of the marrow donor allows a transfer of immunity to the recipient.[14,40] Transferred donor immunity can be long lasting in at least 50% of the patients, but revaccination of the recipient after SCT is needed to ensure long-term immunity.[41] If a patient has evidence of a previously resolved hepatitis B infection (ie HBsAg negative but anti-HBs and/or anti HBc) before transplant, loss of antibody after SCT can result in reactivation of HBV.[42] In these patients, it might be useful to try to induce an early immune response. In a patient lacking antibodies to hepatitis B before transplant, it is usually not a major risk for the patient to wait until 6–12 months after SCT.

The third situation is more difficult since in these patients, immunization should ideally be performed before SCT. Immunization in normal individuals usually requires three injections spread over a couple of months to ensure protective immunity. This might be difficult considering the frequently tight schedule when planning an SCT. Furthermore, a subset of 5–15% of normal individuals will not respond to HBV immunization. No data exist regarding eventual protective efficacy of pretransplant immunization of the marrow recipient:

- Hepatitis B vaccination is recommended for SCT recipients residing in countries where there is a policy recommending general HBV vaccination (BII).
- Hepatitis B vaccination can be given from 6 to 12 months after SCT (BII).
- Early post transplant vaccination of the recipient can be considered in patients positive for anti-HBs before SCT (BIII). In these patients, the response to early vaccination is better if a seronegative donor is vaccinated before donation (BIII).
- Patients lacking antibodies to HBV who are to receive a graft from an HBsAg-positive donor should, if possible, be vaccinated before SCT (BIII).

Hepatitis A vaccine

Hepatitis A is an important infection in many parts of the world. Small outbreaks can occur in any country, but patients residing in or traveling to regions where the infection is endemic are at particular risk. The vaccine is inactivated and therefore safe. Unpublished data from a small series of SCT patients given hepatitis A vaccine show a low response rate (MC Dignani, personal communication). Patients with chronic liver or renal disease are able to respond to the vaccine, although the results are not as good as in normal individuals. Thus, measurement of the antibody response could be considered to confirm immunity.

- Vaccination with two doses of hepatitis A vaccine can be considered for SCT patients living in or traveling to endemic areas (CIII).

Measles, mumps, and rubella vaccines (MMR)

Although in many countries trivalent vaccines are most easily available and therefore used in immunization of SCT recipients, the indications for each vaccine are discussed separately.

Measles vaccine

Measles is still an important infection in many parts of the world. Until recently, the good vaccination coverage in the general population in Europe and the USA reduced the risk of outbreaks and thereby the risk of transfer to SCT recipients. However, during the last few years, the vaccination rates of children in many countries have decreased. Recently, a large epidemic has been reported from Italy and smaller outbreaks from several other countries. Severe and also fatal measles infections have been reported in SCT recipients.[43,44] During a recent large outbreak in Brazil, one of eight patients with measles developed interstitial pneumonia, but all survived.[45]

Most allogeneic SCT patients will become seronegative to measles during extended follow-up.[2,45] Children and young adults given the measles vaccine are at higher risk than adults who have experienced natural measles infection. Children who have been immunized against measles before autologous SCT frequently become seronegative during follow-up, but adults who had experienced the natural infection usually retain their immunity.[46]

The available measles vaccines are live attenuated and are not recommended for use in immunocompromised patients since serious side effects are possible. Thus, immunization can only be considered in allogeneic SCT patients without chronic GVHD or ongoing immunosuppression. Measles vaccine has been given to such patients without severe side effects at 2 years after SCT.[47] The reported efficacy of vaccination to induce a seroconversion varies between published studies.[47–49] and a second dose might be necessary to achieve protective immunity. During the epidemic in Brazil, patients were immunized at 1 year after SCT and preliminary data suggests that this could be done safely.[45] No good evidence regarding timing of immunization after autologous SCT exists, but the risk of side-effects after immunization seems to be low:[46]

- Measles vaccination can be safely administered to allogeneic patients without chronic GVHD or ongoing immunosuppression, and to autologous SCT patients (BII).
- Measles vaccination should normally not be given earlier than 24 months after SCT but earlier vaccination could be considered if there is a high risk of measles (BII).
- Measles vaccination can be considered in seronegative patients, particularly children, who reside in or are traveling to areas where measles is still endemic (BIII).

Rubella vaccine

The risk of severe rubella infection after SCT is likely to be low and there are no reports of severe rubella disease occurring in SCT recipients. The rubella vaccine is live and attenuated and could therefore cause infections in susceptible patients. The risk of severe side effects is, however, likely to be low. The main indication for rubella vaccination is prevention of congenital rubella. The pregnancy potential is low after myeloablative allogeneic SCT. However, with more patients undergoing transplantation after reduced-intensity conditioning regimens, the likelihood of pregnancy for patients may well increase. Rubella vaccine can be given without severe side effects at 2 years after SCT in patients without chronic GVHD or ongoing immunosuppression:[47]

- Rubella vaccine is recommended in female SCT patients who have retained the potential for pregnancy (BIII).
- Rubella vaccine should normally not be given earlier than 24 months after SCT (BII).

Mumps vaccine

There is no evidence that mumps is a severe infection after allogeneic SCT. The vaccine is live and attenuated. The indication for mumps vaccination is therefore weak. However, mumps is included in combination vaccines with measles and rubella and it has been shown that vaccination can be performed safely at 2 years after SCT in patients without ongoing chronic GVHD of who were not given immunosuppressive medication:[47]

- There is no indication for routine mumps vaccination after SCT (CIII).
- If mumps vaccination is considered, it should not be given to patients with chronic GVHD or ongoing immunosuppression and not before 2 years after SCT (CIII).

VZV vaccine

The existing vaccine is live and attenuated and therefore there is a risk of side effects after SCT. However, in contrast to other live viral vaccines, antiviral drugs, in particular acyclovir, could be used to treat infections caused by the attenuated vaccine strain.

VZV seronegative patients – prevention of varicella. Since varicella (chickenpox) is a common childhood infection, children are more likely than adults to be VZV seronegative. Varicella can be very severe early after SCT and post-exposure management of seronegative patients is therefore a significant practical problem for many pediatric transplant units. Since the history of VZV exposure is often difficult to verify, prophylactic measures with zoster immune globulin or antiviral drugs are therefore frequently initiated. The induction of protective immunity in a seronegative patient could therefore be of practical value despite the availability of effective antiviral drugs.

The vaccine has been proven to be safe and effective in children with leukemia in remission and in children awaiting solid organ transplantation. It would therefore be logical to consider vaccination of seronegative patients before SCT providing that enough time will elapse between vaccination and the transplant procedure. This will often prove difficult in patients with malignancies but, for example, in children with thalassemia or inborn errors of metabolism, it might be feasible. There is, however, no information as to the minimum interval required between immunization and transplantation and this strategy has not been tested in a clinical study. The other option would be to vaccinate seronegative patients after SCT. It is important to recognize that patients who were seropositive before SCT can become seronegative and therefore vulnerable to a second 'primary' infection with a clinical picture of chickenpox.

One small study of eight children who were immunized after allogeneic SCT has been published.[50] The vaccine was well tolerated but only three of eight children developed an antibody response against VZV. Furthermore, the data are too limited to allow any conclusions regarding protection against primary VZV infection in allogeneic SCT recipients:

- If there is enough time, seronegative patients can be immunized before SCT (CIII).
- Seronegative family members of SCT recipients should be vaccinated with the varicella vaccine (BIII).

- If there is no chronic GVHD or ongoing immunosuppression, vaccination of VZV seronegative SCT patients could be considered at two years after SCT (CIII).

Seropositive patients – prevention of zoster. A high proportion of seropositive SCT patients develop herpes zoster that occasionally becomes severe and the risk is strongly influenced by the presence of GVHD. Long-term antiviral prophylaxis with acyclovir or valacyclovir can substantially reduce the risk of developing herpes zoster. The use of a heat-inactivated vaccine is effective[51] and the risk was significantly reduced in the vaccinated group (13%) compared to the nonvaccinated group (33%; $P = 0.01$). Unfortunately, this vaccine is not available for routine use:

- Since effective and safe prophylactic alternatives with antiviral drugs exist, vaccination of seropositive SCT patients with VZV – vaccine to prevent zoster is not indicated (CIII).

Yellow fever vaccine

Yellow fever is a life-threatening infection primarily occurring in Central America and South America, and southern and central Africa. The question regarding vaccination of SCT recipients with yellow fever vaccine usually arises when patients plan to travel to an endemic area. It seems logical to make a careful assessment of the risk for yellow fever in the area to which the patient is traveling since several factors including season influence the risk.

The existing vaccine is live attenuated and can cause severe and sometimes fatal side effects even in healthy individuals. This risk seems to be genetically determined. Rio *et al*[52] published a report describing three patients immunized at 5 years after SCT without severe side effects occurring. This experience has now been extended to approximately 25 patients without incident (B Rio, personal communication):

- Immunization should only be considered in SCT patients who must travel to endemic regions for yellow fever (CIII).
- If contraindications for the vaccine exist, the patient should be advised not to travel to endemic areas (CIII)
- It seems likely that, as for other live virus vaccines, the same limitations regarding GVHD, ongoing immunosuppression, and timing of vaccination should apply (CIII).

Serological testing

Testing for antibody levels can be used to determine the need for vaccination (ie if the patient lacks immunity) or the response to vaccination. The techniques vary for different organisms and the antibody levels conferring 'protective' immunity are poorly defined for some. Routine serology for several infectious agents increases costs, and the recommendations therefore take into account the likelihood that the results will influence patient management, for example, the decision to vaccinate, to give additional doses, or to change to another vaccine:

- Immunity testing before vaccination:
  - For many vaccines recommended for all SCT recipients (ie tetanus toxoid, diphtheria toxoid, polio, influenza, pneumococcal, HIB) immunity testing before SCT is not necessary (BIII).
  - Immunity testing before eventual vaccination is recommended for HBV, measles, rubella, and varicella (BIII).
- Response to vaccination:
  - For vaccines that elicit a good immune response in the most patients (ie tetanus toxoid, diphtheria toxoid, polio, HIB), antibody testing is not necessary (BIII).
  - Post-vaccination testing is not recommended for influenza since the interpretation of the results is difficult and a second dose only has a marginal effect (CIII)
  - Post-vaccination testing is recommended for hepatitis B, measles, and varicella (BIII).
  - Post-vaccination testing can be considered for patients receiving pneumococcal polysaccharide vaccine who are at an increased risk of a poor response (BIII)

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