Four fatal cases of viral hemorrhagic fever linked to a New World arenavirus that had never before been acquired by humans in North America were summarized by the Centers for Disease Control and Prevention (CDC) in the Morbidity and Mortality Weekly Report (MMWR) [1]. “This virus is not likely to spread,” said Thomas Ksiazek, PhD, DVM, medical epidemiologist at the National Centers for Infectious Diseases, CDC.

According to the CDC, all 3 patients were female residents of California (none had a history of travel during the 4 weeks preceding their illness) who experienced onset of illness during June 1999 to May 2000. They were aged 14, 30, and 52 years. In the first week of hospitalization, lymphopenia (lymphocyte count, 25±700 cells/mm³) was seen in all 3 patients, and thrombocytopenia (platelet count, 30,000±40,000 cells/mm³) was seen in 2. All 3 patients had acute respiratory distress syndrome, and 2 had liver failure and bleeding consistent with viral hemorrhagic fever. The patients died 1–8 weeks after the onset of illness.

The sequence homology (87% identical PCR-product nucleotide sequence) of the 3 patients is similar enough to be designated as a strain of Whitewater Arroyo virus, Ksiazek explained. According to the MMWR, the Whitewater Arroyo virus is found in North American woodrats.

According to Ksiazek, Whitewater Arroyo virus already occupies a niche in a natural association with a rodent to which it is well adapted. “The virus and the rodent have a stable relationship that has developed in the evolution of the two species together. The virus can infect other rodents, but these infections do not lead to the other rodent species becoming a new reservoir for the virus; otherwise, this would have likely happened already,” he explained.

Ksiazek compared the abundance and habits of woodrats (Neotoma albigula) with those of the deer mouse. “The rodents are widely distributed in the United States, but they are not as abundant in absolute numbers as are such rodents as Peromyscus maniculatus, the deer mouse that is the reservoir/vector of hantavirus pulmonary syndrome. The woodrats also are not generalists in their habits and therefore do not readily use human habitations and outbuildings as their home in the way the deer mouse does. In the aggregate, this suggests that the amount of contact between humans and the various species of Neotoma will not be expected to be as great as, for instance, the amount of contact between humans and the deer mouse,” he said.

“Although rare, person-to-person transmission has been documented for some New World viruses; nosocomial transmission can occur through direct contact with an infected patient’s blood, urine, or pharyngeal secretions,” states the MMWR. However, person-to-person transmission of arenavirus has not been detected in North America. In 1988, the CDC published the article “Management of Patients with Suspected Viral Hemorrhagic Fever” [2]. According to Ksiazek, an interim update of these CDC guidelines was published in 1995 [3], and these updated guidelines still apply, as mentioned in the August 20th issue of MMWR.

Unfortunately, detection of serological evidence of arenavirus infections in humans is difficult. “The natural evolution of the antibody response to most arenavirus infections is delayed (in relation to other viral infections). These patients all died. It would not be unusual, for instance, to not have found antibody in patients who had died of Lassa fever virus or Machuputo virus,” explained Ksiazek.

According to the MMWR [1], efforts are under way to evaluate additional laboratory diagnostic tests for the detection of arenavirus. “The experience of 3 cases doesn’t provide any confidence for the use of any particular diagnostic test,” Ksiazek said. “The fact that these are all based on reverse transcriptase-PCR is also somewhat difficult to disseminate to commercial and hospital laboratories. Although there are PCR-based diagnostic tests for HIV and hepatitis C that have been commercially distributed, the technology is probably not so robust, particularly for this agent, that I would feel comfortable with it being used as the sole means of diagnosis.”

Effective treatment may be available for arenavirus infections, noted Ksiazek. “Ribavirin has been used for Lassa fever infections, and it has also been used, to a lesser extent, for Junin (Argentine hemorrhagic) fever. The drug is worthy of clinical evaluation under appropriate conditions.” For more information, see the CDC Fact Sheet on Arenaviridae that is available at http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/arena.htm
References


Misuse of and Resistance to Antibacterial Drug Products Addressed in Labeling

The Food and Drug Administration (FDA) has proposed that the professional labeling of all systemic antibacterial drug products (for human use) contain information about the inappropriate use of antimicrobial drugs and its relation to the emergence of drug-resistant bacterial strains. The proposed rule is published in the September 19th issue of the Federal Register.

“Our hope is that the rule and requirement for standard language in antibiotic labels will be one step toward improving the ways that physicians and consumers think about antibiotic use,” said Sandra Kweder, MD, deputy director of the Office of Drug Evaluation IV, Center for Drug Evaluation and Research, FDA.

According to the proposed rule, the labeling (e.g., package inserts and Physician’s Desk Reference [PDR] entries) would include the following reminders for physicians:

1. Antibacterial drugs should only be used in situations in which a bacterial infection is either proven or strongly suspected.
2. The type of bacteria involved in an illness and its antimicrobial susceptibility pattern should be used to direct the initial choice of an antibacterial drug product.
3. Antimicrobial therapy should be modified once microbiological results (both the pathogen involved and the susceptibility patterns) are available.
4. Patients should be counseled about the proper use of antibacterial drugs and the importance of taking them only as directed.

Some critics of the proposed rule have questioned whether these messages will be read by physicians. “Most research in this area tells us that physicians do not routinely read these at the time of prescription,” concurred Kweder. “On the other hand, they do look to labels and the PDR when they need specific pieces of information, including, typically, information on dose, administration schedule, or adverse events. That is why our proposed rule includes a requirement for appropriate statements to be placed throughout the label, so that the statements will be relevant to those sections wherein they lie,” she explained.

How will the FDA evaluate whether this is an effective way of relaying this message to physicians? Kweder’s response to this question was, “We do not have a specific plan in place, because we are but one of many public health organizations attempting to address the problem of misuse of antibiotics as a root cause of antimicrobial resistance. It will make it difficult to evaluate any one action’s impact. Nonetheless, we are confident that, by taking this step, the FDA can make a difference. By virtue of their appearance in labeling, some of the statements we are requiring will ultimately appear in drug companies’ advertising and promotional materials.”

Kweder also noted that the proposed rule includes a provision to require corollary statements to the professional labeling in the “Information to Patients” section of the label. These patient-directed sections are often used by commercial pharmacies and patient education organizations to “translate” professional labeling into consumer-friendly materials, she said.

The Federal Register document includes sections with background information on antimicrobial resistance, factors contributing to the emergence of resistance, what can be done to respond to the resistance problem, and cost-benefit analyses of the proposed rule.

The proposed rule may affect up to 761 drug products, according to the FDA. Antifungal, antiviral, antiparasitic, and topical antimicrobial products would not be subject to the labeling requirements. According to industry consultants, the estimated cost of changing professional labeling is $2,600 per product. In the first year, therefore, firms may incur a one-time cost of approximately $2 million, the FDA says.

Written comments about the proposed rule should be submitted to the following address by December 4, 2000: Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. A final rule would become effective 1 year after the date of its publication in the Federal Register. After that date, all new systemic antibacterial drugs and generic drugs, including drugs that have already been approved and that are currently on the market, would have to comply with the labeling requirements.