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Rabies post-exposure prophylaxis in the emergency department: A monocentric retrospective observational study

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ABSTRACT

Background: Emergency departments (ED) are frequently visited after suspected rabies exposure (SRE) and the potential need for rabies post-exposure prophylaxis (R-PEP). However, data on the number of visits, patients' demographics, travel history and the medical treatment is still rare. Therefore, the aim of this study was to assess the number of R-PEP and the appropriateness of medical management including wound treatment, vaccination regime and immunoglobulin application following SRE in a university hospital ED.

Method: We conducted a monocentric retrospective observational study on emergency patients treated in the ED of the LMU University Hospital, Ludwig-Maximilians-University Munich, Germany, between June 1st, 2023 and January 31st, 2024. Patients requiring post-exposure prophylaxis due to SRE abroad or in Germany were included. Demographic data, travel history, clinical findings, wound treatment, and R-PEP vaccination regimen were recorded.

Results: During the observation period of 245 days 43 patients presented to our ED for R-PEP. There was a total of 51 presentation appointments, as 5 patients returned for further treatment. Most patients (27, 52.9 %) presented at the ED on a Saturday, Sunday, or a public holiday. 17 (39.5 %) patients had a category II exposure, and 26 (60.5 %) had a category III exposure. In our ED, there were 28 (55.0 %) active vaccinations and 23 (45.0 %) both active and passive vaccinations.

Conclusions: Our data show that patients frequently present for R-PEP in ED. Therefore, there is a high need for education on indication for R-PEP and for implementation of precise R-PEP treatment guidelines in daily clinical practice.

1. Introduction

Human rabies is a fatal viral disease caused by lyssaviruses of the family Rhabdoviridae leading to an acute progressive encephalitis. Rabies is still widely spread across the globe and is responsible for up to 60,000 human deaths each year [1]. Today, most cases occur in Asia and Africa whereas rabies cases in Europe are rare. In Germany the last endemic rabies case was seen in a fox in 2006 and Germany is officially declared free of terrestrial rabies since 2008 [2,3]. However, re-emergences of rabies in Italy and Greece in the last decades underline the high need of awareness and knowledge of appropriate R-PEP implementation. Moreover, a recent review reported on 122 breakthrough infections although R-PEP has been started after suspected exposure highlighting the persistent importance of medical education regarding human rabies and correct management of potential rabies exposures [4]. In this context, Gautret et al. reported on up to 157 suspected rabies exposures (SRE) per 1000 travellers per month leading to frequent consultations for R-PEP, especially in emergency departments (ED) [5]. Failures with R-PEP can occur if it is not performed in a timely and complete way [6]. Several studies have reported that deviations from R-PEP treatment guidelines occur in up to 8 % of cases and up to 13 % never complete the initiated vaccination series [7,8].

For this reason, detailed instructions and workflows are highly necessary to help ensure that appropriate treatment is performed in the ED. Adequate rabies post-exposure treatment consists of thorough wound treatment, correct vaccination following implemented R-PEP regimes and passive immunization by administration of rabies immunoglobulin (RIG). According to the Robert Koch Institute (RKI) guidelines the rabies post-exposure vaccination is recommended after SRE

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Abbreviations

ED	Emergency departments
ESI	Emergency Severity Index
R-PEP	Rabies post-exposure prophylaxis
RIG	rabies immunoglobulin
RKI	Robert Koch Institute
SRE	Suspected rabies exposure
WHO	World Health Organization

defined as a bite, scratch or licking of a wound or mucous membrane by a mammal. Although potentially all mammals can serve as a source, there is a clear preponderance for carnivores and bats. In some cases, individual decision may need to be made. Non-immunized persons immediate should receive intramuscular vaccination either according to the *Essen regimen* on days 0-3-7-14-28 or the *Zagreb regimen* on days 0-0-7-21. Rabies immunoglobin should be administered to provide passive immunity in a recommended dose of 20 IU/kg body weight with as much dose as possible closely around the wound as soon as possible, latest within seven days. The rest should be administered intramuscularly at a distant site from the vaccine, preferably in the vastus lateralis muscle. The R-PEP process is the same for both adult and paediatric patients [9]. Data on the R-PEP of international travelers in two major German travel clinics were recently described [10].

Currently, there is only limited literature reporting on the administration of R-PEP in ED although there seems to be a high need of awareness and knowledge regarding this rare but fatal disease. Therefore, the aim of our study was to characterize demographic data, the vaccination regimen and the wound treatment of all patients receiving R-PEP in the ED of a university hospital in Germany.

2. Material and methods

2.1. Characteristics of patients presenting for rabies post-exposure prophylaxis in the emergency department

We conducted a monocentric retrospective observational study on emergency patients treated in the ED of the LMU University Hospital, Ludwig-Maximilians-University Munich, Germany, located in the city center between June 1st' 2023 and January 31st' 2024. Patients requiring R-PEP due to SRE abroad or in Germany were included. Patients who had no indication for R-PEP (category I) were not included. The initial assessment in the ED was performed using the Emergency Severity Index (ESI), a five-level triage algorithm that assesses the urgency of treatment based on the severity of the illness an anticipated resource need. The lower the assigned level, the higher the urgency of treatment [11,12]. The data were extracted from the clinical information system and analysed anonymously.

2.2. Definitions and treatment guidelines

According to the World Health Organization (WHO) and Robert Koch Institute (RKI), SRE was defined as a bite, scratch or licking of a wound or mucous membrane by a mammal [7,9]. Indication for R-PEP was evaluated using the RKI recommendations. According to the German RKI recommendations, R-PEP is completed after a series of at least three vaccine doses administered in the appropriate interval [9]. If an indicated administration of rabies immunoglobin (RIG) was missed at first vaccination, it can still be given until 7 days after the first dose of rabies vaccine according to the German recommendation [9,10].

2.3. Administration of the rabies post-exposure prophylaxis

The R-PEP is usually carried out by surgical doctors at specialist level who work in the ED. If necessary, a senior surgical consultant can be involved. Internal medicine junior doctors at specialist level are also present in the ED and can be involved as needed. Infectious disease specialists are available either on-site or on-call for specific questions. We have a hospital-wide SOP for the administration of R-PEP, which is based on the RKI guidelines. Additionally, we regularly conduct training sessions on rabies disease.

2.4. Ethics

The study was approved by the Ethics Committee of Ludwig-Maximilians-Universität München (LMU). Procedures were performed in accordance with ethical standards (institutional and national) for human experimentation and the 1975 Helsinki Declaration.

2.5. Statistical analysis

Median and interquartile ranges (IQR) and mean and standard deviation (SD) were calculated for continuous data and counts and percentages were used for categorical data.

3. Results

3.1. Characteristics of patients presenting for rabies post-exposure prophylaxis in the emergency department

Over the 245-day observation period, 43 patients presented to our ED for R-PEP. There was a total of 51 presentation appointments, as 5 patients returned for further treatment. Among them, 2 patients revisited once, one patient revisited twice, and one patient revisited four times. Of the total, 23 (53.5 %) patients were female, and 20 (46.5 %) were male. The median age was 29.5 years (IQR 14.0–39.5 years). 7 (16.3 %) patients were between 0 and 9 years old, 2 (4.6 %) between 10 and 17 years, 15 (34.9 %) between 18 and 30, 10 (23.2 %) between 31 and 45, and 9 (21.0 %) patients between 46 and 60 years old. Patients over 60 years of age did not present. Most patients (41, 95.3 %) had their residence in Germany, while 2 (4.7 %) patients resided in the USA. There were no presentations from patients residing in other countries

Table 1
Characteristics of patients presenting for rabies post-exposure porphylaxis in the emergency department.

	n	%
No. of cases	51	
Follow-up presentations	8	
Patients with follow-up	5	
One-time follow-up	2	
Two-time follow-up	1	
Three-time follow-up	0	
Four-time follow-up	1	
Patients	43	
Gender (n = 43)		
female	23	53.5
male	20	46.5
Age in years (n = 43)		
Median (IQR)	29.5 (14.0–39.5)	
0-9	7	16.3
10-17	2	4.6
18-30	15	34.9
31-45	10	23.2
46-60	9	21.0
>60	0	0
Region of residence (n = 43)		
Germany	41	95.3
USA	2	4.7
Other	0	0

(Table 1).

3.2. Circumstances of patient presentation for rabies post-exposure prophylaxis in the emergency department

49 (96.1 %) presentations occurred as self-referrals to the ED. Only 2 (3.9 %) presentations were made via emergency medical services, which were transfers from an external clinic. In the initial triage assessment using the Emergency Severity Index (ESI), 8 (15.7 %) patients were assigned level 3, 34 (66.7 %) level 4, and 9 (17.6 %) level 5. Most patients presented on Saturday (13, 25.5 %), followed by Sunday (12, 23.6 %). On Monday, 5 (9.8 %) patients presented, 6 (11.8 %) on Tuesday, 2 (3.9 %) on Wednesday, 9 (17.6 %) on Thursday, and 4 (7.8 %) on Friday. Most patients (27, 52.9 %) presented at the ED on a Saturday, Sunday, or a public holiday. 17 (33.3 %) patients presented between 8 a.m. and 4 p.m., 28 (54.9 %) patients between 4 p.m. and 12 a.m., and 6 (11.6 %) patients between 12 a.m. and 8 a.m. The mean duration of treatment time was 2.77 ± 1.98 h. The mean waiting time until medical treatment after initial assessment was 1.07 ± 1.27 h. For further treatment after the initial presentation in the ED, 45 (88.2 %) of the cases were recommended to follow up with their primary care physician or paediatrician. Only 1 (2.0 %) patient was advised to return to our ED for a follow-up. The treatment for 5 (9.8 %) patients was concluded after their presentation in our ED (Table 2).

3.3. Characteristics of suspected rabies exposure

28 (65.1 %) study participants reported being bitten, 12 (28.0 %) reported being scratched, and 3 (6.9 %) reported being licked on an open wound or mucous membrane. After medical examination, 17 (39.5 %) patients had a category II exposure, and 26 (60.5 %) had a category III exposure. Two of the bites reported in the medical history were downgraded to category II. The most common risk contact occurred in Germany (23, 53.5 %). In 5 (11.6 %) patients, the contact occurred in Turkey, in 3 (7.0 %) patients in Albania, and in 2 (4.7 %) each in Bulgaria, Italy, and Thailand. One (2.3 %) risk contact each occurred in Bali, Bosnia, Colombia, Georgia, India, and Romania. The most common contact was with dogs (25, 58.2 %), followed by bats (7, 16.3 %) and cats (7, 16.3 %). 2 (4.6 %) patients had a risk contact with horses, and 2 (4.6 %) with monkeys. Contacts with bats were assigned to category III according to the guidelines. The horse contact occurred in 2 female siblings. In one of the siblings, there was contact with the horse's blood on a wound on the hand, and in the other, there was blood contact on the oral mucosa and eyes. The contact occurred in Germany. The horse had to be euthanized due to behavioural issues. One monkey bite occurred in Thailand, and the other in Bali. 19 (44.2 %) patients presented to our ED within 24 h after the risk contact. 18 (41.9 %) patients presented after one day but still within one week. 3 (7.0 %) patients presented within two weeks, 2 (4.6 %) patients within three weeks, and 1 (2.3 %) patient within four weeks. Most risk contacts occurred through exposure to the hand (23, 53.5 %), followed by the lower leg (10, 23.2 %) and arm (3, 7.0 %). 2 (4.7 %) risk contacts occurred at the thigh and 1 (2.3 %) at the foot. 4 (9.3 %) contacts occurred at another body location. For 3 (7.0 %) patients, a more extensive surgical wound care was necessary. In 2 cases, the risk contact occurred abroad (Albania/Romania), and the surgical care was already provided there. 1 patient required extensive surgical treatment in our ED following a dog bite on the hand (Table 3).

Table 2
Circumstances of patient presentation for rabies post-exposure prophylaxis in the emergency department.

	n	%
Presentation pathway (n = 51)		
Self-presentation	49	96.1
Admission by emergency medical service	2	3.9
ESI triage level (n = 51)		
1	0	0
2	0	0
3	8	15.7
4	34	66.7
5	9	17.6
Day of the week at presentation (n = 51)		
Monday	5	9.8
Tuesday	6	11.8
Wednesday	2	3.9
Thursday	9	17,6
Friday		7.8
Saturday	13	25.5
Sunday	12	23.6
Presentation on Saturdays, Sundays, and public holidays	27	52.9
Time of presentation in the emergency department (n = 51)		
8:00 a.m.–4:00 p.m.	17	33.3
4:00 p.m.–12:00 a.m.	28	54.9
12:00 a.m.–8:00 a.m.	6	11.8
Total duration of treatment in the emergency department (hours) (n = 51)		
Mean (SD)	2.77 ± 1.98	
Waiting time until medical treatment after initial assessment (hours) (n = 51)		
Mean (SD)	1.07 ± 1.27	
Recommendation for further treatment after the (n = 51) emergency department		
General practitioner/Pediatrician	45	88.2
In our emergency department	1	2.0
Treatment completed	5	9.8

3.4. Treatment after suspected rabies exposure

Of the 43 patients who presented to our ED for R-PEP, 33 (76.7 %) had not received R-PEP before. 10 (23.3 %) patients had already received R-PEP, with 9 (90.0 %) of them abroad and 1 (10.0 %) in

Table 3
Characteristics of suspected rabies exposure.

	n	%
Exposure (n = 43)		
Bitten	28	65.1
Scratched	12	28.0
Licked	3	6.9
Country exposure (n = 43)		
Germany	23	53.5
Turkey	5	11.6
Albania	3	7.0
Bulgaria	2	4.7
Italy	2	4.7
Thailand	2	4.7
Bali	1	2.3
Bosnia	1	2.3
Colombia	1	2.3
Georgia	1	2.3
India	1	2.3
Romania	1	2.3
Bitten, scratched or licked by (n = 43)		
Dog	25	58.2
Bat	7	16.3
Cat	7	16.3
Horse	2	4.6
Monkey	2	4.6
Time point of exposure (n = 43)		
< 1 day	19	44.2
> 1 day, <1 week	18	41.9
< 2 weeks	3	7.0
< 3 weeks	2	4.6
< 4 weeks	1	2.3
Body location of exposure (n = 43)		
Hand	23	53.5
Lower leg	10	23.2
Arm	3	7.0
Thigh	2	4.7
Foot	1	2.3
Other	4	9.3
Category of exposure (n = 43)		
Category II	17	39.5
Category III	26	60.5
Need for more extensive surgical wound care (n = 43)	3	7.0 %

Germany. Among these 10 patients, 7 (70.0 %) received only active vaccination, and 3 (30.0 %) received both active and passive vaccination. Of these, 9 (90.0 %) patients received the first vaccination within a week after the risk contact, and 1 (10.0 %) patient before the end of the 4th week. In total, 39 (90.7 %) patients were treated with the Essen regimen, and 4 (9.3 %) with the Zagreb regimen. As some patients presented again to our ED for further treatment, there were more patient contacts (51) than the total number of patients. In our ED, there were thus 28 (55.0 %) active vaccinations and 23 (45.0 %) both active and passive vaccinations. There was no evidence of immunosuppression in any of the patients (Table 4).

4. Discussion

Our results could demonstrate that there was a high number of patients presenting in our ED with SRE and the need for post-exposure prophylaxis within a very short period. The number of R-PEP consultations corresponds to one patient visit every five days due to R-PEP.

Human rabies remains a public health concern with a relatively high number of rabies caused deaths worldwide [2]. Especially in many low- and middle-income countries rabies is maintained and still spread, as R-PEP is relatively expensive leading to limited availability and delayed access in these countries [13,14]. It is primarily caused by infected dogs in rabies-endemic regions and only a smaller proportion is due to transmission through bats, foxes, cats, or monkeys [15]. Therefore, one of the main strategies of rabies control is ensuring high vaccination coverage in the dog and fox population successfully performed in Germany with the last endemic rabies case seen in a fox in 2006. In 2008 Germany was officially declared as free from terrestrial rabies [16]. As for native animals, today only bats are a reservoir for European bat lyssaviruses (EBLV-1 and EBLV-2) in Germany. However, previous studies documented that potentially rabies-transmitting animal contacts in travellers are high with up to 4 % per month of stay [10,17–19]. However, animals that are brought in through refugee movements, such as from Ukraine, or generally imported, must also be considered as potential sources of infection. Furthermore, a study of GeoSentinel clinics reported a four times increased number of R-PEP between 2003 and 2012 indicating that there was either a higher number of travels to rabies-endemic countries or a higher number of reported incidents [20].

The most effective strategy to prevent rabies after SRE is the timely and appropriate administration of R-PEP in cases of a potentially rabies-transmitting animal contact. Hampson et al. estimated three million people worldwide would die every year from rabies without R-PEP [2]. However, preventive measures through vaccination can also be implemented before traveling to rabies-endemic areas. Therefore, before traveling to high-risk areas, travelers should seek appropriate vaccination advice to determine if a protective vaccination is necessary.

Considering these facts on the one hand and the nearly 100 % case fatality of human rabies infection on the other, it becomes evident that physicians working in ED must be well informed and educated in the field of R-PEP [21].

When analysing our data, 43 patients consulted our ED for R-PEP. Compared to the only other German study reporting on R-PEP in ED there were a 5-fold higher number of visits per month in our clinic [22]. This high number of patients might be due to several factors. The Emergency Department of the LMU University Hospital is located centrally and Munich airport is one of the most important central airports in Germany with a passenger volume of about 37 million people per year [23].

Furthermore, most patients presented at the ED on a Saturday, Sunday, or a public holiday which means outside the opening times of for example specialized travel clinics. In this context, Saffar and colleagues reported on R-PEP visits in two German travel clinics (Munich and Hamburg) including 75 patients over a period of 16 months with 31 patients included in Munich [10]. Compared to these data, the number of visits due to R-PEP in our ED was relatively high irrespective of the availability of a specialized travel clinic in Munich. However, in the study by Saffar et al., only residents who had an indication for R-PEP due to a risk contact abroad were included. In our study, we also included patients who had a risk contact domestically.

In our opinion, these findings underline the need for well-educated physicians and standard treatment algorithms in the ED as our data could demonstrate that exposed patients frequently visit the ED first for advice and treatment.

When analysing all R-PEP visits within 245 days, half of the patients had their exposure in Germany whereas the other half were travellers from several countries, mainly Europe and Asia. Only one fourth of the exposed travellers had already received R-PEP, with 9 (90.0 %) of them abroad and 1 (10.0 %) in Germany when consulting our ED. Among these 10 patients, only 3 (30.0 %) received both active and passive vaccination simultaneously. This finding is in line with previous observations of only 4%–25 % of international travellers receiving RIG in the country of exposure when indicated [7,10,20,24]. This is most likely since RIG might not be widely available or accessible abroad [7,25].

The study by Meyerhoff et al. has shown that even in Germany, within the scope of emergency care, in half of the cases, R-PEP was not performed according to guidelines. In some cases, the indication was incorrectly established. In some cases, R-PEP was not correctly administered, or the vaccination schedule was not followed correctly [22]. Findings from this evaluation have important implications for R-PEP practice. First, the vaccination completion rate is much lower than expected in a country of high-standard health care. This indicates the need for a national surveillance system following two variables: initiation of R-PEP and vaccine completion rates. Second, refresher trainings of health care providers distributing R-PEP should be regularly performed to keep a consistent standard of care. Third, before traveling abroad international travellers should receive rabies risk assessment, seek advice for travel vaccination and be educated by health-care practitioners about avoiding contact with animals and behaviour after animal bites. Meanwhile we should strengthen communication on rabies knowledge, vaccination schedule, R-PEP guidelines and make sure that the guidelines are followed correctly. In particular, there should be increased education by health authorities on how to handle bats. Bats should never be touched without gloves or similar protective measures. This could prevent most of these incidents and the subsequent costly and complex R-PEP following bat contact.

A particular concern with monkey bites, which medical doctors should be aware of, is the indication for antiviral prophylaxis against Herpes-B-virus infection, in addition to R-PEP. There is a significant risk of herpes encephalomyelitis in these cases. The recommended antiviral prophylaxis consists of administering valaciclovir 1g orally three times a

Table 4
Treatment after suspected rabies exposure.

	n	%
PEP already received before presentation to the ED (n = 43)		
No	33	76.7
Yes	10	23.3
Only active vaccination	7	70.0
Only passive vaccination	0	0.0
Active and passive vaccination	3	30.0
Location of PEP administration (n = 10)		
Abroad	9	90.0
Domestic	1	10.0
Time period between PEP and presentation to ED (n = 10)		
< 1 week	9	90.0
< 4 weeks	1	10.0
PEP administered in the ED (n = 51)		
Only active vaccination	28	55.0
Only passive vaccination	0	0.0
Active and passive vaccination	23	45.0
PEP regimen (n = 43)		
Essen	39	90.7
Zagreb	4	9.3

day for a total of 14 days. Additionally, blood samples should be collected and tested if the patient develops symptoms. For such specialized issues, it may be necessary to consult an infectious disease specialist who is also experienced in travel medicine. This expertise may not be available in every ED. Therefore, university hospital ED play a crucial role, as they typically have the necessary personnel and resources.

Our study is a retrospective single centre study and therefore our results cannot be easily transferred. Furthermore, the number of patients that were not qualified for R-PEP was not available in our study and therefore these data could not be analysed.

5. Conclusions

Despite rabies elimination in Germany patients frequently present for advice concerning R-PEP in ED. Following our results there is a high need for education on indication and management regarding R-PEP during and after travel and for implementation of precise R-PEP guidelines in daily clinical practice to ensure medical correct treatment for each exposed patient. Our findings suggest that continuing education is needed for both medical doctors and patients, as adherence to R-PEP guidelines is the most beneficial way to reduce infection rates.

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CRediT authorship contribution statement

Mareen Braunstein: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Data curation, Conceptualization. **Markus Wörnle:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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