BMJ Best Practice

Herpes B virus infection

The right clinical information, right where it's needed



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Summary

- Human infection is rare, but often fatal; therefore, prompt management of likely exposure is critical to preventing disease progression.
- Should be suspected when illness follows exposure to macaque monkeys or their body fluids or tissues. Immediate thorough cleansing of the exposed area combined with antiviral prophylaxis may prevent infection.
- Untreated infection often leads to CNS disease and death, with a mortality rate of approximately 80%. Early and aggressive antiviral treatment may prevent death.

Definition

Herpes B virus infection in humans is caused by the zoonotic *Macacine herpesvirus* 1 (MHV-1), previously known as *Cercopithecine herpesvirus* 1 (CHV-1). It is mainly found in macaque monkeys and they appear to be its natural host. [1]Of all the simplex herpesviruses identified in non-human primates, only B virus is known to be pathogenic for humans.[2]

Infection in humans is usually caused by the bite or scratch from an infected animal, a percutaneous injury contaminated by macaque body fluids, or from mucosal or non-intact skin contact with infected body fluid or tissue (e.g., in a laboratory or animal handling facility).[3]

Infection in humans is rare, but when it does occur it often presents with flu-like symptoms (fever, muscle aches, fatigue, and headache). Neurological symptoms usually develop, which result in fatal encephalomyelitis or severe neurological impairment if not treated early.[3] [2]

Epidemiology

Reported cases of B virus infection in humans are rare. There have been around 50 reported cases of human infection since the virus was first identified in 1932; among these cases, 21 have been fatal.[5]

The majority of infections have originated from the bite or scratch from an infected macaque monkey, from a percutaneous injury contaminated by macaque body fluids (e.g., via needlestick or cut in the laboratory or veterinary setting), or from infected body fluid or materials entering broken skin. There has also been at least one published report of fatal B virus infection resulting from a splash to intact mucosa without associated injury.[3]

In the US, a large number of non-human primates are kept as pets despite strong opposition to the importation of exotic animals by a number of US organisations, including the Department of Agriculture and Centers for Disease Control and Prevention.[6]Pet macaque bites inflicted on people visiting a pet macaque owner or inflicted by pet macaques that have escaped confinement are occasionally reported to the CDC. There have been at least two published reports of children bitten by macaques; a 2-year-old boy bitten by a bonnet macaque kept by a neighbour as a pet, [6]and a 7-year-old girl bitten while trying to feed a macaque in a park.[7] One small study revealed that 4 of 6 pet macaques involved in biting humans were seropositive for B virus; the owners of the remaining two macaques refused requests for testing.[8]Analysis of the history of these macaque encounters with adults and children revealed that 4 of 9 (44%) children were bitten compared with only 3 of 12 (25%) adults.

Bites from macaques who roam freely in temples, parks, and other settings in southern Asia (most notably Indonesia, Nepal, and India) are periodically reported to the CDC and B Virus Research and Resource Laboratory (BVRRL), and there has been at least one reported case of a macaque bite in a temple in Bali.[9] Two studies of temple macaques in Indonesia and Nepal showed that 64% and 82% of temple macaques, respectively, were infected with B virus.[10] [11]

Only one case of human-to-human transmission has been documented; the case, which was reported in a study of a B virus outbreak involving 4 people in Florida, resulted from direct physical contact with lesions.[12] Among the four people, 3 were animal handlers (two suffered bite wounds and one had close contact with the sick macaque, but was not injured or exposed to other body fluids and did not develop symptoms). The fourth person was the wife of one of the animal handlers. She used an ointment to treat her husband's lesions and subsequently used it on herself to treat contact dermatitis. The dermatitis progressed

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to pruritic lesions that were laboratory confirmed to contain B virus. All symptoms and viral shedding resolved with treatment. The study found no evidence of B virus infection among 130 close contacts of the 4 patients, healthcare workers, or primate workers. Moreover, even though B virus seroprevalence among adult macaques is >70%, only a few people in the study developed laboratory evidence of B virus infection. Thus, transmission of this virus, both human to human and primate to human, is quite rare.

Aetiology

Infection in humans is caused by the zoonotic *Macacine herpesvirus* 1 (MHV-1), previously known as *Cercopithecine herpesvirus* 1.[13] The virus is commonly called the B virus, but is also known as herpes B, monkey B virus, herpesvirus simiae, and herpesvirus B. The virus is a member of the Alphaherpesvirus family (genus: *Simplexvirus*) and is closely related to the human herpes simplex virus (HSV). It is a large (approximately 160-180 nm), double-stranded DNA virus surrounded by an icosapentahedral capsid and a lipid-protein envelope.

The natural hosts for B virus are species of macaque monkeys (e.g., rhesus macaques, pig-tailed macaques, cynomolgus monkeys), a genus of Old World monkeys. Non-macaque monkeys (all New World monkeys and all other Old World monkeys) pose no risk for B virus infection. One noteworthy exception involves monkeys from other genera that have been housed together with macaques. One study described an outbreak of B virus infection in DeBrazza's monkeys (same family but distinct genus from macaques). Eight monkeys had been housed with lion-tailed macaques, but were separated by concrete walls. The means of transmission was not identified. All 8 monkeys were B virus positive by PCR and serology; all of the animals developed symptoms consistent with herpesvirus infection, 3 of the 8 animals died. [14]Another study described B virus infection in a colony of brown capuchin monkeys that had been housed together with macaques.[15] B virus can cause fatal infections in capuchin monkeys, but in this instance 7 apparently healthy monkeys were confirmed by both serology and PCR to be asymptomatically infected with B virus. For non-macaque species that have had no contact with macaques, however, there is no risk of B virus exposure.

One species of macaque, the Barbary macaque (Macaca sylvanus), is native to North Africa (Algeria and Morocco) and Europe (Gibraltar), where it was introduced. The other 15 species of macaque are found in Asia. However, rhesus macaques are the most common non-human primates used in research around the world and thus are widely geographically disseminated via the research industry. Rhesus macaques now exist in free-living colonies introduced in the US and possibly other countries.[16]Macaques roam freely in a large number of temples, parks, and other settings in southern Asia, most notably in Indonesia, Nepal, and India. These monkeys have religious significance to Hindu worshippers and have adapted readily to living among humans. In recent years, some temples have been made into popular tourist attractions called monkey forests, where macaques are the main attraction. Local photographers make their living by coaxing macaques to climb onto visitors for souvenir pictures. The monkeys also frequent shopping areas, where tourists may be tempted to feed, pet, or tease the monkeys.

The virus may be present in body fluids or tissues (e.g., saliva, faeces, urine, or nervous tissue) of infected monkeys; it may also be found in cell cultures from infected monkeys.[3] There is a higher prevalence of shedding of B virus in infected primates that are stressed, breeding, immunosuppressed, or unwell.[4]Monkeys become infected via exposure of mucosa or broken skin to oral or genital secretions from other infected monkeys, or due to bites from other infected monkeys. Most infected monkeys are asymptomatic or have only mild symptoms; however, in some cases a disease similar to human HSV infection is seen (e.g., vesicular lesions on the tongue and lips, and sometimes on the skin).[3] [1]

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BASICS

Of all the simplex herpesviruses identified in non-human primates, only B virus is known to be pathogenic for humans.[2]Infection in humans is usually caused by the bite or scratch from an infected macaque monkey, a percutaneous injury contaminated with macaque body fluids, or from mucosal contact with infected body fluid or tissue.[3]

Human infections have resulted from bites or injuries resulting in injection of B virus-containing body secretions from a macaque monkey, but also from mucous membranes or non-intact skin exposure to fluid without associated injury. Human infections have also resulted from injuries associated with laboratory exposure to B virus-infected cell lines, necropsy materials from macaque monkeys, sharp objects contaminated by macaque body fluids or tissues, and contact of non-intact skin with lesions from a B virus-infected person.[4] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] Two cases of B virus infection were possibly associated with aerosols. Only one case of human-to-human transmission has been documented.



Rhesus monkey (Macaca mulatta)

CDC/Dr Roger Broderson

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Pathophysiology

Following initial infection, the B virus replicates at the site of inoculation and then spreads along the peripheral nervous system to the spinal cord and brain. The virus can spread from cell to cell without contacting the extracellular environment. It can also spread between nerve ganglia by axonal transport.[2] [35]The incubation period from confirmed exposure to onset of clinical symptoms ranges from a few days to 5 weeks, but symptoms generally appear between 1 to 3 weeks post-exposure.[2] [4]

The virus rapidly enters the peripheral nervous system during the early stages of disease;[36]some patients develop initial tingling, itching, pain, or numbness at the site of infection. A vesicular rash may also develop at the site of infection. There have also been reports of lymphadenopathy close to the site of infection.[4]

Initial systemic symptoms are generally flu-like (e.g., fever, muscle aches, fatigue, or headache). Neurological symptoms (e.g., meningismus, confusion, diplopia, dysphagia, dizziness, dysarthria, cranial nerve palsies, or ataxia) usually develop as infection progresses to the CNS.[4] CNS symptoms may be gradual or abrupt in onset.[4]If the virus reaches the brainstem, the usual outcome is death.[36]Brainstem encephalomyelitis develops in the terminal stages of infection.

Based on the characteristics of other alphaherpesviruses, B virus is presumed to persist in the peripheral nervous system (usually the nerve ganglia) for the lifetime of the host. In at least two instances, symptomatic B virus infection has presented in a manner suggestive of recurrent disease.[37] [17]The virus has not been found to be present at detectable levels in the blood or serum of infected hosts, but has been identified in other sites such as the buccal mucosa, saliva, genital fluids, or CSF.

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Primary prevention

There are no vaccines available for B virus. The most effective preventative measures against B virus infection are to avoid contact (feeding or petting) in settings where macaques are permitted to roam freely and, in the laboratory setting, to establish a safe laboratory and animal care environment using appropriate personal protective equipment (PPE).

Prevention in the natural setting:

- Macaques should not be kept as pets.
- Close contact with free-roaming macaques in public settings, such as parks or temples, should be avoided both domestically and internationally.

Prevention in the laboratory setting:

- B virus is classified as a biosafety level-4 (BSL-4) biological agent; therefore, laboratory workers handling B virus either directly or indirectly (via infected materials) should do so in facilities with BSL-4 capabilities in order to prevent infection.
- Macaques housed in research facilities may have very high rates of B virus infection. A survey of monkeys in one such colony revealed a B virus seroprevalence of 97%.[39]
- Direct handling of animals should be minimised. Workers should not attempt to handle fully conscious macaques; procedures should be conducted using appropriate physical and chemical restraining methods.
- Macaque handlers should remove physically active animals from cages using arm-length reinforced leather gloves. A long-sleeved garment and face shield are also recommended to protect against scratches. Cages and other potentially contaminated equipment should be free of sharp edges and corners that could cut or scratch animal workers. Areas where macaques are housed should have access limited to properly trained personnel.
- Macaques with lesions consistent with B virus infection should be quarantined until the lesions have healed, reducing transmission risk to both humans and other macaques.
- Workers handling macaques must be trained in proper methods of restraint and in the use of appropriate PPE.
- Personnel handling macaques should be educated about B virus, the risks of exposure, the nature of illness due to B virus infection, and appropriate first aid procedures.
- The occurrence of an eye splash without cutaneous injury leading to a B virus fatality resulted in the additional recommendation that protective eyewear (goggles or glasses with solid side shields) and a mask, or a chin-length wrap-around face shield and a mask should be used to protect mucous membranes in area where macaques are kept. Face shields or glasses must be able to prevent splashes from running or dripping down into the eyes.[40]
- Guidelines for the prevention of B virus exposure have been published.[3] [4] [40]The guidelines recommend that, while exposure involving unpredictable, aggressive animals is not completely preventable, adherence to appropriate laboratory and animal facility protocols will greatly reduce the risk of infection. The following recommendations are published by the US Centers for Disease Control and Prevention:[3]
    - Handling B virus-susceptible monkeys should be done using humane restraint methods to reduce the potential for bites and scratches
    - Proper PPE, including a laboratory coat, gloves, and a face shield, must be used when working with macaque monkeys
    - All bites, scratches, or exposure to the tissues or secretions of macaques must be cleansed immediately. The first few minutes after an exposure are considered the most critical period

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for reducing the risk of infection. For skin exposure, the exposed area should be thoroughly cleansed by washing and scrubbing with soap, concentrated solution of detergent, povidone-iodine, 0.25% hypochlorite, or chlorhexidine and water for 15 minutes. The exposed area should then be irrigated with running water for 15 to 20 minutes. Mucosal exposed areas (nose, eyes, mouth) should be flushed with sterile saline solution or water for 15 minutes

- The cleansed wound should be evaluated by a third party for adequacy of washing, and repeated if necessary. The date, time, location, nature, and site of injury, and the type of fluid or tissue exposure should also be recorded.

- Following exposure, acute and convalescent serum specimens from the exposed human should be sent for serological testing to evaluate for B virus infection. Sending serum specimens from the implicated macaque can also be considered if safe to do so, and if the outcome of testing will affect how that macaque or the colony is managed. Results of macaque testing will not impact management of the exposed human.
- In humans, collection of PCR or viral culture specimens from the site of exposure may be considered only after it has been thoroughly cleansed to prevent risk of driving virus into the wound and increasing the risk of infection; however, collection of wound specimens at the time of exposure is not recommended.

Secondary prevention

Preventing human-to-human transmission:

- Human-to-human transmission of B virus is rare. B virus has been transmitted from human to human in one documented report. Transmission occurred from husband to wife following the repeated use of lotion that the wife used for both her husband's open herpetic lesions and her own dermatitis. [23]The husband's herpetic lesions were subsequently confirmed to have been shedding B virus.
- Patients confirmed or suspected to be infected with B virus should be assumed to be shedding virus from open wounds at the site of virus inoculation, any herpetic-like lesions, and possibly oral and genital mucosa. Serial PCR testing of these sites should guide infection control practices, which should be determined in consultation with infectious disease and infection control specialists. Positive cultures taken from the conjunctiva and buccal mucosa of a patient with B virus infection receiving intravenous aciclovir treatment has shown that shedding of infectious B virus can occur for up to 11 weeks following treatment initiation.[4] [23]
- Those who are infected with B virus should avoid exposing their body fluids or skin lesions to others during the incubation period. Standard precautions should be practiced for all humans infected with B virus until absence of shedding of virus has been confirmed.

Post-exposure prophylaxis (PEP):

If B virus exposure is suspected, PEP can be instituted. The following diagram outlines when PEP should be considered in patients with suspected B virus exposure:

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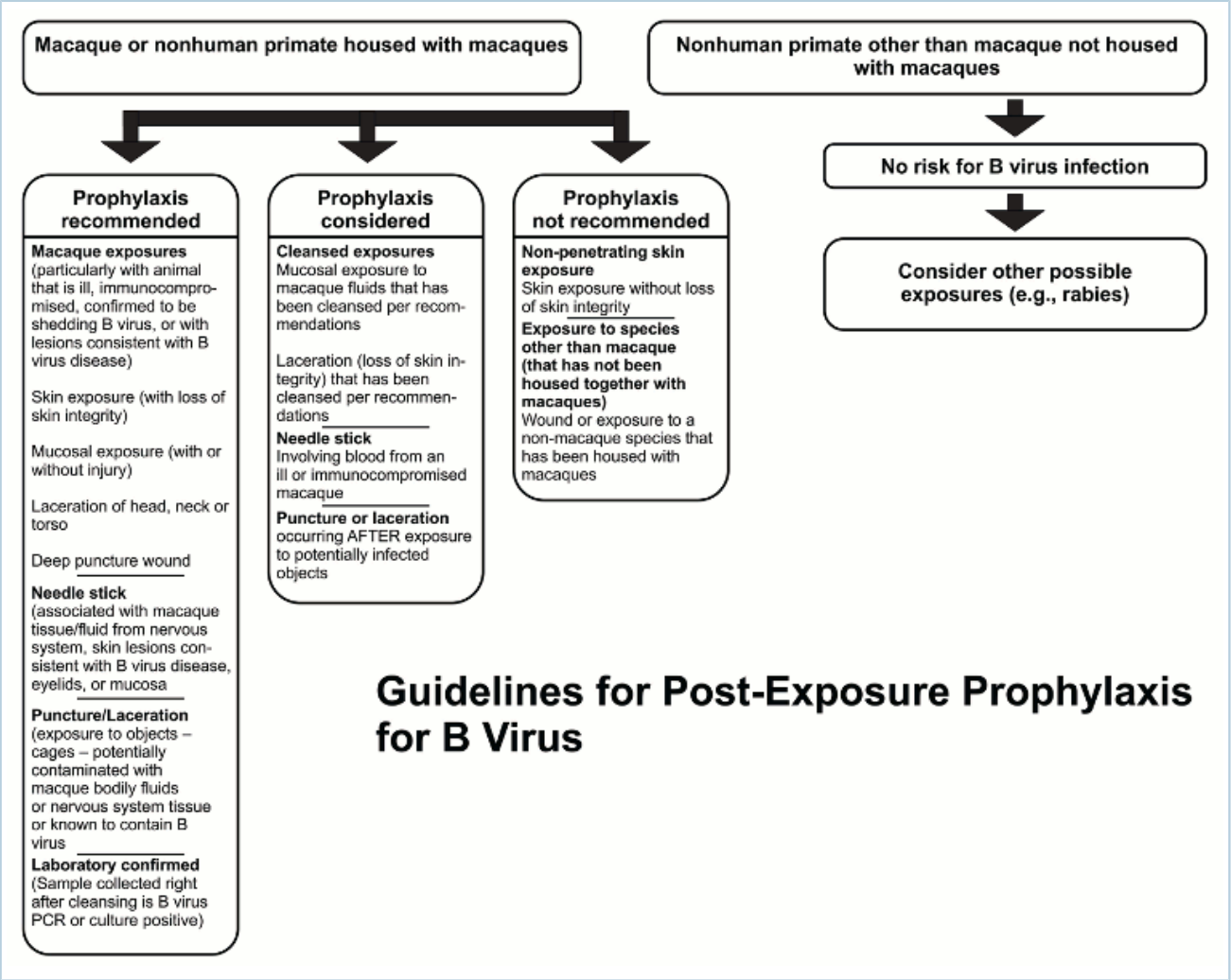

Guidelines for post-exposure prophylaxis for suspected B virus infection
CDC

Fatal B virus infections have occurred in people who recall no exposure or who had minimal exposures. For this reason, ranking the risk of exposure is discouraged. All potential exposures should be assumed to present risk and managed appropriately. However, it is not feasible or recommended to provide antiviral prophylaxis for every possible exposure.

Antiviral prophylaxis is recommended for exposures that present for medical evaluation within 5 days of exposure. Prophylaxis is not recommended for those who present more than 5 days after exposure. The following factors should be considered in determining the advisability of providing prophylaxis:[4]

- Source of the exposure
- Timeliness and adequacy of first aid for wounds or splashes
- Type of wound or exposure
- Evaluation of exposure to materials that were in contact with macaques.

The severity and the nature of the wound and the area affected by the splash or other exposure are relevant. Bites or scratches that break the skin, and especially deep puncture wounds such as from a severe bite or an accidental stick from a contaminated needle, that are difficult to cleanse are assumed to result in a higher risk than superficial injuries that are more easily cleansed. Wounds and exposures of the head, neck, or torso are at risk for rapid transport of virus to the CNS (reasoning by analogy from rabies virus experience) and should thus be regarded as high-risk exposures. Prophylaxis for potential exposures to these parts of the body is recommended, regardless of the severity of the wound or the extent of the exposure to fluids. Antiviral prophylaxis should be administered immediately once the wound or exposure site on the head,

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neck, or torso has been thoroughly cleansed, and specimens have been taken for serology, PCR, and/or culture.[4]

Superficial wounds to the extremities that have been immediately and properly cleansed are presumed to be less likely to lead to fatal disease. Scratches from cages in which macaques are housed are also considered to carry a lower level of risk, again assuming that the wound has been properly cleansed. For these exposures, antiviral prophylaxis should be considered on a case-by-case basis.[4]

Bites and other exposures involving non-macaque primates that have not been housed with macaques are regarded as having no risk for B virus transmission. However, such wounds should be evaluated for bacterial infection as well as for other viruses of concern, such as rabies.

It should be stressed, however, that in none of the potential exposures mentioned can the risk of infection be regarded as zero. As such, the decision to initiate prophylaxis or treat a patient with anti-herpes antivirals should be made at the physician's discretion, with consideration of the patient's wishes and concerns.

Oral antivirals (aciclovir, valaciclovir, famciclovir) are recommended for PEP. In the US, none of these antivirals have been approved by the Food and Drug Administration for treatment of B virus infections. Valaciclovir and famciclovir are oral pro-drugs; each is metabolised in the liver and intestine to aciclovir and penciclovir, respectively. Both drugs have substantially higher bioavailability than oral aciclovir.[59] [60]The preferred antiviral drug for post-exposure B virus prophylaxis is oral valaciclovir (in adults, including non-pregnant women) due to the superior bioavailability compared with aciclovir.[4] [23]However, aciclovir can be used as an alternative. There are no available studies (animal or in vitro) for the efficacy of famciclovir at inhibiting B virus replication. However, famciclovir and valaciclovir have comparable efficacy for the treatment of herpes simplex and herpes zoster, and might also be expected to be similarly efficacious against B virus.[4]

PEP should be started within a few hours and no later than 5 days after exposure, but only after the completion of the first aid protocol. Prophylaxis should be continued for 14 days.[4] If the patient is asymptomatic at the end of 14 days of prophylaxis, antiviral treatment can be stopped, but careful follow-up of the patient is necessary to observe for late onset of symptoms. If symptoms of B virus disease develop, PEP should stop and treatment for B virus disease should be started.[4]

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Case history

Case history #1

A 22-year-old female laboratory worker sustains a splash to her right eye with material (possibly faeces) from a macaque. She immediately wipes the eye with a paper towel and after 45 minutes washes the eye for 2 to 3 minutes with tap water. Swelling and redness develops in her right eye, and on day 10 she presents to the emergency department with ocular lesions. She reports possible B virus exposure; however, lesions are judged inconsistent with herpesvirus infection and she is prescribed sulfonamide eye drops. On day 12, an ophthalmologist suspects infected cat scratch disease and she is prescribed doxycycline; however, she is subsequently found to be seronegative for Bartonella. On day 14, her symptoms persist and she is admitted for B virus treatment. Her temperature is normal on admission, but increases to 38.5°C during first day of admission. She begins intravenous aciclovir within 2 hours of admission. On day 15, treatment is changed to intravenous ganciclovir. Vesicular eruption develops in the vicinity of her right trigeminal nerve. MRI of the head is normal. Sharp mid-cervical/high thoracic back pain is reported on day 21, which abates over 8 hours. On day 26 all symptoms resolve and she is discharged on ganciclovir. On day 27 she develops weakness in her right foot, inability to urinate, and lower abdominal pain, followed by rapidly progressing ascending myelitis. On readmission, she is found to have right leg weakness, moderate left leg weakness, decreased hand grip strength, abdominal pain, and urinary retention. MRI reveals abnormalities extending from the cervical spinal cord to the upper thoracic spinal cord. Flaccid paralysis from C2 caudad develops, and she is then intubated. Neurology consultants consider a diagnosis of post-viral acute demyelinating encephalomyelitis and a short course of plasmapheresis is performed, and a corticosteroid is administered. On day 32 she develops seizure activity (involuntary facial and eye movements), and foscarnet is added to ganciclovir therapy. From days 33 to 41 she develops nosocomial pneumonia with bacteraemia, followed by adult respiratory distress syndrome. MRI reveals abnormalities extending from the midbrain through the thoracic spinal cord. She dies on day 42 from refractory respiratory failure. B virus is recovered from brainstem samples during postmortem.

Case history #2

A 29-year-old male animal handler is bitten by an apparently healthy macaque. The bite wound is immediately rinsed under tap water for a few minutes with soap. He develops a local and general infection (staphylococcus and streptococcus) the next day, which is treated with antibiotics. He then develops intermittent low grade fever over the next 10 days, which is followed by symptoms of CNS involvement, including paralysis of the lower extremities and paraesthesia. The paralysis ascends to 1 inch above the nipple line. A temperature of 40.2°C is recorded on day 12 following the bite. MRI and CT scan do not reveal lesions on the brain or spinal cord.

Other presentations

There have been about 50 documented cases of B virus infection published to date, 21 of whom have been fatal.[4] Thus, limited numbers preclude solid data about typical presentation, particularly for early signs and symptoms. Patients may present with herpetic lesions at the site of exposure, which then progresses to CNS disease. Other presentations include dysaesthesias at the exposure site, which may evolve into ascending paralysis or CNS disease. In one case report, a patient presented with herpetic

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lesions associated with the ophthalmic nerve suggestive of reactivation disease. Various patients have presented in the initial stage of disease with some combination of generalised flu-like symptoms, fever, vesicles proximal to the exposure site, or conjunctivitis. Subsequent neurological involvement can manifest with dizziness, weakness, dyspnoea, severe persistent headache, and, with advancing disease, ascending paralysis and attending complications. Most surviving patients suffer from life-long moderate to severe neurological impairments.

Step-by-step diagnostic approach

Diagnosis is based on clinical suspicion and confirmed by serological testing combined with PCR or viral culture. Early suspicion, recognition, and management of potential exposure, and rapid identification and treatment of B virus infection are critical to the prevention and management of human disease. An immediate evaluation of the patient should focus on a detailed history of exposure risks, a physical examination targeted to areas relevant to the exposure history (including a neurological examination), and an evaluation for the presence of any skin lesions.

First aid and initial evaluation

If a potential B virus exposure occurs, the critical first step is immediate and thorough cleansing of the exposed area to prevent exposure from progressing to infection. The Centers for Disease Control and Prevention has published guidance for wound cleansing.

[CDC: B virus first aid and treatment]

Immediate and thorough cleansing of the wound or other exposed areas should not be delayed to seek medical care. Although potential exposures are frequent and human infections are rare, each potential exposure should be treated as an emergency until the wound or other exposed areas have been thoroughly cleansed. The exposed area should be cleansed on presentation for medical evaluation regardless of whether or not it was previously cleansed. The exposed area should be thoroughly washed and gently scrubbed with soap, povidone-iodine, detergent, or chlorhexidine and water for 15 minutes, followed by irrigating the area with running water for 15 to 20 minutes. Mucosal exposure (nose, eyes, mouth) should be flushed with sterile saline solution or water for 15 minutes. Specimens should not be collected before washing the area as it could force virus more deeply into the wound.[41]

For those exposed while working with macaque monkeys, for example in a laboratory or zoo, the occupational healthcare provider should be contacted immediately after cleansing the exposed area. The occupational healthcare provider should provide an initial evaluation, assistance with first aid, counselling, and education about the signs and symptoms of B virus infection. They should also facilitate rapid access to an infectious disease specialist with knowledge of B virus.

The diagram below provides an overview of the initial steps that should be carried out following B virus exposure:

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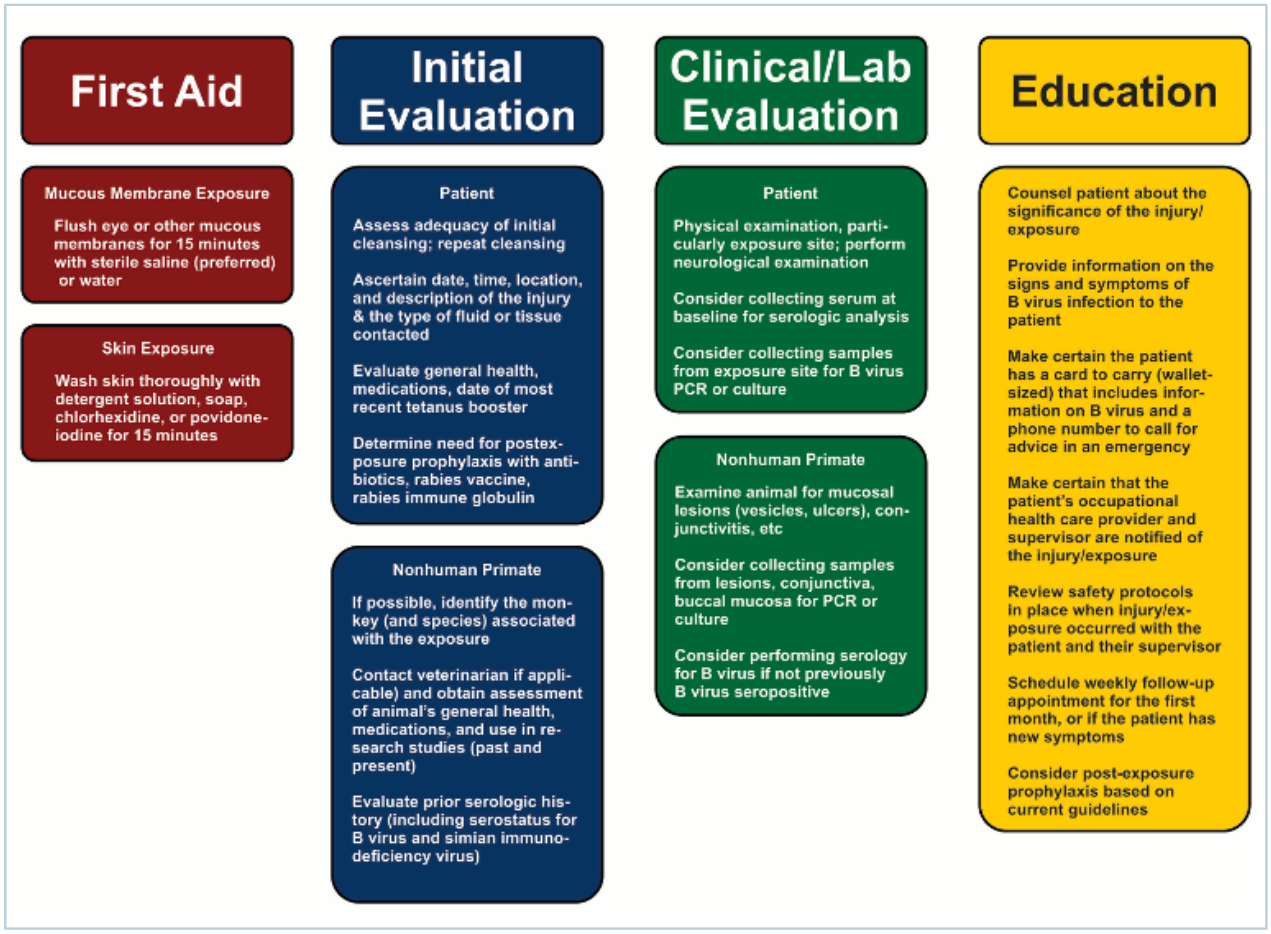

Overview of the steps for managing putative B virus exposures

CDC

DIAGNOSIS

History

A detailed history should be carried out to identify the following:[4]

- Date, time, and (geographical) location of exposure
- Source of exposure (e.g., macaque monkeys [which includes rhesus, cynomolgus, and other macaque monkeys], body secretions or tissues from macaque monkeys, laboratory cell lines or necropsy material from macaque monkeys, objects contaminated with body fluids or tissues from a macaque monkey). If the source of exposure is an animal, the general health of the animal should be ascertained
- Type of exposure (e.g., scratch, bite, percutaneous injury contaminated with macaque body fluids, or mucous membrane or non-intact skin contact with infected body fluid or tissue without injury) and site of infection (on the body)
- Cleansing of wound performed following exposure, including how soon after the exposure, if done
- Safety protocol in place at the time of exposure
- General health, medications taken, and date of most recent tetanus booster.

Identifying the source of exposure

Macaque monkeys (family: Cercopithecidae; subfamily: Cercopithecinae; genus: Macaca) are the only natural hosts for B virus; therefore, identifying the type of monkey responsible for a suspected exposure is important. Non-macaque monkeys (all New World monkeys, and all other Old World monkeys) pose no

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risk for B virus infection unless they have been co-housed with macaques. If they have been co-housed at any time, latent B virus infection of non-macaques cannot be ruled out.[14] [15]

For potential exposures to monkeys that are free-roaming, such as in parks and temples in Asia, it will usually be impossible to determine the type of monkey responsible for the bite or scratch; however, most monkeys in Asia are macaques. Only one species of macaque is native to North Africa (Algeria and Morocco) and Europe (Gibraltar), the Barbary macaque (Macaca sylvanus). Monkeys responsible for bites in Asia should be presumed to be macaques in the absence of any other descriptive evidence. Free-roaming monkeys in Central or South America can generally be presumed not to be macaques. Macaques are not endemic to the western hemisphere, although colonies of imported animals in parts of the US (including animals that are free-roaming) may pose an infection risk to visitors. Such colonies could also exist elsewhere.

Ascertaining general health of the animal responsible

If possible, the medical record of the animal responsible for the exposure should be ascertained to identify its current health status. The medical record should include any history of exposure to infectious agents, and any appearance of active lesions compatible with B virus infection. These mucosal lesions resemble those observed in people infected with HSV-1 or HSV-2. If exposure was in a laboratory setting, the type of research the animal was involved in should be identified where possible.

B virus infection in macaques is usually asymptomatic or only mildly symptomatic, and infected macaques shed virus only intermittently. However, it is important to remember that, while the presence of herpetic skin lesions implies active shedding, B virus-infected macaques with no visible mucosal lesions can still shed virus, similar to humans infected with HSV-1 or HSV-2. As with most mammalian herpesviruses, active shedding of the virus is periodic and, in the case of B virus and closely related alphaherpesviruses (e.g., HSV), may or may not be accompanied by symptoms.[42] Macaques with B virus infection can shed the virus from mucosa (e.g., conjunctiva, buccal) and/or genital surfaces. Macaques appearing unwell, that have been immunologically suppressed (e.g., for research purposes), or have been recently stressed are even more likely to be shedding B virus. B virus can also be deposited on surfaces; therefore, infection of humans and other animals can occur via fomites. Any scratch, bite, percutaneous injury contaminated with macaque body fluids, or mucous membrane or non-intact skin contact with infected fluid from macaques should be regarded as a potential exposure.

Physical examination

A physical examination of the patient should be performed on presentation immediately after cleansing of the exposure site. In the immediate aftermath of exposure, the goal remains to prevent exposure from progressing to infection. Physical examination is aimed at identifying, documenting, and thoroughly cleansing all potentially exposed areas. If the patient presents days after exposure, thorough cleansing of exposed areas should be performed, but is less likely to be of benefit than if performed immediately after exposure.

The type of exposure, appearance of the exposed area, and site of exposure should be carefully examined, but precise risk stratification is discouraged because the limited number of known human B virus disease cases makes it impossible to accurately quantify relative risk of an exposure. Cases of fatal B virus infection in people who could recall no obvious high-risk exposure to macaques or their fluids and tissues have occurred, as have cases among people with exposures that are considered to carry a low risk. The site of infection on the body may, however, impact how the disease progresses. By analogy with rabies, which also spreads by retrograde transport along neural pathways, B virus entry through the head

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and neck may allow more rapid access to the CNS, where neurological symptoms may precede, or at best coincide with, other symptoms.

A medical examination is focused on gathering evidence of infection. Patients with B virus infection may present with the following:

- Signs/symptoms localised to the site of exposure (e.g., herpetic lesions) that worsen or spread to additional locations
- Signs/symptoms limited to the peripheral nervous system or the CNS
- Systemic flu-like illness (e.g., fever, chills, general malaise, headache, or myalgia) without localising symptoms.

Those with potential exposure should, therefore, be evaluated for the presence of any skin lesions, fever, or neurological symptoms, as these may suggest B virus infection. All presentations can progress to abrupt onset of CNS symptoms. A neurological examination to establish a baseline status and, if the patient is symptomatic, appropriate clinical evaluation of the CNS (e.g., lumbar puncture, brain MRI, EEG) should be carried out to identify and characterise infection and to further characterise the neurological status of the patient.

The history and physical/medical examination should be considered before deciding on whether to administer post-exposure prophylaxis (PEP).[43] Prophylaxis is most likely to be effective in the immediate aftermath of exposure. It is unlikely to be effective more than 5 days after exposure, as demonstrated in rabbit models.[44] [45]

Signs and symptoms

All documented human infections with B virus to date have been symptomatic. However, there have been only about 50 documented cases of B virus infection published to date, 21 of which have been fatal.[4] Thus, limited numbers preclude solid data about typical presentation, particularly for early signs and symptoms.

Disease onset in humans typically occurs within 5 weeks of exposure, but may be early and abrupt (3-7 days).[3] Clinical presentation of a B virus-infected person may vary, and patients may progress rapidly to CNS symptoms. Patients with B virus infection should have a history of risk factors for infection and may show one or more of the following signs and/or symptoms at initial presentation, depending on the time post-exposure and the site and nature of infection:

- Systematic signs/symptoms
    - Fever (≥37.5°C) and/or chills
    - Non-specific flu-like symptoms (e.g., malaise, fatigue, listlessness)
    - Lymphadenitis associated with site of infection
    - Lymphangitis associated with site of infection
    - Nausea/vomiting
    - Abdominal pain
    - Headache (may indicate CNS involvement)
- Focal neurological signs/symptoms
    - Paraesthesia at the site of infection
    - Paraesthesia in the lower limbs

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- Hyperaesthesias
- Ocular pain (for infections resulting from splash exposure of the eye or reactivation via the optic nerve)
- Persistent hiccups (suggests neurological involvement at the level of the diaphragm)
- Muscle weakness (paresis)

- Central neurological signs/symptoms (CNS signs/symptoms are most alarming)
  - Severe persistent headache
  - Dizziness
  - Dyspnoea
  - Gait disturbances (if present presume CNS origin)
  - Ataxia (if present presume CNS origin)
  - Diplopia
  - Nystagmus
  - Agitation
  - Meningismus
  - Ascending or acute flaccid paralysis
- Dermatological signs
  - Vesicular skin lesions at the site of infection (similar to those caused by HSV infection)
  - Rash, possibly pruritic, at the site of exposure
  - Conjunctivitis.

Numbness and/or tingling at the site of exposure and/or flu-like symptoms (e.g., fever, muscle aches, fatigue, malaise, and listlessness with or without nausea and vomiting) tend to occur first. Some patients may also present initially with vesicular skin lesions at the site of infection, rash that may be pruritic, lymphadenitis (inflamed lymph nodes), lymphangitis (inflammation of lymphatic vessels), abdominal pain, or persistent hiccups (which may suggest neurological disease at the level of the diaphragm).

Neurological signs (e.g., meningismus, hyperaesthesias, ataxia, diplopia, agitation, and ascending or acute flaccid paralysis) may develop as the virus progresses through the peripheral nervous system to infect the CNS. CNS involvement may progress rapidly to paralysis and death, even with antiviral therapy and supportive care. Respiratory failure, often associated with ascending paralysis, is a common cause of death in those with CNS involvement. Those who survive usually have long-term neurological sequelae.

Specimen collection

Specimen collection for serological analysis should be done when there has been an exposure to macaque body fluid regardless of the risk assessment of the exposure, and regardless of whether or not the patient is receiving PEP.

In asymptomatic patients, acute serum should be collected immediately after an exposure (at initial evaluation) to establish a baseline profile, and again at 3 to 6 weeks after the exposure to evaluate whether or not seroconversion to B virus has occurred or, when the baseline is not negative, whether a substantial (≥4-fold) rise in antibody titre has occurred.[3] [4]In symptomatic patients, it may be informative to collect serial specimens for serological testing.

Prophylactic antiviral drugs may suppress seroconversion and delay onset of symptoms without preventing infection. Therefore, if antiviral drugs are administered as prophylaxis, an acute serum sample

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should be taken at baseline, and convalescent samples should be taken at 3 to 6 weeks and 3 months post-exposure (and potentially serially, thereafter) since seroconversion may be delayed. The patient should be followed during this time for onset of symptoms compatible with B virus infection. Patients in whom prophylactic antivirals have been discontinued should be closely monitored for onset of signs and symptoms that suggest B virus infection.[4]

Collection of wound specimens at the time of exposure is not recommended. If specimens for PCR or viral culture are collected at the time of exposure, they should be taken from the site of exposure only after it has been thoroughly cleansed in order to reduce the risk of forcing the virus more deeply into the wound. Specimens for PCR or culture are usually only obtained if clinical symptoms are present, or if antibody-positive serology suggests infection. It should also be recognised that specimens collected for PCR or culture from the site of exposure at the time of exposure are often negative due to removal of free viral particles during cleansing and, therefore, may lack diagnostic or clinical significance for infection.

Specimens must be sent to specialist diagnostic laboratories with expertise in testing for B virus. B virus is a Risk Group 4 agent requiring a biosafety level class 4 (BSL-4) laboratory for handling; therefore, the specialist laboratory must have BSL-4 biocontainment facilities as well as established capacity and certification to perform diagnostics for B virus.

Initial laboratory investigations

Serological analysis performed in an expert BSL-4 laboratory is the standard first-line test for diagnosing B virus infections. It is also the most effective (and cost effective) laboratory evaluation for following exposed patients. When B virus infection is suggested by serology, infection is ideally confirmed using PCR of specimens collected from herpetic lesions, or, in the absence of infected sites, conjunctiva, buccal mucosa, or CSF. Virus culture remains an option for confirming B virus infection, but its utility in guiding clinical management is limited. Furthermore, there are potential hazards associated with growing the virus in the laboratory; an expert laboratory with BSL-4 capabilities is required. A positive culture must be confirmed using an agent-specific test (e.g., PCR, sequencing, restriction endonuclease analysis, sodium dodecyl sulfate-polyacrylamide gel electrophoresis [SDS-PAGE] analysis of viral proteins). PCR is preferred as it is faster, more sensitive, has a lower hazard risk, and is more cost effective than culture. Thus, serological analysis with confirmation by PCR is a more feasible clinical approach. If a patient is symptomatic, PCR should be the first investigation to order. Culture is not required for clinical confirmation, but it may be helpful in confirming the presence of viable virus and for assessment of drug sensitivity.[46]

Serological analysis:

- Serological testing should be carried out to evaluate for B virus infection, but will not inform immediate treatment decisions owing to the time required to develop detectable virus-specific antibodies. Immediate treatment decisions must be made based on clinical judgement.
- Testing of paired acute and convalescent serological specimens will be most meaningful, but testing of single specimens might be considered if clinical signs or symptoms of B virus infection are present.
- Documentation of seroconversion or of a ≥4-fold rise in antibody titre strongly suggests that exposure has progressed to infection. Alternatively, the absence of either of these findings by serology at 3 to 6 weeks following exposure can provide some reassurance of the absence of infection.

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- Although seroconversion temporally associated with B virus exposure can identify infection with relative confidence, cross-reactions with antibodies from other herpes viruses, particularly HSV-1, can occur. This can complicate diagnostic interpretation through false-positive reactions.[47] Thus, serological rises in titre not definitively correlated with B virus exposure might identify a new infection, or seropositivity not directly associated with a new exposure may identify a past infection, but both are less definitive than seroconversion after exposure.
- People with a history of possible exposure should not be diagnosed as infected on the basis of serological reactivity alone in the absence of symptomatic disease or laboratory confirmation of virus shedding (e.g., by PCR or culture). Expert assistance with diagnostic testing and interpretation is essential.

PCR and viral culture:

- In the absence of established infection, a positive PCR or viral culture from samples collected from the exposed area shortly after exposure indicates that B virus exposure has occurred. However, a negative result does not rule out exposure, and neither positive nor negative results can identify whether an exposure has progressed to infection. Thus, results of these samples have limited diagnostic value.
- In symptomatic patients, specimens collected for PCR or culture from skin lesions or elsewhere do have clinical value as they may establish the diagnosis, document infection, and inform both clinical management of the patient and infection control practices. For example, a specimen for PCR or culture collected from sites associated with the appearance of early symptoms such as vesicular skin lesions or distant sites implicated by clinical syndromes (e.g., the CSF when CNS infection is suspected) is more likely to produce a positive result and can confirm an initial diagnosis that was based on serological testing and clinical presentation.[4]
- A positive PCR test or culture at the exposure site at a time distant from exposure or at a site not exposed to the virus (e.g., lesions, conjunctivae, oropharynx, CSF) at any time and in association with symptoms concordant with B virus disease indicates infection.[4]
- In a setting with clinical symptoms compatible with infection and seropositivity supporting B virus infection, PCR is adequate to confirm the diagnosis of B virus infection.
- Symptomatic patients who have been documented to be PCR or culture positive for B virus should have the tests repeated weekly until two consecutive negatives have been obtained to monitor treatment response and confirm viral shedding has ceased.
- During the follow-up period, samples for PCR can be obtained from crusted lesions. Samples from lesions that have not yet crusted can be used for culture.

Other investigations to consider

- If possible and if safe to do so, and under veterinary consultation, laboratory testing (e.g., serological analysis, PCR, culture) of the animal responsible for exposure can be considered to identify B virus infection. Decisions to test animals associated with possible B virus exposures should take into consideration that, while test results from the animal may inform management of that animal or the larger troop from which it comes, they are unlikely to substantially inform patient management. Decisions on the evaluation and management of patients must be initiated before these results will be available and continued based on the evidence of the patient, not the exposure source. Thus, clinical management of the patient will not justify the cost or risk of culture of animals associated with possible exposures.

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- Pregnancy testing should be carried out in women of childbearing age with suspected or known B virus exposure to aid in the decision of which antiviral drugs to choose. Experience with aciclovir in pregnancy is limited but there is no evidence of an increased risk to the developing fetus. Experience with other antivirals is less extensive.[4]
- Brain MRI can be performed to look for evidence of encephalomyelitis if neurological symptoms develop.[48] [26] [27]A CT scan of the brain can be performed if MRI is unavailable, but CT is less sensitive than MRI for brainstem encephalitis; to have utility it should be done with contrast.
- If neurological symptoms develop, a lumbar puncture should be performed and CSF analysed for routine chemistry and cell counts, and for identification of B virus (e.g., culture, PCR, or serology).[49] [50]
- Under neurological consultation, EEG can be considered if needed to further characterise the encephalitis. B virus encephalitis usually presents as a brainstem encephalitis that becomes diffuse over time, in contrast to HSV encephalitis which is usually a unilateral temporal lobe encephalitis. Both HSV and B virus encephalitis are treated with intravenous aciclovir so treatment should not be delayed. Treatment should be initiated at the higher B virus levels, and adjusted if subsequent evaluation suggests HSV is the aetiology, or consideration should be made to switch to ganciclovir if evaluation suggests a B virus aetiology.
- Guided by neurological consultation, additional useful information about brainstem or upper spinal cord function may be obtained with brainstem auditory evoked responses (patient conscious) or somatosensory evoked potentials (patient unconscious).

Risk factors

Strong

occupational exposure

- Animal handlers (e.g., veterinarians, laboratory personnel) working in facilities that house macaques have the highest degree of risk for B virus exposure, due to high rates of infection history among captive macaques, and daily or frequent close contact with potentially infected animals and to possibly infectious fluids and tissues. Infection can be transmitted through bites or scratches from an infected macaque or injuries exposed to body fluids from an infected macaque, but also through splashes without injury to exposed mucous membranes or open wounds.[4] [18]
- Infections have occurred in laboratories via exposure to cell lines infected with B virus. Infections have occurred after injury or following exposure to cages, sharp objects, and other objects contaminated with macaque body fluids or tissues. Aerosols were suspected as the exposure source for at least one infection.[19] [20] [21] [22] [23] [24] [25]

travel to countries with free-roaming macaques

- Macaques roam freely in a large number of temples, parks, and other settings in southern Asia, most notably in Indonesia, Nepal, and India. Many temples and parks in Asian countries encourage visitors to pose with monkeys for photos and to bring food for the monkeys.[11] [10] [38]Visitors should avoid direct contact with monkeys as macaques in these settings have high rates of infection. Studies indicate that rates of B virus infection among these primate populations is similar to those of captive macaques.[2] [11] [39] [38]
- Macaques live in social hierarchies defined by aggression by dominants against subordinates, and macaque monkeys (especially females) can be aggressive towards humans, especially small children. Rhesus monkeys have been observed to swarm a tiger.[16]

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keeping macaques as pets

- Macaques grow more aggressive with age, but if they have never been housed with other macaques they have a lower risk of being B virus infected. However, a small study found that around 66% of pet macaques are B virus seropositive.[8] Unless a pet macaque has been tested and documented to be B virus negative, it should be assumed to be infected and intermittently shedding B virus.

Weak

exposure to non-macaque species that have been housed with macaques

- There is no risk of B virus exposure in non-macaque species if they have never been housed with macaques. However, other non-human primates can be infected with B virus if housed with macaques and, presumably, are capable of harbouring infection with periodic shedding.[14] [15]

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include close contact with macaque monkeys, macaque body fluids, or tissues or objects contaminated by macaque body fluids or tissues.

fever (≥37.5°C) (common)

- Presenting symptom in most patients with B virus infection. Fever is often >39.0°C with a remitting pattern.[3]

flu-like symptoms (common)

- Majority of diagnosed cases of B virus infection report malaise, fatigue, muscle aches/pains, and listlessness, which typically occur at onset of acute disease.

paraesthesias (common)

- Numbness and/or tingling at the site of infection is a presenting symptom in many patients with B virus infection, and typically occurs within hours to days post-exposure.
- Numbness and/or tingling in the lower limbs may be a symptom of peripheral or CNS involvement, and are reported in more than half of patients with B virus infection.
- Symptoms indicating CNS involvement are most alarming.

hyperaesthesias (common)

- A sign of neurological involvement; may be peripheral rather than CNS involvement.

severe persistent headache (common)

- A symptom that may indicate CNS invasion. Symptoms indicating CNS involvement are most alarming.
- Reported in most patients with B virus infection entering the acute phase of infection.

dizziness (common)

- A symptom that may indicate CNS invasion. Symptoms indicating CNS involvement are most alarming.
- Reported in most patients with B virus infection entering the acute phase of infection.

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ocular pain (common)

- A symptom of CNS involvement. Symptoms indicating CNS involvement are most alarming.
- Typically associated with splash injury to face and neck (specifically exposure of the eye and mucous membranes).

gait disturbances (common)

- A sign of peripheral nervous or CNS involvement. Signs indicating CNS involvement are most alarming.
- Reported in most patients with B virus infection during advancing acute infection.

ataxia (common)

- May be a sign of CNS involvement. Signs indicating CNS involvement are most alarming.

diplopia (common)

- A symptom of CNS involvement. Symptoms indicating CNS involvement are most alarming.

agitation (common)

- A sign of CNS involvement. Signs indicating CNS involvement are most alarming.

meningismus (common)

- A sign of CNS involvement. Signs indicating CNS involvement are most alarming.

muscle weakness (paresis) (uncommon)

- A sign of infection progressing to CNS involvement. Signs indicating CNS involvement are most alarming.
- May be the first presenting symptom in late-onset B virus infections.

persistent hiccups (uncommon)

- A sign of CNS involvement. Signs indicating CNS involvement are most alarming.
- May suggest neurological disease at the level of the diaphragm. Not frequent, but an important sign when present.

dyspnoea (uncommon)

- A symptom of CNS involvement. Symptoms indicating CNS involvement are most alarming.
- Only reported in some patients.

ascending or acute flaccid paralysis (uncommon)

- A sign of infection progressing to CNS involvement. Signs indicating CNS involvement are most alarming.
- Ascending flaccid paralysis reported in a substantial minority of patients with B virus infection.
- May be the first presenting symptom in late-onset infections.

vesicular lesions (uncommon)

- Typically localised to site of exposure.
- Characteristics of lesions similar to lesions caused by HSV infection.

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Other diagnostic factors

nausea/vomiting (common)

- Reported in a large proportion of patients with B virus infection.
- Occurs within days, weeks, or months post-exposure.

conjunctivitis (common)

- Occurs in the majority of patients who are in the midst of advancing acute infection.
- Also occurred in a patient infected via a splash exposure to the eye without injury.

rash (uncommon)

- Reported in some patients with B virus infection. May be due to non-specific inflammation at the site of infection, reaction to replication of herpes virus locally, or may be unrecognised herpetic lesions. May be pruritic.

lymphadenitis (uncommon)

- Reported rarely in some patients.

lymphangitis (uncommon)

- Reported rarely in some patients.

abdominal pain (uncommon)

- Reported in some patients.
- Occurs within days, weeks, or months post-exposure.

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Diagnostic tests

1st test to order

Test	Result
serology • Serological analysis aimed at the detection of anti-B virus antibodies, usually using ELISA, is the standard first-line test for diagnosing B virus infections. It is the most clinically feasible way to assess for infection. However, due to the time required to develop detectable virus-specific antibodies, it will not inform immediate treatment decisions, which must be made based on clinical judgement. • Neither serological testing nor virus detection are used to guide a decision on whether to offer antiviral prophylaxis. Again, this decision must be made on clinical grounds. • An acute serum sample for serological analysis should be obtained immediately after exposure to serve as a baseline. A second convalescent sample should be obtained 3 to 6 weeks following exposure to document seroconversion to B virus. If the patient is receiving prophylaxis with an antiviral drug, a third serum sample should be obtained 3 months after the initial exposure as seroconversion may be delayed. • Acute and convalescent serum samples should be tested at the same time using paired samples when feasible. Testing of single specimens might be considered if clinical signs or symptoms of B virus infection are present. • For patients for whom initial baseline serum is not negative, a substantial rise in B virus antibody titre (>4-fold) in temporal association with potential B virus exposure is highly suggestive of infection. • Serological testing for B virus is complicated by the cross reactivity of serological results with those from other herpes viruses (e.g., HSV), which can result in false-positive reactions. PCR or viral culture should be undertaken alongside serological testing and is used to confirm B virus infection suggested by serological testing. PCR is preferred to viral culture as it is quicker, more sensitive, and more cost-effective. People with a history of possible exposure should not be diagnosed as infected on the basis of serological reactivity alone in the absence of symptomatic disease or laboratory confirmation of virus shedding by PCR or culture. Expert assistance with diagnostic testing and interpretation is essential. • For symptomatic patients, it may be informative to collect serial specimens for serological testing. • B virus is a biosafety level 4 (BSL-4) pathogen; therefore, specimens must be sent to a specialist diagnostic laboratory with BSL-4 capabilities as well as established capacity to perform diagnostics for B virus.[1]	**positive for B virus-specific serum antibodies IgM and subsequently IgG**

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Test	Result
PCR • If the patient is symptomatic, a rapid diagnosis is paramount to ensure appropriate management. PCR should be the first investigation to order in this situation. In an asymptomatic patient, a positive PCR from the exposure site does not confirm infection. However, a positive PCR from the exposure site at a time distant from exposure in association with symptoms concordant with B virus infection, or a positive PCR from a site not exposed to the virus (e.g., lesions, conjunctivae, oropharynx, CSF) at any time with symptoms concordant with B virus disease indicates infection.[4] • Serological results suggestive of B virus infection must be confirmed if possible using an agent-specific test, such as PCR or viral culture. PCR is the most expedient and reliable approach to confirming the DNA present is that of B virus and not another herpes virus that can cross react serologically with B virus (e.g., HSV). It is also preferred over virus culture due to the potential hazards associated with growing the virus in the laboratory as well as the time required for viral culture. Virus culture is also less sensitive than PCR. Thus, serological analysis with confirmation by PCR is the most feasible clinical approach. • Specimens for PCR should be collected from symptomatic patients potentially infected with B virus regardless of the risk assessment of the exposure and regardless of whether or not the patient is receiving post-exposure prophylaxis (PEP). Collection of wound specimens for PCR testing should only be done after the site has been thoroughly cleansed to reduce the risk of forcing the virus more deeply into the wound; however, collection of wound specimens at the time of exposure is not recommended. • It should also be recognised that specimens collected for PCR from the exposure site at the time of exposure are often negative due to removal of free viral particles during cleansing. Even if positive, presence of virus at the exposure site does not confirm infection in the absence of symptoms. Thus, specimens collected from the exposure site at the time of exposure may lack diagnostic or clinical significance for infection. • For symptomatic patients with positive PCR, serial PCR tests of the shedding sites should be followed to inform management decisions and infection control practices. Follow-up PCR testing should be repeated weekly until two consecutive negative PCR or culture results are obtained. Crusted lesions can be used to provide samples for PCR. • B virus is a biosafety level-4 (BSL-4) pathogen; therefore, specimens must be sent to a specialist diagnostic laboratory with BSL-4 capabilities as well as established capacity to perform diagnostics for B virus.[1]	**positive for B virus DNA**

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Other tests to consider

Test	Result
viral culture • Serological results suggestive of B virus infection must be confirmed if possible using an agent-specific test, such as PCR or viral culture. Viral culture remains an option to confirm B virus infection. However, the utility of viral culture to guide clinical management is limited as it is slower, less sensitive, and more costly than PCR. • There are potential hazards associated with growing the virus in the laboratory. Thus, serological analysis with confirmation by PCR is the most feasible clinical approach. Collection of wound specimens at the time of exposure is not recommended. • Collection of specimens for culture can be considered for symptomatic patients potentially infected with B virus regardless of the risk assessment of the exposure, and regardless of whether or not the patient is receiving PEP. Collection of wound specimens for culture should only be done after it has been thoroughly cleansed to reduce the risk of forcing the virus more deeply into the wound. • It should also be recognised that specimens collected for culture from the exposure site at the time of exposure are often negative due to removal of free viral particles during cleansing. The presence of virus at the time of exposure indicates exposure, not infection. Thus, specimens collected at the time of exposure lack diagnostic or clinical significance for infection. • In an asymptomatic patient, a positive culture at the site of exposure does not confirm infection. However, a positive culture from the exposure site at a time distant from exposure in association with symptoms concordant with B virus infection, or a positive culture from a site not exposed to the virus (e.g., lesions, conjunctivae, oropharynx, CSF) at any time with symptoms concordant with B virus disease indicates infection.[4] • Positive cultures from symptomatic patients should be repeated weekly (or PCR testing from the same site repeated instead) until there are two consecutive negatives to monitor response to treatment, inform infection control practices, and confirm cessation of virus shedding. During follow-up visits on symptomatic patients, samples for culture can be obtained from any lesions that have not yet crusted. • Positive growth of B virus must be confirmed using an agent-specific test (e.g., PCR, DNA sequencing, restriction endonuclease analysis, or sodium dodecyl sulfate-polyacrylamide gel electrophoresis [SDS-PAGE] analysis of viral proteins). • Culture is not required for clinical confirmation of B virus infection, but it may be helpful in confirming the presence of viable virus and for assessment of drug sensitivity.[46] • B virus is a biosafety level-4 (BSL-4) pathogen; therefore, specimens must be sent to a specialist diagnostic laboratory with BSL-4 capabilities as well as established capacity to perform diagnostics for B virus.[1]	**positive growth of B virus**
brain MRI • Carried out to assess for encephalomyelitis or other CNS infection if neurological symptoms develop.	**brainstem encephalomyelitis**

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Test	Result
brain CT • If MRI is unavailable, a brain CT with contrast can be carried out to assess for brainstem encephalomyelitis if neurological symptoms develop. However, CT findings are less sensitive than MRI for brainstem encephalitis.	**brainstem encephalomyelitis**
CSF tests • If neurological symptoms develop, a lumbar puncture can be carried out and CSF sent for routine chemistries, cell count, and for B virus detection (typically PCR).[49] [50]	**positive PCR or serology for B virus; cell counts or chemistries outside the normal range**
EEG • Guided by neurology consultant. • EEG can be considered if help is needed to differentiate B virus encephalitis (a brainstem encephalitis that becomes diffuse over time) from HSV encephalitis (a unilateral temporal lobe encephalitis).	**brainstem encephalitis becoming diffuse over time**
brainstem auditory evoked responses • Guided by neurology consultant. • In conscious patients, additional useful information about brainstem or upper spinal cord function may be obtained with brainstem auditory evoked responses. Should be done under neurological consultation.	**abnormal results suggesting B virus infection**
somatosensory evoked potentials • Guided by neurology consultant. • In unconscious patients, additional useful information about brainstem or upper spinal cord function may be obtained with somatosensory evoked potentials. Should be done under neurological consultation.	**abnormal results suggesting B virus infection**
laboratory testing of animal specimen • Guided by veterinary consultant. • Laboratory testing (e.g., serological analysis, PCR, culture) of the animal responsible for exposure can be considered to identify B virus infection. • Samples for testing should only be collected from the animal if possible and safe to do so, and under veterinary consultation. • Decisions to test animals associated with possible B virus exposures may inform management of that animal or the larger troop from which it comes; they are unlikely to substantially inform patient management. Decisions on evaluation and management of the patient must be initiated before these results will be available and continued based on the evidence of the patient, not the exposure source.	**positive for B virus infection**

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Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Herpes simplex encephalitis	• Temporal lobe symptoms (e.g., memory loss, olfactory hallucinations, behavioural abnormalities).	• PCR of CSF: positive for HSV. • Brain CT or MRI: presence of temporal lesions. • EEG: presence of unilateral temporal lobe encephalitis.
Herpes zoster encephalitis	• Usually presents as a stroke or TIA.	• PCR of CSF: positive for varicella-zoster virus. • Serology of CSF: positive for antibodies to varicella-zoster virus. • Magnetic resonance angiography: presence of vasculitis or aneurysm of cerebral arteries.
West Nile virus	• Residence in/travel from West Nile virus-endemic region. • Signs or symptoms may mimic B virus infection. • May present with flaccid paralysis, especially in the elderly.	• Serology of CSF: positive for antibodies to West Nile virus.
Epstein-Barr virus (EBV) encephalitis	• Cerebellar signs predominate (e.g., personality changes).	• Serology: positive for EBV-specific antibodies to EBV. • PCR: positive for EBV.
Viral meningitis	• No definite differentiating signs or symptoms.	• PCR of CSF: positive. • Brain CT or MRI: absence of brainstem encephalitis.

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Step-by-step treatment approach

The goal of medical management of herpes B virus exposure is to prevent progression to infection, to document infection if it has occurred, and to manage infection to prevent a potentially fatal encephalitis. Infection control is critical for the management of all patients confirmed or suspected to be infected with B virus.

Cleansing the exposed area

If a potential B virus exposure occurs, the immediate response should aim at preventing exposure from progressing to infection. Thus, the critical first step is immediate and thorough cleansing of the exposed area. The area should be cleansed on presentation for medical evaluation regardless of whether or not it was previously cleansed. The exposed area should be thoroughly washed and gently scrubbed with soap, povidone-iodine, detergent, or chlorhexidine and water for 15 minutes, followed by irrigating the area with running water for 15 to 20 minutes.[41]Mucosal exposure (nose, eyes, mouth) should be flushed with sterile saline solution or water for 15 minutes.

Post-exposure prophylaxis

If herpes B virus exposure is suspected and the patient presents for medical evaluation within 5 days of potential exposure, post-exposure prophylaxis (PEP) with a high-dose oral antiviral should be considered while diagnostic tests are being carried out to confirm infection. Since the goal of prophylactic antivirals is to prevent exposure from progressing to infection, and since animal models of B virus infection show that antivirals prevented disease if given within 5 days after infection,[44] [45]antiviral prophylaxis is not recommended for patients who present for medical evaluation more than 5 days after exposure.

The recommended first-line antiviral for B virus prophylaxis is high-dose oral valaciclovir. The alternative is high-dose oral aciclovir.[4]In one animal study, aciclovir administered within 24 hours after infection with B virus prevented mortality.[44] High-dose aciclovir administered to humans within hours after exposure may prevent progression to infection or may modify symptomatic B virus disease.[4]

Prophylactic administration of antibiotics or rabies vaccine and rabies immune globulin may also be considered depending on the cause and severity of exposure and the risk that exposure presents for infections other than B virus. Non-human primates housed outside can be exposed to rabies-infected animals and transmit rabies. Non-human primate bites carry similar risks of bacterial infections as bites inflicted by humans. If the animal associated with exposure has been used in research, specific infections that may have occurred during the research history may be clinically relevant (e.g., simian immunodeficiency virus [SIV], HIV) and should be investigated.

All patients who have experienced B virus exposure should be monitored for changes in serological titres and onset of clinical signs and symptoms suggestive of B virus infection. Patients who present more than 5 days after exposure should be followed with monitoring alone.

Infection control measures

In order to protect healthcare personnel and family members from exposure to potentially infectious tissue or body fluids, anyone treating or attending to patients with B virus infection must follow standard precautions.[51] Infection control practitioners should be consulted for further instruction. Observance of these standard precautions should occur regardless of whether the patient is receiving antiviral treatment. B virus has been isolated from skin lesions and buccal mucosa of patients actively receiving high-dose

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intravenous aciclovir.[33]The number of well documented human infections is too small to confidently predict what findings are atypical based on case reports or what findings are more likely to be common for most human infections. Asymptomatic human infection with B virus has never been documented. The one documented case of human-to-human transmission of B virus occurred in a spouse who treated a skin lesion on her B virus-infected husband prior to his diagnosis. She used the same cream to treat her dermatitis. He succumbed to B virus disease. She developed a pruritic rash subsequently laboratory confirmed as B virus, but responded to aciclovir treatment with no subsequent recurrences.[23]

Treatment of infection

Patients who develop signs and/or symptoms consistent with B virus disease after exposure must be treated with high-dose intravenous antiviral therapy. Patients already receiving an oral antiviral as PEP who have onset of symptomatic disease compatible with B virus should be switched to high-dose intravenous antiviral therapy immediately. Treatment should continue until B virus infection has resolved or can be excluded.

If CNS disease is present, high-dose intravenous ganciclovir is the recommended first-line treatment.[4] High-dose intravenous aciclovir is the recommended first-line treatment for B virus disease in the absence of CNS disease. High-dose intravenous ganciclovir can be used as an alternative to aciclovir, and should be preferred in any patient who appears to progress on aciclovir or who develops signs and symptoms of CNS disease.[4]Higher antiviral doses than those used to treat HSV infection are required to ensure effectiveness against B virus, since B virus is less sensitive to aciclovir than HSV in vitro.

Patients receiving aciclovir should be well hydrated to prevent precipitation of the drug in the renal tubules and renal insufficiency. Creatinine levels also need to be monitored, and dosage adjusted accordingly. If patients develop additional symptoms while being treated with aciclovir clinical evaluation is needed to consider whether treatment should be switched to ganciclovir.

B virus is more susceptible to ganciclovir compared with aciclovir, both in vitro and in animal models. Ganciclovir was used in the only case documenting complete recovery of B virus infection with brainstem encephalitis.[33] While ganciclovir is more toxic than aciclovir, the decision whether or not to use ganciclovir should be balanced against its potential benefit. As is the case with aciclovir, the dosage of ganciclovir needs to be adjusted for renal insufficiency. White blood cell and platelet counts should be monitored closely due to the myelosuppressive effects of ganciclovir.

Valganciclovir has been used successfully to manage a B virus patient with recurrent ocular lesions.[37]

The routine use of antivirals for prophylaxis following potential exposure and for the treatment of early-stage B virus disease, including those with early symptoms associated with CNS involvement, may have prevented infections and improved survival rates among infected patients over recent decades.[23] [33]Recognition of the importance of non-injury associated exposures of mucous membranes or non-intact skin, along with improvements in routine use of protective equipment and practices, combined with efforts to develop B virus-free macaque colonies have also likely contributed to the rarity of B virus cases in recent decades.

Supportive care

Beyond the described recommendations for antiviral therapy and diagnostic testing, management of B virus-infected people is largely supportive: for example, adequate hydration, use of antipyretics for fever, anti-emetics for vomiting, and analgesia for headaches.

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Intensive care (ICU) is usually indicated for patients with encephalitis. Death is often associated with respiratory failure. However, management decisions must be made at the bedside based on clinical judgement of the treating physician in association with engaged infectious disease specialists.

Some people who were laboratory confirmed to be infected with B virus survived the acute illness. For these patients, long-term supportive and rehabilitative care has contributed to restoration of mobility and recovery following acute, ascending paralysis. However, recovery from this stage of disease remains an uncommon event and is usually incomplete.[37] [31]

Pregnant women

Fairly extensive clinical experience suggests that administering aciclovir during pregnancy is reasonably safe. A registry of women who received the drug during pregnancy showed no increase in congenital abnormalities, although numbers were limited and insufficiently powered to detect low-incidence adverse outcomes.[52] [53] [54]Aciclovir is the antiviral therapy against herpesvirus with the most evidence for safety during pregnancy. If a woman of childbearing age presents with suspected B virus exposure or known B virus infection, a pregnancy test should be carried out to aid in the decision of which antiviral to choose. The relative safety of treatment with aciclovir compared with ganciclovir for the fetus must be weighed against the risk of B virus encephalitis for the mother during clinical decision making. Ganciclovir is indicated in any CNS infection.

Children

Potential B virus exposures of children and infants have occurred.[6]The social hierarchy among macaques, based on establishment of dominance by attacks against subordinates, may put children at increased risk of attack when in the vicinity of free-ranging macaques. Specific recommendations for treating B virus exposures and disease for children do not exist. Management of potential B virus exposures or disease suggestive of B virus infection should involve an infectious disease specialist who can provide advice on adaptation of existing guidelines in adults and antiviral dosing in children. Because valaciclovir is recommended for the treatment of varicella in children aged 2 to 18 years, and a recent study of the pharmacokinetics and safety of valaciclovir oral suspension showed that the drug was well tolerated and safe in children aged 3 months and older,[55] valaciclovir may be considered for prophylaxis of children exposed to B virus.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Initial		(summary)
potential exposure		
	1st	**cleansing exposed area**
	plus	**infection control measures**
	plus	**consider high-dose oral antiviral prophylaxis**

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Initial		(summary)
	plus	consider prophylaxis for potential co-infections

Acute		(summary)
confirmed infection and/or symptomatic		
	1st	high-dose intravenous antiviral therapy
	plus	infection control measures
	plus	supportive care
■ with encephalitis	plus	ICU care

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Treatment options

Initial

potential exposure

1st **cleansing exposed area**

» If a potential B virus exposure occurs, the immediate response should aim at preventing exposure from progressing to infection. Thus, the critical first step is immediate and thorough cleansing of the exposed area. The area should be cleansed on presentation for medical evaluation regardless of whether or not it was previously cleansed. The exposed area should be thoroughly washed and gently scrubbed with soap, povidone-iodine, detergent, or chlorhexidine and water for 15 minutes, followed by irrigating the area with running water for 15 to 20 minutes.[41]Mucosal exposure (nose, eyes, mouth) should be flushed with sterile saline solution or water for 15 minutes.

» The cleansed exposure area should be evaluated by a third party for adequacy of washing, and repeated if necessary. The date, time, location, nature, and site of injury, and the type of fluid or tissue exposure should also be recorded. The first few minutes after an exposure are considered the most critical period for reducing the risk of infection.

plus **infection control measures**

» Infection control is critical for the management of all patients with suspected B virus infection. Anyone treating or attending to patients with suspected infection must follow standard blood and body fluid precautions.[51]Infection control practitioners should be consulted for further instruction.

» Infection control measures should be carried out regardless of whether the patient is receiving antiviral treatment. B virus has been isolated from skin lesions and buccal mucosa of patients actively receiving high-dose intravenous aciclovir.[33]

plus **consider high-dose oral antiviral prophylaxis**

Primary options

» valaciclovir: children: consult specialist for guidance on dose; adults: 1 g orally every 8 hours for 14 days

OR

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Initial

» aciclovir: children: consult specialist for guidance on dose; adults: 800 mg orally five times daily for 14 days

» Post-exposure prophylaxis (PEP) should be considered if B virus exposure is suspected based on history and physical examination, and the patient presents within 5 days of potential exposure. It is not recommended for patients who present more than 5 days after potential exposure.

» The recommended first-line antiviral is high-dose oral valaciclovir. The alternative is high-dose oral aciclovir.[4]

» All patients who have experienced B virus exposure should be monitored for changes in serological titres and onset of clinical signs and symptoms suggestive of B virus infection. Patients who present more than 5 days after exposure should be followed with monitoring alone.

» PEP should be administered while diagnostic tests are being carried out to confirm infection. Prophylaxis should continue for 14 days or until B virus infection can be excluded.

» In women of childbearing age who present with suspected B virus exposure, a pregnancy test should be carried out to aid in the decision of which antiviral to choose. Extensive clinical experience suggests that administering aciclovir during pregnancy is reasonably safe. A registry of women who received the drug during pregnancy showed no increase in congenital abnormalities, although numbers were limited and insufficiently powered to detect low-incidence adverse outcomes.[52] [53] [54]

» In children exposed to B virus, oral valaciclovir may be considered for prophylaxis owing to its recommended use in treating varicella infection in children aged 2 to 18 years. Furthermore, studies investigating the pharmacokinetics and safety of valaciclovir oral suspension have shown it to be well tolerated and safe in children aged 3 months and older.[55] There are no specific recommendations for treating B virus exposures and disease in children; therefore, an infectious disease specialist should be consulted for advice on adaptation of existing guidelines in adults and antiviral dosing in children.

plus **consider prophylaxis for potential co-infections**

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Initial

» Exposure from the bite or scratch from monkeys may lead to co-infections such as tetanus, rabies, or bacterial infections.

» Reviewing the vaccine history of a patient may be useful to determine whether further vaccinations are required.

» Antibacterial treatment of bites should be considered. Prophylactic administration of antibiotics or rabies vaccine and rabies immune globulin may also be considered depending on the cause and severity of exposure and the risk that exposure presents for infections other than B virus.

» If the animal associated with exposure has been used in research, specific infections that may have occurred during the research history may be clinically relevant (e.g., simian immunodeficiency virus [SIV] or HIV) and should be investigated.

Acute

confirmed infection and/or symptomatic

1st **high-dose intravenous antiviral therapy**

Primary options

» aciclovir: children: consult specialist for guidance on dose; adults: 12.5 to 15 mg/kg intravenously every 8 hours

OR

» ganciclovir: children: consult specialist for guidance on dose; adults: 5 mg/kg intravenously every 12 hours

» Patients with confirmed B virus infection or who develop signs and/or symptoms consistent with B virus disease after exposure should be treated with intravenous antiviral therapy. Higher antiviral doses than those used to treat HSV infection are required to ensure effectiveness against B virus.

» If CNS disease is present, high-dose intravenous ganciclovir is the recommended first-line treatment.[4]High-dose intravenous aciclovir is the recommended first-line treatment for B virus disease in the absence of CNS disease. High-dose intravenous ganciclovir can be used as an alternative to aciclovir, and

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Acute

should be preferred in any patient who appears to progress on aciclovir or who develops signs and symptoms of CNS disease.[4]

» Patients already receiving an oral antiviral as PEP who have onset of symptomatic disease compatible with B virus should be switched to high-dose intravenous antiviral therapy immediately. Treatment should continue until B virus infection has resolved.

» Patients receiving aciclovir should be well hydrated to prevent precipitation of the drug in the renal tubules and renal insufficiency. Creatinine levels also need to be monitored, and dosage adjusted accordingly. If patients develop additional symptoms while being treated with aciclovir, clinical evaluation is needed to consider whether treatment should be switched to ganciclovir. As is the case with aciclovir, the dosage of ganciclovir needs to be adjusted for renal insufficiency. White blood cell and platelet counts should be monitored closely due to the myelosuppressive effects of ganciclovir.

» In women of childbearing age with confirmed B virus infection, a pregnancy test should be carried out to aid in the decision of which antiviral to choose. Extensive clinical experience suggests that administering aciclovir during pregnancy is reasonably safe. A registry of women who received the drug during pregnancy showed no increase in congenital abnormalities, although numbers were limited and insufficiently powered to detect low-incidence adverse outcomes.[52] [53] [54]However, the theoretical risk of ganciclovir to the fetus must be weighed against the documented risk of B virus encephalitis for the mother during clinical decision making. Ganciclovir is indicated in any CNS infection.

» There are no specific recommendations for treating B virus infection in children; therefore, an infectious disease specialist should be consulted for advice on adaptation of existing guidelines in adults and antiviral dosing in children.

plus **infection control measures**

» Infection control is critical for management of all patients with confirmed B virus infection, and/or those who have symptoms suggesting B virus infection. There has been no documented case of asymptomatic human B virus infection.

» Anyone treating or attending to patients with confirmed infection must follow standard blood

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Acute

and body fluid precautions.[51] Infection control practitioners should be consulted for further instruction.

» Infection control measures should be carried out regardless of whether the patient is receiving antiviral treatment. B virus has been isolated from skin lesions and buccal mucosa of patients actively receiving high-dose intravenous aciclovir.[33]

plus **supportive care**

» Beyond the described recommendations for antiviral therapy and diagnostic testing, management of B virus-infected people is largely supportive.

» Adequate hydration, use of antipyretics for fever, anti-emetics for vomiting, and analgesia for headaches may be instituted in symptomatic patients.

» Management decisions must be made at the bedside based on clinical judgement of the treating physician in association with engaged infectious disease specialists.

with encephalitis **plus** **ICU care**

» Usually indicated for patients with encephalitis. Death is often associated with respiratory failure. Management decisions must be made at the bedside based on clinical judgement of the treating physician in association with engaged infectious disease specialists.

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FOLLOW UP

Recommendations

Monitoring

ost-exposure monitoring:

- Patients who have been exposed to B virus should be monitored for at least 2 months despite the fact that disease onset usually occurs within 5 weeks of exposure. Patients should also receive counselling. The need for monitoring and counselling remains regardless of whether antiviral prophylaxis has been prescribed. Follow-up appointments should be scheduled to monitor for potential infection and/or disease progression. Initial appointments can be scheduled for 1, 2, and 4 weeks post-exposure, or immediately if the patient reports the development of symptoms consistent with B virus infection. For occupational exposures, the patient's supervisor at work or their occupational healthcare provider should monitor the clinical status of the patient at least weekly during the first month following exposure. During the follow-up appointments, the site of infection and the signs and symptoms of B virus infection should be evaluated. Adherence with medication should also be determined. Patients who have received post-exposure prophylaxis (PEP) should have their monitoring extended owing to the potential delay with the antibody response to B virus or suppressed viral shedding. Serological testing should be carried out again at 3 to 6 weeks following exposure; serum specimens from patients receiving PEP should be tested at later points in time (e.g., 3 months after exposure). For those patients with positive PCR or cultures from the initial wound, additional PCR or cultures may be done 1 to 2 weeks after antiviral therapy has been discontinued in order to check for viral shedding.[4]

Antiviral treatment monitoring:

- Serum creatinine should be monitored in patients receiving aciclovir at high doses, and doses should be adjusted accordingly. Patients receiving ganciclovir should be closely monitored for myelosuppression.[4]

Monitoring following treatment of active disease:

- Based on what is known about the pathophysiology of B virus infection and reasoning by analogy from other alphaherpesvirus infection, those who survive B virus disease are presumed to remain latently infected. The virus is presumed to persist in the peripheral nervous system (usually the nerve ganglia) for the lifetime of the host; it is not present in blood or serum of infected hosts. The virus can be detected in other body fluids (vesicular lesions, CSF, oral and genital secretions) during symptomatic illness and continuing for a duration while on antiviral therapy. For these reasons, active viral shedding should be demonstrated to have stopped before intravenous antivirals are discontinued.
- Monitoring for recurrence of clinical signs and symptoms suggesting recurrent active infection and for recurrence of B virus shedding is important following successful treatment of active B virus disease. Many physicians have advised a transition from intravenous antiviral therapy to ongoing oral valaciclovir or aciclovir maintenance therapy after symptoms and active virus shedding have been documented to have stopped.[4] However, there is a lack of good data on when or whether treatment should be discontinued; therefore, this should be done with expert consultation.[4]
- Long-term monitoring of patients who have recovered from B virus disease should include some plan for periodic monitoring to confirm that virus shedding has not reactivated. Reactivation of treated B virus infection in survivors is rare, but at least two cases of ocular disease similar to zoster, one recurrent, have been interpreted as recurrent B virus infection.[37] [17] Recurrent ocular B virus disease was treated with valaciclovir.[37]

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Patient instructions

Laboratory workers and animal workers who are in close contact with macaques (or their body fluids) are at high risk of exposure to B virus. These people should be informed of the hazards associated with macaques and the importance of notifying senior personnel (including occupational health personnel) if bites, scratches, or mucocutaneous exposures occur. They should also be educated on administering first aid and the need for rapid evaluation by occupational health personnel.

Administering first aid:

- Immediate first aid following any high-risk contact with a macaque (bite, scratch, percutaneous injuries contaminated with macaque body fluids, or mucous membrane or non-intact skin exposure to potentially infectious fluid or other material without injury) is crucial.
- Wounds and fluid exposures that have been thoroughly cleansed within 5 minutes of the exposure are likely to have a reduced risk for B virus infection. Washing of the affected site should be performed for a minimum of 15 minutes. Possible skin exposures should be washed with povidone-iodine, chlorhexidine, or detergent soap. All of these agents are known to be capable of inactivating viruses such as herpesviruses that have a lipid envelope.[56] [57] [58] Gentle massaging of the wound during cleansing can improve penetration of the antimicrobial solution. Dakin's solution, a 1:20 bleach to water solution, is more toxic than either chlorhexidine or povidone-iodine and can irritate the skin. Bleach solutions are relatively unstable, and should be prepared at the time of use. If Dakin's solution is used, the affected area should be washed with detergent subsequently as described above.
- Skin wounds should not be incised, biopsied, or swabbed as these actions could act to drive the virus more deeply into tissues.
- None of the solutions and detergents discussed for use on skin lesions should ever be used to cleanse eyes or other mucous membranes. For such exposures the affected area should be irrigated without delay with sterile saline solution or water for a minimum of 15 minutes. If the nearest eye wash station cannot be reached in less than a few minutes, a 1-litre bag of sterile saline should be kept at the work site. If workers are based at a remote location with no available wash solution, a 1-litre bag of sterile saline should be carried with them to the site to avoid any delay in cleansing the wound or mucosa.

On-site evaluation by occupational health personnel:

- Immediately after cleansing a potential B virus exposure, the affected person should report to their occupational healthcare provider for counselling and education, and to receive written materials describing the signs and symptoms of B virus infection.
- It is also important for the occupational healthcare provider to facilitate rapid access to a local medical consultant familiar with both human B virus infection and other infectious agents associated with non-human primates.
- Formal education and written protocols for engaging with both the occupational healthcare provider and with local medical experts should be available at the work site. Written information about human B virus infection should also be made available to area physicians in case exposures occur after hours when on-site medical assistance may be unavailable.

Travel:

- Information about the risks associated with macaques freely roaming in parks and temples should be made readily available to tourists and others who plan to travel to countries or areas where contact with these monkeys is likely. Such information should also include instructions for first

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aid in case of a potential exposure, and for the need to visit a medical expert familiar with B virus infections at the earliest opportunity.

Complications

Complications	Timeframe	Likelihood
respiratory failure associated with ascending paralysis	**short term**	**high**
A frequent progression of B virus infection that begins peripherally and ascends the spinal cord. This is frequently the immediate cause of death.		
extremity paresis or plegia	**long term**	**high**
May be an outcome of B virus infection in survivors depending on what part of the CNS was involved.		
aphasia	**long term**	**high**
May be an outcome of B virus infection in survivors depending on what part of the CNS was involved.		
dysarthria	**long term**	**high**
May be an outcome of B virus infection in survivors depending on what part of the CNS was involved.		
residual chorioretinitis	**long term**	**high**
May be an outcome of B virus infection of the eye.		
co-infections	**variable**	**medium**
Exposure from the bite or scratch from monkeys may lead to co-infections such as tetanus, rabies, or bacterial infections. Reviewing the vaccine history of a patient may be useful to determine whether further vaccinations are required. Bites inflicted by non-human primates carry risks for bacterial infections similar to those inflicted by human primates. Antibacterial treatment of bites should be considered.		

Prognosis

B virus exposure may or may not lead to infection, but B virus infection almost always results in disease in humans, which usually occurs within 1 month of exposure.[2] [4]How the disease progresses depends on several factors, including the site of infection and the amount of virus transmitted during infection. In the absence of intervention, human infection typically progresses from localised signs or non-specific flu-like symptoms to neurological symptoms as the virus infects the CNS.[4] Neurological symptoms may be gradual or abrupt in onset.[4] Encephalomyelitis develops as the virus infects the CNS, and the usual outcome is death, which is often attributed to respiratory failure due to ascending paralysis.[36] The mortality rate with B virus infection is approximately 80% in untreated humans. The mortality rate is reduced if aggressive antiviral treatment is instituted in a timely manner.

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Based on what is known about the pathophysiology of B virus infection and reasoning by analogy from other alphaherpesvirus infection, those who survive B virus disease are presumed to remain latently infected. However, recurrence of symptoms is rare; only two reports of presumed clinical recurrence of pre-existing B virus infection exist.[37] [17] Many survivors do suffer lifelong moderate-to-severe neurological sequelae, sometimes requiring institutionalisation.[31] The virus is presumed to persist in the peripheral nervous system (usually the nerve ganglia) for the lifetime of the host; it is not present in blood or serum of infected hosts. The virus can be detected in other body fluids (vesicular lesions, CSF, oral and genital secretions) during symptomatic illness and continuing for a duration while on antiviral therapy. For this reason, active viral shedding should be demonstrated to have stopped before intravenous antivirals are discontinued. Many physicians have advised a transition from intravenous antiviral therapy to ongoing oral valaciclovir or aciclovir maintenance therapy after symptoms and active virus shedding have been documented to have stopped.[4] However, there is a lack of good data on when or whether treatment should be discontinued; therefore, this should be done with expert consultation.[4] Long-term monitoring of recovered patients should include some plan for periodic monitoring to confirm that virus shedding has not reactivated. At least one case of B virus infection presenting similar to ocular zoster in a person who was reported not to have had contact with macaque monkeys for many decades has been described and was interpreted as a late clinical presentation of a long-term silent B virus infection.[17] Recurrent ocular B virus disease has also been described in a patient treated with valaciclovir.[37]

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Diagnostic guidelines

International

Health information for international travel (Yellow Book): B virus

Published by: Centers for Disease Control and Prevention **Last published:** 2017

Recommendations for prevention of and therapy for exposure to B virus (Cercopithecine Herpesvirus 1)

Published by: B Virus Working Group **Last published:** 2002

Treatment guidelines

International

Health information for international travel (Yellow Book): B virus

Published by: Centers for Disease Control and Prevention **Last published:** 2017

Recommendations for prevention of and therapy for exposure to B virus (Cercopithecine Herpesvirus 1)

Published by: B Virus Working Group **Last published:** 2002

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Online resources

1. CDC: B virus first aid and treatment *(external link)*

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Key articles

- Cohen JI, Davenport DS, Stewart JA, et al. Recommendations for prevention of and therapy for exposure to B virus (cercopithecine herpesvirus 1). Clin Infect Dis. 2002 Nov 15;35(10):1191-203. Full text

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Images



Figure 1: Rhesus monkey (Macaca mulatta)

CDC/Dr Roger Broderson

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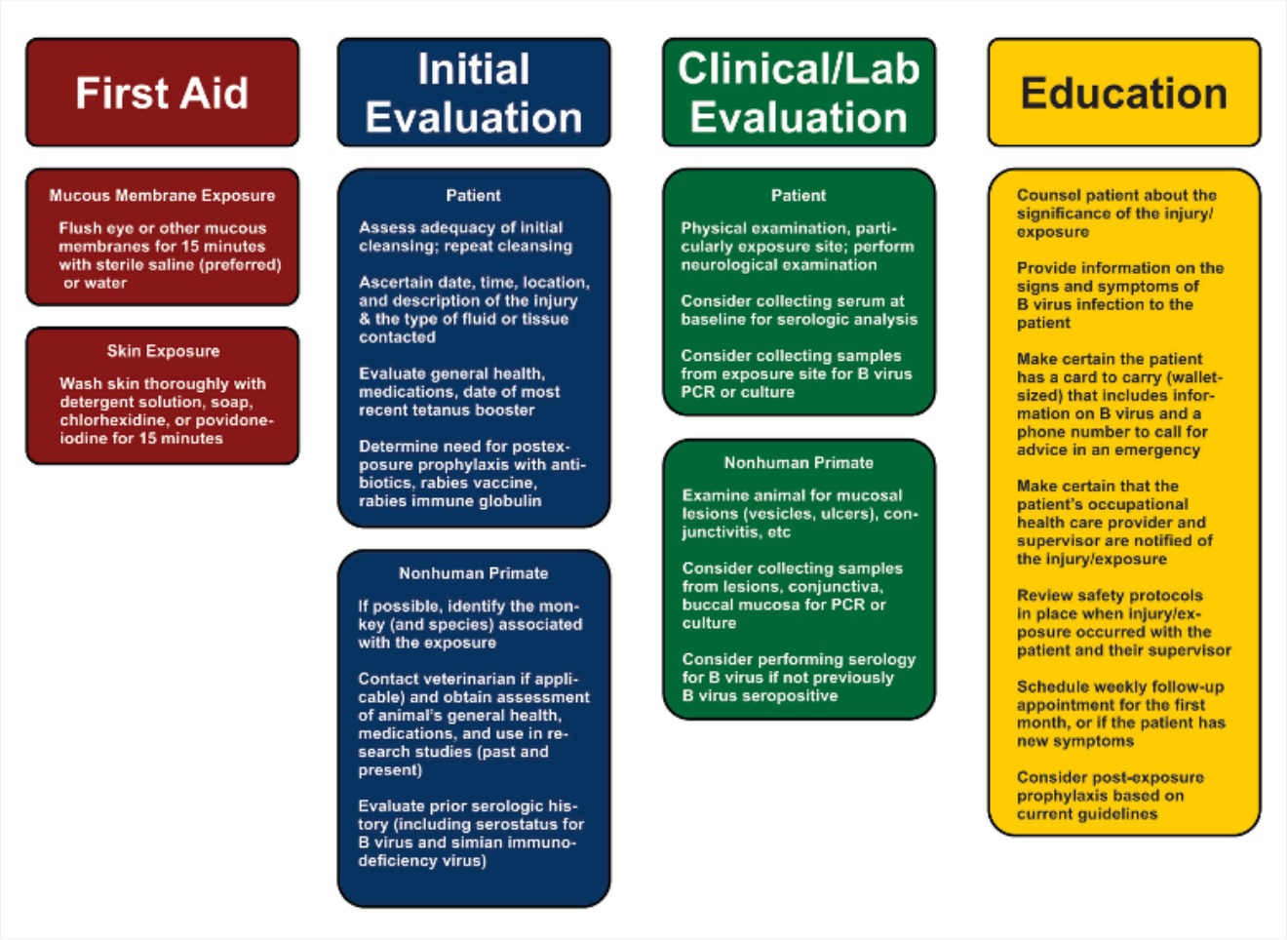

Figure 2: Overview of the steps for managing putative B virus exposures

CDC

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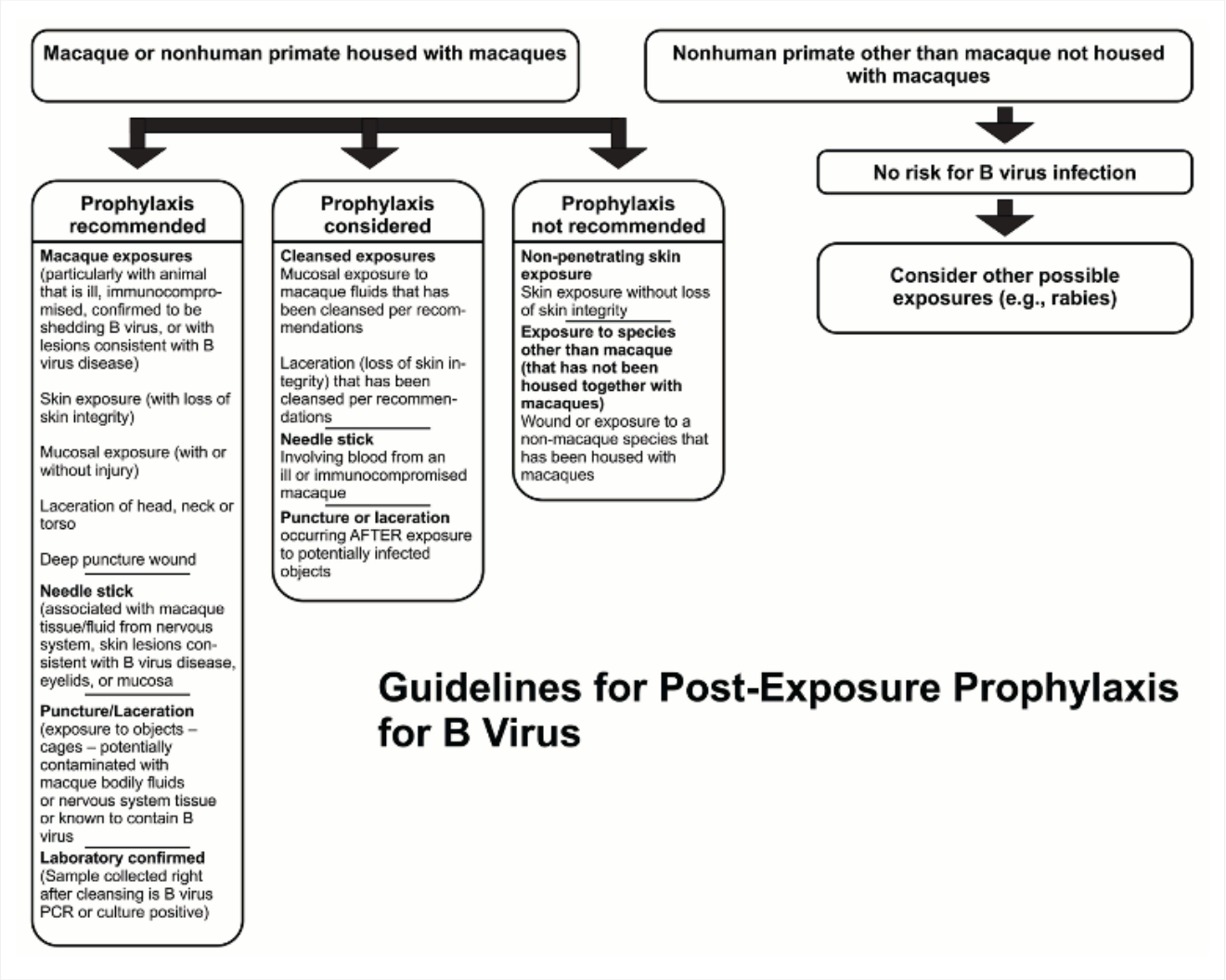

Figure 3: Guidelines for post-exposure prophylaxis for suspected B virus infection

CDC

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