



## Addressing the Most Common Reasons for Patient Refusal of Lifesaving Rabies PEP Treatment

Patient refusal of treatment is the most common reason for not administering human rabies immunoglobulin (HRIG) when it is appropriate and reasonable for disease prevention. Here we address the three primary reasons for patient refusal: fear of needles, concerns about plasma-based therapies, and insurance coverage or cost worries.<sup>1</sup>

### Patient refusal based on fears or concerns about:



*Needles*



*Plasma-based therapies*



*Insurance coverage/costs*



### *Needles*

When it comes to rabies, fear of needles can be deadly.<sup>2</sup> During a rabies outbreak in Bali, Indonesia (2008-2011), two patients died because of their refusal of treatment due to fear of needles, according to ProMED, the Program for Monitoring Emerging Diseases. In the first case, a man was bitten by a stray dog in the outbreak area—a clear indication for postexposure prophylaxis (PEP). He received one rabies shot but declined the rest of the postexposure series because of his fear of needles. In the second case, a woman was bitten by both a stray dog and a pet dog, again clear indications of the need for postexposure treatment. However, she also refused treatment because of a fear of needles. Two completely preventable deaths resulted. The decision to forgo treatment because of fear of needles almost certainly cost these people their lives: rabies is preventable with appropriate and timely postexposure treatment.

Contributing to this fear of needles is the misperception that rabies PEP requires multiple painful intra-abdominal injections over a 1-month period. In fact, PEP requires *intramuscular* injections of rabies vaccine plus injection of HRIG into and around the wound area, followed by a series of vaccine doses that depend on previous vaccination history. (Patients who were previously vaccinated require only one more vaccine dose; patients who were never previously vaccinated require three more vaccine doses for a total of 4.) For immunocompromised patients, an additional fifth vaccine dose is recommended.<sup>3</sup> With the availability of a higher concentration HRIG, there is now potential for fewer injections in the delivery of the full HRIG dose.<sup>4</sup>

**For patients who show a fear of needles, it is important to correct any misperceptions they may have and help them understand the risks of refusing PEP care.**



### *Plasma-based Therapies*

The anti-vaccine movement is founded on the widely debunked belief that ingredients contained in vaccines are harmful and linked to development of neurodevelopmental disorders such as autism in children. While all medicines embody risk—which should be appropriately communicated to patients—understanding how medicines are made and the safety protocols and procedures in place might help some patients balance these risks with the benefits.

In the case of HRIG, for example, patients may have concerns related to the plasma-based nature of these products and the overall viral safety. Versions of HRIG used before the 1970s were manufactured using horse serum to produce equine RIG. Purified versions as well as the development and availability of HRIG preparations produced using human plasma improved safety over the years.<sup>5</sup> To make HRIG, healthy human donors are professionally immunized with the vaccine against rabies; their plasma is then collected and purified to make the immunoglobulin (see figure).<sup>6</sup>

### HRIG Manufacturing



*Donor vaccination*



*Plasma donation*



*Plasma*



*Purification*

Epidemiological controls of the donor population and selection of individual donors based on medical screening are also utilized to reduce risk of transmission of pathogens.<sup>4</sup>

HRIG is manufactured using a sophisticated process that significantly reduces product impurities and is subject to the highest quality and safety standards.<sup>4,7</sup> It is a lengthy and complex process that takes up to 12 months from the time of donation until ready for use.<sup>8</sup> Grifols—the maker of HyperRAB<sup>®</sup> (rabies immune globulin [human])—provides a step-by-step overview of the manufacturing process employed in the development of their plasma medicines that is available at <https://www.grifols.com/en/plasma-journey#>. These steps include plasma collection, testing, manufacturing, and formulation before the final product is available to patients.<sup>8</sup>

The manufacturing process incorporates steps with the capacity to inactivate and remove pathogens if present in the starting material. These complex processes incorporate advanced technologies and employ multiple purification and safety steps that contribute to the product's overall quality.<sup>9</sup>

**For patients who exhibit concern about vaccines and plasma-derived products, it is important to reassure them that processes and protocols are in place to maximize safety.**

Plasma-derived products carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk. This also applies to unknown or emerging viruses and other pathogens.

**Please see Important Safety Information at the end of this article and accompanying full Prescribing Information for HyperRAB<sup>®</sup> (rabies immune globulin [human]).**



### *Insurance Coverage and Costs*

Patients have also expressed concerns about insurance coverage and the costs of PEP. These worries may be based on news stories about uninsured individuals who have received unexpectedly high hospital bills following emergency department (ED) care, treatment, and consultation.<sup>10</sup> Articles and studies have shown discrepancies in ED charges that are so great that patients feel they have no way of knowing how much they can expect to be billed, a somewhat rational fear.<sup>11</sup>

Cost of ED care varies not only across the US depending on region, but also across medical conditions.<sup>11</sup> For example, there is an almost 5-fold variation in charges among the top 10 health conditions that present to the ED, from ~\$700 for an upper respiratory infection to ~\$3500 for a kidney stone.<sup>11\*</sup> Factors such as facility fees, the need for multiple visits, and the need for various consults (eg, plastic surgery) can play a role in ED cost variation. According to the CDC, the cost of rabies PEP treatment—a course of HRIG and four doses of vaccine given over a two-week period—is on the upper end of this cost scale at approximately \$3000.<sup>12</sup>

\*Based on over 8,000 ED encounters across the US, representing more than 76 million visits.

Most insurance plans cover emergency PEP rabies treatment, and some plans with preventive benefits may even cover travel-related vaccinations that are deemed elective.

**For patients who do not have insurance, do not qualify for Medicaid or Medicare, and whose financial resources are strained, assistance programs may be available; see the CDC website at [https://www.cdc.gov/rabies/medical\\_care/programs.html](https://www.cdc.gov/rabies/medical_care/programs.html) or contact the manufacturers of HRIG and rabies vaccine before administering the product to determine if assistance is available.**

**In some states, like New York, Florida, and Texas, state and county health departments help patients regarding costs and may give product to patients at cost or supplement part of the bill that's not covered by insurance.<sup>13</sup>**

## REFERENCES

1. Data on file, ATU Report, Grifols. **2.** Weese S. Fatal needle phobia: Rabies in Bali. Worms & Germs Blog. University of Guelph. <https://www.wormsandgermsblog.com/2009/04/articles/diseases/rabies/fatal-needle-phobia-rabies-in-bali/>. Published April 2, 2009. Accessed May 17, 2019. **3.** Rupprecht CE, Briggs D, Brown C, et al. Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies: Recommendations of the Advisory Committee on Immunization Practices [published correction appears in *MMWR Recomm Rep*. 2010 Apr 30;59(16):493]. *MMWR Recomm Rep*. 2010 Mar 19;59(RR02):1-9. **4.** Grifols. <https://www.grifols.com/en/plasma-journey#>. Accessed May 1, 2019. **5.** World Health Organization. Other rabies biological products. [https://www.who.int/rabies/resources/other\\_rabies\\_biolog\\_product/en/](https://www.who.int/rabies/resources/other_rabies_biolog_product/en/). Accessed April 20, 2019. **6.** Scott D. *Scientific Basis for Approval of Human Rabies Immune Globulin in Combination with Rabies Vaccine*. Silver Spring, MD: Center for Biologics Evaluation and Research, US Food and Drug Administration, US Dept of Health and Human Services; 2017. <https://www.fda.gov/media/106255/download>. Accessed April 20, 2019. **7.** HyperRAB® (rabies immune globulin [human]) Prescribing Information. Grifols. **8.** Kedrab Prescribing Information. Kedrion Biopharma Inc. **9.** Farrugia A, Cassar J. Plasma-derived medicines: access and usage issues. *Blood Transfus*. 2012;10(3):273–278. **10.** Kliff S. Why a simple, lifesaving rabies shot can cost \$10,000 in America. *Vox*. <https://www.vox.com/policy-and-politics/2018/2/7/16851134/rabies-treatment-expensive-emergency-room>. Published February 7, 2018. Accessed May 17, 2019. **11.** Caldwell N, Srebotnjak T, Wang T, Hsia R. “How much will I get charged for this?” Patient charges for top ten diagnoses in the emergency department. *PLoS One*. 2013;8(2):e55491. **12.** Centers for Disease Control and Prevention. Cost of Rabies Prevention. <https://www.cdc.gov/rabies/location/usa/cost.html>. Updated August 3, 2015. Accessed April 19, 2019. **13.** Goodman B, Miller A. The High Cost of Surviving Rabies. *WebMD*. <https://www.webmd.com/a-to-z-guides/news/20180220/the-high-cost-of-surviving-rabies>. Published February 20, 2018. Accessed May 17, 2019.

## ***Indication and Usage***

HYPERRAB® (rabies immune globulin [human]) is indicated for postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies.

### Limitations of Use

Persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine.

For unvaccinated persons, the combination of HYPERRAB and vaccine is recommended for both bite and nonbite exposures regardless of the time interval between exposure and initiation of postexposure prophylaxis.

Beyond 7 days (after the first vaccine dose), HYPERRAB is not indicated since an antibody response to vaccine is presumed to have occurred.

## ***Important Safety Information***

### **For infiltration and intramuscular use only.**

Severe hypersensitivity reactions may occur with HYPERRAB. Patients with a history of prior systemic allergic reactions to human immunoglobulin preparations are at a greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available for treatment of acute allergic symptoms, should they occur.

HYPERRAB is made from human blood and may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

The most common adverse reactions in >5% of subjects during clinical trials were injection-site pain, headache, injection-site nodule, abdominal pain, diarrhea, flatulence, nasal congestion, and oropharyngeal pain.

Do not administer repeated doses of HYPERRAB once vaccine treatment has been initiated as this could prevent the full expression of active immunity expected from the rabies vaccine.

Other antibodies in the HYPERRAB preparation may interfere with the response to live vaccines such as measles, mumps, polio, or rubella. Defer immunization with live vaccines for 4 months after HYPERRAB administration.

**Please see accompanying full Prescribing Information for HYPERRAB.  
You are encouraged to report negative side effects of prescription drugs to the  
FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088.**