Vaccine Recommendations for Patients on Chronic Dialysis

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Despite improvements in infection control practices and dialysis techniques, bacterial and viral infections are a major cause of morbidity and mortality among patients on long-term hemodialysis or peritoneal dialysis (1–4). Several studies have documented that infections contribute to as many as 30–36% of deaths in patients on long-term dialysis (1, 3); many of these deaths are vaccine preventable. The incidence of pneumonia in dialysis patients has been reported to be as high as 4.9 episodes per 1,000 patient-months; of these, 53% were due to *Streptococcus pneumoniae* (1, 5). Acute hepatitis B virus (HBV) infection in uremic patients on dialysis is generally mild or asymptomatic, but these patients have a higher incidence of chronic HBV infection compared to immunocompetent persons (6, 7). Infection control measures and the use of hepatitis B vaccine have significantly reduced the annual incidence of HBV infection among patients on dialysis, from 3.0% to 0.05% between 1976 and 1997 (8). However, chronic dialysis patients are at increased risk of HBV infection because of their constant exposure to blood, frequent transfusions, and sharing of dialysis equipment (8–11).

The increased susceptibility to infections among these patients is indicative of a complex and varied state of immunodeficiency manifested by abnormal phagocytosis, T- and B-lymphocyte abnormalities and impaired responses to T-cell-dependent pathogens such as hepatitis B and influenza viruses (12, 13). These immunologic abnormalities are complicated by the use of immunosuppressive drugs to treat and control underlying diseases and exacerbated by nutritional deficiencies, the dialysis procedure, and the disruption of cutaneous and mucosal barriers to infection (2, 14–18).

While vaccines and toxoids can play an important role in attenuating the risk of infections among patients with chronic renal failure (14, 19, 20), the immune response to vaccination is limited by the same immunodeficiencies that limit immune response to disease (21–25). Thus the response to vaccines varies by the type and course of the underlying disease that led to renal failure, as well as by the treatment and stage of renal disease (14, 19, 20). Lower seroconversion rates following vaccination (26–28), lower peak antibody titers (27, 29), and a rapid decline of antibody levels (27, 30–32) are common among patients on dialysis.

According to the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP), patients on dialysis can safely receive all live attenuated vaccines, except the oral polio vaccine, as well as all inactivated vaccines on the same schedule recommended for immunocompetent persons (Fig. 1 and Table 1) (19, 33–35). However, since response to vaccination may be suboptimal, higher doses or an increased number of doses may be needed to ensure protection (33, 36, 37).

The purpose of this article is to summarize the current recommendations of the ACIP and the AAP regarding the use of vaccines and toxoids among persons on chronic dialysis. The current ACIP recommendations for the three main vaccines specifically recommended for dialysis patients—hepatitis B, pneumococcal, and influenza—will be discussed first, followed by recommendations regarding other routinely used vaccines.

Vaccines Specifically Recommended for Dialysis Patients

Hepatitis B Vaccine

Patients on dialysis should receive three doses of hepatitis B vaccine as early in the course of the renal disease as possible (33, 38). Two yeast-derived recombinant hepatitis B vaccines are currently licensed in the United States for use in dialysis patients: Recombivax HB® (Merck, Sharp & Dhome) and Engerix-B® (Smith-Kline Beecham) (38). Pediatric patients on dialysis should receive the standard dosage (5 μg of Recombivax HB or 10 μg of Engerix-B) on the same schedule as recommended for healthy children by the ACIP and AAP (34, 35, 38). The recommended dosage for adults on dialysis is 40 μg of either Recombivax HB or Engerix-B given intramuscularly in the deltoid (38, 39). Several studies conducted between 1985 and 1996 used the intradermal (ID) route to enhance the seroconversion of dialysis patients to the hepatitis B vaccine (40–43). However, there are no data regarding long-term protection

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TABLE 1. Summary of ACIP recommended vaccines for patients on chronic dialysis

Vaccine	Age group	Dose volume	Route of administration*	Number of doses	Boosters
Hepatitis B (Recombivax HB®)	<20 years	5 μg (0.5 mL)	IM	3	Yes, when anti-HBs
	≥20 years	40 μg (1.0 mL)†	IM	3	<10 mU/mL
Hepatitis B (Engerix-B®)	<20 years	10 μg (0.5 mL)	IM	3	Yes, when anti-HBs
	≥20 years	40 μg (2.0 mL)‡	IM	4	<10 mU/mL
Pneumococcal	>2 years	0.5 mL	IM or SC	1	No (revaccination in 3–5 years)
Influenza	6–35 months	0.25 mL	IM	1 or 2§	No
	3–8 years	0.50 mL	IM	1 or 2§	
	9–12 years	0.50 mL	IM	1	
	>12 years	0.50 mL	IM	1	
Measles, mumps, rubella (MMR)	12 months–18 years	0.5 mL	SC	2	No
	>18 years	0.5 mL	SC	1	No
Varicella	1–12 years	0.5 mL	SC	1	No
	>12 years	0.5 mL	SC	2	No
Inactivated poliovirus (IPV)	<18 years	0.5 mL	SC	3 or 4	No
Diptheria and tetanus toxoids, and pertussis vaccine (DTP/DTaP)	2 months–7 years	0.5 mL	IM	5	No
Diptheria and tetanus toxoids (DT)	2 months–7 years	0.5 mL	IM	3	No
Tetanus and diphtheria toxoids (Td)	7 years	0.5 mL	IM	3	Every 10 years
Haemophilus influenzae type B (HbOC)	2 months–5 years	0.5 mL	IM	1–3**	One at 15 months
Haemophilus influenzae type B (PRP-OMP)	2 months–5 years	0.5 mL	IM	2	One at 12 months
Haemophilus influenzae type B (PRP-D)	2 months–5 years	0.5 mL	IM	1	No
Hepatitis A (HAVRIX®)	2–18 years	0.5 mL	IM	2	No
	>18 years	1.0 mL	IM	2	No
Hepatitis A (VAQTA®)	2–17 years	0.5 mL	IM	2	No
	>17 years	1.0 mL	IM	2	No

* IM = intramuscular, SC = subcutaneous.
† Special formulation for dialysis patients.
‡ Two 1.0 ml doses at one site in a 4-dose schedule at 0, 1, 2, and 6 months.
§ Two doses administered at least 1 month apart are recommended for children less than 9 years of age who are receiving influenza vaccine for the first time.
** Depending on age at first dose.

following ID vaccination. The ID route for hepatitis B vaccination is not currently recommended by the ACIP, and the vaccine is not licensed for the ID route of administration. In children on dialysis, postvaccination protective antibody rates as high as 91% have been reported (44). Among adult patients on dialysis, only 50–75% develop protective antibody levels against hepatitis B surface antigen (anti-HBs) after three doses of vaccine (≥10 mU/mL) (27–29, 32, 45–47) compared to more than 90% of healthy adults (28, 45).

Revaccination with up to three additional doses is recommended for susceptible persons who do not develop protective antibody levels after an initial three-dose vaccination series (38). The ACIP recommends postvaccination anti-HBs testing for dialysis patients to demonstrate protective antibody levels 1–2 months after the primary series is completed and annually thereafter (38). A booster dose is recommended if the anti-HBs titer falls below 10 mU/mL (38). The vaccine has been shown to be safe for patients on chronic dialysis, with only minor local reactions, including pain, redness, or swelling at the injection site (31, 32, 44, 46, 47).

Pneumococcal Polysaccharide Vaccine

The ACIP currently recommends that a single 0.5 mL dose of the 23-valent pneumococcal polysaccharide vaccine be administered intramuscularly or subcutaneously to all dialysis patients 2 years of age or older (33, 48, 49). More than 75% of dialysis patients have an adequate response to the vaccine, measured by a twofold or greater increase in postvaccination antibody titer and/or a geometric mean greater than 200 ng/mL (50–53), but their antibody levels are considerably lower than those of healthy vaccinated adults (26, 30, 50–52).

In healthy adults, antibody levels to most pneumococcal vaccine antigens remain elevated for at least 5 years, decreasing to prevaccination levels after 10 years (54, 55). In children and adults with chronic renal disease requiring dialysis, a rapid decline in antibody level (within 6 months–5 years after vaccination) has been reported (30, 50–53, 56). Revaccination is recommended 3 years after the previous dose for children with chronic renal failure who will be 10 years old or younger at the time of revaccination (49). Revaccination is also recommended for other dialysis patients, provided that at least 5 years have elapsed since the first dose of pneumococcal vaccine (49). The pneumococcal vaccine is generally well tolerated, with minor side effects such as pain, erythema, itching, and burning at the site of the injection (49, 52).

Influenza Vaccine

Patients with chronic renal failure requiring dialysis should receive the influenza vaccine because of their

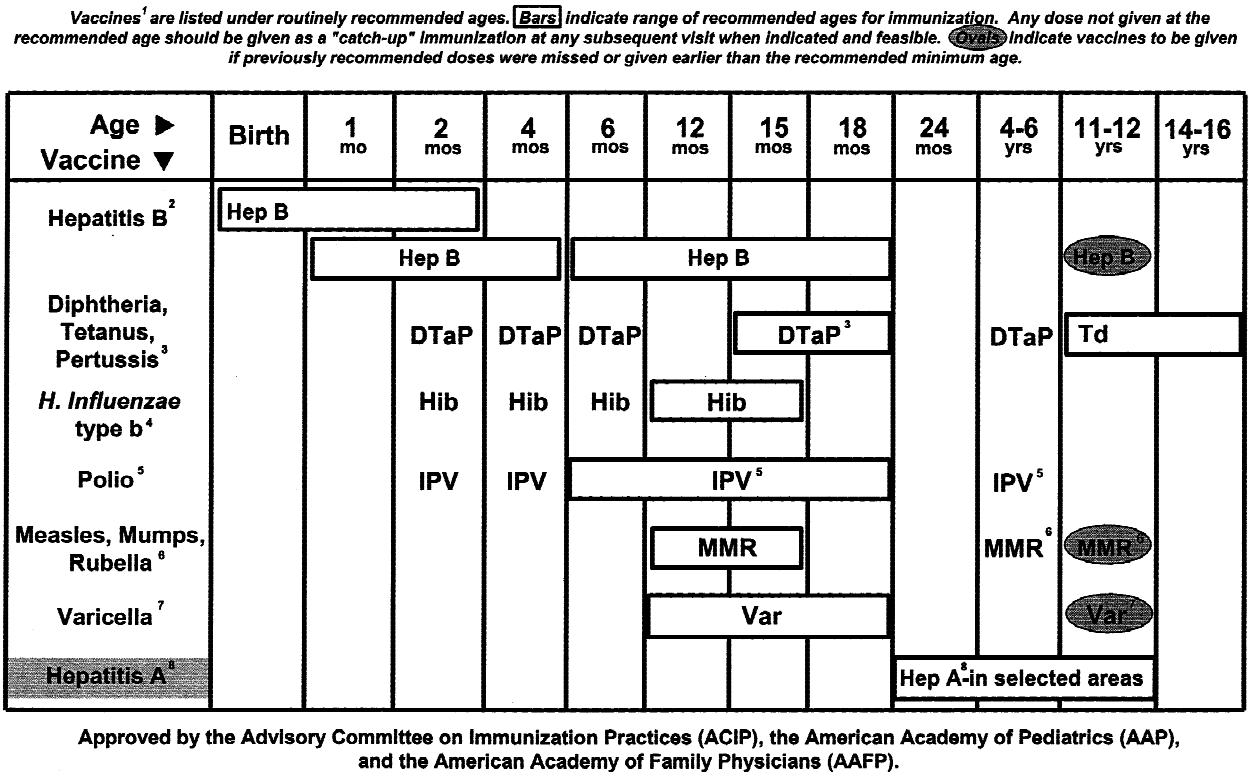

FIG. 1. Recommended childhood immunization schedule, United States, January–December 2000. On October 22, 1999, the Advisory Committee on Immunization Practices (ACIP) recommended that Rotashield® (RRV-TV), the only U.S.-licensed rotavirus vaccine, no longer be used in the United States (*MMWR*, Volume 48, Number 43, Nov. 5, 1999). Parents should be reassured that their children who received rotavirus vaccine before July are not at increased risk for intussusception now. **(1)** This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines as of 11/1/99. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and its other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations. **(2)** Infants born to HBsAg-negative mothers should receive the 1st dose of hepatitis B (Hep B) vaccine by age 2 months. The 2nd dose should be at least one month after the 1st dose. The 3rd dose should be administered at least 4 months after the 1st dose and at least 2 months after the 2nd dose, but not before 6 months of age for infants. Infants born to HBsAg-positive mothers should receive hepatitis B vaccine and 0.5 mL hepatitis B immune globulin (HBIG) within 12 hours of birth at separate sites. The 2nd dose is recommended for infants at ages 1–2 months and the 3rd dose at 6 months of age. Infants born to mothers whose HBsAg status is unknown should receive hepatitis B vaccine within 12 hours of birth. Maternal blood should be drawn at the time of delivery to determine the mother's HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than 1 week of age). All children and adolescents (through 18 years of age) who have not been immunized against hepatitis B may begin the series during any visit. Special efforts should be made to immunize children who were born in or whose parents were born in areas of the world with moderate or high endemicity of hepatitis B virus infection. **(3)** The 4th dose of DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine) may be administered as early as 12 months of age, provided 6 months have elapsed since the 3rd dose and the child is unlikely to return at age 15–18 months. Td (tetanus and diphtheria toxoids) is recommended at 11–12 years of age if at least 5 years have elapsed since the last dose of DTP, DTaP or DT. Subsequent routine Td boosters are recommended every 10 years. **(4)** Three *Haemophilus influenzae* type b (Hib) conjugate vaccines are licensed for infant use. If PRP-OMP (PedvaxHIB® or ComVax® [Merck]) is administered at 2 and 4 months of age, a dose at 6 months is not required. Because clinical studies in infants have demonstrated that using some combination products may induce a lower immune response to the Hib vaccine component, DTaP/Hib combination products should not be used for primary immunization in infants at 2, 4 or 6 months of age, unless FDA-approved for these ages. **(5)** To eliminate the risk of vaccine-associated paralytic polio (VAPP), an all-IPV schedule is now recommended for routine childhood polio vaccination in the United States. All children should receive four doses of IPV at 2 months, 4 months, 6–18 months, and 4–6 years. OPV (if available) may be used only for the following special circumstances: 1. Mass vaccination campaigns to control outbreaks of paralytic polio. 2. Unvaccinated children who will be traveling in <4 weeks to areas where polio is endemic or epidemic. 3. Children of parents who do not accept the recommended number of vaccine injections. These children may receive OPV only for the third or fourth dose or both; in this situation, health-care providers should administer OPV only after discussing the risk for VAPP with parents or caregivers. 4. During the transition to an all-IPV schedule, recommendations for the use of remaining OPV supplies in physicians' offices and clinics have been issued by the American Academy of Pediatrics (see *Pediatrics*, December 1999). **(6)** The 2nd dose of measles, mumps, and rubella (MMR) vaccine is recommended routinely at 4–6 years of age but may be administered during any visit, provided at least 4 weeks have elapsed since receipt of the 1st dose and that both doses are administered beginning at or after 12 months of age. Those who have not previously received the second dose should complete the schedule by the 11–12-year-old visit. **(7)** Varicella (Var) vaccine is recommended at any visit on or after the first birthday for susceptible children, i.e. those who lack a reliable history of chickenpox (as judged by a health care provider) and who have not been immunized. Susceptible persons 13 years of age or older should receive 2 doses, given at least 4 weeks apart. **(8)** Hepatitis A (Hep A) is shaded to indicate its recommended use in selected states and/or regions; consult your local public health authority. (Also see *MMWR* Oct. 01, 1999/48(RR12); 1–37).

increased risk of influenza-related mortality (57, 58). The ACIP recommends the influenza vaccine annually, before the beginning of the influenza season for persons 6 months of age or older on dialysis (58). Household members and health care workers in contact with persons on dialysis should also be vaccinated annually to decrease influenza transmission to high-risk patients (58). For previously unvaccinated children less than 9 years of age, two doses of the influenza vaccine administered intramuscularly at least 1 month apart are recommended to achieve satisfactory antibody response (35, 58). Children 9–12 years old should receive one dose of the split-virus vaccine, while patients older than 12 years can receive one dose of either the whole-virus or split-virus vaccine (Table 1) (58).

The post-influenza vaccination geometric mean titer is often lower in dialysis patients than in immunocompetent persons (59–62). A fourfold increase in serum antibody titer against influenza antigens has been observed in 50% of dialysis patients compared to 64% of healthy controls; no systemic reactions among dialysis patients have been reported following vaccination (60).

Recommendations Regarding Other Routine Vaccines

Live Attenuated Vaccines

Although live vaccines are generally contraindicated in immunocompromised patients due to the risk of vaccine-induced infections (33), several studies of their use in patients with chronic renal failure reported no adverse reactions (63–66). However, due to a theoretical risk, the oral polio vaccine is not recommended for children who have a known or suspected immunodeficiency, including those with chronic renal failure.

Measles, Mumps, and Rubella Vaccine

The measles, mumps, and rubella (MMR) vaccine should be given to all children, including those on dialysis, between 12 and 15 months of age, with a booster dose between 4 and 6 years of age (34, 67). Among healthy children, the seroconversion rate for one dose of MMR vaccine is more than 90% (63, 67, 68). For children on dialysis, the seroconversion rate for all three antigens is approximately 30%, for mumps alone 50%, and for measles and rubella combined 80% (63). Therefore some have suggested children on dialysis may benefit from postvaccination testing to assess seroconversion (63).

Varicella Vaccine

Children 1 year or older on dialysis who have not had chickenpox previously should receive one subcutaneous dose of the varicella vaccine as recommended by the ACIP for healthy children 13 years of age or younger (34, 69). Due to the high risk of complications and death associated with chickenpox infection in adulthood, susceptible adolescents and adults should receive two doses of the varicella vaccine subcutaneously, with the second injection at least 4 weeks after the first (69, 70).

Among patients undergoing dialysis, data on the immunogenicity of the varicella vaccine are limited. A recent report, however, showed that up to 85% of children on dialysis developed protective antibody levels (geometric mean titer 1:640) within the first 6 months following a single dose of the vaccine (71), which is comparable to the seroconversion rate among healthy children (69). The varicella vaccine has been reported to be safe for children on dialysis, with no systemic adverse reactions reported (71).

Oral Poliovirus Vaccine

There are no data discussing the use of oral poliovirus vaccine (OPV) in children undergoing dialysis. However, because of a theoretical risk that they will not be able to effectively limit the replication of the vaccine virus, OPV should not be used to immunize immunocompromised children, including children on dialysis (33). Also OPV should not be used on household members or health care staff in close contact with these patients (33).

To eliminate the risk of vaccine-associated paralytic polio, on June 17, 1999, the ACIP recommended that effective January 1, 2000, OPV no longer be used in the United States (34, 72).

Inactivated Vaccines and Toxoids

All inactivated vaccines and toxoids are safe and effective when used in dialysis patients, and should be administered to children and adults on chronic dialysis using the same doses and schedules recommended for immunocompetent persons (14, 18, 19, 33–35).

Inactivated Poliovirus Vaccine

Inactivated poliovirus vaccine (IPV) is the only poliovirus vaccine that should be routinely administered to infants and adolescents including those who have or are suspected to have, an immunodeficiency (33). Routine vaccination of adults (persons 18 years old or older) residing in the United States is not necessary because most adults have a minimal risk of exposure to poliovirus (33). However, vaccination with IPV is recommended for certain adults who have a greater risk of exposure to poliovirus than the general population (i.e., travelers to poliovirus endemic areas, laboratory workers, and persons in close contact with patients who may be excreting poliovirus). This recommendation applies to both immunologically normal and immunocompromised adults (73). For children, the polio vaccination series consists of four doses of vaccine at 2, 4, 16–18 months, and 4–6 years of age. All children who have received their third dose of IPV after their fourth birthday do not need an additional dose at school entry.

For unvaccinated adults on dialysis at increased risk of exposure to poliovirus, a primary series of IPV is recommended (33). IPV is highly immunogenic and pro-

duces a fourfold increase in antibody titer to all three polio virus serotypes in 86% of children on chronic dialysis, with no side effects reported (74).

Diphtheria and Tetanus Toxoids and Pertussis Vaccine

Children on dialysis should receive the diphtheria and tetanus toxoids and pertussis (DTaP) vaccine as recommended for healthy children (Fig. 1). Booster doses of tetanus-diphtheria toxoids (Td) should follow every 10 years after completing the primary series (33, 75). The seroconversion rate for these antigens has been shown to be lower in children on dialysis (69–88%) (24, 76) than in healthy children (93–100%) (75); however, the toxoids and vaccine are well tolerated (24, 76). Further, the persistence of immunity in patients on dialysis is comparable to that among healthy persons (24, 76).

Haemophilus influenza Type B Conjugate Vaccine

There is limited information on the use of *H. influenza* type b (Hib) vaccine in children on chronic dialysis. The ACIP recommends the vaccine for these patients beginning at 2 months of age using the same dosage and schedules used for healthy children and adults (33, 34, 77). The vaccine is safe: a study of children on continuous ambulatory peritoneal dialysis has shown seroconversion rates of 90%, with a persistence of immunity for 22 months after vaccination (78).

Hepatitis A Vaccine

The ACIP recommends hepatitis A vaccine for persons who are at increased risk of infection and for any person wishing to obtain immunity. Persons at increased risk are travelers to countries of intermediate or high endemicity of infection, children 2 years of age and older living in areas where rates of hepatitis A are at least twice the national average, users of injecting and noninjecting drugs, men who have sex with men, persons with chronic liver disease or clotting-factor disorders, and persons working with non-human primates (79). Children who should be routinely vaccinated are those who live in states, counties, or communities where the average hepatitis A rate during 1987–1997 was greater or equal to 20 cases per 100,000 population. These states are Arizona, Alaska, Oregon, New Mexico, Utah, Washington, Oklahoma, South Dakota, Nevada, California, and Idaho. The ACIP also recommends that routine hepatitis A vaccination may be considered in states, counties or communities with reported hepatitis A average annual rate greater than 10 cases per 100,000 but less than 20 cases per 100,000 population. The states are Mississippi, Texas, Colorado, Arkansas, Montana, and Wyoming (79).

Two hepatitis A vaccines are currently licensed in the United States, one formulation for children and one for adults. Vaccination schedules and doses differ according to the vaccine formulations, vaccinee's age, and type of vaccine (Table 1). Both children and adults should receive two doses of the vaccine intramuscularly (79). Data on immunocompetent persons show that the hepatitis A vaccines are highly immunogenic in children, adolescents, and adults, with up to 100% of recipients developing protective levels of antibodies greater than 20 mU/mL, persisting for up to 48 months following vaccination (79–81). A small study of hemodialysis patients showed similar geometric mean titer responses at 7 months post-vaccination in dialysis patients (1,330 mU/mL) and healthy subjects (1,355 mU/mL), with only a few mild side effects reported (82).

Summary

Pediatric patients on dialysis should receive all the vaccines currently recommended by the ACIP and the AAP for healthy children, except the oral polio vaccine (34, 35). Adult patients should receive the hepatitis B vaccine series, pneumococcal vaccine, yearly influenza vaccinations, tetanus-diphtheria toxoids, and varicella vaccine, if they are susceptible (33, 48, 69). Vaccines are well tolerated by these patients (33), but higher doses and/or additional boosters may be required periodically to adequately protect dialysis patients from vaccine-preventable diseases (33, 36, 37, 82, 83). Following vaccination, antibody concentrations for hepatitis B vaccine should be measured annually and booster doses administered when antibody concentrations fall below protective levels (33, 38).

Although both children and adults on dialysis may show an impaired and/or delayed immunologic response to certain antigens, particularly hepatitis B virus and *S. pneumoniae*, appropriate immunizations can significantly reduce the risk of serious complications from vaccine-preventable diseases (11, 84). Because the protection these vaccines provide may be incomplete or transient, infection control strategies at hospitals and other health care facilities should be implemented simultaneously. Health care providers are encouraged to assess each patients need for vaccinations individually and formulate immunization strategies early in the course of progressive renal disease, ideally before the patient requires dialysis.

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