B Virus – Clinical Management

IDIC Forum

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Introduction

- B virus is an alpha herpesvirus commonly found among macaques
- Named after the first patient W.B., a researcher who was bitten by a healthy-looking rhesus macaque (Macaca mulatta) and died of progressive encephalomyelitis 15 days later
- Also known as herpes B, monkey B virus, herpesvirus simiae, herpesvirus B, Macacine (formerly Cercopithecine) herpesvirus, 猴疱疹病毒, B 病毒
- Without treatment, mortality up to 70-80%
- About 50 people documented to have been infected globally since 1932 (CHP website)
- No cross-protection from HSV 1 and 2 antibodies in humans

B virus infection in monkeys

- Naturally carried in Old World monkeys (such as rhesus, cynomolgus, pig-tailed, Japanese macaques)
- Infection usually mild and self-limiting in macaques – results in either no symptom or oral or genital lesions similar to HSV in humans
- Virus remains latent; can reactivate and shed from oral, nasal, or genital mucosa during stress or immunosuppression
- Transmission amongst monkeys – through mating, scratching, or biting

B virus infection in monkeys

- Prevalence study, depending on survey, ~ 20% of animals < 2.5 years of age were seropositive, and nearly 100% of captive macaques ≥ 2.5 years were seropositive
- ~2% of seropositive rhesus monkeys can shed the virus → 1 in 50 to 1 in 250 contacts with macaques can result in exposure to B virus

Transmission to humans

- Majority of B virus infection cases has occurred in persons who work macaques monkeys, in animal facilities or laboratories
- Documented sources of infection – monkey bites, injury by contaminated fomites e.g. monkey cage scratches, needlestick injuries, exposure of mucous membranes to infectious materials
- Travelers exposed to free-ranging monkeys that can be seropositive for B virus

Cohen JI, Davenport DS, Stewart JA, et al. Recommendations for prevention of and therapy for exposure to B virus. Clin Infect Dis. 2002;35(10):1191-1203.

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

[a] Cultures involved monkey kidney cells.

[b] In one case, a needle had been used to inject the tissues around the eye, and, in the other case, a needle "may have been used previously to inject monkeys" [4, p. 974].

[c] In one case, aerosol may have been generated during autopsies performed on macaques, and, in the other case, the patient presented with respiratory symptoms.

[d] The patient applied cream to her husband's herpes vesicles and to areas of her own skin that were affected by contact dermatitis.

[e] The patient was splashed in the eye with material, possibly feces, from a macaque.

One case of human to human transmission has been reported

Patient 2

On about 10 March 1987, a 37-year-old male biological technician at NAMRL suffered a penetrating wound on the left forearm that later appeared to observers to be an animal bite. On the day of the injury, he had frequently handled monkey X, the monkey that bit Patient 1, and coworkers later reported that this animal inflicted the injury to Patient 2 as well. It is not known what protective gear he was wearing at the time of the injury. Five days after the injury, herpetiform vesicles developed at the site of the wound. On 26 March, after the lesions had become crusted, he was seen by a dermatologist who detected giant cells with distinct viral inclusions in a Tzanck preparation of scrapings from the lesions. Topical acyclovir cream was prescribed, but the patient never filled the prescription; he used instead a zinc oxide preparation on the lesions, changing later to an over-the-counter 0.25% hydrocortisone cream. During the next several days, left arm numbness, chest pain, dyspnea, fever, confusion, lethargy, diplopia, and dysphagia developed, and he was hospitalized on 30 March. He had respiratory arrest and was intubated later that day. Infection with B virus was suspected, and a culture of a skin biopsy specimen later confirmed this diagnosis. High-dose intravenous acyclovir, followed by ganciclovir therapy, was administered without response. The patient died on 28 April 1987.

Patient 4

Beginning about 18 March 1987, the 29-year-old wife of Patient 2 regularly applied zinc oxide cream to her husband's herpetic skin lesions, also applying it to an open area of contact dermatitis on her left ring finger. On 25 March, she began applying 0.25% hydrocortisone cream to both her and her husband's lesions. Although she had frequently visited the NAMRL facility, she denied having had direct contact with monkeys or monkey products. Her dermatitis failed to resolve, becoming pruritic and slightly ulcerated. On 1 April, a dermatologist took a punch biopsy specimen from the site and prescribed oral acyclovir. On 6 April, a herpesvirus was identified in the culture and she was hospitalized for intravenous acyclovir therapy. On 13 April, B virus infection was confirmed. The lesion remained virus-positive for more than 1 month and then healed without any associated progressive signs or symptoms. During this interval, the patient developed culture-confirmed asymptomatic conjunctival shedding that lasted for 18 days. Subsequent cultures for B virus were consistently negative, and she has had no documented B virus-related symptoms since her discharge on 17 May 1987. As of 31 January 1990, she remained asymptomatic while continuing daily oral acyclovir therapy.

Holmes GP, Hilliard JK, Klontz KC, et al. B virus (Herpesvirus simiae) infection in humans: epidemiologic investigation of a cluster. Ann Intern Med. 1990;112(11):833-839.

B Virus Disease in Humans

- No serologic evidence that B virus causes asymptomatic infections in humans in several studies, including one study involving 321 primate handler: 224 (70%) recalled exposure to Macaca monkeys over an extended period and 166 (52%) of 321 primate handlers reported potential BV exposures

  Freifeld AG, Hilliard J, Southers J, et al. A controlled seroprevalence survey of primate handlers for evidence of asymptomatic herpes b virus infection. Journal of Infectious Diseases. 1995;171(4):1031-1034.

- Most cases with CNS complications will die – even with antiviral and supportive care
- Survivors usually have long-term neurological sequelae
- Respiratory failure with ascending paralysis the most common cause of death, which can occur 1 day to 3 weeks after symptom onset

B Virus Disease in Humans - Clinical features

Incubation Period	5 days to 3 weeks (range 2 days to 5 weeks)
Initial Symptoms	**Flu like illnesses** Fever, myalgia, fatigue, headache
Progressive Symptoms	**Local** Vesicular or ulcerative lesion, lymphadenopathy, pain and tingling sensation
	Systemic Nausea and vomiting, abdominal pain, hepatitis, pneumonitis, sinusitis conjunctivitis
	CNS involvement Ataxia, cranial nerve palsies, nystagmus, diplopia, agitation, dysarthria and dysphagia, ascending flaccid paralysis, respiratory failure, coma

Who are at risk of B virus?

1. Source of exposure
   - Macaques or other primates that have history of contact with macaques
   - At risk: ill animals, stressed animals, breeding animals
2. Timeliness and adequacy of first aid
   - At risk: Wounds not adequately cleaned
3. Type of wound or exposure, depth of wound, location of wound
   - At risk: deep puncture wounds, needlestick injuries
   - At risk: Wounds involving head, neck and thorax (more rapid transmission to central nervous system before local symptoms developed)
   - Exposure that involve intact skin are not thought to pose a risk of infection
4. Exposure to materials that have come in contact with macaques
   - At risk: exposure to Macaque oral, genital, ocular secretions, or central nervous system tissue
   - Contact with monkey blood has not been reported to cause B virus disease in humans – viremia in macaque monkeys not common

Post Exposure Wound Management

First aid

- Wash area thoroughly with soap, detergent (e.g. chlorhexidine), or povidine-iodine for at least 15 minutes – can readily inactive the virus
- Mucous membranes – flush with water or saline for at least 15 minutes

Then run water over area for 15-20 min more

- First aid of injured or contaminated sites plays a major role in infection control

- Antibiotics prescription, tetanus and rabies vaccination if indicated

Post Exposure Prophylaxis – Antiviral Medications

- Valaciclovir 1g oral every 8 hours OR
- Acyclovir 800mg oral 5 times per day (pregnancy)

For 14 days

PEP with acyclovir and ganciclovir has been shown effective in rabbits

So far, no cases have occurred for patients who have received postexposure prophylaxis with antiviral medication within 3 days of B virus exposure

PEP should be started soon (within hours) after the exposure, and preferably within 5 days of exposure

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

Prophylaxis recommended
Skin exposure[a] (with loss of skin integrity) or mucosal exposure (with or without injury) to a high-risk source (e.g., a macaque that is ill, immunocompromised, or known to be shedding virus or that has lesions compatible with B virus disease)
Inadequately cleaned skin exposure (with loss of skin integrity) or mucosal exposure (with or without injury)
Laceration of the head, neck, or torso
Deep puncture bite
Needlestick associated with tissue or fluid from the nervous system, lesions suspicious for B virus, eyelids, or mucosa
Puncture or laceration after exposure to objects (a) contaminated either with fluid from monkey oral or genital lesions or with nervous system tissues, or (b) known to contain B virus
A postcleansing culture is positive for B virus
Prophylaxis considered
Mucosal splash that has been adequately cleaned
Laceration (with loss of skin integrity) that has been adequately cleaned
Needlestick involving blood from an ill or immunocompromised macaque
Puncture or laceration occurring after exposure to (a) objects contaminated with body fluid (other than that from a lesion), or (b) potentially infected cell culture
Prophylaxis not recommended
Skin exposure in which the skin remains intact
Exposure associated with nonmacaque species of nonhuman primates

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

Cohen JI, Davenport DS, Stewart JA, et al. Recommendations for prevention of and therapy for exposure to B virus. Clin Infect Dis. 2002;35(10):1191-1203.

Barkati S, Taher HB, Beauchamp E, Yansouni CP, Ward BJ, Libman MD. Decision tool for herpes B virus antiviral prophylaxis after macaque-related injuries in research laboratory workers. Emerg Infect Dis. 2019;25(9).

Figure. Decision tool used at McGill University Health Centre, Montreal, Canada, for herpes B virus antiviral prophylaxis after macaque monkey–related injuries in research laboratory workers.CNS, central nervous system; IV, intravenous.

Centre universitaire de santé McGill — McGill University Health Centre

TROPICAL DISEASES CLINIC
Decision tool for anti-viral prophylaxis

Monkey bite	**Source: macaque** ☐ **Yes** ☐ **No** **If no, do not proceed. No prophylaxis indicated**
Employer	

Score (Maximum 12 points)	
0-1 points	**Low-risk exposure; prophylaxis not routinely recommended**
2-3 points	**Moderate-risk exposure; consider prophylaxis**
4-7 points	**High-risk exposure; prophylaxis recommended**
More than 7 points	**Very high-risk exposure; prophylaxis recommended and consider treatment with IV Acyclovir**

Designed for assessment of laboratory workers; may not be relevant for other groups such as travelers

First aid			Point(s)	Score
☐	Adequate	Skin:washed with soap X 15 min.	0 pt	
☐	Adequate	Membranes : flushed with saline / water X 15 min	0 pt	
☐	Inadequate		2 pts	

Type of exposure (choose one only)		Point(s)	Score
☐	Any exposure to skin with no loss of integrity	0 pt	
☐	Mucosal splash with other bodily fluids (e.g.: blood, urine, stool)	1 pt	
☐	Needlestick associated with other bodily fluids	1 pt	
☐	Scratch with loss of skin integrity	2 pts	
☐	Puncture / laceration with object potentially contaminated with bodily fluid (e.g.: cage)	2 pts	
☐	Bite with loss of skin integrity	3 pts	
☐	Mucosal splash (including eye) with saliva / CNS tissue or fluid / fluid from oral or genital lesions	4 pts	
☐	Needlestick or other puncture associated with CNS tissue or fluid/macaque mucosa / macaque eyelid/fluid from oral or genital lesions	4 pts	

Depth of exposure		Point(s)	Score
☐	Superficial scratch / bite / puncture / splash	0 pt	
☐	Deep (e.g.: More than 5 mm) scratch / bite / puncture / splash	1 pt	

Body part(s) exposed		Point(s)	Score
☐	Limbs / extremities	0 pt	
☐	Head / neck / torso	2 pts	

Source risk factors		Point(s)	Score
☐	Healthy macaque	0 pt	
☐	Macaque new to colony / ill / breeding / immunocompromized / lesions compatible with B-virus disease	2 pts	
☐	Macaque known to be B - virus seropositive	3 pts	
		Total	

Follow up after the exposure

- PEP may delay the development of antibody response to B virus or suppress viral shedding

- Consider repeat serological testing 3-6 weeks, and at later points in time e.g. 3 months after exposure

- Cultures of material obtained from the conjunctivae, oropharynx, and any unhealed skin lesions 1-2 weeks after discontinuation of antiviral medication to detect viral shedding

Patient Education

- Counseling on the significance of the injury
- Provide information on the signs and symptoms of B virus infection
- Ensure patient, carer and health care provide +/- supervisor are informed of the injury
- Consider a card that include information on B virus and phone call for advice in case of emergency
- Review of safety precaution in place at the time of injury

Management of cases with compatible symptom and signs of B virus illness

- History and physical examination – watch out for neurological symptoms and signs

- Routine chemical and hematological studies
- Urine or serum pregnancy test if appropriate

Specific investigations for suspected B virus cases

- Serum for B virus serology (obtained before or at time of exposure, and at presentation - ≥ 4 fold rise diagnostic)
- B virus cultures (BSL4 agent) / PCR of lesions, conjunctivae, and oropharynx
- MRI brain (or CT if MRI not available) for brain stem encephalomyelitis
- Lumbar puncture – send for cell count, biochemistry, B virus culture / PCR, B virus serology
- EEG (electroencephalography) – help differentiate B virus encephalitis (brainstem encephalitis that becomes diffuse) from HSV (usually focal encephalitis involving unilateral temporal lobe)

Antivirals against B Virus

- Higher IC50 for B virus than HSV
- Ganciclovir (GCV) lower IC50 than Acyclovir (ACV)

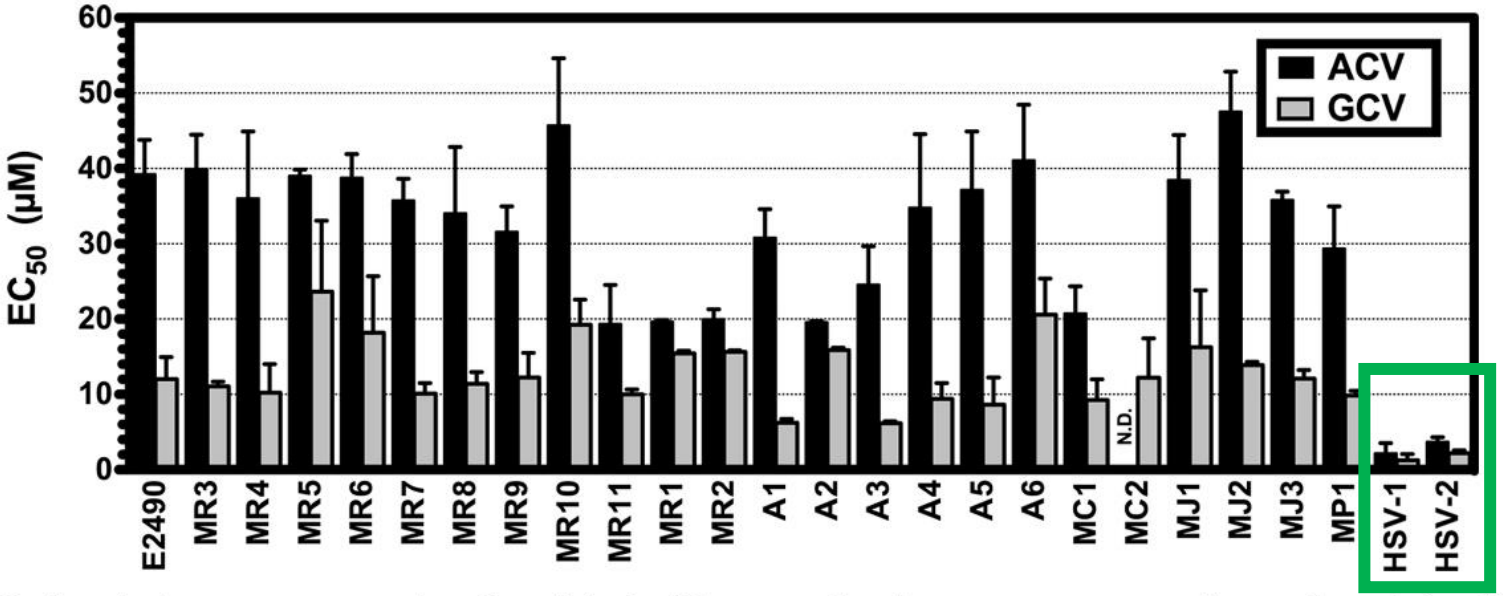

FIG. 4. Sensitivities of B virus isolates to conventional antivirals. Plaque reduction assays were performed, and the 50% effective concentration (EC_{50}) of each drug against each isolate was determined. Each bar corresponds to the mean EC_{50}; error bars, standard deviations. Each isolate was tested against each drug in at least two independent experiments. N.D., not done.

MR, rhesus macaque isolate; E2490, prototype laboratory strain; A, human isolate; MJ, Japanese macaque isolate; MC, cynomolgous macaque isolate; MP, pigtail macaque isolate.

Krug PW, Schinazi RF, Hilliard JK. Inhibition of B virus (Macacine herpesvirus 1) by conventional and experimental antiviral compounds. Antimicrob Agents Chemother. 2010;54(1):452-459.

Treatment of B Virus Disease

First line, without without peripheral or central nervous system involvement

- IV Acyclovir 12.5-15mg/kg Q8H

With nervous system involvement or progression with acyclovir

- IV Ganciclovir 5mg/kg Q12H

Duration: at least 2 to 3 weeks until symptoms resolve, and and ≥ 2 sets of cultures yield negative results

Then switch to oral valacyclovir, famciclovir, or acyclovir at a dose used for post exposure prophylaxis – for at least 6 months to 1 year, followed by suppressive therapy

Suppressive Therapy for B Virus Disease

Lifelong suppressive therapy has been advocated by some experts to protect patients from B virus reactivation, with the following regimen:

- Valacyclovir 500mg oral once to twice daily or
- Acyclovir 400mg oral twice daily

If therapy is discontinued, patient should be followed closely with regular checking for any evidence of B virus shedding e.g. conjunctivae and oral mucosa cultures at least weekly during the first few weeks

Infection Control

In patient care, standard blood and body fluid precautions should be used

B virus can be inactivated with heat, formaldehyde, detergents, and bleach

Summary

- B virus infection, although not a common zoonotic infection, can cause fatal meningoencephalitis if left untreated
- B virus infection should be considered in cases with known exposure to macaque monkeys or their tissues, especially with neurological or dermatological complaints
- Early antiviral use – as treatment or prophylaxis – reduces the morbidity and mortality of B virus infection
- Acyclovir is the first line treatment for confirmed cases. Ganciclovir is recommended with CNS involvement

Summary

Prevention of B virus

- Precautions when working with nonhuman primates
- Adequacy of first aid
- Thorough evaluation
- Post exposure prophylaxis if indicated

Seek early medical attention for any injury from macaques

Stay away from wild monkeys and avoid touching or feeding them

References and Resources

- CDC herpes B virus website (https://www.cdc.gov/herpes-b-virus/)
- CHP B virus infection (https://www.chp.gov.hk/en/healthtopics/content/24/107789.html)
- 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;35(10):1191-1203.
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- Hilliard J. Monkey B virus. In: Arvin A, Campadelli-Fiume G, Mocarski E, et al., editors. Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Cambridge: Cambridge University Press; 2007. Chapter 57. Available from: https://www.ncbi.nlm.nih.gov/books/NBK47426/