

Rabies Treatment Protocol (Checklist)

Please note

Rabies mimics brain death, reversibly.

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

Rabies causes laboratory correlates of brain death, reversibly

- **BH4 deficiency is found regularly (5 of 5) 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, that we require for cure	Section B
Propofol	Has led to acutely flat EEG in 2 patients.	Section B
Topiramate	Has led to acutely flat EEG in 2 patients.	Section B
Vasopressors	May lead to unopposed vasoconstriction with BH4 deficiency	Section E
Diuretics	Confound management of SIADH, DI, salt wasting and subacute cerebral edema	Appendix II

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.

1. **Sedate until the diagnosis is confirmed (24 hours)**, preferably with benzodiazepines.
2. **Confirm the diagnosis.** You need serum, cerebrospinal fluid (CSF), saliva and biopsy of hairy skin.
 - Call CDC rabies branch or your national reference laboratory to request assistance
 - CDC: 404 639 1050 www.cdc.gov/ncidod/dvrd/rabies/professional/Prof.forms/antem.htm
3. **Get treatment drugs in hand.**
 - **We no longer recommend IV ribavirin, although the original protocol used it.**
 - BH4 is occasionally needed acutely and always needed during rehabilitation. BH4 is available through
 - Schircks Laboratories
http://www.schircks.com/tablets/sys/tetrahydrobiopterin_tab_frame40.htm.
 - BioMarin Pharmaceuticals/Merck-Serono
1-866-906-6100 <https://www.kuvan.com/Common/ContactUs.aspx>
 - **As last recourse**, contact Dr. Willoughby at Medical College of Wisconsin to request BH4 (414) 266 2000 rewillou@mcw.edu or rabies@chw.org
 - BH4 can be obtained as an emergency loan to other hospitals from Children's Hospital of Wisconsin Investigational Pharmacy. The investigational pharmacist can be reached by pager at 414 266 2000.
 - World Courier will deliver anywhere in the world, *7 days a week*. 1 800 221-6600
www.worldcourier.com
4. **Plan for key ancillary diagnostics.**
 - You will **need continuous EEG monitoring or a BIS monitor** to properly care for rabies. Plan for 1-2 weeks of continuous EEG or BIS monitoring.
 - Get **daily transcranial Doppler ultrasound (TCD)** of middle cerebral arteries. Plan for 2 weeks of daily monitoring.
CT angiography is indicated for confirmation of severe spasm by TCD.
 - **Contact Medical Neurogenetics to request 3 collection kits** for biopterin & neurotransmitter analyses of cerebrospinal fluid, and notify them of imminent need for rapid reporting for active case of rabies. 678.225.0222 www.medicalneurogenetics.com
 - **Call Neurosurgery** in order to familiarize them with recent advances in treatment of rabies, so that considerations of futility and fear of rabies can be addressed ahead of any emergent need for their services.
 - **Call Neuroradiology** in order to familiarize them with recent advances in treatment of rabies, especially anticipated requirements for CT angiography around day 6-10 and day 13-17 in association with generalized cerebral vasospasm.

Basic treatment

1. Central venous pressure targeted to the normal range.
2. Consider placement of external cardiac pacing wires for first 3-5 days.
3. Patients should be intubated or undergo tracheotomy with cuffed tubes in order to protect the airway from aspiration secondary to profuse salivation, bulbar paresis, or rabies-associated or induced coma.
4. Placement of nasojunal feeding tube.
5. Fever is tolerated below 39.0C without medication.
Antipyretics were not effective in some cases.
Consider modifying ambient room temperature for severe hypothermia (<36.0C) or hyperthermia (>39.5C).
6. Heparin 10 U/kg/hour is administered as prophylaxis.
Consider support hose or inflatable stockings as prophylaxis against deep vein thrombi.

7. Physical therapy should be regularly scheduled during the periods of general anesthesia and rabies-associated paresis to avoid contractures.
8. The patient should be frequently repositioned to avoid pressure ulcers.
9. Patients should receive prophylactic supplementation for reported cofactor deficiencies.

Vitamin C	500 mg daily
Consider zinc sulfate	50 mg PO every 8 hours (pediatric 1 mg/kg Q8h).
10. Consider red cell transfusion to maintain hemoglobin > 10 mg%, appropriate volume loading, and mechanical ventilation targeting arterial normoxia and mild hypercapnia.
11. Consider prophylaxis against vasospasm with oral nimodipine: Enteric dose: 60 mg PO Q4h x 21 days. [This is about 1.5 mg/kg/dose in children.] Can be given sublingually. IV formulation (adults and children): start 7.5-10 ug/kg/h initially, increasing over a few hours to 30 ug/kg/h (max 45 ug/kg/h).
12. We recommend deep sedation-anesthesia during the 7-10 days of acute encephalitis
 - a. Ketamine is dosed aggressively at 1-2 mg/kg/h, achieved over first 24 hours..
 - b. Midazolam at a ratio of 2:1 to 1:1 of ketamine: midazolam.
13. Consider topical application of 1% lidocaine to the hypopharynx and trachea if reflex spasms or dysautonomia occur with care of the endotracheal tube
14. Paralyze for apneustic breathing/spasms that affect ventilator.
15. The patient is best followed over the first 2 weeks by assessing amplitude of the EEG tracing.

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.
16. We recommend discontinuation of aggressive sedation-anesthesia when (a) anti-rabies titers in CSF exceed 1:40 (about 0.3 IU) 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 by cardiac monitor.

Antiviral treatment

17. No medications are given intrathecally
18. Avoid rabies immunization of the patient after onset of clinical symptoms.
19. Avoid administration of rabies-specific antiserum
20. Avoid administration of IFN α
21. Ribavirin is no longer recommended.
22. Amantadine is administered by nasogastric tube at a dose of 2.5 mg/kg every 12 hours (100 mg every 12 hours if >40 kg).

Monitoring:

23. CSF should be assayed initially and then twice weekly for rabies titers, cell count, protein, glucose, lactate.

Pterins (biopterin, neopterin), HVA and 5-HIAA require special tubes.
CSF antibody usually follows serum antibody by 2-3 days: consider LP at that time
24. Saliva should be collected every other day by rayon swab, into standardized 1.0 mL viral media, frozen
25. Serum should be collected every other day for rabies titers

Anticipatory monitoring:

26. Continuous EEG monitoring
27. Daily transcranial doppler screening of MCA velocity and resistive indices bilaterally.

We recommend TCD of posterior circulation when possible as well.
28. Serum sodium should be measured at least daily.

29. Urine output should be assessed every 4-6 hours.

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 may 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 80 mg (2 mg/kg in children) every 8-12 h of oral BH4 and daily monitoring of cerebral blood supply by TCD.

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

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

Consider fosphenytoin for seizures. Avoid topiramate.

Emergency TCD.

Emergency CT angiography to confirm vasospasm if detected by TCD.

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”.

If bilateral MCA decreased velocity/high resistance:

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

Check for rabies-specific immune response (serum)

Lumbar puncture for opening pressure, cell count, protein, glucose, lactate, rabies antibody titers. Pterins (biopterin, neopterin), HVA and 5-HIAA require special tubes for collection.

Consider ventriculostomy to monitor ICP

Strongly consider brain biopsy if intracranial pressure abnormally low to minimize futile care.

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

Consider “triple H therapy”

EEG voltage declines with unchanged TCD and MRI imaging:

Lumbar puncture for cell count, protein, glucose, lactate, rabies antibody titers. Pterins (biopterin, neopterin), HVA and 5-HIAA require special collection tubes.

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