Recommendations for Prevention of and Therapy for Exposure to B Virus (*Cercopithecine Herpesvirus* 1)

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B virus (*Cercopithecine herpesvirus* 1) is a zoonotic agent that can cause fatal encephalomyelitis in humans. The virus naturally infects macaque monkeys, resulting in disease that is similar to herpes simplex virus infection in humans. Although B virus infection generally is asymptomatic or mild in macaques, it can be fatal in humans. Previously reported cases of B virus disease in humans usually have been attributed to animal bites, scratches, or percutaneous inoculation with infected materials; however, the first fatal case of B virus infection due to mucosal splash exposure was reported in 1998. This case prompted the Centers for Disease Control and Prevention (Atlanta, Georgia) to convene a working group in 1999 to reconsider the prior recommendations for prevention and treatment of B virus exposure. The present report updates previous recommendations for the prevention, evaluation, and treatment of B virus infection in humans and considers the role of newer antiviral agents in postexposure prophylaxis.

B virus (*Cercopithecine herpesvirus* 1) is a naturally occurring infectious agent that is endemic among macaque monkeys (including rhesus macaques, pig-tailed macaques, cynomolgus monkeys, and other macaques) [1–3]. Animals become infected with the virus primarily through exposure of the mucosa or skin to oral or genital secretions from other monkeys. Vertical transmission of the virus to neonates is rare. Infected monkeys often have no or very mild symptoms, although oral and genital lesions may develop. The virus persists in the sensory ganglia for the lifetime of the animal and can reactivate, resulting in the shedding of infectious virus from the oral, conjunctival, or genital mucosa of animals with or without visible lesions.

Infections due to B virus in humans are rare and occur as a result of exposure to either macaques or their secretions or tissues. The incubation period for infection in humans after an identified exposure is reported to range from 2 days to 5 weeks; most well-documented cases present 5–21 days after exposure. Some patients present with a progression of symptoms that first appear near the site of exposure; others present with symptoms limited to the peripheral nervous system or CNS. A third presentation involves flulike illness with fever, chills, myalgias, and other nonspecific symptoms, with no focal findings, and it may later be followed by the abrupt onset of CNS symptoms.

After infecting humans, B virus replicates at the site of exposure and may result in the development of a vesicular rash at this site. Additional symptoms can include tingling, itching, pain, or numbness at the site; however, many patients have no symptoms at the site of infection. Some patients develop lymphadenopathy proximal to the site of inoculation. Within the first 3 weeks after exposure, paresthesias may develop and

proceed proximally along the affected extremity. Associated symptoms can include fever, myalgias, weakness of the affected extremity, abdominal pain, sinusitis, and conjunctivitis. Other organs, including the lung and liver, may be involved.

The virus spreads along the nerves of the peripheral nervous system to the spinal cord and then to the brain. Symptoms of infection can include meningismus, nausea, vomiting, persistent headache, confusion, diplopia, dysphagia, dizziness, dysarthria, cranial nerve palsies, and ataxia. Seizures, hemiplegia, hemiparesis, ascending paralysis, respiratory failure, and coma more commonly occur later in the course of infection. Some patients have presented with symptoms within 48 h after exposure to the virus [4]. The overall presentation of late-stage disease is that of brain stem encephalomyelitis that may evolve into diffuse encephalomyelitis during its terminal stages. This presentation is in contrast to the more focal neurologic disease observed in association with herpes simplex encephalitis. Among untreated humans, the mortality rate associated with B virus infection is estimated to be 80% [3]. The mortality rate has declined since the advent of antiviral therapy.

TYPES OF EXPOSURE

Humans have become infected after exposure to the infectious tissues or fluids of monkeys. The ocular, oral, or genital secretions of monkeys, as well as the CNS tissues and CSF of monkeys, are potentially infectious. Primary cell cultures derived from macaque kidneys are a potential source of virus. Exposure to peripheral blood from monkeys has not been reported to cause infection in humans. Although ∼50 cases of B virus infection in humans have been identified to date, only 26 cases have been well documented (table 1). Documented routes of B virus infection include animal bites and scratches, exposure to tissue culture material, exposure to tissue obtained during autopsies of monkeys, needlestick injuries, cage scratches, mucosal splash, and human-to-human transmission. The only case of person-to-person transmission occurred in a woman who applied medication (hydrocortisone cream) both to areas of her skin that were affected by contact dermatitis and to her husband's vesicular lesions (which contained B virus) [10]. B virus was subsequently cultured from samples of her skin lesions and conjunctiva. The only documented case of B virus infection resulting from mucosal exposure without percutaneous injury occurred in a person who worked with primates and who was splashed in the eye with material from a rhesus monkey [19]. She washed her eye briefly 45 min after the exposure occurred, but she developed conjunctivitis 10 days later and died of B virus encephalomyelitis 6 weeks later. Because it appears that mucocutaneous contact with the body fluids of nonhuman primates (hereafter known as "primates") is common among persons who work with or near nonhuman

Table 1. Well-documented cases of B virus infection in humans.

Exposure	No. of cases	Reference(s)
Monkey bite	10	[4–11]
Monkey scratch	2	[4, 12]
Wound contamination with monkey saliva	1	[13]
Tissue culture-bottle cuts[a]	1	[7]
Needlestick injury[b]	2	[4, 14]
Possible aerosol[c]	2	[15, 16]
Cleaned monkey skull	1	[4]
Needle scratch and monkey bite	1	[4]
Cage scratch	2	[10, 17]
Possible reactivation of B virus	1	[18]
Human-to-human contact[d]	1	[10]
Mucosal splash[e]	1	[19]
Unknown	1	[20]
Total	26	

[a] Cultures involved monkey kidney cells.
[b] In one case, a needle had been used to inject the tissues around the eye, and, in the other case, a needle "may have been used previously to inject monkeys" [4, p. 974].
[c] In one case, aerosol may have been generated during autopsies performed on macaques, and, in the other case, the patient presented with respiratory symptoms.
[d] The patient applied cream to her husband's herpes vesicles and to areas of her own skin that were affected by contact dermatitis.
[e] The patient was splashed in the eye with material, possibly feces, from a macaque.

primates ("primate workers") [19], the risk of B virus infection due to percutaneous exposure to infectious body fluids (primarily saliva) appears to be greater than that of B virus infection due to mucosal splash exposure.

Of importance, many cases of B virus infection in humans have been associated with exposures that were considered trivial. In other cases, multiple exposures had occurred over a period of years, although patients could not recall having had a recent exposure at the time of infection [8, 12, 20]. One case of B virus disease was reported to have occurred in a worker whose last documented exposure to primates occurred >10 years before infection developed [18]. The patient was reported to have had reactivation of latent B virus infection; however, it is possible that infection resulted from a more recent exposure that had seemed trivial at the time and that had not been reported.

RISK FOR TRANSMISSION OF B VIRUS TO PRIMATE WORKERS

The prevalence of shedding of B virus is increased among primates that are stressed, breeding, immunosuppressed, or ill. In one survey, nearly 100% of captive macaques ⩾2.5 years of age were seropositive for the virus, whereas ∼20% of animals <2.5 years of age were seropositive [21]. On a given day, ∼2% of

one group of seropositive rhesus monkeys shed B virus [22]. Thus, multiplication of these rates ($1 \times \frac{1}{50}$ or $\frac{1}{5} \times \frac{1}{50}$) indicates that from 1 in 50 to 1 in 250 contacts with macaques have the potential to result in exposure to material contaminated with B virus.

How frequently disease occurs after exposure to B virus–contaminated material is unknown. However, although hundreds of monkey bites and scratches occur among primate workers in the United States each year, B virus infection in humans is rare. Asymptomatic infection of humans has not been documented [23]. In a study of 321 primate workers, potential exposures to B virus, including those resulting from bites and scratches, were reported by 166 workers; however, none of the workers were considered to be B virus seropositive, as defined by positive results of both ELISA and Western blot analysis [23]. In a study of household contacts of patients with B virus infections, hospital workers, and primate workers that was performed when a cluster of cases of B virus infection occurred in Florida, 0 of 130 asymptomatic persons tested were found to be seropositive for B virus [10]. Similarly, in a study of animal workers that was performed when a group of cases of B virus infection occurred in Michigan, 0 of 116 asymptomatic employees were found to be seropositive [11].

Analysis of cases of B virus infection among primate workers suggests that certain types of exposures may pose greater risks. These exposures include deep puncture wounds that are difficult to clean, inadequately cleansed wounds, and wounds sustained on the face (especially wounds to the eye), neck, or thorax. Because the virus replicates at the site of infection and then ascends to the CNS along the axon, inoculation of the head or thorax with the virus allows little time for the development of symptoms that do not involve the CNS, and it may be difficult to recognize and treat the disease before the CNS is infected.

RATIONALE FOR POSTEXPOSURE PROPHYLAXIS

Postexposure prophylaxis is defined as administration of antiviral medication to a person potentially exposed to B virus but not known to be infected. The use of postexposure prophylaxis to prevent B virus infection in humans has not been proven to be effective. However, postexposure prophylaxis prevents disease in rabbits experimentally inoculated with B virus. There are several reasons why these experiments are not a perfect model for infections in humans. First, the amount of inoculum used in experiments in animals may be greater than the inoculum during human exposure to a primate. Second, in rabbits, the animal most commonly used in studies, B virus infection results in more rapid progression of virus to the CNS than has been noted in humans. Third, one of the most com-

monly recommended antiviral agents, acyclovir, has a shorter plasma half-life in rabbits than in humans. For all these reasons, postexposure prophylaxis might be more effective in humans than in experimental studies of rabbits; however, it is not known if this is the case.

Boulter et al. [24] evaluated the efficacy of intravenous acyclovir given for 5–14 days to rabbits inoculated with lethal doses of B virus. Treatment that began within 24 h after exposure to B virus and that lasted for 2 weeks resulted in complete protection from death, whereas treatment initiated up to 5 days after exposure yielded a significant decrease in mortality. To be effective, treatment was required every 8 h for 14 days. A shorter duration of treatment resulted in delayed onset of ultimately fatal infection.

Zwartouw et al. [25] compared oral acyclovir and oral ganciclovir for the treatment of rabbits for a period of 3 weeks that began the day after the rabbits were inoculated with B virus. Although animals that received acyclovir at a dosage of 500 mg/kg/day for 3 weeks survived, a dosage of 700 mg/kg/day was required to prevent animals from developing disease. In contrast, ganciclovir was more effective than acyclovir for the prevention of disease; animals required only 2 weeks of treatment with ganciclovir given at a dosage of 100 mg/kg/day beginning 1 day after inoculation for the prevention of disease. Furthermore, all animals that received ganciclovir at a dosage of 170 mg/kg/day within 5 days after inoculation with B virus survived.

Few data exist to assess the effectiveness of postexposure prophylaxis for B virus infection in humans. To our knowledge, there have been no cases in which humans who received postexposure prophylaxis within 72 h of exposure developed disease; however, as previously noted, the number of persons with potential exposure to B virus is large, and the number of cases of documented infection is small, even without the use of prophylaxis.

RECOMMENDATIONS FOR THE MANAGEMENT OF PERSONS EXPOSED TO B VIRUS

Planning before Exposure

Previous recommendations for the prevention of B virus infection in humans [1, 26] were published before the fatal case transmitted by an ocular splash was reported [19]. In view of this case, the use of either protective eyewear (e.g., goggles or glasses with solid side shields) and a mask or a chin-length wraparound face shield and a mask is recommended to protect the mucous membranes of workers in areas where captive macaques are located. Furthermore, face shields or glasses with side shields must be able to prevent splashes to the head from running down into the eyes.

Table 2. Laboratories that perform tests for B virus.

Physician, laboratory, and contact information	Available tests for B virus
Dr. Julia Hilliard B Virus Research and Resource Laboratory Georgia State University PO Box 4118 Atlanta, GA 30302-4118 Phone: 404-651-0808 E-mail: biojkh@panther.gsu.edu Internet address: http://www.gsu.edu/~wwwvir/ index.html	Culture, serologic testing, and PCR analysis of specimens from humans or nonhuman primates
Dr. David Brown Enteric, Respiratory, and Neurological Virus Laboratory Central Public Health Laboratory 61 Colindale Ave. London NW9 5HT, England Phone: 44-208-200-4400 E-mail: dbrown@phls.org.uk	Culture, serologic testing, and PCR analysis of specimens from humans or nonhuman primates
Dr. Seymour S. Kalter Esoterix 7540 Louis Pasteur Dr., Ste. 200 San Antonio, Texas 78229 Phone: 210-614-7350 E-mail: sy.kalter@esoterix.com	Culture and serologic testing of specimens from nonhuman primates only

An occupational health care system should be made available to primate workers for documentation of potential exposures, for counseling, and, in some cases, for treatment of workers who have been exposed; follow-up should also be provided for such workers. Animal workers who care for macaques should be informed of the biohazards associated with these monkeys and the importance of notifying their supervisors and occupational health care personnel if bites, scratches, or mucocutaneous exposures occur. All macaques should be treated as if they are seropositive for B virus, regardless of their origin. Workers must receive training about B virus and other biohazards before working with primates, and additional education should be provided on an annual basis, whenever there is a change in job responsibilities, and whenever an exposure has occurred. Training should include practice in or demonstrations of eye washing and wound cleansing, in addition to didactic training. So that baseline serum levels are available for comparison in the event of an exposure, the occupational health care provider should consider collecting and then storing serum samples obtained from primate workers at the time of employment.

Materials including supplies used for first aid and specimen collection, copies of written instructional materials, and treatment protocols for exposures should be available in areas where exposure can occur. The primate facility is responsible for making these materials available and for educating employees regarding their use. In a field station, where access to emergency evaluation and care will be delayed, an exposure kit (reviewed in [1]) should be in place. Signs that indicate the proper actions to take in the event of exposure should be posted in areas in which exposures to macaques may occur.

Because confirmed cases of B virus infection have occurred in animal caretakers who work with macaques but who do not recall obvious exposures, workers need to be aware that any episode of prolonged fever (for >48 h), flulike symptoms, or symptoms compatible with B virus infection, even in the absence of a known exposure, needs to be reported to their supervisor and to occupational health care personnel. Primate workers should be given a card to carry in their wallet that indicates the symptoms of B virus infection, contact information for a local health care provider who is knowledgeable about B virus, contact information for expert clinical and laboratory consultation regarding B virus (e.g., the state health department, the Centers for Disease Control and Prevention [Atlanta, GA], or a B virus diagnostic laboratory) (table 2), and a reference for prophylaxis and therapy guidelines. In addition, both the worker and the primate facility should have access to a physician who has specific knowledge about B virus, so that delays do not occur during evaluation of the worker.

Intervention after an Exposure

First aid. The most critical period for the prevention of B virus infection and other infections is during the first few minutes after an exposure occurs. Both the adequacy and the timeliness of wound or mucosa cleansing are the most important factors for reducing the risk of infection. Primate workers should be instructed to immediately cleanse the skin or mucosa affected by bites, scratches, or exposure to any poten-

Table 3. Initial management of B virus exposure.

First aid

  Mucous membrane exposure: flush eye or mucous membranes with sterile saline solution or water for 15 min

  Skin exposure

    Wash skin thoroughly with a solution containing detergent soap (e.g., chlorhexidine or povidone-iodine) for 15 min

    Consider washing skin with 0.25% hypochlorite solution, followed by detergent solution, for 10–15 min (see the "First aid" subsection of the Recommendations for the Management of Persons Exposed to B Virus section of the text for precautions)

Initial evaluation

  Human

    Assess the adequacy of cleansing; the health care provider should repeat cleansing

    Determine the date, time, location, and description of the injury, and the type of fluid or tissue contacted

    Evaluate general health (including medications) and determine when the last tetanus booster was received

    Determine the need for postexposure prophylaxis with antibiotics or rabies vaccine and immunoglobulin

  Nonhuman primate

    Identify the monkey associated with the exposure, the species of that monkey, and the responsible veterinarian

    Assess general health (including medications and involvement in past and present research studies)

    Evaluate prior serologic history (including infection with B virus or simian immunodeficiency virus)

Examination and laboratory testing

  Human

    Physical examination, especially evaluation of the site of the exposure and neurologic examination

    Consider obtaining serum samples at baseline for serologic analysis

    Consider culturing specimens from the site of the wound or the exposed mucosa

  Nonhuman primate

    Examine the animal for mucosal lesions (e.g., vesicles, ulcers), conjunctivitis, etc.

    Consider culturing specimens from the lesions, conjunctiva, and buccal mucosa

    Consider serologic testing for B virus (if the animal is not known to be seropositive)

Education and treatment

  Counsel the patient regarding the significance of the injury

  Provide the patient with information on the signs and symptoms of B virus infection

  Ensure that the patient has a card (to carry in his or her wallet) that includes information on B virus and a phone number to call for advice in an emergency

  Ensure that the patient's occupational health care provider and supervisor are notified of injury

  Review with the patient and his or her work supervisor the safety precautions in place at the time of injury

  Schedule a follow-up appointment

  Consider postexposure prophylaxis (see table 5)

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tially infected material from macaques (table 3). Washing of the involved site should last for at least 15 min.

Eyes or mucous membranes potentially exposed to B virus should be irrigated immediately with sterile saline solution or water for 15 min. If reaching the nearest eye-washing station requires a delay of more than a few minutes, then a kit that contains a 1-L bag of sterile saline should be available at the work site. If the worker is based at a remote location, he or she should transport a 1-L bag of saline to that site, so there will not be a delay in cleansing the wound or mucosa.

Potentially exposed skin should be washed with povidone-iodine, chlorhexidine, or detergent soap. These solutions can destroy the virus lipid envelope and inactivate virus on the skin; however, they are too harsh to use when washing the eye or mucous membranes. In addition to being washed, wounds may be gently massaged to increase their contact with the

cleansing solutions. Incision of wounds or biopsy of wound sites is not recommended.

Use of a 0.25% hypochlorite solution (Dakin's solution) can cause rapid inactivation of herpesviruses. However, this solution is more toxic than are the previously mentioned detergents, and the risk of harming tissues needs to be balanced against the benefit of increased antiviral activity. Hypochlorite solution (0.25%) is not stable for long periods; it should be prepared, when needed, by diluting standard household bleach 1:20 in water. If hypochlorite solution is used, the exposed area should subsequently be washed with detergent as previously described. Hypochlorite solution should *never* be used to wash mucous membranes or the eye, and, therefore, caution should be exercised when hypochlorite solution is used to wash areas near the eye.

Initial evaluation by the health care provider. Persons with potential exposure to B virus should report to their occupational health care provider for counseling and education and to receive written materials about the signs and symptoms of B virus infection. In addition to providing counseling, the occupational health care provider should facilitate rapid access to a local medical consultant who is knowledgeable about B virus and other hazards associated with primates. The person who has been exposed to B virus should have the information needed to gain direct access to the occupational health care provider as well as to a local medical consultant for follow-up.

A procedure should be in place to handle exposures to B virus that occur after regular working hours. If the person who has been exposed prefers to be evaluated by his or her personal physician, the occupational health care provider should be available for consultation. The person who has been exposed should be aware that his or her personal physician is unlikely to have any knowledge of or experience in treating or preventing B virus infection, and the occupational health care provider should make written information about B virus available to the physician.

The health care provider should obtain a detailed history, which should note the time, source, and type of exposure; the safety procedures that were in place at the time of exposure; and the time and adequacy of cleansing after the exposure. To ensure that cleansing is done properly, the exposed area should be cleaned again (as described in the "First aid" subsection above), regardless of a history of having been cleaned. The area that may have been exposed should be carefully examined, and the likelihood that an exposure has occurred should be determined.

The monkey's medical record should be reviewed to determine the following information: the monkey's current state of health, history of exposure to infectious agents, and the type of research in which the monkey has been involved. The referring facility should provide information about the monkey's health status to the physician. The monkey should be examined for active lesions that are compatible with B virus infection, if this can be done safely. Both the circumstances of the human exposure and information on the health status of the monkey should be considered when decisions are made regarding evaluation and treatment. These decisions include whether to perform cultures for the detection of B virus; whether to collect blood samples for serologic analysis; whether to administer postexposure prophylaxis, a tetanus booster, rabies immunoglobulin and vaccine, or antibiotic prophylaxis for bacterial infections [27]; and whether other potential exposures (e.g., to retroviruses) may have occurred.

Although only 1 case of person-to-person transmission of B virus has occurred, positive results of cultures from the conjunctiva and buccal mucosa of an infected patient receiving intravenous acyclovir therapy demonstrated shedding of infectious B virus for >1 week after the onset of therapy ([10]; L.E.C. and J.K.H., unpublished data). Thus, potentially infected persons should be counseled to avoid exposing others to body fluids or skin lesions during the incubation period.

LABORATORY TESTING OF THE EXPOSED WORKER

Culture

B virus is classified as a Biosafety Level–4 biologic agent (belonging to the same group as Ebola virus and Marburg virus). Work involving concentrated stocks of B virus should be performed at Biosafety Level–4 facilities, whereas testing of material known or suspected to contain B virus should done at a facility designated as having a Biosafety Level of 3 or higher [28]. Cultures must not be sent to routine diagnostic laboratories but, rather, to a facility that has expertise in testing for B virus. There are 3 laboratories that perform diagnostic testing for the agent (table 2). The B Virus Research and Resource Laboratory at Georgia State University (Atlanta) is the major reference laboratory in the United States for diagnostic testing for B virus in humans. Materials sent for B virus culture and PCR analysis, which may contain infectious material, must be sent in approved packaging [1].

It is important to determine how the information obtained from culture or other diagnostic tests (e.g., PCR analysis for viral DNA) will be used and interpreted *before* it is obtained. Decisions regarding postexposure prophylaxis need to be made before the results of cultures are available, because several days may be required for cultures to yield positive results if virus is present.

Culture of material from the wound or the site of exposure before cleansing is not recommended because it delays cleansing, may force virus on the surface of the wound further into the wound, and may further contaminate the wound with in-

fected material located nearby. Cultures of specimens from the wound or the site of exposure that are performed after cleansing (even cultures of material from wounds that have resulted in known infections) are usually negative for B virus, and some authorities do not believe that performance of such cultures is worthwhile, except in unusual circumstances. Conversely, positive results of cultures of wounds or other exposure sites do not confirm infection with B virus. Positive wound culture results do confirm that a high-risk exposure has occurred and that postexposure prophylaxis is indicated. The use of PCR for the detection of B virus might provide more-rapid results than does culture; however, there is less experience in how to interpret a positive PCR result, because it is not clear that replication-competent virus is present if a wound is found to be positive for viral DNA by PCR analysis. B virus was not detected by PCR in a published study of wound swab samples [29].

Identification of virus at the site of exposure or in a wound does not prove infection with the virus. However, a positive culture or PCR result indicating the presence of viral DNA either at a site not directly associated with the exposure (e.g., the conjunctiva, in the case of a bite), or in a wound or at a site of exposure concurrent with symptoms compatible with B virus disease should be considered indicative of infection.

Serologic Analysis

The employer and the occupational health care provider should have a policy in place for determination of when serologic testing should be performed. In some cases, it may be appropriate to collect and store serum samples at the time of the exposure and again 3–6 weeks after exposure occurred, and to send them for testing if warranted. In the United States, human serum samples obtained for B virus testing should be sent to the B Virus Research and Reference Laboratory at Georgia State University (table 2).

Asymptomatic seroconversion has not been reported in the literature. Although some authorities recommend performing serologic testing only for symptomatic persons, others recommend testing serum samples obtained from asymptomatic but potentially exposed persons if the health care provider and/or the primate worker believe that the results would be helpful in making additional management decisions or providing peace of mind to the exposed worker.

Assessment of serum antibody levels is most useful if serologic analysis has been performed at the time of exposure and its results can be compared with those of serologic analysis performed at a later date. The initial serum sample obtained should be frozen at a temperature of –20°C or lower, preferably in a freezer that does not go through freeze-thaw cycles. A second serum sample should be obtained 3–6 weeks later or at the onset of clinical symptoms. If sent for testing, these serum samples should be analyzed simultaneously. Seroconversion or a significant (≥4-fold) increase in titer is highly suggestive of acute infection. In some cases, a third serum sample, obtained 3 months after exposure, may be useful, particularly if postexposure prophylaxis is given (see the Follow-up after Exposure section below). If a baseline serum antibody level has not been obtained, serial testing of serum samples can be performed to detect a change in titer and, thus, the likelihood of the presence of a new infection. Serologic analysis should involve the testing of paired samples. Testing of single specimens might be considered if clinical signs or symptoms of B virus infection are present. Even if signs and symptoms are present, it is important to obtain a second specimen at a later date to allow for testing of paired (acute- and convalescent-phase) serum samples. Because of the cross-reactivity of B virus with herpes simplex virus, a serologic test that is positive for B virus should be confirmed with a Western blot (immunoblot) or competition ELISA [23].

LABORATORY TESTING OF THE PRIMATE

Culture

The possible benefits of obtaining specimens from the primate must be balanced against the risks incurred by other workers in obtaining these specimens. In less-controlled settings and in the absence of expertise in capturing animals, it may be more advisable to observe the primate and look for obvious lesions, rather than to trap the animal to obtain for blood for testing. However, it is important to note that oral or genital lesions are rarely visible when an animal is shedding B virus, and that not all lesions are due to the virus.

The sites from which specimens can be obtained from primates for B virus culture include the buccal mucosa (for exposures that involve oral secretions), the conjunctiva, or the urogenital area (if contaminated urine or feces are implicated in the exposure). Cultures are subject to sampling error, and shedding of virus can be intermittent.

Serologic Analysis

Currently, all macaque monkeys should be considered seropositive for B virus. Interpretation of negative serologic test results may be misleading. Monkeys found to be seronegative when tested weeks before an exposure occurred could be seropositive at the time of the exposure. Animals that are seronegative at the time of exposure could be undergoing primary infection and may not yet have seroconverted; thus, retesting of the animals several weeks after the exposure may be required to rule out acute infection at the time of the exposure.

POSTEXPOSURE PROPHYLAXIS

Although fatal cases of B virus disease in humans have occurred in primate workers who do not recall an obvious exposure or who have had what would be considered a low-risk exposure, it is not reasonable to provide prophylaxis for every potential exposure (table 4). We are currently unable to accurately quantify the risk associated with all exposures. Thus, these recommendations can only be considered as guidelines. For certain "low-risk" exposures, postexposure prophylaxis may be appropriate when the primate worker and/or the occupational health provider would be more comfortable with the use of prophylaxis.

For each primate exposure, 4 major variables need to be assessed. First, the source of the exposure should be determined. Macaques are the only primates known to transmit B virus. Other primates pose no known risk unless they have had the opportunity to acquire infection directly from a macaque. Macaques that have lesions compatible with B virus or that are known to be culture positive for the virus are more likely to be shedding virus. Immunocompromised or otherwise ill animals, stressed animals, breeding animals, and recently acquired primates that are still in quarantine are all more likely to shed B virus [30].

Second, the timeliness and adequacy of first aid for the wound should be assessed. Was the wound cleansed within 5 min of exposure, and was the duration of cleansing a full 15 min? Mucosal splashes or wounds that are inadequately cleansed are more likely to become infected, because there is an increased duration of exposure to infectious material.

Third, the type of wound or exposure, the depth of the wound, and the location of the wound should all be determined. Infections that occur as a result of exposure of the head, torso, or neck may result in no signs or symptoms before the CNS is involved and should be classified as high risk (see the Risk for Transmission of B Virus to Primate Workers section). Studies of rabies virus, which progresses along neural pathways from a peripheral site to the CNS, have shown that animal bites to the head and neck are more likely to result in fatal disease (percent mortality, 30%–100%) than are bites to the fingers or hands (percent mortality, 15%–20%) [31]. Because B virus also travels to the CNS by these pathways, we recommend postexposure prophylaxis for potential exposures to B virus when the head, neck, or torso is involved. Superficial wounds and scratches are easily cleansed and, therefore, usually are considered low risk. Deep punctures—in particular, those caused by bites—are likely to result in inadequately cleansed wounds and pose a higher risk. Studies of rabies virus indicate that superficial wounds and scratches to the extremities are less likely to result in fatal disease (percent mortality, 0.5%–5%) than are deeper bites (percent mortality, 15%–20%) [31]. Thus, we recommend postexposure prophylaxis for persons with potential B virus exposures involving deep wounds or punctures.

Fourth, exposure to materials that have come in contact with macaques, in addition to direct exposure to the animals, must be evaluated. B virus is latent in the CNS of macaques and is shed intermittently from the mucosa of infected animals. Therefore, punctures with needles that contain material from the CNS, eyelids, or mucosa of macaques are considered high-risk exposures. Although a case of viremia in an ill monkey has been reported [32], viremia rarely occurs in healthy animals [33]. Therefore, punctures with needles contaminated with peripheral blood from monkeys are considered exposures of much lower associated risk. Needlestick injuries were associated with 2 of the cases of B virus presented in table 1. One of the injuries involved a needle that had been exposed to the ocular tissues of a monkey [14], whereas the other injury involved a needle that "may have been used previously to inject monkeys" [4, p. 974].

Using the aforementioned principles, we have identified 7 different exposures for which postexposure prophylaxis is recommended (table 5). If postexposure prophylaxis is administered, it should be started soon (within hours) after the ex-

Table 4. Pros and cons of postexposure prophylaxis for persons exposed to B virus.

Pros

    Initiation of acyclovir therapy within 24 h after exposure to B virus prevents death among animals [24]

    Initiation of acyclovir therapy within hours of exposure may prevent or modify symptomatic B virus disease

Cons

    Infection with B virus is very rare relative to the number of possible exposures

    There are no controlled studies that document the ability of immediate empirical therapy to prevent infection or symptomatic B virus infection in humans

    Acyclovir therapy can suppress virus shedding and seroconversion, which may make diagnosis more difficult [25]

NOTE. Adapted from [1].

Table 5. Recommendations for postexposure prophylaxis for persons exposed to B virus.

Prophylaxis recommended

Skin exposure[a] (with loss of skin integrity) or mucosal exposure (with or without injury) to a high-risk source (e.g., a macaque that is ill, immunocompromised, or known to be shedding virus or that has lesions compatible with B virus disease)

Inadequately cleaned skin exposure (with loss of skin integrity) or mucosal exposure (with or without injury)

Laceration of the head, neck, or torso

Deep puncture bite

Needlestick associated with tissue or fluid from the nervous system, lesions suspicious for B virus, eyelids, or mucosa

Puncture or laceration after exposure to objects (a) contaminated either with fluid from monkey oral or genital lesions or with nervous system tissues, or (b) known to contain B virus

A postcleansing culture is positive for B virus

Prophylaxis considered

Mucosal splash that has been adequately cleaned

Laceration (with loss of skin integrity) that has been adequately cleaned

Needlestick involving blood from an ill or immunocompromised macaque

Puncture or laceration occurring after exposure to (a) objects contaminated with body fluid (other than that from a lesion), or (b) potentially infected cell culture

Prophylaxis not recommended

Skin exposure in which the skin remains intact

Exposure associated with nonmacaque species of nonhuman primates

[a] Exposures include macaque bites; macaque scratches; or contact with ocular, oral, or genital secretions, nervous system tissue, or material contaminated by macaques (e.g., cages or equipment) (see the Postexposure Prophylaxis section of the text for details).

posure. Prophylaxis should be initiated by the occupational health care provider, who should determine whether first aid and cleansing has been appropriate, properly document the injury, provide counseling and education about B virus, and ensure appropriate testing of the worker and the primate. In addition, the risks of the medication should be discussed, and the medication given to and used by the patient should be documented. Careful evaluation of the history of a presumed exposure has, on occasion, indicated that an exposure has not occurred (e.g., the wrong species of primate was involved or the instruments were not actually used on primates) and that postexposure prophylaxis was not indicated.

Postexposure prophylaxis is administered if the exposure occurred within the previous 5 days, because animals have benefited from prophylaxis given as late as 5 days after infection occurs. We also recommend postexposure prophylaxis if wound cultures done after cleansing are positive for B virus. Although this may result in administration of prophylaxis beyond 5 days after the exposure occurred, a positive wound culture result indicates that a high-risk exposure to B virus has occurred.

Antiviral Agents for Postexposure Prophylaxis

Three orally administered agents—acyclovir, valacyclovir, and famciclovir—are currently available for postexposure prophylaxis of B virus infection. These drugs have not been approved by the US Food and Drug Administration for treatment of B virus infection. The IC_{50} of acyclovir for B virus is 18 μg/mL, and that of ganciclovir is 9 μg/mL [25]. Famciclovir is the prodrug of penciclovir; the IC_{50} of penciclovir for B virus is ~15 μg/mL (J.K.H., unpublished data). These values are approximately 8–14-fold higher than the corresponding IC_{50} values for herpes simplex virus. Oral ganciclovir is poorly absorbed and should not be used for prophylaxis. Oral valganciclovir is well absorbed; however, we do not recommend this agent for prophylaxis because of its potential for toxicity, compared with that of other oral agents.

Although acyclovir has been the mainstay for postexposure prophylaxis of B virus [1], 2 newer drugs have been approved for the oral treatment of herpesvirus infections. Valacyclovir is the 6-valine ester of acyclovir and is metabolized to acyclovir in the liver and intestine. Serum levels of acyclovir are ~4-fold greater when oral valacyclovir, 1 g q8h, is given than when oral acyclovir, 800 mg 5 times daily, is given. Famciclovir is an esterified form of penciclovir and is converted to penciclovir in the intestine and the liver. Inside cells, both acyclovir and penciclovir are phosphorylated to the monophosphate form by the viral thymidine kinase and, then, to the active triphosphate form by cellular kinases. Famciclovir is administered orally because it is better absorbed than is penciclovir. Compared with acyclovir triphosphate, penciclovir triphosphate is less active in

inhibiting the herpesvirus polymerase; however, penciclovir triphosphate is present in higher concentrations and has a longer intracellular half-life than does acyclovir triphosphate. Famciclovir and valacyclovir have similar efficacy in the treatment of herpes zoster and therefore might be expected to have similar effectiveness when used for prophylaxis of B virus infection.

Antiviral Agents Recommended for Postexposure Prophylaxis

We recommend oral valacyclovir, 1 g given 3 times daily, as the preferred drug for postexposure prophylaxis of B virus in adults and nonpregnant women (table 6), because valacyclovir results in much higher serum levels of acyclovir than does oral acyclovir, the previously recommended drug [1]. The choice of valacyclovir is supported by animal studies that show that acyclovir (the active metabolite of valacyclovir) is effective in postexposure prophylaxis. In addition, valacyclovir is given 3 times daily, whereas acyclovir is required 5 times daily; therefore, compliance may be better with valacyclovir. Dosages may need to be adjusted for renal insufficiency. The first alternate choice is oral acyclovir given at a dosage of 800 mg given 5 times daily. Although 500 mg of oral famciclovir given 3 times daily might be equally as efficacious as valacyclovir, the lack of animal studies evaluating famciclovir (or its active metabolite penciclovir) provides some concern regarding the effectiveness of the drug for postexposure prophylaxis.

Antiviral medication should be given soon after potential exposure to virus (preferably within the first few hours after exposure) but only after first aid has been provided and cleansing has been done. Postexposure prophylaxis should be given for 2 weeks, on the basis of the previously cited animal studies. If the patient remains asymptomatic, antiviral medication should be discontinued at 2 weeks, and careful follow-up (see the Follow-up after Exposure section below) should be performed. In the event that the patient develops symptoms compatible with B virus infection, postexposure prophylaxis should be discontinued and treatment of B virus disease should be initiated.

Antiviral Agents for Pregnant Women

Of the available orally administered antiherpesvirus agents, acyclovir is the agent for which clinical experience is most extensive, especially when it is used during pregnancy. Although the use of acyclovir should be limited during pregnancy, findings from a registry of women receiving the drug have not shown an increase in the incidence of congenital abnormalities. However, the number of pregnant women who have received acyclovir is not large enough to detect a small increase in congenital problems. Few data are available on the use of valacyclovir or famciclovir during pregnancy; thus, acyclovir would be the preferred agent if postexposure prophylaxis is recommended for a pregnant woman. If a woman is of childbearing age, a urine or serum pregnancy test should be considered to help direct the choice of the antiviral medication.

Side Effects of Antiviral Agents

Oral acyclovir usually is very well tolerated. The most frequently reported adverse effects are nausea, headache, diarrhea, and rash. Renal insufficiency has not been associated with use of oral acyclovir. Neurologic side effects, including confusion and dizziness, occasionally have been reported in association with oral acyclovir use, but such side effects are less common than those associated with use of intravenous acyclovir.

Valacyclovir is generally well tolerated. High-dose (8 g/day), prolonged therapy (median duration, 54 weeks) with oral valacyclovir has been associated with thrombotic microangiopathy that presented as thrombocytopenic purpura or hemolytic uremia syndrome in patients with AIDS [34]. These patients, however, were receiving numerous other drugs, and it is unclear whether valacyclovir or another drug or associated condition was responsible for the microangiopathy [35]. High-dose, prolonged therapy with valacyclovir has also been associated with CNS disturbances in renal transplant recipients [36]. Such side effects are unlikely to occur in otherwise healthy persons who are receiving much lower doses of valacyclovir (3 g/day) for 2 weeks as postexposure prophylaxis. Resistance of B virus to antiviral agents has not been reported or extensively studied.

Table 6. Summary of recommendations for prophylaxis and treatment of B virus infection.

Clinical setting	Drug of first choice	Alternative drug
Prophylaxis for exposure to B virus	Valacyclovir, 1 g po q8h for 14 days	Acyclovir, 800 mg po 5 times per day for 14 days
Treatment of B virus disease		
CNS symptoms are absent	Acyclovir, 12.5–15 mg/kg iv q8h[a]	Ganciclovir, 5 mg/kg iv q12h[a]
CNS symptoms are present	Ganciclovir, 5 mg/kg iv q12h[a]	

[a] To be given until symptoms resolve and the results of 2 cultures are negative for B virus; see the Discontinuation of Treatment of B Virus Infection section of the text for additional therapy used after intravenously administered therapy has been completed.

FOLLOW-UP AFTER EXPOSURE

After counseling has been completed, questions have been answered, and, in some cases, postexposure prophylaxis has been initiated, follow-up appointments should be scheduled for a primate worker who has been exposed to B virus. A suggested schedule for follow-up appointments might include visits occurring at 1, 2, and 4 weeks after the exposure and at any time there is a change in the clinical status of the exposed primate worker. If the worker does not report for a follow-up appointment, attempts should be made to contact him or her to verify that the worker has remained healthy and to emphasize the potential seriousness of the exposure. In addition, the worker's supervisor or occupational health care provider should ask the worker about his or her clinical status at least weekly during the first month after the exposure occurs. Similar procedures should be in place in the event that a supervisor is exposed to B virus or becomes ill.

At follow-up visits, the wound and the signs and symptoms of B virus infection should be evaluated, compliance with medication should be determined, questions that the patient may have should be answered, and the worker's supervisor should be asked whether corrective measures have been taken to prevent future exposures. Blood samples should be obtained from selected patients for serologic testing.

Postexposure prophylaxis may delay the development of the antibody response to B virus or suppress viral shedding. Thus, follow-up of patients receiving postexposure prophylaxis should be extended. Serologic testing should be performed 3–6 weeks after the initial exposure occurs, and, in addition, serum specimens from patients receiving postexposure prophylaxis should be tested at later points in time (e.g., 3 months after exposure). Furthermore, for patients who had an initial wound culture that was positive for B virus, cultures of material obtained from the conjunctivae, oropharynx, and any unhealed skin lesions might be performed 1–2 weeks after the discontinuation of antiviral medication, to detect virus shedding.

TREATMENT OF B VIRUS DISEASE

The presence of any signs or symptoms of B virus disease (see the first 4 paragraphs of the present report) or laboratory confirmation of a positive culture result (*not* a positive result of the postcleansing wound culture referred to in the Laboratory Testing of the Exposed Worker section) necessitates treatment with intravenous antiviral therapy, not with orally administered medication used for postexposure prophylaxis. For any patient with symptomatic B virus infection, a thorough evaluation (including a detailed history and physical examination) should be done, with particular attention given to the presence of any skin lesions and to the neurologic status of the patient. Laboratory tests should include cultures of specimens of lesions, conjunctiva, and oropharynx for B virus, serologic testing of serum for B virus (preferably along with analysis of serum samples obtained either at the time of or before the presumed exposure), routine chemical and hematologic studies, and a urine or serum pregnancy test, when appropriate. Neurologic tests should include lumbar puncture and MRI of the brain; electroencephalography (EEG) should also be considered. CSF samples should be sent for culture, PCR detection of viral DNA, and serologic testing. PCR has been used to detect B virus in the CSF of a patient with meningitis caused by B virus [37], as well as in human necropsy specimens [29]. CT of the brain should be performed if an MRI is not immediately available. However, CT findings have been negative in recent cases of B virus meningoencephalitis. The primary usefulness of EEG is to help differentiate herpes simplex virus encephalitis (which most often presents as focal encephalitis involving the temporal lobes) from B virus disease (which usually presents as brain stem encephalitis). Brain stem auditory evoked responses in a conscious patient or somatosensory evoked potentials in an unconscious patient may provide useful information about brain stem or upper spinal cord function in patients with suspected CNS involvement.

Some experts recommend intravenous acyclovir for the initial treatment of B virus infection in patients without CNS disease [1]. Other authorities recommend ganciclovir for all symptomatic B virus infections because of the unpredictability of rapid and life-threatening brain stem involvement. When acyclovir is used, a higher intravenously administered dosage (12.5–15 mg/kg q8h) is recommended because B virus is less susceptible to acyclovir than is herpes simplex virus. It is critical to ensure proper hydration and to administer the drug slowly to avoid precipitation of the drug in the renal tubules and renal insufficiency. In addition, it is important to monitor the serum levels of creatinine in patients receiving high-dose acyclovir therapy and to adjust doses accordingly. If patients develop further symptoms while receiving acyclovir, intravenous ganciclovir should be used.

For patients with definitive signs and symptoms of peripheral nervous system or CNS involvement, intravenous ganciclovir, 5 mg/kg q12h, is recommended. As previously noted, B virus is more susceptible to ganciclovir than to acyclovir both in vitro and in an animal model. In addition, the only case of documented brain stem encephalitis for which the outcome was complete recovery occurred in a patient treated with ganciclovir [11]. The increased toxicity (especially myelosuppression) associated with ganciclovir must be balanced against the potential benefit of the drug. The dose of ganciclovir needs to be adjusted for renal insufficiency, and WBC and platelet counts should be monitored closely.

In recent years, the use of acyclovir and ganciclovir therapy for patients with the early stages of B virus disease, including

patients with early signs of CNS disease, has probably been responsible for an increased survival for some patients [10, 11]. However, antiviral therapy generally has not been effective in patients with advanced encephalomyelitis.

Standard blood and body fluid precautions should be used in the care of patients undergoing treatment for B virus infection or those otherwise known or suspected to be shedding virus, so that health care personnel and family members are not exposed to potentially infectious blood, body fluids, or skin or mucosal lesions. B virus has been cultured from the buccal mucosa and skin lesions of infected patients receiving intravenous acyclovir ([10], L.E.C. and J.K.H., unpublished data); thus, precautions must be continued during therapy.

DISCONTINUATION OF TREATMENT OF B VIRUS INFECTION

Intravenous therapy for B virus infection should be continued until symptoms resolve and ≥2 sets of cultures yield negative results after having been held for 10–14 days. Most experts believe that therapy should not be discontinued but, rather, should be switched to oral valacyclovir, famciclovir, or acyclovir administered at the dosages used for postexposure prophylaxis.

No good data exist to aid in the determination of when or whether treatment should be discontinued. Some experts suggest that after oral therapy has been administered using the doses recommended for postexposure prophylaxis for 6 months to 1 year, the dose can be further reduced to a "suppressive" level to reduce the risk of reactivation of B virus. Although oral acyclovir has been given in suppressive doses for many years to prevent reactivation of genital herpes, less is known about the long-term toxicities of valacyclovir and famciclovir. Nevertheless, any risks associated with prolonged administration of antiviral medication must be balanced against the possible devastating effects of B virus reactivation.

Some experts believe that lifelong suppressive therapy is needed, while others recommend that it be discontinued at some point. The latter opinion is based on the observation that, over time, patients with frequently recurring genital herpes have a diminishing rate of recurrences and, therefore, less need for long-term suppressive therapy [38]; however, it is not known whether this finding applies to B virus infection in humans. The decision to discontinue therapy is often difficult and requires careful deliberation and discussion with the patient. If therapy is discontinued, the patient should give his or her informed consent and should be followed closely. Because B virus remains latent in the sensory ganglia of monkeys and can reactivate, discontinuation of therapy has the potential for leaving the patient "unprotected" in the event that the virus reactivates. There has been at least 1 case [18]

in which B virus was interpreted by some, but not all, experts to have reactivated months to years after primary infection.

Most experts recommend that cultures of the conjunctivae and oral mucosa be performed at least weekly during the first few weeks after discontinuation of therapy, to check for shedding of B virus. If shedding is not present for ≥2 weeks after therapy has been discontinued, shedding can be assessed at less-frequent intervals, with an ultimate goal of assessment being done only once or twice yearly. If neurologic symptoms develop at any time, cultures for B virus should be obtained.

THE B VIRUS WORKING GROUP

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