VACCINATION STRATEGIES IN PATIENTS WITH BONE MARROW TRANSPLANTATION

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Effective prevention against infectious diseases is more useful and life-saving measure than to treat them. Vaccination seems more effective preventive approach in decreasing the incidence of some important infectious diseases in immunocompromised patients most likely healthy individuals. Bone marrow transplantation presents prototypic clinical manifestations for immunocompromised patient. Also, vaccination of BMT donors to protect the recipient against a variety of infections is an appealing approach. In this paper, vaccination strategies have been reviewed and evaluated to give most useful and cost-effective approach in patients (and their donors) with bone marrow transplantation.

***Key words**: Immunocompromised patient, bone marrow transplantation, vaccination*

Kemil iliği nakillerinde aşılama protokolleri

Infeksiyon hastalIklarından aşı ile korunma, onların tedavi edilmeleri ile karşılaştırılamayacak kadar avantajları olan bir yaklaşımdır. Bu durum immun sistemi baskılanmış olan hastalarda daha da önem kazanır. Bu çalışmada, immun sistemi baskılanmış olan hastalar için güzel bir örnek olan kemik iliği nakli yapılmış olan hastaların ve onların vericilerinin bazı infeksiyonlara karşı aşılanmaları ile korunmaları yönünde yapılan çalışmalar değerlendirilerek ortak bir yaklaşım ortaya konulmaya çalışılmıştır.

***Anahtar kelimeler**: Immun kompremize hasta, kemil iliği nakli, aşılama*

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Immunisation is the act of artificially inducing immunity to prevent from serious infectious diseases. While "vaccination" and "immunisation" are often used synonymous, immunisation refers to the provision of immunity by any means; either active or passive. Passive immunisation refers to administration of antibody-containing immunoglobulin preparations to provide temporary protection. Active immunisation consists of inducing the body to develop defences against infections refers to the administration of a vaccine or toxoid that stimulate the body's immune system to produce antibodies and/or cell-mediated immunity (CMI) [1].

The antigens available for routine or widespread use in children include diphtheria-pertussis-tetanus (DPT), trivalent polio, measles-mumps-rubella

(MMR), *Haemophilus influenzae* type b (Hib), hepatitis B, and tuberculosis. Adult vaccines include diphtheria-tetanus (DT), hepatitis B, influenza virus, and pneumococcus. A number of other vaccines are available for special circumstance[1] .

After a while, most allograft and a large proportion of autograft recipients loose their immunity to DPT and measles[2-7] . Additionally, transplant recipients are at increased risk of infections with encapsulated microorganisms such as *H. influenzae* and S. *pneumoniae*[8-10] . Secondary to these reasons, it is essential to re-immunise peripheral blood stem cell/bone marrow transplant (BMT) recipients at their convenience following the transplantation[11,12] .

Systematic re-immunisation after BMT is a relatively neglected area. A survey of re-immunisation practices in Europe found wide variations in practice[11] .Tetanus toxoid vaccination was the most common practice, with 65% of the surveyed centres administering this to allo, and 37% to auto recipients. By the way, vaccination for pertussis was the less common practice, with only one center application[11] .

PRINCIPLES OF VACCINATION IN PATIENTS UNDERGOING BONE MARROW TRANSPLANTATION

Immune reconstitution following BMT continue with general pattern, developing from immature to mature immune functions[13-19] . Immune reactivity during the first month post-BMT is extremely low. Cytotoxic and phagocytic functions recover by day 100, but the more specialised functions of T and B-lymphocytes may remain impaired more than one year. After a long time, the various components of the immune systems of most healthy BMT recipients begin to work synchronously, whereas the immune systems of patients with chronic graft-versus-host disease (GvHD) remain suppressed.

There are preliminary data showing faster immune reconstitution after autologous[20] as well as allogeneic[21] peripheral blood stem cell transplantation (PBSCT) rather than marrow transplantation. Because of this and the significantly large amount of inoculum of cells infused during PBSCT[22,] it is possible that blood stem cell graft recipients may have an earlier and a better response to vaccines. However, all the data available so far on post-transplant immunisation have been gathered on recipients of marrow grafts, and it is probably reasonable to treat PBSCT recipients in the same way as marrow transplant recipients for the purposes of post-transplant re-immunisation.

The most important factor, which needs to be taken into account while considering vaccination after BMT, is the immune status of the host. Inactive, subunit or recombinant vaccines may be, at the worst, ineffective in BMT recipients, whereas live vaccines may be dangerous in immunocompromised patients[1] .

Table 1. Patients who should not be considered eligible for live vaccination after blood/marrow transplantation.

1.	All autograft recipients for two years (a)
2.	All allograft recipients for two years (a,b)
3.	Immunosuppressive therapy for any reason
4.	Chronic-GvHD (requiring therapy or not)
5.	Recurrent malignancy after transplantation

(a) These recommendations are based upon patients with marrow transplantation. Preliminary data suggest that immune reconstitution is faster in patients transplanted using blood stem cells.

(a, b) It is possible that immune recovery may take longer in recipients of T-cell depleted, HLA-mismatched, or unrelated donor transplants. If there is any question about immune competence, serum immunoglobulin levels and the number of CD4+/CD8+ cells should be determined. Patients in whom these parameters are normal are likely to be immunocompetent.

There are limited data on the effect of donor and recipient ages, underlying disease and conditioning regimen on the indications for re-immunisation and its outcome. The general principles underlying vaccination of BMT recipients are shown in table 2.

Table 3 shows a recommended re-immunisation schedule for transplant recipients excluding those with chronic GvHD, whose schedule is given in table 4.

Table 2. General principles of vaccination after blood or marrow transplantation

Principles	Why?
Avoid; • All vaccines for at least 4 months after BMT • Live vaccines (Adenovirus, BCG, oral polio*, MMR**, typhoid, yellow fever) • Spreadable live vaccines such as oral polio in household contacts	As a result of compromised immune responses, inactive vaccines are unlikely to elicit a response, and live vaccines may life-threatening infections.
Measure antibody titers after vaccination to ensure efficacy	After BMT, responses to vaccines are often compromised
Repeat doses/courses until optimal titers achieved	Response is often inadequate with a single dose or course
IVIG may interfere with the immune response to vaccine	There is evidence to suggest suboptimal response to vaccines in immunoglobulin recipients

(*): When healthy household members are immunised against polio, inactive polio vaccine should be given to avoid spread of live oral poliovirus to patient.

(**): Live attenuated virus vaccines (MMR) should be avoided except in those in remission who have received no chemotherapy for at least 3 months; but these patients should receive *Influenza* and *Pneumococcus* vaccines.

Table 3. Recommended immunization schedule in blood/marrow transplant recipients excluding those with chronic GvHD

Vaccine	Schedule	Time post-BMT	Comments
Diphtheria toxoid	3 doses; monthly intervals	1 year	All patients
Haemophilus influenzae (Hib)	3 doses; monthly intervals	4 months	All patients
Influenza	1 dose annually	6 months	At least 2 years; in patients with lung problems, vaccinate household contacts
Pneumococcus*	1 dose	2 years	Additional drug prophylaxis needed
Poliovirus** (inactivated-Salk)	3 doses; monthly intervals	1 year	All patients
Measles	3 doses; monthly intervals	2 years	Not for general purposes
Mumps	3 doses; monthly intervals	2 years	Not for general purposes
Rubella	3 doses; monthly intervals	2 years	In potentially fertile females
Tetanus toxoid	3 doses; monthly intervals	1 year	All patients

*: With variable antibody response

**: Do not use Sabin vaccine

Table 4. Recommended immunization schedule in blood/marrow transplant recipients to whom those with chronic GvHD

Vaccine	Schedule	Time post-BMT	Response
Diphtheria toxoid	3 doses; monthly intervals	1 year	?
Haemophilus influenzae (Hib)	3 doses; monthly intervals	4 months	Good
Influenza	1 dose annually	6 months	?
Pneumococcus	1 dose	2 years	Poor
Poliovirus (inactive)	3 doses; monthly intervals	1 year	Good
Tetanus toxoid	3 doses; monthly intervals	1 year	Good

CURRENTLY AVAILABLE VACCINES AND TOXOIDS FOR BMT-RECIPIENTS

Diphtheria toxoid

Diphtheria has recently emerged as a problem in a number of countries where immunisation coverage has been high. High mortality rates, a high proportion of cases in adults, and an increased incidence of complication have characterised these outbreaks[23] . Lum et al. showed that while antibodies to diphtheria toxoid were present in all patients within day 100 post-allo-BMT, only two-thirds of normal long-term survivors with immune donors had antibodies. This reduced further to 40% among patients with chronic-GvHD who were transplanted from immune donors[2] .

Chronic-GvHD patients have been shown to have an impaired cellular immune response to diphtheria toxoid when vaccinated as early as 4 months period following BMT[24] . However, immunisation with multiple doses of diphtheria toxoid has been reported to result in adequate immune response in paediatric patients autografted[23] using bone marrow depleted of B lymphocytes 38-54 months after BMT[5] , and in allografted thalassaemia patients without chronic GvHD 2-6 years following BMT[25] .

Haemophilus influenzae

H. influenzae accounts for a significant proportion of pulmonary infections in long-term BMT survivors including those on penicillin prophylaxis[9,26] . Unlikely, almost all severe

disease is related to one capsular serotype (type b). *H. influenzae* b (Hib) vaccine is very effective for preventing infections[1] .

The tetanus toxoid-conjugated Hib capsular polysaccharide vaccine is more immunogenic than the unconjugated capsular polysaccharide vaccine, and induces protective antibodies in 85% allo-BMT recipients including patients with IgG2-deficiency[26] . Between 4 and 18 months of post-BMT period, the response to the conjugate vaccine did not correlate with GvHD, Immunosuppressive therapy, or the time of vaccination. Beyond 18 months post-BMT, response correlated with time (increasing efficacy with longer time interval) [26] . Auto as well allo recipients receiving a Hib-conjugate vaccine at 12 and 24 months or 24 months only developed protective antibodies 80% and 50% of the time[27] .

Donor and recipient immunisation using the Hib-conjugate vaccine pre-BMT resulted in higher antibody concentrations in patients as early as 3 months post-BMT compared with immunisation of patients after BMT (28). Higher antibody levels in the early stages post-transplant could potentially decrease the incidence of respiratory tract infections in patients with lung disease or chronic-GvHD.

Hepatitis B

While the risk of hepatitis B virus (HBV) infection is not significant in regions with a low prevalence of the virus, the risk and morbidity of the infection in high-prevalence areas is considerable. The risk of infection may be high in the early post-transplant phase due to infectivity risk of transfusions. Pre-BMT vaccination of donors can result in adoptive transfer of protective immunity to the recipient[4,29] . Wimperis et al. showed that immunisation of the donor alone resulted in transfer of an antibody response to the recipient following T-cell depleted BMT, whereas immunisation of donor as well as recipient resulted in a higher antibody response of a longer duration[4] . Ilan et al. confirmed that pre-BMT immunisation of donors could result in adoptive transfer of immunity to non-immune marrow recipients[29] . Roughly two-thirds of autograft recipients vaccinated peri-transplant developed low-titer antibody responses which could have been protective against HBV-associated complications during post-BMT period[30] .

Interestingly, it is possible to resolve the HBV carrier state and chronic hepatitis B through an allografts from an immune donor, who could have acquired immunity either through a natural infection[31] or through vaccination[32] . Outlines an approach to hepatitis B immunisation in the setting of BMT depending upon the type of graft, and the immune status of the recipient and the donor can be seen in table 5.

Table 5. Suggested approach to hepatitis B immunization in patients with BMT

	Recipient		
Donor ⇓	**HBsAg + (carrier/ hepatitis)**	**Anti HBs + (immune)**	**No HBV marker**
HBsAg + (Carrier/ hepatitis)	-	Multiple-dose boosters immediately after BMT	Vaccinate prior to BMT, then as soon as the left
Anti HBs + (Immune)	1. Donor WBC infusions if patient remains HBsAg + 2. Booster doses if immune with low level titers	Booster doses if titers decline	Booster doses if titers decline
No HBV marker	1. Immunize donor 2. Ensure Anti-HBs antibody + prior to harvest	3. Revaccinate if antibodies lost 4. Booster doses if titers decline	1. Immunize donor pre-BMT in areas with high prevalence of HB 2. Booster doses post-BMT if titers decline
Auto-BMT	-	Booster doses to ensure titers convenient	1. Immunize donor pre-BMT in areas with high prevalence of HB 2. Booster doses post-BMT if titers decline

Influenza

BMT recipients can acquire influenza infections during annual community epidemics[33,34] , and secondary bacterial infections including pneumonia may lead to serious complications[34] . Influenza vaccination within the first 6 months following BMT has been found to be ineffective[35]. However, in patients receiving the vaccine two or more years after BMT, the efficacy was similar to that described in

immunocompetent hosts[35] , with a positive correlation between longer BMT-immunisation interval and seroconversion. Patients with chronic GvHD responded well to two of the virus strains and poorly to one.

It would also be worthwhile vaccinating household contacts of BMT recipients to prevent transmission of influenza through them to patients; especially for those to whom still in the early post-transplant phase.

Measles

A substantial proportion of allograft recipients and some autograft recipients, especially children, loose immunity to measles over a period of time[3,6,36,37] . Measles is an important pathogen in developing countries[38] , but apart from occasional outbreaks, it is not a problem elsewhere because of immunisation. Although severe measles can occur in immunocompromised patients, there are no reports of measles following BMT.

The attenuated trivalent MMR vaccine has been administered to non-immunocompromised allograft recipients after two years following BMT with seroconversion[6] , and in autografted children[36] . It is not generally recommended for all BMT recipients; but on an individual basis for patients from high-prevalence geographic areas or where the risk for measles is increased[11] .

Mumps

As with measles, a large number of allo and autograft recipients loose immunity to mumps [6,36,37] . Mumps has not been described to be a problem in patients undergoing BMT.

Rubella

As with measles and mumps, a number of allograft and autograft recipients loose immunity to mumps[6,36,37] . Although, rubella has not been reported to be a problem in BMT patients, a number of pregnancies have been reported in transplant recipients[49] . The offspring of these women could be at risk of the congenital rubella syndrome, and it would therefore be advisable to re-vaccinate women with childbearing potential. The attenuated trivalent MMR vaccine has been administered to non-immunocompromised allo-BMT recipients beyond two years from the transplant with development of immunity to rubella[6] , and in autografted children[36] .

Pneumococcus

Functional hyposplenism is a consequence of total-body irradiation (TBI) and chronic GvHD Although pneumococcal infections are generally an important problem in patients with chronic GvHD[8] because of their inability to mount an antibody response to the pneumococcal polysaccharide antigen[39] , other patients can also be affected. Splenectomized patients and those autografted for Hodgkin's disease and multiple myeloma may be particularly at high risk. In a study of the 14-valent pneumococcal vaccine in allo-BMT recipients, Winston et al. [40] found that both pre- and post-immunisation antibody levels for all serotypes were lower in patients compared with normal people. Antibody responses of patients not on steroids and vaccinated more than six months after BMT improved with time.

Lortan et al.[41] found that the titers of specific IgG, IgG1 and IgG2 pneumococcal antibodies fell significantly after allogeneic BMT compared with pre-transplant levels in children. Their response to immunisation with a 23-valent vaccine one year or longer post-BMT was not significantly different from normal controls except for weak IgG2 response. Despite responding, the patients did not achieve a high specific antibody titer after immunisation in any immunoglobulin subclass because of the lower pre-immunisation levels. The pre-immunisation antibody levels and the response to immunisation in these patients were not affected by previous splenectomy or chronic GvHD. Immunisation of donors before the marrow harvest did not influence the levels of specific antibody a year or more after BMT. Molrine et al.[28] confirmed the observation that pre-BMT pneumococcal vaccination of the donor did not affect the recipient's antibody response to post-transplant vaccination.

Some investigators found that all auto or allografted children vaccinated more than two years beyond BMT responded to pneumococcal polysaccharide compared with 20-50% of those vaccinated within two years[42] . Although chronic GvHD influenced the response rate in univariate

analysis, only the time between marrow transplant and immunisation was a powerful predictor of response in multivariate analysis. The improving response to pneumococcal vaccination with increasing time after transplant seems to suggest that B-cell ontogeny follows a sequential program in which polysaccharide antigens are amongst the last to evoke antibody responses.

Interestingly, some other investigators found that over the first year post-BMT, pneumococcal antibody levels decreased in most allograft recipients, but not in autograft recipients[43] . None of the patients with chronic GvHD showed normal levels of antibodies at one year. Of the patients who lost immunity after BMT and were vaccinated with a polyvalent pneumococcal vaccine, 34% showed a rise in IgG2 antibodies, 28% with an increase in IgG1, and 38% did not respond at all. None of the patients with chronic GvHD showed an elevation in IgG2 antibodies and 75% did not respond at all.

The 23-valent polysaccharide vaccine, apart from being poorly immunogenic, also does not cover 20% of the commonly encountered pathogenic pneumococcal strains, and immunised individuals remain susceptible to them. Life-long prophylaxis with penicillin V (250 mg bid, orally) is therefore recommended for all patients who have had TBI prior to an auto/allograft, patients with chronic GvHD, and splenectomized patients[8,11] . Erythromycin (250 mg bid, orally) or Clarithromycin (250 mg qd, orally) may be substituted in penicillin-allergic patients.

The covalent linkage of a polysaccharide antigen to a protein such as tetanus or diphtheria toxoid results in a more immunogenic molecule, which evokes a T-cell-dependent immune response that is stronger in an immature immune system and is longer duration. Conjugated pneumococcal vaccines are being developed.

Poliovirus

Poliomyelitis continues to remain a serious problem in a number of developing countries, with sporadic outbreaks in non-immunised individuals[44,45] . Immunity to polio is gradually lost after BMT[46-48] .

Engelhard et al.[46] showed that 68-80% of BMT recipients had protective antibodies against the three serotypes of poliovirus 6-96 months post-BMT compared with 92-96% before transplant. Immunization with two doses of inactivated polio vaccine 6-96 months after BMT produce increased antibody titers in all patients. Presence and degree of GvHD, pre-BMT polio antibody titers, age, and the type of graft affected response to the vaccine, but the time from BMT to vaccination did not. Ljungman et al.[47] found that although almost 70% of allo recipients were seropositive to all poliovirus types one year after BMT, at least a four-fold decrease in antibody levels was seen in roughly half of the patients from their pre-transplant levels. Half of the patients receiving three inactivated polio vaccine doses responded, and the presence of chronic GvHD did not affect the response. Almost 20% of autograft recipients were found to have lost antibodies to at least one type of poliovirus after one year of auto-BMT[48] . This time-dependent decrease in antibody titers continued in unvaccinated patients in the second and third years. A high proportion of seronegative patients re-immunised with three doses of the inactivated vaccine responded[48] .

The inactivated polio vaccine has been successfully administered to paediatric patients autografted using bone marrow depleted of B lymphocytes[5] , and in patients allografted for thalassaemia who did not have chronic GvHD[25.]

Tetanus toxoid

There are data, which suggest that tetanus toxoid-specific immunity can be transferred by allografting, and can persist in long-term survivors without immediate pre-transplant toxoid administration to donors or to recipients pre/post-transplant[2] . Contrasting observations were made by Ljungman et al.[7] who found that half of the patients who were immune to tetanus before BMT had lost their immunity by one year post-BMT. All the patients who were not re-immunised with tetanus toxoid were seronegative for two years.

Response rates were relatively poor and loss of immunity common in patients immunised with one or two doses of toxoid after BMT[7] . However, primary immunization with three

doses of toxoid resulted in 100% response and sustained immunity[7] . Amongst patients receiving tetanus toxoid 3, 6, and 12 months following T-cell-depleted BMT, only those who had been immunised pre-transplant along with their donors responded effectively[50] . Tetanus toxoid administration resulted in adequate immune response in paediatric patients autografted using B-lymphocytes depleted bone marrow[5] , and in thalassemic patients who did not have chronic GvHD[25] .

In children, who were routinely re-immunised early after BMT, the antibody response was quantitatively more to that in adults who were not re-immunised early[51] . In the majority of patients, the time required to reach peak antibody level was prolonged and the number of tetanus toxoid-specific B-cell clones was significantly decreased in comparison with controls. Unlike the controls, production of relatively high concentrations of homogeneous antibodies against a heterogeneous background was seen in BMT recipients. These abnormalities were present up to 10 years after transplantation, irrespective of the age, the type of transplant, or the re-immunization schedule. Their data indicate that routine re-immunization early after BMT may improve the specific immune response, but because of dysregulated antibody production, long-lasting qualitative defects may be present even after normalisation of antibody titers.

MEASUREMENT OF THE IMMUNE RESPONSE

The level of specific immune response following vaccination can be measured in the serum. Although sero-conversion does indicate an immune response, it does not necessarily signify protection[1] . For some viral vaccines, such as measles, rubella, HBV, the presence of circulating antibodies correlates with clinical protection. The absence of measurable antibody may not mean that the individual is unprotected. By contrast, with some vaccines and toxoids, the presence of antibodies is not sufficient to assure clinical protection, but rather a minimal circulating level of antibody is required (e.g., 0.01 IU/ml of tetanus antitoxin).
Routine measurement of antibody titers prior to vaccination is not recommended in all transplant recipients[11] . Post-vaccination determination of antibody levels is useful to monitor antibody response and protection.

ADOPTIVE TRANSFER OF PROTECTIVE IMMUNITY

Although immunity can be transferred adoptively from the donor to the recipient through an allogeneic blood or marrow graft, the durability of this immune response is uncertain, and most data in clinical practice suggest fail in the antibody titers over a period of time[2-7] . Therefore, adoptive transfer of immunity with allogeneic BMT probably does not overcome the need for routine re-immunization in the majority of cases.

In a murine model, Shepherd and Noelle showed that while the adoptive transfer of immune splenic B cells or immune peripheral blood mononuclear cells, effectively transferred antigen-specific IgG1 antibody responses of donor origin to recipients, marrow from immune animals did not transfer a memory response[52] . They suggested that the transfer of immunological memory observed in human BMT, might be a consequence of peripheral blood contamination of the harvested donor marrow. The number of B cells in blood stem cell harvests from healthy donors is 2.7 to 15.8 times (mean 7.9) higher than marrow[22] . Therefore it is possible that peripheral blood stem cell allografts may transfer immunity more effectively and this may be durable.

Serious infections are common in the early phase following allogeneic BMT. Augmentation of immunity to some of the common pathogenic organisms by adoptive transfer could conceivably reduce infection-related mortality and improve outcome. However, adoptive transfer of antibody responses is possible only for recall antigens. Transfer of responses to priming antigens, which would broaden the range of organisms against which patients can be protected, is not successful[53.]

Gottlieb et al. immunised marrow donors and/or recipients pre-transplant with a polyvalent *Pseudomonas* 0-polysaecharide-toxin A conjugate vaccine[54] . When either donor or recipient alone was vaccinated, no increase in

specific antibody titers was observed in the recipient post-BMT. However, when both donor and recipient were vaccinated before transplant, antibody titers elevated to levels shown to be protective in animal models of gram-negative sepsis[54] . The requirement for both donor and recipient immunization[53,54] reflects the need for primed donor B-lymphocytes in the marrow inoculum to be transferred into an antigen-containing environment for maximum B cell proliferation and antibody production.

The adoptive transfer of virus antigen-specific cytotoxic T lymphocytes from the donor to establish immunity has been shown to be effective for the prevention of cytomegalovirus (CMV) infections[55] , and prevention and treatment of Epstein-Barr virus (EBV)-induced lymphoproliferation[56] in allograft recipients.

PASSIVE IMMUNIZATION

The indications for passive immunization of BMT recipients using specific immunoglobulin preparations are similar to those in otherwise healthy individuals[1] . Administration of high-dose intravenous immunoglobulin (IVIG) is commonly employed for up to four months after BMT, especially allogeneic transplantation, for its beneficial effects on viral and bacterial infections and GvHD (by inhibiting of cytokines) have been reported[57] . In allogeneic BMT, prophylactic IVIG decreases bacterial sepsis, CMV disease, interstitial pneumonitis and acute GvHD in recipients of HLA-matched sibling BMT over age 20. It may also decrease platelet transfusion requirements. There is no significant benefit on autograft transplant patients. However, there is evidence that prolonged administration of immunoglobulin (for one year) is associated with delayed immune reconstitution and an increased incidence of infections after discontinuation of immunoglobulin[58] . While re-immunizing BMT recipients, possible interference of immunoglobulin administration with response to vaccination must be borne in mind. Response to the MMR vaccine in healthy children has been shown to be suboptimal for 3 months after the administration of 80 mg/kg of immunoglobulin. A similar observation has been made in adult immune globulin, but to a much smaller extent[59] .

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