

## Protocol That Saved Life of a Rabies Patient Requires Further Study

BY SHARON WORCESTER  
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The doctors who treated the first known patient to survive rabies without prior vaccination have published their aggressive and previously untested treatment protocol, but they caution that it requires further study.

"Clearly, our experience with this patient requires replication in other patients and proof-of-concept experiments in animal models," said Rodney E. Willoughby Jr., M.D., of the Medical College of Wisconsin, Milwaukee, and his colleagues.

The 15-year-old patient developed confirmed clinical rabies 1 month after being bitten on the left index finger by a bat. She was treated with a strategy that involved induction of therapeutic coma, and antiexcitatory and antiviral drug therapy under supportive intensive care. The concept was to protect the brain from injury while allowing the launch of a natural immune response against the virus (N. Engl. J. Med. 2005;352:2508-14).

The patient was treated with ketamine, midazolam, ribavirin, and amantadine. Doses were adjusted as needed due to responses and probable drug-related toxicities, which included hemolysis, pancreatitis, acidosis, and hepatotoxicity. She did not receive rabies vaccine or rabies immunoglobulin because she demonstrated im-

mune response and because of concern regarding harm from a potentiated immune response.

On the 8th day, a lumbar puncture indicated an increased level of rabies antibody, and sedation was tapered. On hospital day 31, the patient was determined to be cleared of transmissible rabies and was removed

from isolation. She was discharged to home on hospital day 76.

At a follow-up visit 131 days after her initial hospitalization, the patient was progressing, and had returned to school part time. She continues to experience dysarthrotic speech, buccolingual choreoathetosis with generalized choreoathetosis and intermittent dystonia and ballismus, which affect her gait and fine-motor skills.

Prior to this case, five cases of survival following rabies had been well documented, but all received occupationally related preexposure rabies vaccination or postexposure prophylaxis; this is the first known patient to survive with only naturally acquired immunity. It should be noted that the



The 15-year-old rabies survivor was treated with ketamine, midazolam, ribavirin, and amantadine.

patient was young and athletic, and may have received a limited quantity of inoculum, the investigators stressed, adding that since the bat was not recovered, it is unclear if the patient's survival was due to an "unusual, more temperate or attenuated variant of the virus, or a rare host polymorphism."

"Therapy may have been more effective than in past cases because of the inferred limited exposure to rabies virus, early recognition of the disease, and aggressive management," the investigators said, noting that the survival of this patient does not change the fact that rabies has the highest case fatality ratio of any infectious disease. ■

## Better Drugs in Sight For Hepatitis in Kids

BY ROBERT FINN  
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SAN FRANCISCO — Although some therapies are available for treating chronic viral hepatitis, it remains unclear whether children should be treated, Frank R. Sinatra, M.D., said at a meeting on clinical pediatrics sponsored by the University of California, San Francisco.

There are good arguments on both sides of the issue, said Dr. Sinatra, director of the pediatric gastroenterology division at the University of Southern California, Los Angeles.

The arguments for treatment include:

- ▶ Early treatment can prevent fibrosis and cirrhosis.

- ▶ Children do at least as well as—and perhaps better than—adults, with current drugs.

- ▶ Treatment can help prevent the spread of chronic hepatitis B and hepatitis C.

- ▶ Many clinicians believe any chronic viral infection must be eradicated.

The arguments against treatment include:

- ▶ Most children with chronic viral hepatitis are asymptomatic. "It's very hard to make an asymptomatic patient feel good," Dr. Sinatra said.

- ▶ Fibrosis typically develops slowly.

- ▶ The side effects from current treatments are significant, and include growth retardation.

- ▶ Current therapy has a success rate of only 50%.

- ▶ Even without treatment, a small number of children will experience spontaneous resolution of their chronic infection.

- ▶ In Dr. Sinatra's view, the best argument against treating children who appear to be doing well is that there are better drugs on the horizon. He knows of at least eight that are in phase I, phase II, or phase III clinical trials.

Whether or not a clinician decides on treatment, these children need to be followed closely for evidence of progressive liver disease and the development of hepatocellular carcinoma, he said. ■

## HHV-6 Infection Peaks Between 9 and 21 Months

BY MARK S. LESNEY  
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The peak age of acquisition of primary human herpesvirus 6 infection is between 9 and 21 months, according to results of a population-based study of 277 children followed from birth to 2 years.

Of the 277, 130 (47%) of the children were infected by the age of 24 months (N. Engl. J. Med. 2005;352:768-76). Human herpesvirus 6 (HHV-6) acquisition was associated with female sex (adjusted hazard ratio of 1.7) and having older siblings (adjusted hazard ratio of 2.1). Of the 227 children, 46% were female, and 52% had at least one sibling, said Danielle M. Zerr, M.D., of the department of pediatrics, University of Washington, Seattle, and her colleagues.

HHV-6 infection was monitored using polymerase chain reaction on saliva samples obtained weekly by parents using precut filter-paper strips. Serological de-

tection of anti-HHV-6 antibodies was performed whenever a blood sample was taken from the child for other purposes.

Of the 81 children with a well-defined time of HHV-6 acquisition, 93% showed symptoms, most commonly fussiness (69%), rhinorrhea (65%), and fever (57%), with less-frequent occurrences of cough (33%), rash (31%), and diarrhea (26%).

Roseola, a clinical syndrome considered relatively specific for HHV-6, occurred in only 23% of the 81 children.

No seizures were reported. This was "in contrast to emergency department-based studies, in which seizures occurred in as many as 13% of children with primary HHV-6 infection," they wrote.

Previous serologic studies have shown that HHV-6 infects 90% of children by 2 years of age, and it has been estimated that 20% of emergency department visits for fever are due to primary HHV-6 infection. ■

## Consider Musculoskeletal Adverse Effects When Using Fluoroquinolones in Children

BY SHARON  
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BAL HARBOUR, FLA. — Fluoroquinolones must be used judiciously in children, Sarah S. Long, M.D., said at the annual Masters of Pediatrics conference sponsored by the University of Miami.

These drugs are increasingly available, and they are being widely prescribed to children. More than 520,000 prescriptions for fluoroquinolones were written for this population in 2002—with more than 16,000 written for those under age 6 years and nearly 3,000 written for those under age 2 years, said Dr. Long, professor of pediatrics at Drexel University, Philadelphia.

And that was before ciprofloxacin received Food and Drug Administration approval for use in those under age 18 years with complicated urinary tract infections, pyelonephritis,

and inhalation anthrax exposure, Dr. Long said.

The FDA granted this approval last year, but there is little guidance beyond that for the use of fluoroquinolones in the pediatric population.

The advantages of fluoroquinolones include oral administration, excellent oral bioavailability, and a gram-negative spectrum, but these drugs are associated with adverse musculoskeletal events. The potential for spontaneous Achilles tendon rupture is of particular concern, Dr. Long commented.

Tendon rupture is a rare event, but it is definitely "above the radar," she said.

"These drugs do have some effect on cartilage—there is no question," she added.

In addition, there is some concern about whether they are associated with long-term arthropathy, she noted.

Central nervous system, hepatic, and metabolic effects are also possible, and some patients

experience photosensitivity and rashes after taking fluoroquinolones.

Therefore, the use of these drugs in children should be limited mainly to serious gram-negative rod infections for which there are no other treatment alternatives, Dr. Long said.

Conditions for which fluoroquinolones may be appropriate in children—other than the approved uses—include chronic otitis, chronic or acute *Pseudomonas aeruginosa* osteomyelitis, cystic fibrosis exacerbations, certain mycobacterium infections, and multidrug-resistant shigella, salmonella, or vibrio infections.

Topical treatment is acceptable for conjunctivitis and otitis externa that are refractory or resistant to other treatments, but fluoroquinolones should not be used for plain conjunctivitis or otitis media or for community-acquired bronchitis and pneumonia, Dr. Long said. ■