



# RABIES WATCH

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## Addressing Challenges to Administration of Human Rabies Immune Globulin

US clinicians whose responsibilities include rabies management know that current approaches to using rabies vaccines and human rabies immune globulin (HRIG) have been broadly successful in reducing the burden of this disease.<sup>1</sup> However, human cases do occur, including situations in which rabies postexposure prophylaxis (PEP) with rabies vaccine and HRIG was incompletely or incorrectly administered.<sup>1</sup> Therefore, these clinicians may wonder whether any recent technical advances in science and clinical practice may help to further improve PEP administration for patients who were not previously vaccinated against rabies.

As a starting point in this discussion, it is important to recall that researchers and clinicians agree on the goal for HRIG administration in PEP regimens: to deliver the optimal amount of exogenous rabies virus-specific antibodies into wound sites soon after a potential rabies virus exposure and neutralize rabies virions before they reach and enter nerve cells.<sup>2-4</sup> This form of immediate passive immunity forestalls the development of infection through the period during which a patient's own immune system responds to rabies vaccination by actively producing endogenous antibodies to neutralize the virus.<sup>2,4</sup>

*“There is a dose-response effect with HRIG administration into and around the wound. If the dose is too low, the HRIG concentration is inadequate to prevent rabies virus infection and death may result. But, if the volume of the HRIG infusion required to deliver an effective dose is too large for the specific wound area, such as a finger, the patient may be at risk of compartment syndrome.”—Charles E. Rupprecht, VMD, MS, PhD*



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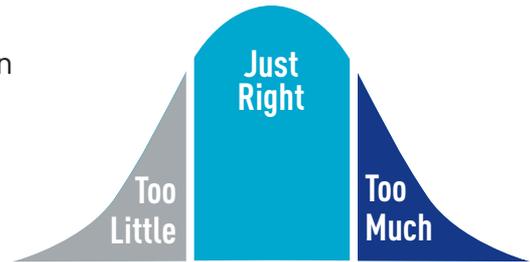
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A key challenge for clinicians is achieving optimal delivery of HRIG through correct administration of the appropriate dose.<sup>4</sup> That is, to deliver an HRIG dose and volume of infusion in the right range—not too little and not too much—into and around the wound area. This can be a challenge because each patient’s presentation may be different with respect to exposure to different potentially rabid animals, location/ extent of wounds, and the patient’s age and body size.

As noted in various guidelines, administration of HRIG at a dose that is too low will likely not be sufficient to neutralize all rabies virions present and block virus invasion.<sup>4</sup> Conversely, administration of HRIG at a dose above the recommended dose poses 2 potential risks: Excessive levels of exogenous HRIG may partially suppress the active immune response to vaccination and consequent production of endogenous antirabies antibodies<sup>1</sup>; and, administration of an excessive volume of HRIG in relation to a small-volume wound puts the patient at risk for development of compartment syndrome, with compromised blood flow into the affected area.<sup>4</sup> Compartment syndrome may develop when blood and related fluids become trapped within a closed space, such as hand or foot. As the pressure of fluid trapped within the tissue increases, normal arterial blood flow is substantially reduced, which prevents excess fluid from perfusing out of the space. At this point, loss of normal oxygenation of the affected tissue increases the risk of ischemia and may require surgical intervention to dissipate the excess fluid load.<sup>5</sup>



Given the need to find the right HRIG dose and volume between the extremes, clinicians would be well advised to “First, do no harm” and “Use your best judgement for individual patients.” The first challenge is to calculate the patient’s dose. The maximum HRIG dose should be calculated at 20 IU/kg lean body mass with adjustment for obese patients.<sup>2</sup> The total volume to be infused will be determined on the basis of the calculated dose and the concentration of antibodies within the HRIG solution.

*“What I tell emergency department people who administer HRIG is, ‘Do the best you can’. That’s the mantra. Do the right thing without causing harm in the process.”*

*—Stephen J. Scholand, MD*

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The next challenge is to plan how to infiltrate the wound site(s) and deliver the full dose based on an evaluation of the individual patient's wounds. Ideally, the full HRIG dose would be administered directly into and around the wound for maximal effect.<sup>2</sup> Each wound may be different with respect to type of animal exposure and location/extent of the wound and associated potential introduction of rabies virus.<sup>1,4</sup> For example, dog bites typically involve large and potentially gaping wounds, whereas cat bites are typically smaller puncture wounds. Bat exposures are smaller still, involving bites or scratches that may not even be evident to the patient.<sup>1,4</sup> Exposures may occur at small body areas on the face, neck, or fingers, or at larger body areas, such as arms, legs, or feet. Exposures at small body sites that are highly innervated with numerous peripheral nerve endings increase the risk of rabies virus entry into the nerves and consequently are areas of particular concern for HRIG administration.<sup>1,4</sup>

Clinicians must successfully address these critical challenges when planning to administer HRIG across the continuum of possible scenarios of the patient's body size and HRIG dose/volume in relation to the size of the wound area.

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### ***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 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.**



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All quotations in this article were provided by Charles E. Rupprecht, VMD, MS, PhD, and Stephen J. Scholand, MD, in personal interviews.

## REFERENCES

**1.** Manning SE, Rupprecht CE, Fishbein D, et al; Advisory Committee on Immunization Practices Centers for Disease Control and Prevention (CDC). Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2008;57(RR-3):1-28. **2.** Rupprecht CE, Briggs D, Brown CM, et al; Centers for Disease Control and Prevention (CDC). Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2010;59(RR-2):1-9. **3.** World Health Organization. Summary of the October 2017 meeting of the Strategic Advisory Group of Experts on Immunization. [http://www.who.int/immunization/policy/sage/SAGE\\_oct\\_2017\\_meeting\\_summary.pdf?ua=1](http://www.who.int/immunization/policy/sage/SAGE_oct_2017_meeting_summary.pdf?ua=1). Accessed January 16, 2018. **4.** World Health Organization. Background paper: proposed revision of the policy on rabies vaccines and rabies immunoglobulins. [http://www.who.int/immunization/sage/meetings/2017/october/1\\_Background\\_paper\\_WG\\_RABIES\\_final.pdf](http://www.who.int/immunization/sage/meetings/2017/october/1_Background_paper_WG_RABIES_final.pdf). September 22, 2017. Accessed January 16, 2018. **5.** Taber's Medical Dictionary. <https://www.tabers.com/tabersonline/view/Tabers-Dictionary/735826/all/compartments%20syndrome>. Accessed February 21, 2018.

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