**SUMMARY**
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# Human Rabies Prevention

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***Please note:** Data and analysis discussed in these presentations were current when presented. Data collection and analysis are ongoing in many cases; therefore updates may be forthcoming elsewhere on this website, through publications such as **CDC's Morbidity and Mortality Weekly Report** or other venues. Presentations themselves will not be updated. Please keep this in mind when citing data from these presentations.*

## Part I -- Overview:

### *Common Rabies Misconceptions*

Rabies in the United States, particularly in domestic animals, has been extremely well-controlled since the 1950s and 1960s, when regulations for vaccination of dogs and stray animal control were implemented.

A common misconception is that dogs are still a primary rabies problem in the United States, but that is no longer true:

- Worldwide, dogs are the most important and common source of human exposure and of human rabies; it remains uncontrolled in many parts of Africa and Asia.
- **In the United States**, however, and many other parts of the world where vaccination and control of strays have been widely implemented, the **canine rabies virus variant has been eliminated**.

Another common misconception in the United States is that when you're presented with a bite from a dog, cat, or a ferret, there is an urgent need for human prophylaxis. That is no longer true.

If the animal is healthy and available for observation, then a ten-day observation period should be applied. If the animal develops a clinical illness, it should be examined by a veterinarian. If clinical signs are compatible with rabies, the animal should be humanely euthanized and testing of the brain material should be expedited. Human Post-exposure prophylaxis should be initiated if the brain material tests positive. We've been following this protocol for well over 40 years; it has not failed us in the United States.

### *Rabies in Domestic Animals*

**The most common rabid domestic animals in the United States are cats**; they have supplanted dogs in this role. Cats are less likely to be vaccinated and less likely to be confined, which may account for why there are more rabid cats than dogs in the United States.

### *Increased Prevalence in Wild Animal Populations*

While domestic animal rabies has declined precipitously, we've seen a tremendous coincident rise in rabies among wild animals. **Raccoons are now the leading wild animal with rabies**, **skunks** are second, **bats** are third, and **foxes** are the fourth most common wild animal with rabies.

### *Rabies in Humans*

As you may recall, rabies is:

- a single-stranded RNA virus in the Genus *Lyssavirus*
- neurotropic, causing fatal encephalitis

Again, historically dogs were the most common source in the U.S. That has now changed and most cases occur in wildlife species. Even though we have had raccoon rabies in the United States since the 1950s, we were able to fully prevent spillover of that type of rabies into humans until 2003, when we had our first human case of rabies due to the raccoon rabies virus variant.

**At present, the most common sources of human rabies in the United States are the rabies virus variants associated with bats, perhaps because people are unaware that bats may transmit rabies or because bat bites are often quite small**.

### *Pathogenesis*

Initiation of infection starts most often with a bite. The virus may replicate locally in muscle tissue before going through the peripheral nerves into the spinal cord and up to the central nervous system. When it reaches the brain, manifestations of behavioral abnormalities and illness may be observed.

**Aggression is a common manifestation of behavioral changes**, particularly in the reservoir species to which these viruses have exquisitely adapted. The infection often drives the animal to bite. Virus is typically present in the saliva just before the clinical illness is observed and when the animal is obviously ill. Once the brain is infected, the animal may become very aggressive, then very ill, and ultimately die.

### *Rabies Virus Variants*

There are many different kinds of rabies viruses. These are termed "rabies virus variants" and **can be differentiated by monoclonal antibody patterns** which

reflect antigenic differences and by differences in genetic sequence. They are usually maintained in a single host reservoir species, such as raccoons.

There is a rabies variant virus in raccoons in the eastern US. There are several skunk virus variants in the United States, as well as fox virus variants; although they may be transmitted to any susceptible mammal (this is termed "spillover").

The monoclonal antibody patterns in the United States describe:

- a north central skunk rabies virus variant
- a south central skunk rabies virus variant
- a California skunk virus variant
- two grey fox variants with one focus in Arizona and another in Texas
- a Texas coyote variant that is found in Mexico but occasionally spills across the border
- a raccoon rabies virus variant from Florida all the way up into Canada, and
- Arctic fox rabies in Alaska.

There are a number of rabies virus variants associated with bats and a tremendous variation of **between 15 and 40 different species of bats that may each have their own virus variant**. So that is overlaid on top of those terrestrial animal rabies virus variants. These are geographically widespread throughout the United States. There is also mongoose rabies in Puerto Rico.

***Clinician Resources***

If you need rapid information about rabies, one of the quickest sources to go to is the **main CDC web site, www.cdc.gov** . When you get there:

- click on "**A to Z Index**" to see an alphabetical list
- go to "**R**" and click on "**Rabies**" to get into the rabies Web site
- go to "**Professional Resources**" to find a clinician information line where you can reach service 24 hours a day, seven days a week, for immediate answers. You can also find the ACIP **Guidelines for Human Rabies Prevention and Control in the United States**; the most recent document is the 1999 version. The site also contains the annually updated **Compendium for Animal Rabies Prevention and Control**. These are the primary reference documents.

Additionally, under "Professional Resources" you will find the **Human Rabies Rule-out Guidelines and forms**. If there is a case where the more common causes of encephalitis have been ruled out and something in the history or clinical progression of the patient is suggesting rabies, you can click on these sites and look at the:

- patient information form
- directions for collection and packaging of specimens
- directions for reaching us and going over the case with us, so that we can assist you with the differential diagnostic workup.

***Clinician Concerns***

Some of the most common questions we've had from clinicians are:

- "Is the patient potentially exposed?"
- "Do I need to administer post-exposure prophylaxis?"
- Another common question is where and how is human rabies immune globulin administered. **Human rabies immune globulin is most effective when it is infiltrated (as much as anatomically possible) around the potential viral deposition site (i.e., bite site, even if the bite has healed) with any remaining volume administered at another intramuscular site but distant from the vaccine administration site.** Vaccine is most effective when it is administered in the deltoid (or anterolateral thigh in small children and infants). **The passive immunity supplied by immune globulin bridges the gap in the first week after vaccine administration. RIG is not administered seven days after the first vaccine dose, as patients respond actively with their own antibody induction.**

***Site Exposure Risk***

Understanding the most common routes of exposure and what presents a risk is necessary for determining whether or not human post-exposure prophylaxis is needed.

- **Bite**

  Bite is the most natural and successful way to transmit rabies.

- **Contamination of Open Wounds**

  Direct contamination of fresh, open, bleeding wounds with a live virus source -- such as fresh saliva or tissue from a potentially rabid animal -- that is also considered an exposure, assuming the animal is a suspect or proven rabid animal.

- **Oral Exposure**

  Oral exposure is a potential risk. We know from experimental evidence that if you dose a number of animals with millions of particles of rabies, disease will not occur in the majority of those animals. In a small proportion of those animals you may see immunity to rabies develop. And in 1 - 2% of those animals, if it is a susceptible species and if the titer of rabies virus is high enough, you may see the manifestation of rabies.

  With oral exposure, perhaps the virus is being taken in through deficits in the mucus membrane around the teeth. It may be able to invade further in the tonsillar crypts; however, once it reaches the stomach it is inactivated. So the risk is orders of magnitude lower than a bite or contamination of a fresh, open, bleeding wound or, but it's still a possibility.

- **Inhalation**

  Inhalation of droplets or an aerosol is a possibility, and a potential for exposure to rabies; however, rabies virus does not naturally form an aerosol. There are unusual conditions, for example, laboratory accidents that could

present some risk, but it's low and we'll go over this in more detail in a moment.

- **Ocular Exposure**

  Ocular contamination leading to rabies has not been documented except with corneal transplants. So, if corneas from a donor for whom rabies was not suspected but was present, are surgically implanted into a recipient, sequelae may result.

  If there is a corneal breach, obviously contamination of eyes is a potential exposure. This is a consideration when there is a human who may have contaminated their eyes with a splash from a potentially rabid animal.

As stated in the 1999 ACIP document, rabies is transmitted only when the virus is introduced in the bite wounds or open cuts in the skin or on to mucus membranes. "Bite" is defined as any penetration of the skin by teeth and that includes even a minor bite from a bat that represents a potential risk of rabies transmission. **Non-bite exposures rarely cause rabies**.

### *Non-Bite Exposures*

- **Inhalation of Aerosol**

  We have seen two laboratory accidents where an aerosol was created and the laboratory workers developed clinical rabies. Also there were two cases many years ago where researchers handling bats on a frequent basis in a cave setting developed rabies.

  We are not sure if the investigators may have been bitten by these bats. They were working in caves with several million Mexican Free-tailed bats. It was humid; there were millions of animals jostling each other and taking flight because of the disturbance, so that may have resulted in the creation of an aerosol that may have been the source of transmission to these two researchers, although a bite or other direct exposure cannot be ruled out.

- **Corneal and organ Transplantation**

  Corneas and organs transplanted from infected donors are a source of rabies exposure to recipients.

- Other contact by itself, such as petting a rabid animal and contact with blood, urine, or feces (bats feces are called guano) of the rabid animal does not constitute an exposure and is not an indication for prophylaxis.

### *Determining Potential Exposure*

Helping a patient make a decision as to whether or not they were potentially exposed can be tedious and take some time. Rabies virus is inactivated by:

- drying
- UV irradiation.

It is inactivated very quickly outside of the body. Fomite fomite transmission of rabies has not been documented.

**Rabies prophylaxis is a medical urgency but not an emergency**. There are local and state public health professionals who routinely take calls from members of the public who think they may have been exposed to rabies. These professionals are a good resource for understanding the local transmission patterns of rabies. So it's a complex decision that involves consideration of the:

- animal species
- type of exposure
- availability for animal testing or observation
- condition of the animal (is it healthy or not?)
- circumstances of the exposure (was the animal provoked or not?)
- the local transmission patterns of rabies

Dog, Cat, or Ferret Exposure:

For dogs, cats, and ferrets, as we've already mentioned, simply observe them for ten days if they are available. You will not need to initiate post-exposure prophylaxis unless the animal tests positive.

If the animal is not available for observation, then it's a much more difficult process and in most cases, if rabies is found in terrestrial animals in the locality, then it raises the possibility that the dog, cat, or ferret may be potentially rabid, depending upon the behavior of the animal.

In most cases, post-exposure goes forward. But there are some times when, if the animal appeared healthy, the encounter was provoked, and the risk is low, post-exposure may not be needed.

Wild Animal Exposure:

With wild **carnivores**, such as the most common rabies reservoir species (i.e., raccoons, skunks, foxes), if the source of exposure is obvious -- like a bite or gross contamination of eyes, nose, or mouth with material from the animal -- it's considered high risk. If the animal is available, testing to get a definitive diagnosis will determine post-exposure needs. If the animal is not available, post-exposure is usually needed.

For livestock and small mammals such as **rabbits, hamsters, and guinea pigs,** these generally present low-risk situations. The decision can be made on a case-by-case basis, often in consultation with local and state health officials. Rodents are not a reservoir for rabies. Naturally infected cases are extremely rare. Scenarios leading to infection of domestic rodents are rabbits housed in outdoor hutches, often with a known history of a wound, or the observation of a suspect rabies reservoir rabies species -- such as a skunk or a raccoon -- in the vicinity.

Conversely, large-bodied wild rodents, such as, **ground hogs (woodchucks) or beavers** have been positive for rabies in areas with the raccoon rabies virus variant. They may survive an attack by a rabid raccoon and go on to develop rabies, potential exposure situations with smaller rodents, such as **chipmunks, squirrels, wild mice, pet hamsters and gerbils**, overwhelmingly do not require post-exposure.

### *Post-Exposure Treatment*

- Local wound care is extremely critical; **the wound is to be washed immediately with soap and water**. Simply that alone has been shown to reduce human mortality in developing countries.

- Human rabies immune globulin is dosed according to body weight:

    - as much as is anatomically possible should be infiltrated at the site of exposure
    - the remaining volume should be deposited **intramuscularly**
    - the five doses of vaccine should go intramuscularly in the deltoid on days 0, 3, 7, 14 and 28
    - **the vaccine and human rabies immune globulin should never be mixed and should not be administered anatomically near each other** because they will neutralize each other and you'll see a lower response to vaccination.

- **Post exposure prophylaxis for someone previously immunized is only two doses of vaccine, intramuscularly in the deltoid, one on day zero and one on day three.** Human rabies immune globulin is not needed and is contraindicated because it may suppress an anamnestic response. There has never been a failure of PEP in a previously immunized individual if it was administered, but it is not needed and should not be administered.

- Post-exposure prophylaxis in the United States is extremely effective. A 16-day-old infant who was attacked by a rabid raccoon with virtual intra-cerebral inoculation of virus is a normal child today. Post-exposure was rendered about 12 hours after the animal attack with human rabies immune globulin infiltrated at all sites that were possible, and the five doses of rabies vaccine. **There has never been a failure of post-exposure prophylaxis in the United States since the advent of cell culture vaccine and human rabies immune globulin**.

### *Rabies in the United States*

Rabies is invariably lethal, there are a few survivors, but this is extremely rare. Several cases of human rabies in the United States are occurring due to a lack of prophylaxis with exposure abroad – to a traveler in a foreign country or to an immigrant while in their country of origin -- or exposure in the United States to a bat where the patient was unaware or dismissive of the risk of rabies.

Rabies in bats is widespread geographically throughout the United States. We've had two human rabies cases from bat-associated rabies in the decade from 1980-1990 and then 20 in the following decade.

It is unknown if this is an actual increase, greater detection, or an unusual trend; however it's something that led to the 1999 ACIP recommendations for more caution when dealing with bat exposures.

In the ensuing five years we had another ten cases; the trend has not reversed. There have been:

- ten cases of naturally occurring human rabies from bat rabies virus variant, and
- four cases due to transplantation of infected organs from a donor who died of rabies and for which rabies was not recognized in that donor.

Due to the type of rabies virus variant found in the human cases, the bites may have been from two small insectivorous bats, the Eastern pipistrelle or Silver-haired bat. These bats are:

- small
- have very tiny teeth
- leave a minor bite wound that is unlikely to send anyone to the emergency room.

U.S. Case in 2003:

In the most recent California case in 2003, an adult male dismissed the bite from a bat and decided that the risk of rabies in bats was small enough to not seek post-exposure. He died of rabies several weeks later.

U.S. Cases in 2004:

In the recent Wisconsin case in late 2004, the 15-year-old actually survived rabies. She was bitten by a bat, washed the bite immediately. Later when she showed it to her father, he could no longer observe a wound and commented that it did not look like a bite. Apparently, he understood that if there had been a bite he may have been concerned rabies, but since he could not see a bite, he did not think that rabies would be an issue and perhaps it could be treated if rabies developed. Bat bites can result in a very minor lesion that may disappear within a few days or even hours.

Four cases of rabies occurred in organ transplant recipients from a case in a donor that was unrecognized. In 2004, there was a rabies suspect sheep at a petting zoo with over 750 people exposed and only one available vaccine on the market. At the end of the year the Wisconsin human rabies occurred, with the young woman surviving clinical rabies.

Two of the rabies cases were several months retrospective, where immigrant sfrom El Salvador and Haiti developed clinical rabies in the United States but the diagnosis came only on post-mortem. There was a total of eight cases in the United States in 2004.

Also in 2004 there was a recall of human rabies vaccine due to detection of a residual amount of live rabies virus in lots that had not yet been released. The

vaccine was the product of one of the leading manufacturers for the rabies vaccine in the United States and for the world market. The recall in the United States left only one vaccine on the market.

### *Human Rabies Biologics Available in the U.S.*

- At present, only one licensed vaccine is available for the U.S. market: the manufacturer is Chiron.
- The rabies vaccine absorbed from BioPort is no longer available.
- The Imovax rabies intradermal vaccine formulation was voluntarily removed from the U.S. market by its manufacturer, Pasteur Merieux Connaught (that later became Aventis Pasteur and now Sanofi Pasteur).
- In 2004 the Imovax rabies intramuscular formulation was recalled because of potential contamination with live virus.

Adequate availability of effective vaccines and immune globulins in the United States for an orphan disease such as rabies can be tenuous.

### *Organ Transplant Transmission: Case Study*

The CDC was asked to assist with investigation of the infected donor as to how he was potentially exposed, and to review his clinical presentation. We visited the donor's apartment complex; there was a report of bat problems from residents and sufficient physical evidence at the site to suggest that there had been recent and historic bat colonization there.

Interviews with the donor's contacts identified that the donor had reported to friends that at least one bat had swooped at him. Another friend reported that the donor had said something about a bite and wanted to show where the bat had bit him, but the timeframes quoted were somewhat different.

The donor was the hub of an association of friends and participated in a party at a local club of about 100 people, sharing drinks and smoking materials four days before he presented with nausea and vomiting. He presented at the initial hospital at approximately 9:25 a.m. reporting that he "couldn't even swallow his own spit." When he tried to swallow he became nauseated and vomited. He was treated for a suspected urinary tract infection and was discharged.

He reported back around 6:00 p.m. that night and his family reported that he had collapsed with shallow breathing and wheezing.
Upon presentation, he was:

- hyperventilating
- very anxious
- having difficulty with ambulation

He was eventually discharged and presented to another ER with:

- vomiting of blood
- abdominal pain
- agitation
- confusion

- delirium

At this point the patient required intubation. He tested positive for cocaine and cannabinoids. He developed a mild subarachnoid hemorrhage, which progressed, and eventually there was electrical silence in the brain and a declaration of death. The organs were harvested the following day.

According to the chart review, the patient:

- had been combative
- was biting the endotracheal tube
- had ongoing seizures that were uncontrollable with medications
- had non-reactive pupils
- demonstrated continued obvious motor activity, despite administration of a variety of medications
- had tremendous autonomic instability with very high blood pressure, then very low blood pressure
- had a body temperature that varied substantially from sub-thermic to hyper-thermic

This was an unusual case with the clinical presentation of rabies potentially complicated by the substance abuse history.

The organs were donated as follows:

- the lungs were transplanted to a recipient in Alabama who died during surgery, so there were no potential exposures to rabies from the lungs.

- the liver was transplanted and the recipient was discharged within a few days. The recipient was readmitted several weeks later with tremors, lethargy, and manifestations of clinical rabies. It was recognized as an encephalitis. The patient died on June 6th.

- kidney 1 was transplanted and the patient had a relatively uneventful recovery from the transplantation but presented on May 29th, several weeks later with flank pain and then subsequently died.

- kidney 2 was transplanted and the patient discharged after two weeks, but represented two weeks later with myoclonus and confusion and died.

A second liver (from a different donor) was transplanted the following day. The liver recipient later died. The pathologist at this institution reviewed the histopathologic findings and identified encephalitic lesions that were similar to the other cases. With additional testing is was demonstrated that, indeed, this second liver recipient had also died of rabies.

Upon review of their records, the surgeons were able to identify that the second liver donor and recipient both had atherosclerotic vessels, and a vessel that had been banked from the rabid donor was the source of rabies during the second liver transplantation.

These cases were reported in the New England Journal of Medicine.

***Ante-Mortem Testing***

With regard to cases of encephalitis in humans, ante-mortem testing is available. We routinely do this at the Rabies Laboratory at CDC. The workup is useful for obtaining a definitive diagnosis, and to minimize rabies exposures to others.

- The **direct fluorescent antibody test (dFA test)**, may be applied to either fresh skin (a ~4 mm biopsy from the nape of the neck) or sometimes to a brain biopsy. Although the dFA test can be modified for pathologic specimens that have been formalin fixed, the **dFA test on fresh frozen tissue** is the gold standard; it's much faster and easier to perform on fresh tissue and is particularly useful for ante-mortem diagnosis.

- An evaluation for the presence of anti-rabies virus antibodies is conducted on sera and cerebral spinal fluid.

- The **reverse transcriptase-polymerase chain reaction (RT-PCR)** assay for amplification of potential rabies viral nucleic acid may be applied to a number of samples, particularly saliva and skin, with genetic sequencing of products to identify the rabies virus variant.

- **Immunohistochemistry as well as a modified d FA test** on formalin fixed tissues may be preformed.

- Isolation in cell culture or animals may also be used.

***Organ Donor Screening***

There are a number of unresolved issues in human rabies in the United States, particularly on the heels of last year's transplant recipients. And recently we've been notified of human rabies cases in Germany from a rabid donor. The initial rabies case in the donor also went unrecognized until after six recipients received organs and tissues.

**When there is a patient with an encephalitis of unknown etiology, but suggestive of viral etiology and with a precipitous clinical decline, rabies should be on the differential list**. As you are well aware, human rabies is rare in the United States. However, it should be entertained in the differential diagnosis, even in cases where there may not have been a reported bite from an animal. The animal exposure could have occurred several weeks to several months or even six months or more prior to the onset of symptoms. **The incubation period can be very long, so people may not recall their potential exposure to rabies.**

In organ donation cases, diagnostic screening tests are available and there are ongoing discussions with the organ procurement organizations. Additionally, retrospective diagnostic testing is available, so we can assist if there are cases of encephalitis for which pathological specimens exist.

We are concerned in cases like this, where there was immunosuppression. Could there be novel sources of exposure? For example, when the kidneys were transplanted into the recipients, there were drainage sites and urine collection vessels. Although rabies is typically not shed in the urine, when you're implanting an

organ that has rabies virus in it and then allowing urine and tissue fluids to be drained from a surgical site, there is a potential for altered pathogenesis and abnormal portals of exit of the rabies virus from these patients.

### *Vaccine Supplies*

Due to the concern about vaccine and rabies immune globulin supplies, research is onging to develop alternatives. We're working on potential replacements with a combination of monoclonal antibodies that could be grown in cell-culture. In theory, a cell culture product could be produced quickly in response to unusual needs such as a mass human exposure. The production of monoclonal antibodies could be more easily increased than the production of human rabies immune globulin from human donors.

CDC works closely with FDA and the licensed vaccine manufacturers to monitor expected demand and supply.

### *Animal Vaccination Efforts*

**There is a continuing major epizootic of rabies among raccoons from Florida to Maine**. With oral vaccination of wildlife, there is a possibility of containing or perhaps controlling wildlife rabies, which may reduce human and pet exposures in the future.

### *Conclusions*

Since rabies virus variants associated with bats are the most common source of human rabies in the United States, public education is needed to portray the risk of rabies in relation to the benefits of these unique species. In addition to the risk of rabies from ignoring bat bites, there may also be unique viral characteristics that results in easier infection of humans. The rabies virus variant associated with the Silver-haired and Eastern pipistrelle bats has the ability to replicate in epidermal cells and when these cells are held at lower temperatures it also replicates to a higher titer than other rabies viruses.

- Post-exposure is not reportable throughout the United States, because of this, it is difficult to describe the magnitude and epidemiology of it's administration. We conduct pilot studies that are useful in showing that the majority of post-exposures are administered because of bites from dogs and cats in the United States. That may be appropriate, but if we can better educate the public to keep their dogs on leashes and vaccinate their cats, we may achieve a better rate of prevention of the exposure rather than relying on post-exposure prophylaxis.

- There are still questions about the availability of human rabies biologics, and, we are working on novel alternatives to human rabies immune globulin. We are also working on novel approaches to immunizations.

- We're concerned about the importation of animal rabies and the potential for new outbreaks. Domestic animals brought into the U.S. could have rabies from exotic sources. For example:

    - We know that, just last year, we had a rabid animal from Puerto Rico brought into the United States; it was a dog that had a mongoose rabies variant that is easily transmitted dog to dog. The case occurred in Massachusetts.
    - There were two puppies brought on a commercial airliner from Thailand into the United States, of which one was sick with rabies and was diagnosed in California.

- We also know that there are newly described Lyssaviruses, which cause rabies, that have been recently identified in Australia and Asia.
    - Australia bat Lyssaviruses: current human biologics protect against it
    - Four new Asian Lyssaviruses: current rabies biologics do not provide complete protection against them. The viruses are genetically diverse from our traditional rabies viruses. There are a lot of novel things out there among wild animals that we're still learning about.

There needs to be **heightened surveillance** for these potential newly emergent variants, as well as for indigenous and translocated animal rabies cases.

We are working very hard on the development of therapeutics, especially in view of the recent Wisconsin survivor, for which we're not sure whether her survivorship was due to the treatment or if it was because of a peripheral exposure from a potentially low viral burden. If it was a weak bat, the bite may not have been very strong. If the bat was very sick and the mouth was dry, there may not have been much virus in its mouth. The Wisconsin patient was young and in good physical condition. She already had antibodies in her cerebral spinal fluid when she presented for medical care. Perhaps being placed in a chemically induced coma and given antivirals helped allow her to survive this infection. She was never given any rabies vaccine or immune globulin because she was already responding to the infection itself. We are working on that and look forward to the publication of the case managment in *New England Journal of Medicine*.

## Part II: Q& A

**Q: You mentioned that ante-mortem testing is recommended; is it widely used and please comment on cost-effectiveness?**

**A:** Ante-mortem human rabies testing is available sometimes through state health departments, particularly the larger ones, such as Texas, California, and New York, but it is also directly available here at CDC. We have a comprehensive battery of tests that are available. We encourage testing when the clinical course is compatible with a presentation of rabies and when other more common causes of encephalitis have been ruled out.

There is no charge, so we consider it highly cost-effective and it can certainly help in leading you either towards a diagnosis of rabies or away from it.

**Q: What clues can be useful for physicians to look for during the initial history and physical so that human rabies cases can be suspected earlier and included in the differential diagnosis?**

**A:** In the USA, rabies is often a diagnosis of exclusion. A classic presentation, although not always present, is hydrophobia. In one of the cases, the patient reported a phobia to liquids; however he was treated for potential mental disturbances rather than recognition of this abnormality. Many of the classic clinical presentations: hydrophobia, ataxia, manifestation of encephalitis, are present but may be masked by clinical management such as sedation for intubation.

Rabies results in a very precipitous clinical course. Usually when a patient presents, almost invariably they have an outpatient visit and are sent home and then re-present usually within 24 hours, sometimes sooner. If you have patients showing a precipitous decline and re-presenting with signs of encephalitis then that should lead to rule-outs for the most common causes of encephalitis but also rabies.

Paresthesia is often found, but not always. Paresthesia usually starts at the site of the bite, so some of the patients have been treated for potential nerve damage. For example, they may report routinely carrying a backpack with that particular arm, and so may be treated empirically. But if it is rabies, the clinical presentation declines precipitously and progresses rapidly to overt encephalitis.

Once the patient is hospitalized, usually within a few days, it can be as little as 24 hours or upon presentation, but within a few days they are in need of intubation for respiratory secretion control for maintenance of airway protection. Then within hours, they are often comatose without the effect of chemicals. Often, autonomic instability develops over the next four to six days, making it very difficult to maintain the patient. As rule-outs for more common causes come up negative, ante-mortem rabies testing should be pursued.

Only rarely have patients come in with a self-reported potential history of animal exposure, so in cases of encephalitis, it may be worthwhile to explore with the history with the family and friends. In recent human rabies case investigations, often the reports come from the family member, for example that "Yes, he removed a bat from our house several weeks or months ago" - a not uncommon retrospective finding.

**Q: Can you please describe criteria that are used to determine further post-exposure prophylaxis recommended in the health care setting and situations in which rabies infection was not initially suspected?**

**A:** With the human rabies cases or a point-source exposure from a domestic animal or a wild animal with rabies where groups of people have been potentially exposed, the ACIP recommendations and definition of exposure are used for determination of potential exposure.

In hospital settings where human cases have occurred, post exposure prophylaxis is usually not widely needed because the clinical management of this patient has precluded exposure. Exposure typically arises from an accident where contamination of one's eyes, nose, mouth, or an open, bleeding wound has occured, such as through a needle stick or a scalpel injury that was contaminated with the patient's

saliva, or their tissues from an invasive procedure. Additionally, potential creation of an aerosol may result in an exposure to respiratory technicians, and others attendant to intubation. In these cases, the determination for potential exposure would require careful consideration. Generally the need for post-exposure is surprisingly low in a hospital setting but with appropriate routine precautions, the potential for exposure should be quite low, as well. No cases of transmission to rabies to a health care worker have been documented.

**Q: As public health officials, what can we do to assist with rabies public health education. Is it most important that we urge people to take rabies seriously? It sounds like some of the cases developed because folks are not taking the potential exposures seriously. Or is it more important to get the myths out there and dispel them?**

**A:** Probably we need to dispel the myths but we also need to have people understand that rabies surrounds us in the United States. The number of animal cases is quite astonishing and, particularly in bats, it is very widespread, so the potential for exposure is real. The public seems to understand that wild carnivores are a potential source of rabies and possibly domestic animals as well, however the potential exposure from bats is not as widely recognized. We think it has been improving based on some pilot studies showing shifts towards more prophylaxis following bat encounters where there may have been a potential exposure.

Reminding the public that rabies is still present in the United States is critical. The public needs to know that rabies is present in wild animals, particularly in bats, and that seeking post-exposure prophylaxis is critical because if a patient presents with clinical signs of rabies it is invariably lethal. The recent Wisconsin survivor is the only one who didn't receive any vaccination; the other survivors in the United States received vaccination before the onset of illness.

**Q: Is there ever a time when PEP is too late, if they are presenting with symptoms already?**

**A:** It's never too late to administer prophylaxis unless clinical signs are present, and then yes, it is too late. Prophylaxis has been administered in the face of clinical onset of rabies in rabies cases and it has never been successful. This Wisconsin case would lead us the other way in fact, away from prophylaxis, perhaps because of the resulting inflammation from human rabies immune globulin and vaccination in the presence of clinical illness. This treatment may actually accelerate brain inflammation and injury rather than assist in clearing an infection that may already be receding.

With a case of encephalitis that may be a suspect human rabies case, the first thing to do would be to pursue more common differential diagnoses, and then seek a specific human rabies rule-out.

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