

Rabies Postexposure Prophylaxis in Routine Practice in View of the New Centers for Disease Control and Prevention and World Health Organization Recommendations

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(See the Editorial Commentary by Wilde, on pages 206–8.)

Background. New recommendations for rabies postexposure prophylaxis (PEP) were published by the Centers for Disease Control and Prevention and the World Health Organization in 2010. In view of these new recommendations, we investigated the adequacy of rabies PEP among patients consulting our travel clinic.

Methods. A retrospective analysis of the files of all patients who consulted for rabies PEP at the Travel Clinic of the University Hospital in Lausanne, Switzerland, between January 2005 and August 2011 was conducted.

Results. A total of 110 patients who received rabies PEP were identified. The median age of the patients was 34 years (range, 2–79 years), and 53% were women. Ninety subjects were potentially exposed to rabies while travelling abroad. Shortcomings in the management of these patients were (1) late initiation of rabies PEP in travelers who waited to seek medical care until returning to Switzerland, (2) administration of human rabies immunoglobulin (HRIG) to only 7 of 50 travelers (14%) who sought care abroad and for whom HRIG was indicated, and (3) antibody levels <0.5 IU/mL in 6 of 90 patients (6.7%) after 4 doses of vaccine.

Conclusions. Patients do not always receive optimal rabies PEP under real-life conditions. A significant proportion of patients did not develop adequate antibody levels after 4 doses of vaccine. These data indicate that the measurement of antibody levels on day 21 of the Essen PEP regimen is useful in order to verify an adequate immune response.

In case of potential rabies exposure, the recommendation is to clean and disinfect the wound and to administer rabies postexposure prophylaxis (PEP). For the postexposure immunization of nonimmune subjects, the Essen regimen, which includes 5 intramuscular vaccine doses on days 0, 3, 7, 14, and 28, has been widely used. Serological testing on day 21 has usually been advocated if available, to ensure the development of an appropriate

antibody level of at least 0.5 IU/mL. Rabies PEP should also include human rabies immunoglobulin (HRIG) for nonimmune persons with significant wounds [1, 2].

Because of recurrent vaccine shortages, a US National Working Group was created in 2007 to review the justification for the 5 doses of the Essen PEP regimen. This working group reviewed the available data on rabies virus pathogenesis, experimental animal models, human immunogenicity studies, prophylaxis effectiveness in humans, and documented failures of prophylaxis in humans [3]. Following this analysis, the Centers for Disease Control and Prevention decided in 2010 to recommend a rabies PEP with 4 intramuscular doses of vaccine on days 0, 3, 7, and 14 but to abandon the fifth dose, scheduled for day 28 [4]. Serological testing on day 21 was also considered unnecessary. Later that year, the World Health

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Organization (WHO) issued a position paper stating that this 4-dose regimen was an adequate alternative for healthy, fully immunocompetent individuals who had received wound care plus high-quality HRIG [1].

In view of these new recommendations, we aimed to evaluate the adequacy of rabies PEP among patients who consulted the Travel Clinic of the Department of Ambulatory Care and Community Medicine at the University Hospital in Lausanne, Switzerland.

PATIENTS AND METHODS

The study was based on a retrospective review of the files of all patients referred for rabies PEP to the Travel Clinic between January 2005 and August 2011. Patients were included if they had had a potential exposure to rabies in Switzerland or abroad. Details about demographic characteristics, preexposure vaccination, place of potential exposure, type of potential exposure, medical management abroad and in Switzerland, and serological results were recorded. For nonimmune persons, serologic testing was in general done after receipt of the fourth dose of the rabies PEP regimen; for prevaccinated patients, serum specimens were obtained after receipt of 2 postexposure rabies vaccine doses. Additional serologic testing was done when additional vaccine doses were administered.

The patients, who were vaccinated at our center, received either Rabipur (Novartis Pharma) or Rabies Vaccine Merieux (Sanofi Pasteur MSD). The details of the vaccines used for the first 4 doses (for nonimmune persons) or first 2 doses (for prevaccinated patients) are indicated below. Lot numbers, potency, and number of doses of Rabipur vaccine were as follows: lot number 378011A: 6.0 IU/dose, 29 doses; lot number 397011A: 9.0 IU/dose, 39 doses; lot number 422011A: 7.0 IU/dose, 28 doses; lot number 422011C: 7.0 IU/dose, 1 dose; lot number 359011C: 7.0 IU/dose, 10 doses; lot number 416011F: 7.0 IU/dose, 5 doses; lot number 420011C: 9.0 IU/mL, 1 dose; lot number 461011F: 6.2 IU/mL 9 doses; lot number 394011C: 11.0 IU/dose, 35 doses; and lot number 469011C: 5.5 IU/dose, 11 doses. Lot numbers, potency, and number of doses of Rabies Vaccine Merieux were as follows: lot number B0001-9: 2.6 IU/dose, 16 doses; lot number E0042-15: 6.0 IU/dose, 3 doses; lot number E0374-3: 13.7 IU/dose, 1 dose; lot number E0761-1: 5.2 IU/dose, 8 doses; lot number E0761-3: 5.2 IU/dose, 12 doses; and lot number E0762-4: 4.7 IU/dose, 12 doses. For 39 doses administered at our center, the type of vaccine and lot number was not recorded. A total of 159 vaccine doses were administered at other centers. The following vaccines were used: Verorab (80 doses), Rabipur (11 doses), and Abhayrab (2 doses); the vaccine was unknown for 64 doses. Lot numbers of vaccines used in other centers were only available for 5 doses.

Serological testing was done by the Swiss Rabies Center (Bern, Switzerland). The antibody titers were determined by the rapid fluorescent focus inhibition test, as previously described [5,6].

RESULTS

A total of 110 patients consulted the Travel Clinic during the study period (Table 1). The median age of the patients was 34 years (range 2–79 years), and 53% were women. No patient reported any immunosuppressive condition. Eleven patients had received at least 3 doses of rabies vaccine as preexposure prophylaxis. Ninety subjects (82%) were exposed abroad. The principal animals involved were dogs, in 59 cases (54%); monkeys, in 21 (19%); bats, in 11 (10%); and cats, in 11 (10%). Four patients had WHO grade 1 exposure due to bats, 7 patients had WHO grade 2 exposure, and 99 patients had WHO grade 3 exposure.

Of the 90 subjects potentially exposed to rabies abroad, 54 consulted a physician in the visited country, and 36 patients waited to be back in Switzerland before seeking medical care. For patients who consulted abroad, the median delay between exposure and initiation of rabies PEP was 0 days (range, 0–14 days), while for patients who waited to be back in Switzerland before seeking medical care, the median delay was 10 days (range, 0–481 days). Ninety-nine patients (18 locally exposed subjects and 81 travelers) should have received HRIG because they had not received preexposure prophylaxis. All 18 locally exposed persons and 28 of the 31 travelers (90%) who waited for their return to Switzerland received HRIG. On the other hand, of the 50 travelers who consulted abroad, only 7 (14%) received HRIG. The countries in which patients obtained HRIG were Tunisia (2 patients of 3 exposed), Algeria (1 of 1), Thailand (1 of 18), Vietnam (1 of 4), Indonesia (1 of 8), and Brazil (1 of 2).

Five patients were lost to follow-up before antibody levels could be measured to ensure appropriate antibody response: 4 patients were transferred to other medical facilities for further management, and 1 patient could not be reached after the fourth dose of vaccine. Figure 1A and 1B show the antibody titers in the remaining 105 patients. The 11 patients who had received preexposure prophylaxis had serum titers measured after 2 postexposure vaccine doses. The geometric mean titer for these patients was 18.2 IU/mL, with a range of 5.4–33.9 IU/mL and a 95% confidence interval of 11.8–28.0 IU/mL. For 90 of the 94 patients without previous vaccination, the antibody titers were measured after the fourth dose of vaccine of the rabies PEP, and for 4 patients the antibody titers were only measured after the fifth dose of vaccine. Five patients had antibody titers measured >50 days after the start of the rabies PEP. They were therefore excluded from the calculation of the geometric mean titer. For the remaining 85 patients, all of whom had received 4 vaccine doses, the geometric mean

Table 1. Characteristics of Subjects Who Consulted for Rabies Postexposure Prophylaxis, by Exposure Location

Characteristic	Exposed in Switzerland (n = 20) ^a	Exposed Abroad (n = 90)	Total (n = 110)
Age, years	32 (15–79)	36 (2–74)	34 (2–79)
Female sex/male sex, %	45/55	54/46	53/47
Received ≥3 PrEP doses	2	9	11
Animals involved			
Dogs	8	50	58
Bats	7	4	11
Cats	3	8	11
Monkeys	0	21	21
Other	2	7	9
Place of exposure			
Switzerland	20	...	20
Asia	...	47	47
Africa	...	14	14
Europe	...	18	18
North America	...	1	1
Central and South America	...	10	10
Days from exposure to start of rabies PEP	0 (0–14)	10 (0–481)	...
Patients without PrEP who received HRIG, No. ^b	Consulted in Switzerland: 18/18	Consulted abroad: 7/50; consulted after returning to Switzerland: 28/31	...

Data are median (range) or no. of patients, unless otherwise indicated.

Abbreviations: HRIG, human rabies immunoglobulin; PEP, postexposure prophylaxis; PrEP, preexposure prophylaxis.

^a All are Swiss residents.

^b Denominators are no. of patients who did not receive ≥3 PrEP doses.

antibody titer was 3.7 IU/mL, with a range of 0.1–38 IU/mL and a 95% confidence interval of 2.8–4.8 IU/mL.

After 4 doses of vaccine, 6 patients without preexposure prophylaxis had antibody titers <0.5 IU/mL when measured between 21 and 29 days after initiation of rabies PEP (Figure 1B and Table 2). Four of these patients were exposed abroad. Four of these patients received all their vaccine doses at our center. The type and lot numbers of the vaccines used for these patients are shown in Table 2. Ten of the 24 vaccine doses used were Rabipur vaccines with the lot number 397011A. Five patients received HRIG, which was administered 0–5 days after the start of the rabies PEP. All 6 patients developed antibody levels >0.5 IU/mL after additional vaccine doses. A seventh patient, who had received 5 vaccine doses of unknown type in Brazil, had an antibody level of 0.1 IU/mL, but the serologic testing was done only 130 days after initiation of rabies PEP.

DISCUSSION

This study analyzed a large number of patients who needed rabies PEP after potential rabies exposure under very varied circumstances similar to those seen in routine practice. Besides local residents exposed in Switzerland, there was a large

proportion of travelers who had been potentially exposed to rabies abroad. Travelers to Asia were at disproportionate risk of potential rabies exposure, with 43% of all subjects consulting for rabies PEP having visited some Asian country. The principal animals involved in potential rabies exposure were dogs, which have also been the main culprits in other studies [7, 8].

The delay between exposure and initiation of PEP was significantly shorter in subjects who were exposed at home and in travelers who sought care abroad, compared with travelers who waited to be back home before seeking care. For about half of the travelers who waited to return to Switzerland before seeking care, it took >10 days to start the rabies PEP. Considering that incubation times as short as 7 days have been described, travelers should be advised to seek care abroad in case of potential rabies exposure.

Limited availability of HRIG is a well-known problem in many resource-limited countries. In our cohort of 50 patients who sought care abroad, only 7 received HRIG. In none of these countries was HRIG administered systematically when indicated. The availability of HRIG seems to have been very patchy, even within the different countries.

In the absence of formal immunological correlates of protection, antibody levels ≥0.5 IU/mL have usually been considered as evidence of an adequate immune response. Therefore, the

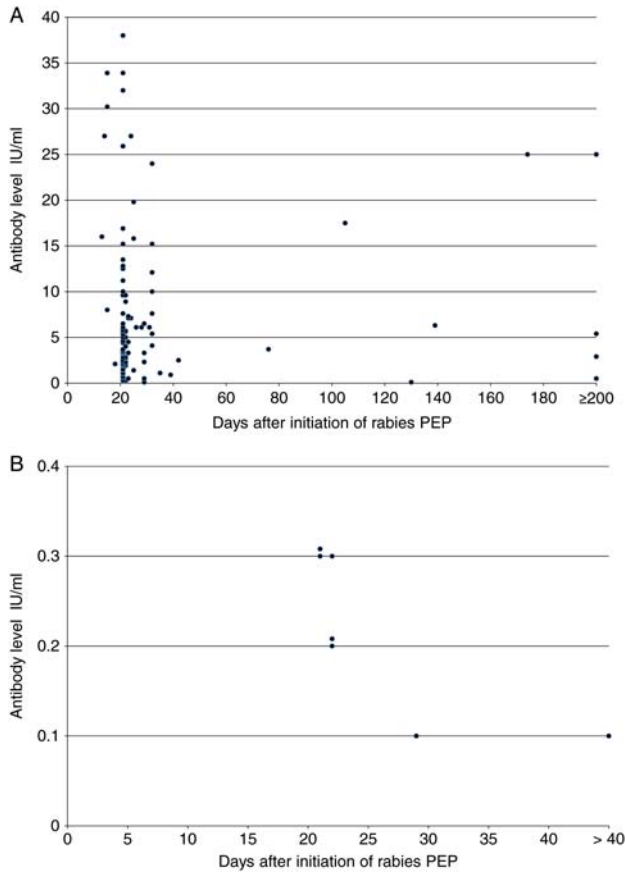


Figure 1. Anti-rabies virus antibody levels, according to time elapsed since start of rabies postexposure prophylaxis, overall (A) and for 7 patients with levels <0.5 IU/mL (B). Abbreviation: PEP, postexposure prophylaxis.

WHO and certain national agencies have recommended until recently to verify the efficacy of rabies PEP by checking the serological response, if serological testing is available. In this cohort, 6 of 90 patients (6.7%) without prior vaccination had antibody titers <0.5 IU/mL after 4 doses of rabies PEP. One additional patient had an antibody level <0.5 IU/mL after 5 vaccine doses, but the serum specimen was collected only on day 130 after the start of the rabies PEP. It could therefore be argued that the antibody level had already declined in this patient.

The antibody levels were measured by the rapid fluorescent focus inhibition test, which is the widely recommended method [5, 6]. Quality issues at the laboratory level are unlikely, as all serological tests were done at the Swiss rabies reference laboratory, where rabies antibody testing has been well established for many years and where quality control analyses are done routinely. Furthermore, because low antibody levels were observed throughout the study period rather than during a limited time, the presence of temporary technical problems was unlikely. What other explanations for the low antibody levels should be considered? First, the antibody

Table 2. Details for Patients Who Did Not Develop Appropriate Antibody Levels After Receipt of 4 Doses of Vaccine

Date	Exposure Location	PEP Initiation Location	HRIG Receipt, Day	Vaccine Received, by Dose				Serologic Test Days, Ab Titer	Ab titer After Additional Doses	
				1st	2nd	3rd	4th			
Dec 2005	India	Switzerland	Yes, D5	Rabipur, lot no. 359011C	Rabipur, lot no. 378011A	Vaccine unknown	Vaccine unknown	D0, 3, 7, 14	D21, 0.3 IU/mL	9.9 IU/mL
Aug 2007	Dominican Republic	Switzerland	Yes, D5	Rabipur, lot no. 397011A	Rabipur, lot no. 397011A	Rabipur, lot no. 397011A	Rabipur, lot no. 397011A	D0, 3, 7, 14	D22, 0.2 IU/mL	2.7 IU/mL
Sep 2007	Switzerland	Switzerland	Yes, D0	Rabipur, lot no. 397011A	Rabipur, lot no. 397011A	Rabipur, lot no. 397011A	Rabipur, lot no. 397011A	D0, 3, 8, 15	D22, 0.3 IU/mL	5.4 IU/mL
Mar 2008	Switzerland	Switzerland	Yes, D0	Rabipur, lot no. unknown	Rabipur, lot no. unknown	Rabipur, lot no. 397011A	Rabipur, lot no. 397011A	D0, 3, 7, 14	D22, 0.2 IU/mL	21.4 IU/mL
July 2009	China	China	No	Verorab, lot no. unknown	Verorab, lot no. unknown	Verorab, lot no. unknown	Verorab, lot no. unknown	D0, 3, 8, 14	D29, 0.1 IU/mL	2.6 IU/mL
Oct 2009	Italy	Italy	Yes, D4	Vaccine unknown	Rabipur, lot no. 422011A	Merieux, lot no. B0001-9	Merieux, lot no. B0001-9	D0, 4, 7, 14	D21, 0.3 IU/mL	13.5 IU/mL

Appropriate antibody levels are defined as levels ≥ 0.5 IU/mL.

Abbreviations: Ab, antibody; HRIG, human rabies immunoglobulin; PEP, postexposure prophylaxis; PrEP, preexposure prophylaxis.

titers could have been measured too late, as the serological tests were done 21–29 days after the start of the rabies PEP. The WHO criterion for adequate immunogenicity is a titer of at least 0.5 IU/mL on day 14 of the PEP. There are, however, studies that showed that anti-rabies virus antibodies are long-lived after vaccination in the vast majority of patients [9]. Second, immunosuppression could have blunted the serological response. In our cohort, no patient reported a history of immunosuppression, although it cannot be excluded that some subjects had an unrecognized immunological deficiency. Under real-life conditions, however, it is hardly realistic to expect a detailed evaluation for immunological deficiencies to be performed before administration of rabies PEP. Third, HRIG could have interfered with the development of the antibody response. None of our patients received HRIG before the start of the vaccination, and therefore a negative interaction is unlikely. In addition, 2 patients did not receive any HRIG. Fourth, the vaccines might have been of poor quality. The fact that 10 of the 24 doses administered to these patients were of the same vaccine type and from the same lot would appear to support this explanation, but Rabipur vaccine lot number 397011A was reported by the manufacturer to have an adequate potency of 6.0 IU/dose. In addition, we also observed poor serological responses with other types of vaccine, both in patients vaccinated abroad and in patients vaccinated in Switzerland.

From these data we have to conclude that some patients are at risk of inadequate antibody response after receipt of 4 doses of rabies PEP under real-life conditions. According to the data collection done by the Swiss rabies reference laboratory since 1997, about 15% of serum specimens drawn after 4 doses of rabies PEP have inadequate antibody levels (R. G. Zanoni, personal communication). Previously published studies that reported data about the immunogenicity of rabies vaccines were mostly done under strict study conditions. The largest immunogenicity study reviewed by the US National Working Group included 680 American veterinary students [10]. A total of 124 subjects received the HDCV vaccine, and the remainder received an experimental vaccine that was never commercialized. Among the other publications reviewed by the US National Working Group, there were only 3 studies done under real-life conditions, using the Essen regimen and HRIG [11–13]. Two of these studies were done in Asian populations, and these studies included a relatively small number of subjects (33 and 57 patients).

In summary, this study shows that patients do not always receive optimal rabies PEP under real-life conditions and that some patients do not develop adequate antibody levels after 4 doses. During routine practice, several factors can probably lead to the observed inappropriate antibody response, but these factors are difficult to identify and therefore avoid. These include unrecognized immunodeficiency, poor quality of vaccines,

inappropriate administration of vaccines, and other as yet unidentified factors. Therefore, we believe that the measurement of antibody levels on day 21 of the Essen rabies PEP regimen is useful in order to verify an adequate immune response, at least in settings where antibody testing is available and until more data on the protective efficacy of the 4-dose regimen on days 0, 3, 7, and 14 under real-life conditions are available. In addition, we recommend administering a fifth dose of vaccine if the antibody level is <0.5 IU/mL, although we cannot rule out that even lower antibody levels are protective.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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