

# **Medical College of Wisconsin: Rabies Treatment Protocol Checklist**

*Please note that this document is provided for information, but readers should not assume any endorsement of the protocol by the HPA*

## Rabies Treatment Protocol (Checklist)

Please note

### **Rabies mimics brain death, reversibly.**

- **Rabies clinically mimics brainstem death** – known a long time.(1)  
*Rabies causes sensory denervation, like Miller-Fisher syndrome/Birkenstaff encephalitis*

### **Rabies causes laboratory correlates of brain death, reversibly**

- **BH4 deficiency is found regularly (3 of 3) in human rabies.**
- **BH4 deficiency should flatten the EEG and reduce cranial artery flow**  
*Loss of EEG in rabies has correlated with middle cerebral artery spasm by transcranial doppler. EEG has returned with improvement in blood velocity.*

Corollary: **Standard criteria for brain death do not apply.** Diagnosis of brain death requires anatomic (biopsy or neuroimaging) evidence for irreversible brain damage or a brain flow scan showing zero flow intracranially.

### **Drugs with relative contraindications in rabies (mostly based on anecdote)**

Barbiturates	Suppress immunity.
Propofol	Has led to acutely flat EEG in 2 patients.
Topiramate	Has led to acutely flat EEG in 2 patients.
Vasopressors	May lead to unopposed vasoconstriction with rabies-associated BH4 deficiency of cerebrovascular circulation.

The materials in this document are intended as general medical information and are not intended to constitute a recommendation as to a course of medical treatment for any individual patient. They are provided for the limited purpose of assisting clinicians as they evaluate available treatment options. These materials represent the insights and opinions of physicians involved in treatment of patients with rabies and are not the result of activities pursuant to an approved research protocol, and they should be evaluated on that basis. The information provided in this document is based on a very limited experience and therefore may not be applicable in any other situation. Each rabies patient is unique, and factors such as general good health, excellent and adaptive medical intensive care, and careful avoidance of mistakes and complications of intensive care may prove to be essential to positive outcomes.

The information, including the identification of key issues, and the recommendations provided remain preliminary in nature. As noted, they do not constitute the current standard of care. This document will be modified as additional data is accumulated. The risks associated with the course of treatment described generally in these materials must be understood and carefully evaluated by physician and patient before treatment decisions are made. Any additional information that other clinicians or researchers may provide related to the treatment of rabies in other patients is greatly appreciated.



- BH4 at vascular (non-CNS) doses: 80 mg every 8 hours (pediatric 2 mg/kg/Q8h).  
 Coenzyme Q10 1200-2400 mg daily (pediatric 30-60 mg/kg/day)
10. Consider zinc sulfate 50 mg PO every 8 hours (pediatric 1 mg/kg Q8h).
11. Consider a full “mitochondrial cocktail” preventively.  
 L-carnitine 330 mg PO daily (pediatric 20 mg/kg every 8 h)  
 Coenzyme Q10 – see above  
 B50 complex pills: 1 pill PO BID  
 Creatine (usually at health food store) 3 g daily  
 Mg Orotate (health food store) 200 mg daily  
 Vitamin E (tocopherol) 200 U daily  
 Vitamin C – see above  
 Some add alpha-lipoic acid 80 mg PO daily (pediatric: 2 mg/kg daily)
12. Consider red cell transfusion to maintain hemoglobin > 10 mg%, appropriate volume loading, and mechanical ventilation targeting arterial normoxia and mild hypercapnia.
13. Consider prophylaxis against vasospasm with oral nimodipine: 60 mg PO every 4 h x 21 days (pediatric dosing uncertain, consider 1.5 mg/kg/dose orally).

### **Sedation**

14. We recommend deep sedation-anesthesia during the first week of acute encephalitis
- Ketamine is dosed aggressively at 2 mg/kg/h.
  - Diazepam or alprazolam while ketamine in use.
15. Consider topical application of 1% lidocaine to the hypopharynx and trachea if reflex spasms or dysautonomia occur with care of the endotracheal tube
16. Paralyze for apneustic breathing/spasms that affect ventilator.
17. The patient is best followed over the first week by assessing amplitude of the EEG tracing and the degree of difficulty in maintaining partial burst suppression using benzodiazepines  
**It is unwise to push to complete burst suppression.** The intent is to suppress severe dysautonomia, and full burst suppression loses the capability to assess trends in EEG over time or in association with acute cerebral artery vasospasm.
18. We recommend discontinuation of aggressive sedation-anesthesia when (a) anti-rabies titers in CSF exceed 1:1024 by IFA or 1:40 by RFFIT, or (b) there is evidence of denervation of the heart as shown by loss of heart rate and blood pressure variability over 24 hour tracings.

### **Antiviral treatment**

19. No medications are given intrathecally
20. Avoid rabies immunization of the patient after onset of clinical symptoms.
21. Avoid administration of rabies-specific antiserum
22. Avoid administration of IFN $\alpha$
23. Ribavirin is no longer recommended based on weak evidence. It was used in the original survivor. Use is optional
24. Amantadine is administered by nasojejun tube at a dose of 2.5 mg/kg every 12 hours (100 mg every 12 hours if >40 kg).

### Monitoring:

25. CSF should be assayed initially and then at least weekly for rabies titers, cell count, protein, glucose, lactate, pterins (biopterin, neopterin), HVA and 5-HIAA.  
 CSF antibody usually follows serum antibody by 2-3 days: consider LP at that time
26. Saliva should be collected every other day by rayon swab, into standardized 1.0 mL viral media, frozen
27. Serum should be collected every other day for rabies titers

***Anticipatory monitoring:***

28. Continuous EEG monitoring
29. Daily transcranial doppler screening of MCA velocity and resistive indices bilaterally.
30. Serum sodium should be measured at least daily.
31. Urine output should be assessed every 4-6 hours.
32. Weekly monitoring for deficiencies in thyroid (TSH, fT4, fT3, T3RU), and cortisol stimulation.
33. Consider weekly monitoring for serum prolactin as index of hypothalamic integrity and brain dopamine metabolism.

***Management of complications:***Dehydration:

The patient should be given normotonic saline or equivalent crystalloid to correct dehydration.

Vasopressors are relatively contraindicated.

SIADH:

Restriction of free water is effective at treating SIADH. *Note that DI will follow within several days.*

DI is cyclical and can be very severe:

We recommend mL/mL replacement of urinary output above 2 mL/kg/hour output with 1 milliUnit arginine vasopressin/500 mL of D2.5, 0.2NS (made as 250 mL D5W + 250 mL 0.45 NS. Final AVP = 0.2 milliU/mL replacement fluid), replaced every 2-4 hours.(21) Max dose 10 milliU/kg/h

Use of vasopressin replacement therapy for DI may result in unopposed cerebral vasoconstriction and so requires supplementation with 2 mg/kg/Q8h of oral BH4 and regular monitoring of intracranial blood supply by TCD.

Evaluate thyroid, adrenal, growth hormone axes if DI occurs.

Progressive bradycardia, hypotension, hypothermia and ileus

Evaluate thyroid, cortisol, growth hormone axes.

Consider replacement therapy as per recommendations for organ donation, while tests are pending. (While this concept is a bit bizarre, rabies can clearly mimic brain death in many ways, so such interventions may be rational.) This includes --for adults -- [T3 3.0 mcg/h OR T4 10 mcg/h] plus methylprednisolone 15 mg/kg/day plus vasopressin 0.4-4.0 U/h plus insulin drip to maintain glucose between 80-150 mg/dL; minimal insulin rate: 1 U/h.

Use of vasopressin replacement therapy for DI may result in unopposed cerebral vasoconstriction and so requires supplementation with 2 mg/kg/Q8h of oral BH4 and regular monitoring of intracranial blood supply by TCD.

Severe dysautonomia (hypertension, tachyarrhythmia, hypersalivation)

Increased sedation

Cardiac echo to assess function

Serum troponin I

Severe dysautonomia (bradycardia, asystole)

Increased sedation

Atropine (*this will not work after cardiac denervation in rabies*)

Electrical pacing

Seizures or decline in EEG voltage

Emergency TCD.

Emergency CT angiography to confirm vasospasm if detected by TCD.

Consider fosphenytoin for seizures. Avoid topiramate.

If bilateral MCA very high velocity/normal resistance:

Confirm by CT angiography. Once confirmed:

Consider ventriculostomy to monitor ICP

Consider IV nicardipine 75 mcg/min (pediatric dose: 0.5 mcg/kg/min)

Consider “triple H therapy”.

Consider BH4 at 2 mg/kg every 8 hours orally

If bilateral MCA decreased velocity/high resistance:

Confirm by CT angiography and exclude diffuse cerebral edema. Once spasm confirmed/edema excluded:

Lumbar puncture for cell count, protein, glucose, lactate & pyruvate, rabies antibody titers, pterins (biopterin, neopterin), HVA and 5-HIAA.

Check for rabies-specific immune response (serum)

Consider ventriculostomy to monitor ICP

Strongly consider brain biopsy at time of drain placement to confirm normal neuron densities

Strongly consider brain biopsy if intracranial pressure abnormally low.

Consider IV nicardipine 75 mcg/min (pediatric dose: 0.5 mcg/kg/min)

Consider “triple H therapy”

Consider BH4 800 mg (pediatric dose: 20 mg/kg/day) divided every 12 h enterally –AND -- 0.5 g/kg/24 h of IV L-arginine.

EEG voltage declines with unchanged TCD and imaging by MRI:

Lumbar puncture for cell count, protein, glucose, lactate & pyruvate, rabies antibody titers, pterins (biopterin, neopterin), HVA and 5-HIAA.

Consider brain biopsy to confirm normal neuron densities.

BH4 at CNS doses 800 mg (pediatric dose: 20 mg/kg/day) divided every 12 h enterally.

### ***Prognosis/continuation of care***

1. Brain biopsy is probably the only way of proving futility of care in most human rabies, absent severe cerebral edema.
2. Clinical recovery is rapid once neutralizing anti-rabies antibody rises in CSF.