

Rabies immune globulin and next steps

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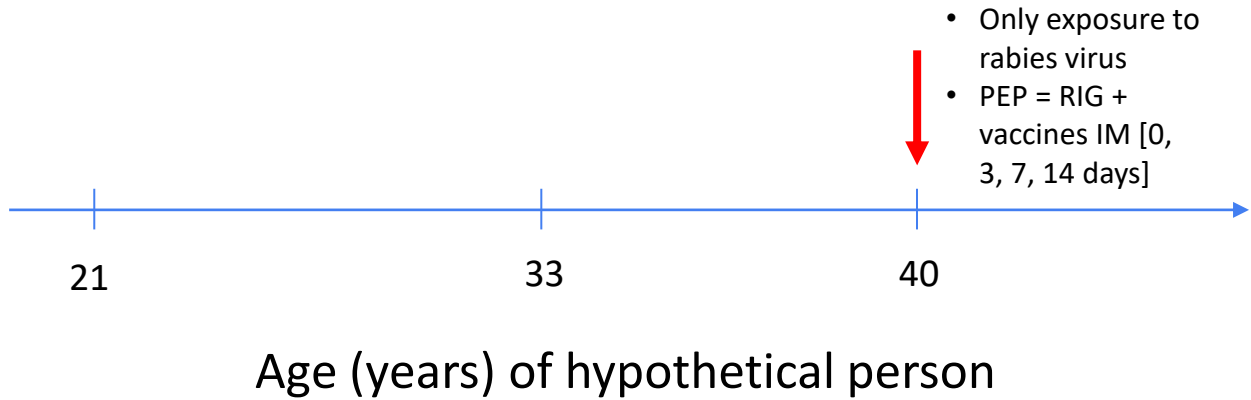
Advisory Committee on Immunization Practices meeting
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Current ACIP recommendation for RIG

- RIG administration within first 7 days of PEP vaccine administration
- Infiltrate maximal amount that is anatomically feasible (i.e., should not cause compartment syndrome)
- For large / multiple wounds, RIG can be diluted

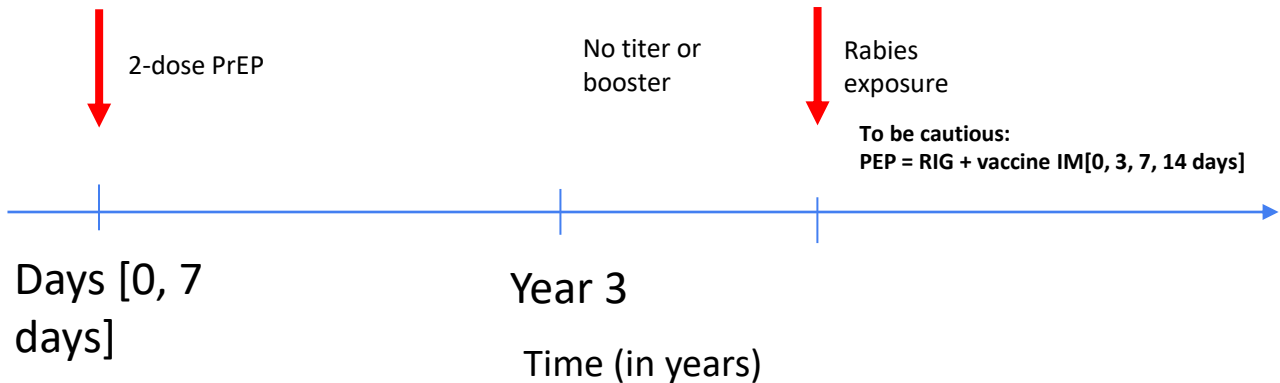
Indications for Rabies Immune Globulin

- Component of PEP for persons who are not considered previously vaccinated
 - A) Persons who did not previously receive PrEP



Indications for Rabies Immune Globulin

- Component of PEP for persons who are not considered previously vaccinated (i.e., did not receive PrEP or PEP)
 - B) Consideration if proposed PrEP guidance is passed



2018 WHO considerations

- RIG in limited supply internationally
 - It is estimated that worldwide, <2% of persons with serious wounds (i.e., WHO Category III), receive RIG
 - RIG is very expensive
 - What can be done when there is no RIG available:
Thorough washing of wound + vaccine has been shown to effective in preventing rabies
- When RIG is available, dog exposures are the most common exposures
 - Maximum infiltration of RIG around wound is effective
- Benefits from additional IM administration of remaining RIG likely limited

2018 WHO Position Statement

- Limit RIG infiltration to RIG that can be infiltrated into and around the wound (i.e., that is anatomically feasible)
- No IM administration of RIG
- Rinsing with diluted RIG can be considered for mucosal exposures with no wound

Questions discussed by WG

- Two newly licensed RIGs: Are these new formulations or new products?
- What is the data in support of limiting RIG to infiltration around wounds? What are the U.S. implications of any proposed changes to the recommendations?

Newly licensed RIG products in U.S.

Human immunoglobulins licensed in U.S.

Product name	Manufacturer	Administration	Potency	Dose
Imogam®	Sanofi Pasteur	Infiltrated around wound and remainder administered intramuscularly	150 IU/mL	20 IU/kg
Kedrab™/ Kedrion	Biopharma and Kamada Ltd		150 IU/mL	20 IU/kg
HyperRab™ S/D	Grifols		150 IU/mL	20 IU/kg
HyperRab®			300 IU/mL	20 IU/kg

HyperRab[®]

- New formulation at higher concentration of product that has been in existence for >46 years
- Improved production and manufacturing processes over the years
- No FDA post-licensure requirements because considered to be new formulation (not new product)

WG Conclusions about Kedrab™ and HyperRab®

- Safety and efficacy: Non-inferiority to previously licensed products
- After review of data, WG concluded
 - “Newly licensed products” are not “new”
 - Preference is for no preferential recommendation of a RIG product

Selection of RIG product should be made by individual institutions

- Indications same for all
- Licensed products are equally efficacious
- HyperRab[®] more potent than others
- Individual institutions can determine which product they stock
- Oversight needed for proper amount of RIG administered; pharmacy often not involved beyond stocking

**WG discussions about RIG administration
around wound and frequently asked
questions about RIG**

U.S. and RIG considerations

- Most rabies cases are from bat exposures
 - These create small or barely visible wounds
 - Limiting RIG to administration around wound could result in very little or no RIG given®
- Role for RIG
 - Studies indicate it can be advantageous
 - In U.S., RIG has always been available and should be administered for persons not previously immunized
- Strong and convincing data needed before WG willing to propose a change

Current ACIP recommendation for RIG infiltration around wound and remainder IM

- RIG infiltrated around wound likely remains at site of injection
 - Limited data cited in WHO Position Statement*
 - Unclear whether IM administration of RIG provides any benefit
- Data insufficient for WG to propose change to current ACIP recommendations

*Madhusudana et al, Saesow et al, and Wilde et al included in background documents

Other WG discussions

- RIG dose of 20 IU/kg can result in multiple needlesticks
 - No data to support a change
- Rinsing with RIG after mucous membrane exposures e.g., after saliva from rabid animal enters mouth of human
 - WG preference is for no recommendation e.g., after saliva from rabid animal enters mouth of human

Frequently asked questions about RIG

- High amount of RIG inadvertently or intentionally administered
 - Antibody titers decrease *slightly* when 21-40 IU/kg given; typically not a clinically meaningful decrease in titer
 - Inadvertent high amount could be administered because less volume is administered for HyperRab
- Risk / benefit should be weighed before administering more than 20 IU/kg

WG's next steps

- Review data for PEP series including fewer doses
- Consider guidance for management of frequent questions
 - Schedule deviations for PreP and PEP series
 - Continuation of PEP when series initiated abroad with 1) non-US licensed vaccine or 2) intradermal administration
- Consider referring to RIG package inserts about reported differences/ benefits between products

Acknowledgements

- Rabies WG
- RIG product sponsors



Thank you