Zoonoses of Nonhuman Primates
B Virus Infection

“B Virus” Synomys
Herpes B
Monkey B Virus
*Herpesvirus simiae*
*Cercopithecine herpesvirus type 1*

Enveloped, double-stranded DNA virus
Alphaherpesvirus subgroup

B Virus Infection

*Alphaherpesvirus*
Neurotropic herpesviruses

B Virus Related Agents
*Herpesvirus simplex* (HSV) – humans
Simian Agent 8 (SA8) – African green monkeys
*Herpesvirus papio-2* (HVP2) – baboons

B virus – only zoonotic NHP alphaherpesvirus
B Virus Infection
Historical

First documented B virus case – 1932
Gay and Holden J. Infect. Dis. 53:287-303; 1933
Patient (W.B.) – bitten by healthy rhesus macaque
Died of progressive encephalomyelitis 10 days later
“B” virus – named for initial of patient’s last name

B Virus Infection
Epidemiology

Natural Hosts
Asian monkeys genus Macaca
16-19 species of macaques

Endemic in captive and wild populations
Prevalence of infection may reach 70-90%
B Virus Infection
Epidemiology

B virus infection
M. mulatta – rhesus macaque
M. fascicularis – cynomolgus macaque
M. nemestrina – pig-tailed macaque
M. cyclopis – Taiwanese macaque
M. radiata – bonnet macaque
M. fuscata – Japanese macaque
M. arctoides – stump-tailed macaque

B Virus
Species-specific Variants

Evidence for species-specific variants of B virus
Close relationship of isolates from Japanese and Rhesus macaques
More distant relationship between rhesus, cynomolgus, and pig-tailed macaques
Macaque isolates more distant from other NHP and human alphaherpesviruses

Figure 7. Phylogenetic analysis of primate α-herpesvirus DNA sequences. Approximately 450 bp of sequence from the UL27 (gB) gene (A) and 1.3 Kbp of sequence from the US region of the genome spanning the US4-6 (gO, gD, and gD) genes

B Virus Infection
Epidemiology – Natural Hosts

Transmission - Direct contact (bite, scratch, sexual)
Shedding - saliva, lacrimal and genital secretions
Peak seroconversion at puberty (3-4 yrs)
Latency - latent virus in trigeminal and lumbosacral ganglia
  Infection life-long
  Intermittent reactivation and shedding
    Infrequent and of short duration
    “Stress” or immunosuppression
*Shedding may occur in the absence of lesions

B Virus Infection
Disease in Natural Host

Primary infection
  Mild, transient disease
  Vesicular lesions – tongue, lips, oral or genital mucosa, muco-cutaneous border
  Conjunctivitis
  Rare systemic disease
    Focal necrosis – multiple organs
B Virus Infection
Disease in Macaques

Table 1  Distribution of B virus seropositive rhesus
by corral and age group

<table>
<thead>
<tr>
<th>Monkey Age Group</th>
<th>Corral 2</th>
<th>Corral 4</th>
<th>Corral 8</th>
<th>Group Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (&gt; 28 days to 6 mon)</td>
<td>1/12a</td>
<td>2/9</td>
<td>2/7</td>
<td>5/28</td>
</tr>
<tr>
<td>Juveniles (&gt; 6 mon to 3 yrs)</td>
<td>2/16</td>
<td>12/18</td>
<td>1/13</td>
<td>15/47</td>
</tr>
<tr>
<td>Young Adults (&gt; 3 yrs to 6 yrs)</td>
<td>11/12</td>
<td>13/13</td>
<td>11/10/10</td>
<td>34/35</td>
</tr>
<tr>
<td>Adults (&gt; 6 yrs to 15 yrs)</td>
<td>12/12</td>
<td>15/15</td>
<td>7/7</td>
<td>34/34</td>
</tr>
<tr>
<td>Aged (&gt; 15 yrs)</td>
<td>2/2</td>
<td>0/0</td>
<td>0/0</td>
<td>2/2</td>
</tr>
</tbody>
</table>

Corral-Wide Prevalence 0.52 0.76 0.54 (0.42, 0.62) (0.68, 0.84) (0.42, 0.66)

aNumerators are seropositive monkeys, denominators are number sampled.

bNumbers in parentheses are lower and upper bounds of the 95% confidence interval for the proportion of sampled monkeys seropositive.
B Virus Infection
Peak Seroconversion at Puberty

**Figure 1**  Age composition of sampled rhesus monkey population relative to B virus antibody status. Values on the x-axis represent midpoints of increasing 6-month age intervals.

B Virus Infection
Seasonal Incidence Patterns

**Figure 1.** Cumulative incidence (risk) per 2-month testing interval for 47 cases of B virus infection in California Regional Primate Research Center north corral 4 rhesus macaques from 20 September 1989 to 22 January 1991. CI = confidence interval.
B Virus Infection

Virus Isolations in a cohort of rhesus macaques

Long lag time from virus isolation to seroconversion

Seasonality of virus isolations from mucosal surfaces

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Table 2. Monkey characteristics associated with 14 isolations of B virus from study cohort of rhesus macaques at the California Regional Primate Research Center from 20 September 1989 to 22 January 1991.

<table>
<thead>
<tr>
<th>Type of infection, monkey no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Month/year</th>
<th>Tissue site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23726</td>
<td>2</td>
<td>F</td>
<td>9/89</td>
<td>Gen/Conj</td>
</tr>
<tr>
<td>25007*</td>
<td>0.3</td>
<td>F</td>
<td>9/89</td>
<td>Gen</td>
</tr>
<tr>
<td>24227</td>
<td>1</td>
<td>M</td>
<td>11/89</td>
<td>Gen</td>
</tr>
<tr>
<td>24727*</td>
<td>1</td>
<td>F</td>
<td>1/90</td>
<td>Oral</td>
</tr>
<tr>
<td>24762</td>
<td>1</td>
<td>F</td>
<td>9/90</td>
<td>Oral</td>
</tr>
<tr>
<td>Recurrent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21782</td>
<td>5</td>
<td>F</td>
<td>9/89</td>
<td>Conj</td>
</tr>
<tr>
<td>23035</td>
<td>3</td>
<td>F</td>
<td>9/89</td>
<td>Conj</td>
</tr>
<tr>
<td>23523</td>
<td>4</td>
<td>M</td>
<td>9/89</td>
<td>Conj</td>
</tr>
<tr>
<td>23037</td>
<td>3</td>
<td>M</td>
<td>9/89</td>
<td>Conj</td>
</tr>
<tr>
<td>19504</td>
<td>8</td>
<td>M</td>
<td>9/89</td>
<td>Gen</td>
</tr>
<tr>
<td>20620</td>
<td>9</td>
<td>F</td>
<td>1/90</td>
<td>Gen</td>
</tr>
<tr>
<td>23726*</td>
<td>3</td>
<td>F</td>
<td>9/90</td>
<td>Gen</td>
</tr>
<tr>
<td>26057</td>
<td>10</td>
<td>F</td>
<td>1/91</td>
<td>Gen</td>
</tr>
<tr>
<td>Unknown*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: F = female; M = male; Gen = genital; Conj = conjunctival. Primary, first infection with B virus; recurrent, evidence of previous B virus infection.

* No antibodies to B virus detectable for subsequent 16 months of study.
* B virus isolated during symptomatic episode of disease.
* Primary infection detected during 9/89 testing.
* Identification label lost in transit.

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B Virus Infection

NHP-related Injuries

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Figure 1. Injury-specific IRR and 95% CI per 3000 person-weeks, 1988 to 1993.
B Virus Infection
Post-infection Seroconversion

Table 4. IgM and IgG antibody response following experimental B virus infection

<table>
<thead>
<tr>
<th>Days post-infection</th>
<th>IgM antibody titer*</th>
<th>IgG antibody titer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>monkey number</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16856</td>
<td>16845</td>
</tr>
<tr>
<td>0</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>6</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>8</td>
<td>6.1</td>
<td>8.2</td>
</tr>
<tr>
<td>12</td>
<td>8.4</td>
<td>11.1</td>
</tr>
<tr>
<td>15</td>
<td>6.1</td>
<td>10.2</td>
</tr>
<tr>
<td>20</td>
<td>5.1</td>
<td>8.4</td>
</tr>
<tr>
<td>29</td>
<td>3.8</td>
<td>7.3</td>
</tr>
<tr>
<td>41</td>
<td>2.4</td>
<td>5.5</td>
</tr>
</tbody>
</table>

*IgM and IgG antibody titers detected by antibody capture radioimmunoassay expressed as positive to negative (P:N) ratios.

B Virus Infection
Infrequent Viral Shedding in Macaques

Table 1. Isolation of virus from the oral cavity following experimental B virus infection

<table>
<thead>
<tr>
<th>Days post-infection</th>
<th>Virus isolated*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>monkey number</td>
</tr>
<tr>
<td></td>
<td>16856</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>29</td>
<td>-</td>
</tr>
<tr>
<td>41</td>
<td>-</td>
</tr>
<tr>
<td>50</td>
<td>-</td>
</tr>
</tbody>
</table>

*Virus isolation by inoculation of oral swabs into 25 cm² flasks of Vero cells.
B Virus Infection
Zoonotic Disease in Humans

Direct Zoonosis
Transmission - bite, scratch, needle-stick, or mucous membrane exposure
Only 43 cases ever documented
Case-fatality rate ~ 70%
Human to human transmission
Direct contact with herpetic lesion

B Virus Infection
Human Cases by Type of Exposure

Direct Exposures
- bites
- scratches
- mucosal contact with body fluids

Indirect Exposures
- needle-stick
- cage scratch

Unknown
B Virus Infection
Zoonotic Disease in Humans

Pathogenesis

Initial replication at site of entry
  Vesicular lesions +/-
  Pruritic if present
  Tingling sensation

Incubation period

  Usually within 30 days of exposure
  As short as 5 days

Development and progression of disease depends on
  site of exposure and viral inoculum

B Virus Infection
Epithelial lysis and Intranuclear Inclusions
B Virus Infection
Zoonotic Disease of Humans

Systemic Disease
Prodrome of “flu-like” illness
Fever, malaise, fatigue, headache, pharyngitis
Neurologic signs (within several days)
Early – paresthesias, disorientation, dysphagia
Late – rapidly progressive ascending paralysis
encephalomyelitis, coma and death

B Virus Infection
Zoonotic Disease of Humans

Survivors – severe, residual neurologic impairment
Antibody to HSV is not protective
No evidence of subclinical infections in humans
Seroprevalence of B virus antibodies in Sangeh Monkey Forest cynomolgus macaques (*M. fascicularis*), Bali, Indonesia

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. (%) Ab Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile</td>
<td>2/8 (25)</td>
</tr>
<tr>
<td>Subadult</td>
<td>2/6 (33.3)</td>
</tr>
<tr>
<td>Adult</td>
<td>28/28 (100)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>31/38 (81.6)</strong></td>
</tr>
</tbody>
</table>

Adapted from *Jones-Engel et al. Emerging Infectious Diseases 8:789-795; 2002*
Prevalence of bite and scratch injuries to humans, Sangeh, Bali, Indonesia

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>No. (%) of persons (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitten</td>
<td>31 (29.5)</td>
</tr>
<tr>
<td>Bitten more than once</td>
<td>7 (6.7)</td>
</tr>
<tr>
<td>Scratched</td>
<td>41 (39.0)</td>
</tr>
<tr>
<td>Scratched more than once</td>
<td>15 (14.3)</td>
</tr>
<tr>
<td>Bitten or scratched</td>
<td>51 (48.6)</td>
</tr>
<tr>
<td>Possessed food at time of injury</td>
<td>48 (45.7)</td>
</tr>
<tr>
<td>Total</td>
<td>105 (100)</td>
</tr>
</tbody>
</table>

Adapted from Jones-Engel et al. Emerging Infectious Diseases 8:789-795; 2002

B Virus Infection Diagnosis

Serology – detection of antibodies by EIA

Confirmatory immunoblot

Virus detection – virus isolation or PCR
B Virus Infection
Treatment and Prevention

Post-exposure Treatment
   Immediate first aid – wound cleansing
   Recognition of potential exposure is critical
   Prophylactic treatment with antiviral drugs
      Acyclovir, Ganciclovir – prevent virus replication
   Potential reactivation with cessation of treatment

For detailed treatment and risk assessment algorithms see:

B Virus Infection
Treatment and Prevention

Prevention Program Components
   Remove source of exposure
      SPF macaque colonies
      Cynomolgus from Mauritius – B virus free
   Medical surveillance
   Training in safe handling practices
   Personal protective equipment (PPE)
      gloves, mask, eye protection
   First aid for bites, scratches, needle sticks, eye splashes
   Post-exposure plan
   No vaccine available
B Virus Infection
Rare But Deadly Zoonosis

Highly endemic in macaques
Opportunities for zoonotic transmission are many
  Thousands of human contact hours
  Thousands of potential exposure injuries
Only 43 cases in 70 years
Human case-fatality rate ~70%
Viral shedding is intermittent and infrequent
  Only 2-3% of infected macaques are shedding
  at any given time