Review Article

Vaccination in Immunocompromised Patients

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INTRODUCTION

With the emergence of newer diagnostic modalities, cancers are being detected more frequently and at an early stage in all age groups from pediatric to geriatric population and patients are living long and fruitful lives with cancers and after its treatment. Vaccinations of such immunocompromised patients is currently a matter of intense debate as there are only a few pragmatic vaccination standards. This article reviews the current vaccination strategy in patients on treatment for malignancies and those who have successfully received treatments like blood and bone marrow transplantation (BMT).

VACCINATIONS IN PATIENTS RECEIVING BMT

Treatment of lymphoma, leukemia, immunodeficiency illnesses, hemoglobinopathies, congenital metabolic defects and myelodysplastic and myeloproliferative syndromes accounts for nearly 25,000 hematopoietic stem cell transplantations (HSCTs) each year.

Three major societies: American Blood and Marrow Transplantation, European Group of Blood and Marrow Transplantation, and Infectious Disease Society of America Vaccination guidelines for recipients of blood and bone marrow transplantation (BMT) have recently been published and it was found that the existing guidelines

- lacked practical dose clarifications in vaccinating patients of varied ages, underlying diagnosis and amount of immunosuppressive therapy,
- provide little or conflicting guidance for certain vaccines regarding their age-related schedules (e.g. tetanus toxoid, reduced diphtheria toxoid, meningococcal and reduced acellular pertussis; and human papilloma virus vaccines) and the time post transplant.
- provide little adjustment regarding the cause for which BMT has been offered e.g. primary immunodeficiency diseases or other factors which are considered at the time of beginning and dosing vaccines.

The new guidelines keep in view:

- time after transplant
- levels of numeric or functional immune reconstitution,
- the intensity of recent or ongoing immuno-suppressive therapy
- age related schedule of some vaccines (e.g. meningococcal, Tdap [tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis], pneumococcal and *human papillomavirus* [HPV]).

HSCT recipients lose protective immunity to vaccine-preventable diseases that had been achieved after childhood vaccination- has been demonstrated by several studies.[1] Although most BMT recipients are vaccinated earlier in life the antibody titers to most of these diseases decline after autologous or allogeneic BMT. It is thought that while some protective immunity may be conferred through the transferred cells of the donor immune system, the function of engrafted memory cells declines with time and patients remain at risk of life-threatening infections. Vaccine-preventable infections cause significant morbidity, re-hospitalization and mortality after successful HSCT and diseases which are potentially preventable by vaccines pose increased risks for recipients of BMT until immunity is fully restored.

It is now well accepted that BMT recipients should be vaccinated even if they already have protective titers. Therefore, with exception of some viruses that are known to exhibit latency outside the hematopoietic system (e.g. varicella), BMT recipients should generally be revaccinated against pathogens which are contained in childhood primary immunization schedules.

It is now understood that some degree of immune competence is necessary for efficient vaccine response and that unlike vaccination in healthy individuals,

vaccination given after HSCT does not ensure complete serological response, more so in chronic Graft versus Host Disease (GVHD) patients with delayed immune reconstitution. Also, early vaccination may sometimes be associated with early response but there are problems with these responses having long-term persistence.[2] Thus, specific antibody levels pre and post vaccination should be measured to assess the immunologic response to vaccination and to ascertain the requirement for subsequent booster immunizations especially in patients suffering from chronic GVHD.[3]

At present, consensus guidelines recommend initiating vaccinations at 3 to 6 months post BMT although this lacks prospective validation.[4-8] Given the variation of Immune Reconstitution, more so in patients who have been transplanted for primary immunodeficiency diseases, the negative impact of moderate to severe GVHD on immune reconstitution and the use of in vivo T- or B-cell depleting therapies, candidates are chosen for "early vaccination" at 6 months after evaluation of favorable responses to a 6-question algorithm (Figure 1). In case of any unfavorable response vaccine administration is deferred (except for flu shots) to at least 1 year post transplant. This is done taking into consideration the fact that vaccine efficacy depends on at least partial reconstitution of adaptive immunity.

Strengths of recommendation (Table 1), evidence levels (Table 2) and immunization schedules (Table 3) in such patients are as under:

VACCINES

DTaP vaccine :

Three doses of DTaP given regardless of age, especially to children less than 7 years of age. However, it is also offered to older BMT recipients, as there is a 10-fold higher dose of diphtheria and pertussis toxoids present in DTaP as compared to Tdap and it elicits better antibody responses.

Hib vaccine :

Before the introduction of Hib conjugate vaccines, *Hemophilus influenzae type b* was a major cause of bacterial meningitis among 5 years old children and was a major cause of other life-threatening infections including pneumonia, epiglottitis, bacteremia, etc.

HAV and HBV vaccine :

There is no difference in HAV vaccination in immunocompetent and immunocompromised individuals. However, HBV vaccine antigen doses need to

Table 1: Recommendation Strength

Strength of recommendation level	Definition of recommendation level
A	Always offered
B	Generally offered
C	Optional • evidence for efficacy is not sufficient to support for or against use, • evidence might not outweigh adverse consequences, • cost of the approach.
D	• moderate evidence due to lack of efficacy or due to adverse outcome supports recommendation against use. • generally not be offered
E	• good evidence for lack of efficacy or for adverse outcome supports recommendation against use. • never be offered

Courtesy: Vaccine 29 (2011) 2825–2833

Table 2: Quality of Evidence Supporting the Recommendation

Strength of evidence level	Definition of evidence level
I	Evidence from $\geqslant$ 1 properly randomized, controlled trail
II	Evidence from • $\geqslant$ 1 well-designed clinical trial without randomization, • Cohort or case-controlled analytic studies (preferable from >1 center) • multiple time series • dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive

Courtesy: Vaccine 29 (2011) 2825–2833

Table 3: Recommendations for Vaccinations after Allogenic HSCT for Adults.

	Type of Vaccine	Start of Vaccination (Months after HSCT)	Number of doses	Strength of recommendation
Bacteria				
H.influenzae type b	Conjugated	6(boost:18)	3+1	BII
B.pertussis	Acellular	6(boost:18)	3+1	BIII
S.pneumoniae	Conjugated	6(boost:18)	3+1	BI
N.meningitidis type c	Conjugated	6-12	3	CIII
Diphtheria/tetanus viruses	Toxoid	6(boost:18)	3+1	BIII
Hepatitis A	Inactivated	6-12	3+1boost	CIII
Hepatitis B	Inactived	6(boost:18)	3+1boost	BII
Influenza	Inactived	(4-)6	1	AII
Measles-mumps-rubella	Live	>24	1-2	CII/III(for immunocompetents) EIII (<24 months post-HSCT, active cGVHD or on immunosuppresion)
Poliomyelitis	Inactivated	6(boost:18)	3+1boost	BII
Human Papillomavirus	Inactivated	6-12	3	CIII
Tick-borne-encephalitis	Inactivated	6-12	3	CIII

Courtesy: Vaccine 29 (2011) 2825–2833

be higher for adult hemodialysis patients to induce protective antibody. The Centers for Disease Control suggests that higher doses or additional doses of HBV vaccine might be necessary for all immunocompromised individuals including BMT recipients at least until they are 6 months off all immunosuppressive therapy.

HPV vaccine :

Among the three currently available HPV vaccines (4vHPV, 2vHPV and 9vHPV), only 9-valent HPV prevents 90% of cervical, vulvar, vaginal and anal cancers, in addition to offering protection against genital warts and cervical cancer. Vaccination is recommended with either 4vHPV or 9vHPV in immunocompromised persons age 9 up to 26 years .[9]Although 2 doses may be sufficient for 4vHPV vaccine in immune competent patients,[10] there is no such data in patients of BMT and thus it is advised that 3 doses be given in these patients. In girls 12–17 years of age, vaccination with three doses of the HPV vaccine is recommended, starting at 6–12 months after HSCT.

Flu Vaccine:

It is given 6 months post-BMT regardless of any conditioning regimen or type of BMT. Although during community outbreaks flu vaccine may be given earlier-at 3 to 4 months post-BMT, in which case a second dose is usually given a month later.[11]

(a) flu vaccination in children aged 6 months to 9 years:
2 shots given at 1 month interval and then 1 dose is given annually. [12]

(b) For healthy family members aged 2 to 8 years:
Live attenuated influenza vaccine (LAIV) or inactivated flu shot may be considered as they are equally effective. LAIV does not spread from person to person easily, but still, patients who require protective isolation or are hospitalized should not be exposed to LAIV. Thus, persons immunized with LAIV should be isolated from immunocompromised patients for at least 1 week following immunization.

(c) flu vaccination adults aged 65:
Intramuscularly administered Fluzone High-Dose offers superior protection against influenza[13] in adults 65 years or more as it contains 4 times as much antigen as the standard inactivated flu shot and has an advantage over traditionally poor antibody response to standard flu vaccination.

Meningococcal vaccine:

All BMT recipients older than 9 months of age and/or 6 months post transplant are given 2 doses of T-dependent conjugated quadrivalent vaccine (MCV4) and not the polysaccharide (MPSV4) vaccine as conjugate vaccines are more immunogenic and stimulate long-lived memory B cells.

MMR vaccine:

It is considered safe to give live attenuated MMR("2-1-8" mnemonic), if recipient is:[14]

- 2 years post BMT
- 1 year off all systemic Immune Suppressive Treatment,

- 8 months out from any prior IVIG dose.

Exception to this rule can be made to some extent in case of community outbreak.

Pneumococcal vaccine:

Invasive pneumococcal disease (IPD) caused by *Streptococcus pneumonia*, results in frequent hospitalizations for fatal pneumonia, bacteremia, or meningitis immunocompromised patients and is the most common vaccine preventable infections encountered after BMT. Adults aged 65 years or more, immuno-compromised individuals, and those with chronic health conditions are most affected.

PPSV23 (Pneumovax) polysaccharide capsular vaccine offers protection against 23 serotypes of pneumococci which are implicated in causing disease in humans. If the patient is not severely immunocompromised, vaccination is started with PCV13 at 6 months, with 3 doses, 1 to 2 months apart [15,16] one dose of the vaccine is then given 6 to 12 months (minimum 8 weeks) after the last PCV13.

If a BMT recipient remains heavily immuno-compromised, a fourth dose of PCV13 is given with PCV13 rather than PPSV23 because it induces better T-cell collaboration and anamnestic response through generation of memory B cells. Elderly BMT recipients also require PPSV23 booster immunization as they are very vulnerable to IPD.

Varicella zoster vaccine:

Vaccination for Varicella for prevention of chickenpox is only recommended for VZV-seronegative recipients who do not have a history of chickenpox or varicella vaccination as BMT does not eradicate latent VZV in the sensory nerve ganglia of a previously infected individuals (ie, those with a history of chicken pox) or previously vaccinated individuals.Also, latent VZV provides ongoing antigen exposure that obviates the need for revaccination. Timing of varicella vaccination is like that of MMR vaccine ("2-1-8" rule). A second dose of varicella vaccine is given 1 month after the initial dose.It is now recommended that live MMR and VZV vaccination should be deferred to at least 3 to 11 months after receiving the last IgG-containing blood products so that there is sufficient time for degradation of potential antibodies that could interfere with viral replication, which is essential for affectivity of live virus vaccination.

Polio vaccine:

All HSCT patients are given four (3 + 1) doses of inactivated polio vaccine starting at 6 months post HSCT. Three doses should be given in monthly intervals, followed by an additional booster dose at 18 months after allogeneic HSCT. Only inactivated polio vaccine should be used in HSCT recipients and their family members

VACCINATION IN PATIENTS OF PRIMARY IMMUNE DEFICIENCY DISEASES UNDERGOING ALLOGENIC BMT

Vaccination in such patients is different because B-cell immune reconstitution is highly variable in these patients after BMT and so vaccination is delayed till there is definite evidence of functional B-cell recovery. Except for seasonal flu all other routine post transplant vaccinations are deferred until at least 1 year after BMT and those are also given only if the following 3 criteria are met:

1. Patient has remained infection free for the past 6 months, and it is thought reasonable to attempt a 3-month trial off IgG replacement therapy
2. There is low community prevalence of influenza, *respiratory syncytial virus, human metapneumovirus,* or parainfluenza during the planned trial of withholding IgG therapy
3. The following laboratory criteria are satisfied:

   (a) Trough IgG (600 mg/dL) on standard IgG dosing, indicating satisfactory numeric IgG reconstitution.

   (b) Detectable serum IgA (6 mg/dL) suggesting ability to "Ig class switch."

   (c) Donor B cells (200/mL) determined by percent donor B-cell chimerism multiplied by the total absolute B-cell count.

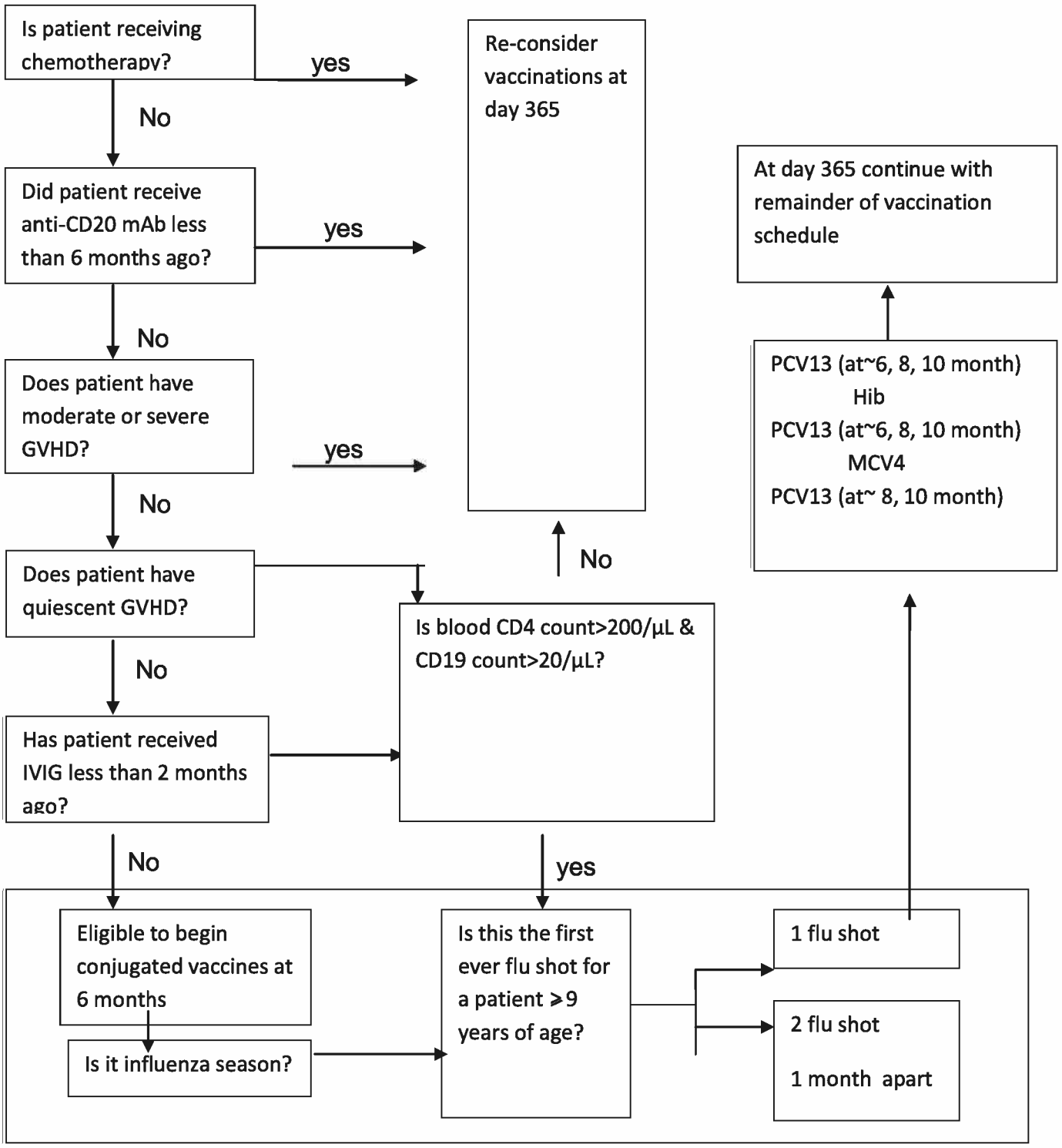
   (d) Donor CD4 cells 200/mL as determined by percent donor CD4 chimerism multiplied by the total absolute CD4 T-cell count.

When all three criteria are satisfied, IgG therapy is withheld for 12 consecutive weeks. Immunization is then started as follows:

Week 0 and 6-8	1 dose PCV13, Hib, DTaP (or Tdap age.10), hepatitis B virus (HBV).
Week 12	Measuring antibody titers to Hib, 23-serotypes of pneumococcus (with response only to PCV13 serotypes expected), tetanus toxoid, HBV surface antibody review

Patients responding well remain off IgG therapy and are given a third dose of each of these vaccines as per the accepted protocol. Patients also receive a standard series of meningococcal, HPV, hepatitis virus (HAV), and inactivated polio vaccines. In case, vaccine response is not satisfactory, IgG therapy is resumed and further vaccination is deferred.

Conjugated vaccines (including Hib, PCV13, and MCV4) are used to initiate vaccinations because of the phenomenon of impaired opsonization.This phenomenon



Courtesy: Paul A. Carpenter*#** and Janet A. Englund#**
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Figure 1: Flow chart for vaccination recommendation for patients undergoing stem cell transplantation.

makes B-cell-deficient patients and BMT recipients without a spleen or with functional asplenia highly susceptible to encapsulated bacteria like *Hemophilus influenzae type b, Neisseria meningitidis, Streptococcus pneumonia,* because of chronic GVHD.

IMMUNIZATION IN PATIENTS OF CANCER WHO ARE NOT ELIGIBLE FOR HSCT

Immunization of patients with impaired immune function due either to primary immunodeficiency or treatment causing immunodeficiency (cancer chemotherapy, corticosteroid, antimetabolite or biologic immuno-modulator therapy) needs special consideration because administration of the required vaccines is an integral part of their treatment before the start of immunomodulatory treatment.

Although, non-live vaccines may be given, recipients may not mount an adequate protective response, depending on the degree of immune suppression at the time of vaccination. With some important exceptions live vaccines should not be given to immunocompromised persons. The risks of vaccine preventable disease in patients of cancer vary depending on exposure, vaccination history and the degree of their immunosuppression. The probability of favourable response to vaccination depends on the disease stage and the degree of immunosuppression.

Whenever possible, recommended vaccines are given before the start of treatment. Vaccination is generally avoided during periods of intense chemotherapy as the vaccine response may be significantly attenuated. In some situations the benefits of live vaccines may outweigh any potential risk, e.g. varicella vaccine for susceptible leukaemia patients who are in remission and/or post chemotherapy.

If non-live vaccines are given during chemotherapy, they are administered again when there is good recovery of immune function, which is usually 6 months post chemotherapy. Re-administration of vaccines given before chemotherapy is usually not necessary except where chemotherapy is followed by haematopoietic stem transplantation (HSCT).

Immunisation of Immunocompromised Persons (August 2015 Recommendations):

• Whenever possible, immunization should be completed prior to chemotherapy as response is attenuated during chemotherapy.

• Tdap should be considered for all adult patients.

• Pneumococcal vaccination is recommended for all cancer patients. As far as possible, vaccination should be completed before chemotherapy

- For patients who are pneumococcal vaccine naive, a single dose of PCV is given followed by PPV23 after at least 8 weeks.
- For patients who have received 1 or more doses of PPV23, a single dose of PCV is given after 1 year
- In children who have received vaccination, a booster dose of PPV23 is given at least 5 years after the previous dose if the patient still remains immunosuppressed
- Hib is not routinely recommended for adult cancer patients unless they are found to be candidates for HSCT

• Annual seasonal inactivated influenza vaccine is recommended for all cancer patients. It is given after a minimum interval of 3 to 4 weeks following a course of chemotherapy and when lymphocyte count is $> 1000 \times 10^9$ /L.

• Polio, MenB, MenC, MenACWY, HAV, HBV and HPV can be given as and when indicated.

• As a general rule, cancer patients should not receive MMR. However, MMR can be given to leukemia or lymphoma patients if they are in remission and have been off chemotherapy for 6 months. In situations where there is a high risk of infection the minimum interval for administration of MMR post chemotherapy is 3 months.

• Varicella vaccine can be administered to susceptible persons with leukaemia, lymphoma or other malignancies who are either in remission or who are off chemotherapy for a minimum of 3 months and generally for 6 months and are considered at high risk for severe or complicated varicella. It should be given under close supervision and with an appropriate protocol for management of vaccine virus infection which may be encountered in up to 20% cases.

• BCG, as vaccination against TB is not recommended for cancer patients.

Immunisation of household contacts and health care workers:

- Household contacts and health care workers who interact with immunocompromised hosts should be administered live attenuated vaccines.
- Routine administration of household contacts with injectable live attenuated MMR or varicella vaccine is indicated if otherwise age appropriate.
- Intranasal live attenuated influenza vaccine (LAIV) is not given to any close contact of seriously immunocompromised hosts because live attenuated influenza virus is shed for several days.
- If a close contact is given LAIV, a 7-day furlough is advised.

- Live attenuated oral polio vaccine should not be used and if at all given to a household contact, a 4- to 6-week furlough is advised.

SUMMARY

Vaccine preventable diseases are a major cause of morbidity and mortality in immunocompromised patients. Patients of cancer who are receiving treatment should be given inactivated vaccines as per protocol and booster doses should be given as per the antibody titres. Patients who undergo Hematopoietic Stem Cell Transplants are considered as vaccine naive and should be vaccinated as soon as permissible. Only inactivated vaccines should be administered to immunocompromised patients.

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