For use within RIDU only

Protocol for Management of Non-Human Primate Injuries and Other Potential Exposures to Herpes-B Virus

Introduction

This Standard Operating Procedure (SOP) aims to be a clinical guide for infection specialists involved in the assessment and management of individuals who have sustained a bite or other exposure injury from a non-human primate, from now on referred to as monkeys. Patients bitten/injured by monkeys are at risk of bacterial skin and soft tissue infection, tetanus, rabies and herpes B virus. Even minor injuries carry risk and warrant thorough risk assessment. This protocol describes the assessment of humans with monkey bites in any clinical setting.

Within NHS Lothian, the main source of monkey bites is within research laboratories and zoos. Charles River laboratories, based in East Lothian, hold macaques for medical research objectives. The majority of their macaques are Mauritian but they also have some Asian macaques. Occasionally injuries are sustained from staff looking after these macaques.

First point-of-contact for medical assessment of injuries sustained at Charles River should be accident and emergency. Infectious diseases (ID) on-call should be contacted if there are concerns following assessment.

Summary of management

Wound care should happen at the time of injury, and be repeated at initial medical assessment.

Figure 1 details the overall management procedure.

Infections that will be discussed in greater detail (with links to relevant sections) are:

- Herpes B
- Rabies
- Tetanus
- Bacterial soft tissue infection
- RIDU follow up referral form (Appendix 1)

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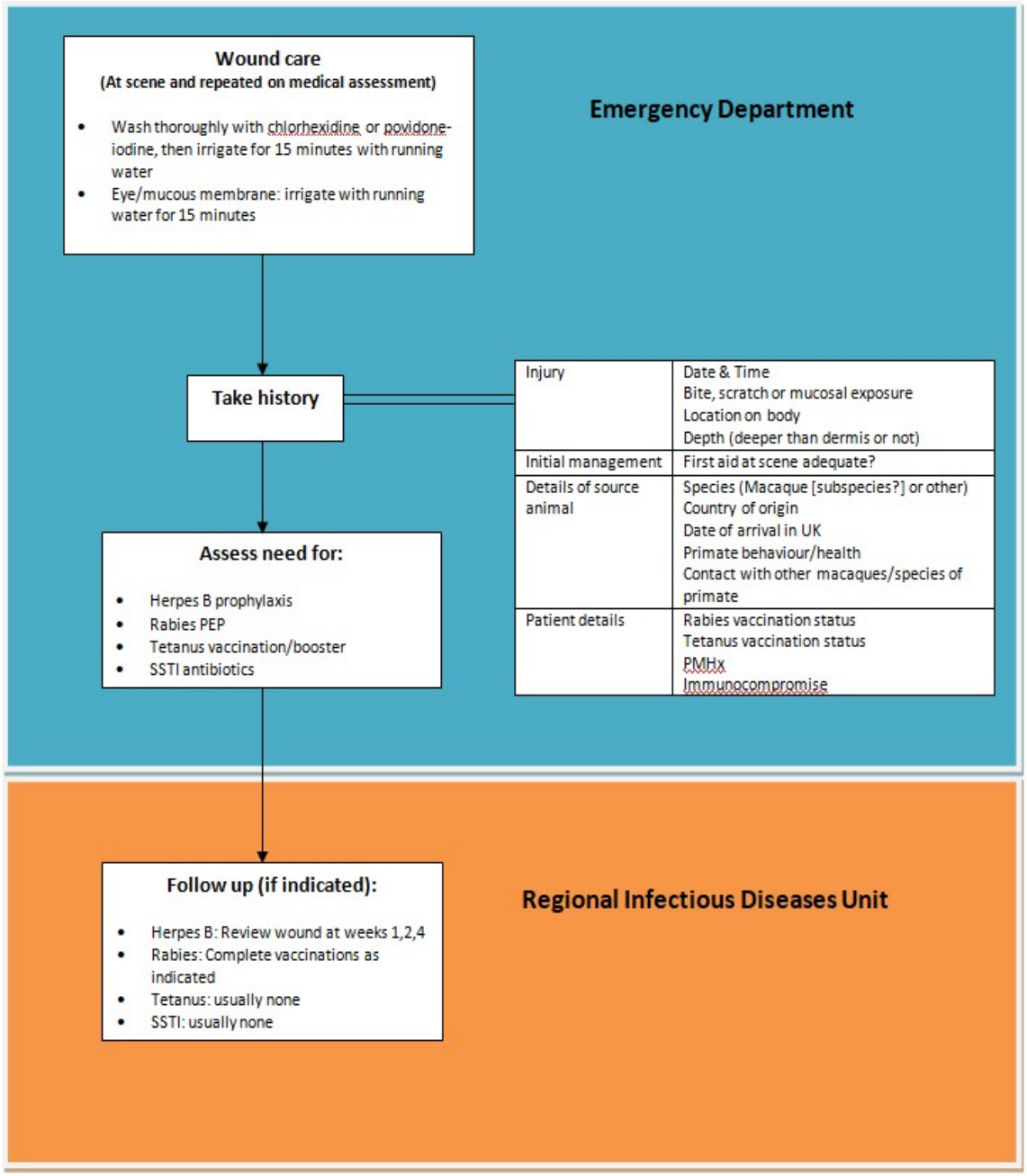
Figure 1: Summary of non-human primate injury management



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Herpes B virus

Herpes B virus is an alphaherpesvirus endemic in Old World macaques, including rhesus macaques (*Macaca mulatta),* pigtailed macaques *(Macaca nemestrina)* and cynomolgus macaques *(Macaca fascicularis)*. These are used in biomedical research laboratories, as well as being found in monkey temples across Asia/South East Asia. Infected monkeys may have oral or genital lesions but are often asymptomatic. Routes of infection include bites, scratches, injury with contaminated fomites or exposure of mucous membranes to infectious material from the macaque. Certain types of injuries are deemed higher risk including wounds that are inadequately cleaned or difficult to be cleaned. Similar to rabies, injuries that involve the head/neck/thorax of the patient are deemed high risk due to the closer proximity to the CNS/shorter distance for the virus to travel. **However, human Herpes B infection has resulted from seemingly trivial exposures, and most human cases have been acquired from asymptomatic macaques. Therefore, any exposure to a potentially infected animal therefore requires careful risk assessment.** (1, 2)

Clinical manifestations in humans typically appear within 5-21 days post-exposure, with a maximum incubation period of 5 weeks (35 days). Initial symptoms may be a flu-like illness and/or local symptoms at the inoculation site (itch, tingling, numbness, pain, vesicular rash). The virus then spreads to the CNS, leading to an acute ascending encephalomyelitis. Untreated mortality is ~75%, but treatment with acyclovir/ganciclovir improves mortality to 20%. (1,3)

Cynomolgus macaques originating from Mauritius and Barbary macaques in Gibraltar are considered to be free of Herpes B infection with no recorded cases. However, cynomolgus macaques and rhesus macaque colonies elsewhere, including in South-east Asia, are at risk of carrying this virus. (4,5)

Injuries associated with wild macaques or monkey temples

There has <u>never</u> been a known case of herpes B virus in humans related to macaque exposure in the wild. Prophylaxis is likely to be most effective when given within 72 hours postexposure and most travellers will be out with this time period. Do not routinely recommend herpes B post-exposure prophylaxis for injuries from wild monkeys. Offer patient reassurance that the risk is negligible, but advise them to seek medical attention if they develop: vesicles at site of the injury; fever; flu-like symptoms; or signs of encephalopathy within 5 weeks of the incident. (1,7)

Monkey bites or injuries from research labs, zoos or pets

There are strict quarantine guidelines for all animals imported to the UK. Residual risk will depend on whether these have been followed, including if the animal has been tested for

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Herpes B virus (where relevant) and/or if there has been contact with an Asian macaque species that has not completed testing.

An animal can be regarded as seronegative if it has had a negative test for B virus antibody on two occasions separated by at least 2 months, during which it has been kept isolated from other animals that may be infected. Serological tests do not completely exclude risk of infection, but the probability of latent infection is low. (6)

Injuries from macaques at Charles River Labs

Located in Tranent, Charles River laboratories hold macaques for medical research objectives. The majority of their macaques are from Mauritius (and are hence not tested for herpes B virus) but they also have some Asian macaques; these must be herpes B virus serology negative before shipment to Charles River Laboratories. Further testing takes place within two weeks and at 3 months post arrival in the UK. If found to be herpes B positive or equivocal then they are euthanised. Mauritian macaques are housed separately from Asian macaques at all times, so there should be no risk of transmission of Herpes B virus between these species.

Charles River employ a number of veterinarians who are able to assess a macaque involved in an exposure incident. Serology and swab samples are taken under anaesthetic; both are sent for testing if the macaque is of Asian origin, whereas the serology sample is tested, and the swab samples stored, for a Mauritian macaque.

Injuries from macaques at other research settings or zoos

It is expected that some form of assessment protocol of the animal/ injury would be in place. Where able, a veterinary assessment/ testing of the animal may be useful similar in approach to that used by Charles River.

Injuries from pet macaques

Macaques kept as pets should be subject to quarantine restrictions, however there is the possibility of animals being illegally entered into the country. Macaques from non-seronegative colonies without reliable test history should be assumed to be positive for Herpes B virus until proven otherwise. (6)

Assessment Steps

1. Prior to arrival at NHSL medical assessment	• First aid as detailed in figure 1 • Vet to assess primate and take samples for herpes B virus testing as appropriate • Charles River Labs will issue a Non-Human Primate (NHP) Incident Report outlining the nature of the incident, the identification of the animal and markers associated with level of risk. • If from Charles River lab, injured staff member to attend A&E at RIE
2. Medical assessment in A&E	• Repeat first aid as above • History (as detailed in figure 1) • Determine animal risk category using NHP Incident form (if relevant) and source animal risk assessment tool (page 6). • If indicated based on source animal risk, proceed to injury assessment category (page 7) and determine if post-exposure prophylaxis is required • Wound swab for viral PCR at initial assessment is not advised as this may force virus further into the wound
3. Follow up	• If patient was injured at Charles River and is being assessed in ED, complete referral form (appendix 1) and email to wgh.infectiousdiseases@nhslothian.scot.nhs.uk • For all patients, advise to seek medical attention if within the 5 weeks following exposure they develop: fever; flu-like illness; vesicles at the wound site; or signs of encephalopathy. • Low risk patients will not be routinely followed up unless they develop symptoms • Moderate or high-risk patients require follow-up at RIDU at weeks 1,2 and 4 post-exposure.
4. Animal testing results	• If testing of the monkey is undertaken, Charles River will contact the infectious diseases registrar via switchboard with any significant results. If these confirm Herpes B infection, the risk assessment and management should be reviewed to determine if any change in advice is required.

Post-exposure prophylaxis of injuries from macaques

1. Assess risk associated with source non-human primate.

Below is the source risk for any macaque from a research or zoo setting. If patient is coming from Charles River laboratory, this information will be on the Non-Human Primate (NHP) Incident Report

See Appendix 1 for source risk for wild macaques, pet macaques and other NHPs.

Any Macaque in research or zoo setting		**Previous herpes B virus serology result**			
		Negative at final 3 month test	**Thought negative** Previously neg, but not had final 3 month test	**Not tested** From a herpes B negative colony (Mauritian/ Gibraltarian)	**Not known** Non-Mauritian/ Gibraltarian and no test results available
Species of NHP	**Mauritian/Gibraltarian macaque** – NO contact with other macaque species ***eg Charles River Mauritian macaque*** OR contact only with other macaques with completed testing	N/A	N/A	Negligible risk	N/A
	Mauritian/Gibraltarian macaque – contact with other macaque species whose test status is incomplete or unknown	N/A	N/A	Possible risk	N/A
	Non-Mauritian/ Gibraltarian macaque OR origin unknown – No contact with other macaques since last test OR Contact only with other macaques that have completed testing ***eg Charles River Asian macaque***	Negligible risk	Possible risk	N/A	Possible risk
	Non-Mauritian/ Gibraltarian macaque OR origin unknown – Since source animal's last test, there has been contact with other macaque species whose test status is incomplete or unknown	Possible risk	Possible risk	N/A	Possible risk

If '**negligible risk'** no further risk assessment is needed.

If '**possible risk'** proceed to **step 2**.

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2. Assess injury risk (based on recommendations from Cohen et al):

Skin exposures where skin remains intact do not carry a risk of transmission and no further assessment or follow up is required.

For all other injuries, proceed to the injury risk assessment below.

Source Animal	
Healthy macaque	0
Macaque that is ill or immunocompromised	1
Macaque that is known to be shedding herpes B virus	1
Macaque that has lesions compatible with herpes B virus disease	1
Test results from vet indicates macaque is infected with herpes B virus	1

Injury	
Skin exposure in which skin remains intact	Not at risk: leave risk assessment
Mucosal exposure	1
Needlestick involving blood	1
Laceration (with loss of skin integrity) in any location other than head, neck or torso	1
Puncture or laceration occurring after exposure to objects (a) contaminated with body fluid (other than that from a lesion), or (b) potentially infected cell culture	1
Laceration of head, neck or torso	2
Deep puncture bite in any location	2
Needlestick associated with tissue/fluid from nervous system, lesions suspicious for B virus, eyelids or mucosa	2
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	2

First Aid	
Adequately cleaned	0
Inadequately cleaned	1

Suggested actions:

Total score	Risk Assessment	Recommended actions
2 or more	High	Commence postexposure prophylaxis: aciclovir 800mg five times daily for 14 days, or valaciclovir 1gram three times daily for 14 days
1	Moderate	No prophylaxis, follow up required
0	Low	No prophylaxis. Give patient advice. No follow up required.

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Treatment of Possible Cases of Herpes B Disease

Any patients presenting with fever, flu-like symptoms, vesicles at site of injury or signs of encephalopathy following an injury with a non-human primate should be immediately discussed with the ID registrar on-call (pager 8161 9am-9pm, ID Consultant on-call via switchboard out with these)

Assessment of a possible case of Herpes B disease

1. Clarify details of exposure incident and any initial management
2. If PEP was given, clarify dosing where able, and compliance with PEP.
3. Any further exposures?
4. History and clinical assessment, with a particular focus on presence or absence of CNS features.
5. Discussion with ID Consultant
6. If ongoing concern about risk of clinical Herpes B infection, discuss with Duty Virologist (63373/via switchboard) including treatment options.
7. Notification to Health Protection Team (HPT)
8. Discuss with Virus Reference Department (VRD) Duty Consultant at Colindale:
    1. Clarify what samples are needed (e.g. any swabs, CSF, blood)
    2. Confirm category of transport (Herpes B virus is a ACDP hazard group 4 pathogen so a Category A courier may be needed).
    3. If local samples are additionally needed e.g. wound swabs for MC&S, this will need discussion with microbiology and appropriate alerts made.

Treatment

- With no CNS symptoms:
    1. acyclovir—12.5–15 mg/kg* intravenously every 8 hours, or
    2. ganciclovir*—5 mg/kg intravenously every 12 hours

    *Doses/ choice may need reviewed e.g. in context of renal function, pregnancy.

- With CNS symptoms
    1. ganciclovir—5 mg/kg intravenously every 12 hours

No good data exist to support decision on duration. Decisions regarding treatment should be made on an individual patient basis, in conjunction with MDT discussion and discussion with national experts at Colindale.

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Rabies

Rabies risk in monkeys varies by country of origin:

Origin	Risk of Rabies
UK	None, unless they have had contact with imported monkeys
Mauritius	No risk of rabies (as of 2021)
Other	Varies by country: check here.

Risk assess and manage as per PHE rabies post-exposure guidelines.
Please contact infectious diseases on-call if risk assessment recommends post-exposure rabies vaccination or HRIG.

Tetanus

All monkey bites are considered "tetanus prone". Recommended actions are given in the table, and are based on PHE guidance.

Vaccination Status	Immediate treatment
Those aged 11 years and over, who have received an adequate priming course of tetanus vaccine with the last dose within the last 10 years	None required
Received adequate priming course of tetanus vaccine but last dose more than 10 years ago (Includes UK born after 1961 with history of accepting vaccinations)	Immediate reinforcing dose of vaccine
Not received adequate priming course of tetanus vaccine (Includes uncertain immunisation status and/or born before 1961)	Immediate reinforcing dose of vaccine One dose of human tetanus immunoglobulin in a different site

If point-of-care tetanus antibody testing if available then we recommend using that facility and following local guidelines instead.

Bacterial infection

Follow NHS Lothian antimicrobial guidelines for management of animal bites (For prophylaxis use the recommendations for human bites).

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RIDU Follow Up

Rabies
ID registrar on-call to arrange post-exposure rabies vaccination or HRIG, if indicated

Herpes B
Emailed referral form should be forwarded by secretaries to infectious diseases registrar on-call on next working day.

Registrar to review the documented risk assessment and verify that they agree with the global risk assessment.

If deemed to be at moderate or high risk of herpes B virus infection then ID registrar to arrange review of wound at weeks 1, 2 and 4 post-exposure.

Results of serology +/- PCR testing of source macaque will be returned to Charles River laboratories. The health safety officer will contact the ID registrar on-call between 9am and 9pm if any of these results suggest herpes B infection in the source macaque.

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Abbreviations

CNS: Central nervous system
C&S: Culture and sensitivity
HRIG: Human rabies immunoglobulin
ID: Infectious diseases
MDT: Multi-disciplinary team
NHP: Non-human primate
NHSL: NHS Lothian
PCR: Polymerase chain reaction
PEP: Post-exposure prophylaxis
PHE: Public Health England
RIDU: Regional infectious diseases unit
SSTI: Skin and soft tissue infection

References and Further Reading

These guidelines are predominantly based on the below references. For further information on assessment and management of herpes B prone injuries, we recommend reading the below articles.

(1) Cohen JI, Davenport DS, Stewart JA, Deitchman S, Hilliard JK, Chapman LE. Recommendations for the prevention of and therapy for exposure to B virus (Ceropithecine Herpesvirus 1). CID 2002:35.
(2) Huff JL, Barry PA. B-virus (Cercopithecine herpesvirus 1) infection in humans and macaques: potential for zoonotic disease. *Emerg Infect Dis*. 2003;9(2):246-250. doi:10.3201/eid0902.020272
(3) 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. EID 25 (9) 2019.
(4) Elmore D, Eberle R. Monkey B virus (Cercopithecine herpesvirus 1). *Comp Med*. 2008;58(1):11-21.
(5) Engel GA, Jones-Engel L, Schillaci MA, et al. Human exposure to herpesvirus B-seropositive macaques, Bali, Indonesia. *Emerg Infect Dis*. 2002;8(8):789-795. doi:10.3201/eid0808.010467
(6) Working safely with simians: Management of infection risks. Advisory committee on dangerous pathogens. HSE Books 1998. https://www.hse.gov.uk/pubns/misc134.pdf
(7) PHE Follow-up of monkey bites. PHE publications gateway number 2016652. March 2017.

Rohman M. Macacine herpes virus (B virus). Workplace health and safety. 64 (1) 2016.

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Appendix 1: Further Herpes B Virus Source Animal Risk Assessments

Wild macaque

Herpes B virus risk	Other info
Negligible risk	There has never been a known case of Herpes B virus infection in humans related to macaque exposure in the wild.

Pet macaque

		Herpes B virus risk
Species of NHP	**Mauritian/Gibraltarian macaque** NO contact with other macaque species OR Contact only with other macaques that have completed testing	Negligible risk
	Mauritian/Gibraltarian macaque Contact with other macaque species whose test status is incomplete or unknown	Possible risk
	Non-Mauritian/ Gibraltarian macaque OR origin unknown Tested negative for Herpes B virus after import. Since then, NO contact with other macaques OR Contact only with other macaques that have completed testing	Negligible risk
	Non-Mauritian/ Gibraltarian macaque OR origin unknown Herpes B virus test status incomplete OR unknown in source animal	Possible risk
	Non-Mauritian/ Gibraltarian macaque OR origin unknown Contact with other macaque species whose test status is incomplete or unknown	Possible risk

Non-macaque NHP (wild or captive)

	Herpes B virus risk	Other info
NO contact with (non-Mauritian/ Gibraltarian) macaques	No risk	Only NHPs with contact with (non-Mauritian/ Gibraltarian) macaques are at risk of Herpes B virus
Contact with (non-Mauritian/ Gibraltarian) macaques AND NO sign of herpes B virus infection	Negligible risk	Non-macaque NHPs are expected to be symptomatic with Herpes B virus
Contact with (non-Mauritian/ Gibraltarian) macaques AND convincing signs of Herpes B virus infection eg oral sores	Possible risk	Animals with suspected infection must be reported to a Vet for assessment/ testing

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