附錄四

Milwaukee Protocol, version 4.0 (updated 9/13/2012)

Protocol

1. Do not administer rabies vaccine or immunoglobulin to a patient with rabies.
   - RIG delays development of rabies antibodies in CSF, essential for survival.
   - Preliminary evidence favors detrimental survival after rabies vaccine in bat rabies.
   - We have administered beta-interferon to a few rabies patients with poor prognostic epidemiology, with evidence for a peripheral effect on viral load. This can be considered in particular for dog rabies, where CSF responses are often poor. It appears to "buy" an additional week for serological response to mature.
2. Maintain patient in isolation.
   - There has never been a laboratory-documented case of human-human transmission of rabies other than by transplantation.
   - Patients can be removed from isolation when saliva is negative by RT-PCR on 3 occasions in the presence of serum neutralizing antibodies > 0.5 IU/ml by RFFIT, FAVN or other test for neutralizing antibodies.
3. Transfer patients with laboratory-confirmed rabies to a tertiary care facility capable of critical care including intracranial pressure monitoring.
   - Institutions in developing countries can handle rabies if they treat head trauma and tetanus with critical care facilities.
   - Treatment also requires access to a rabies reference lab and a rehabilitation facility.
4. Place a central venous catheter, urinary catheter and NG tube. A NJ tube is recommended for nutrition during the brief (5 day) period of ileus encountered in rabies.
5. Administer low-dose insulin drip (1 U/h in adults) with sufficient enteral and intravenous nutrition to maintain euglycemia.
   - Complications in rabies are associated with biochemical markers of gluconeogenesis and ketogenesis in CSF. Promotion of anabolism appears preliminarily to improve the survival curve.
   - Insulin may also minimize alcohol metabolites and lactic acidosis associated with propylene glycol stabilizers in benzodiazepine sedatives used at high dosage.
6. Maintain normovolemia and serum sodium > 145 mEq/L.
   - Use of isotonic solutions is strongly recommended for the first 2 weeks due to salt wasting encountered at 5 days of hospitalization.
   - Administer fludrocortisone 100 mcg (child) – 200 mcg (adult) to maintain normal serum sodium during the first 2 weeks of illness. Otherwise salt wasting may be very difficult to control despite administration of hypertonic saline.
   - There is an unusual form of cerebral edema in rabies, along with cerebral artery spasm on hospital days 6-8 and 13-15. Cerebral edema from hyponatremia exacerbates these processes.
7. Ventilate using normal parameters. Rabies patients maintain CNS responsiveness to changes in pCO_2.

- The tetrahydrobiopterin deficiency repeated measure in human rabies is predicted to abrogate low-pressure autoregulation. It may also contribute to modest pulmonary hypertension.

8. Prevent fatal dysautonomia (20% of rabies patients). Aggressive sedation is essential in the first week of hospitalization:
    - Minimize stimulation, including interval neurological examinations.
    - Recommend use of ketamine at 0.5-1.0 mg/kg/h to prevent fatal dysautonomia in the first 7 days of hospitalization. Patients with rabies have very high levels of quinolinic acid, an excitatory agonist of the NMDA receptor from time of diagnosis. Ketamine blocks these agonists.
    - Ketamine is best balanced by a benzodiazepine, typically midazolam, sufficient to minimize vascular reactivity during endotracheal suction or turning.
    - Sedation should be tapered after the 7th day from first hospitalization. The vagus nerve is no longer functional at this point; atropine ceases to be effective.
    - Propofol has a relative contraindication. It tends to over-sedate rabies patients (to isoelectric EEG) and there is a progressive CSF lactic acidosis in rabies that in theory might be exacerbated by prolonged propofol use.
    - Barbiturates are contraindicated until the immune response to rabies is sufficient for viral clearance (0.5 IU/ml in blood, 1.0 IU/ml in CSF) due to their immunosuppressive properties.
    - Opiates and central alpha-adrenergic agonists have not been used enough for us to comment.
    - Sedation can be monitored by EEG or BIS monitor. We do NOT recommend titration to burst suppression. Sedation should be held temporarily if the EEG is suppressed.
9. Amantadine is given because of its use in the original protocol.
    - There is biochemical evidence of high quinolinic acid in CSF in human rabies, an agonist of the NMDA glutamate receptor. Amantadine in neuroprotective by this mechanism.
10. Ribavirin is no longer recommended because of its immunosuppressive effects.
11. Vasospasm and clinical exacerbations are regularly encountered on days 6-8 and 13-15 of first hospitalization.
    - These are effectively monitored by transcranial Doppler and can be evident by EEG or BIS monitor.
    - Nimodipine is recommended at half to full dose for prophylaxis against vasospasm.
    - Vitamin C (250 mg daily for child and 500 mg for adult, IV or enterally)
    - Sapropterin (5 mg/kg/day enterally), and L-arginine (0.5 gm./kg/day IV or enterally) are preferred over nimodipine when available.
12. Prophylaxis against DVT is recommended.
13. Precautions against pressure ulcers are recommended.

14. General targets:
    - Maintain head of bed elevated 30 degrees
    - mean arterial pressure > 80 mm (adult)
    - central venous pressure 8-12 mm Hg
    - O_2 saturation > 94%
    - $PaCO_2$ 35-40 mm Hg
    - Hemoglobin > 10 mg% (historical observation)
    - Serum sodium 140-150 mEq/L
    - Serum glucose 70-110 mg% with low dose insulin infusion
    - Maintain diuresis > 0.5 cc/kg/h with hydration; avoid diuretics given rapid evolution of salt wasting on day 5 and possible diabetes insipidus in second week
15. Maintain core temperature 35-37C. Patients are poikilothermic.
    - Antipyretics generally have no effect in rabies
    - Ambient temperature has a major effect in rabies.

Laboratory monitoring:

1. Serum sodium twice daily.
    - Urine sodium when serum sodium abnormal or difficult to control
    - Consider serum/urine uric acid as marker of tubular salt wasting
2. Arterial blood gases twice daily or more frequently as needed
3. Serum magnesium daily on hospital days 5-8 and 12-15 to avoid hypomagnesemia during periods of high risk for vasospasm
4. Serum zinc once weekly (inflammatory state, no body stores)
5. MRI or CT at time of seroconversion and then twice weekly until CSF titers stabilize. (MRI and CT are poorly sensitive for increased intracranial pressure present before seroresponse.)
6. Transcranial Doppler ultrasound daily on days 4-8 and days 12-15 after first hospitalization to monitor for degree of vasospasm. TCDs on days 9-11 may detect progressive cerebral edema if no intracranial pressure monitoring is undertaken.
7. Dog rabies: ECG daily to measure PR interval and assess for heart block

Virological Monitoring (clinical samples)

8. Saliva (0.5-1.0 ml, frozen for PCR) every other day until 3 negatives obtained sequentially. Avoid collection after chlorhexidine.
9. Serum (2 ml, frozen for serology) every other day for first 2 weeks, then 1-2 times weekly.
10. CSF (2 ml, frozen for serology) twice weekly. Consider ventricular or lumbar drain.
11. CSF twice weekly for cells, chemistry including lactate
12. CSF for neurotransmitters (special collection, soon after diagnosis and at start of rehabilitation).

Timeline for complications

Timeline seems most exact based on analyses when timed from first hospital admission.

First 3 days after first hospitalization (HD 0-HD 3):

1. Dehydration, electrolyte disturbances, ketosis.
   - volume replacement, isotonic fluids, low-dose insulin drip
2. Increased intracranial pressure (20-35 cm water)
   - Radiologically subtle but can lead to herniation
   - Associated with increased N-acetylaspartate in CSF (? overlap w/ Canavan's disease)
   - Consider intracranial pressure monitoring. Ventricular or lumbar drain provides therapeutic and diagnostic advantages over mechanical monitors.
3. Sudden death from asystole or tachyarrhythmias.
   - minimize stimulation and neurological exams
   - sufficient sedation
   - consider pacer at bedside
   - asystole responds to increased sedation
4. Cardiac stunning from catecholamine storm
   - consider milrinone and beta-blockers

HD 5:

5. Salt wasting, hyponatremia and dehydration
   - fludrocortisone prophylaxis
   - CVP monitoring
   - frequent measures of serum sodium
   - hypertonic saline replacement; watch free water from medications
   - enteric sodium (23%) is more efficacious than 3% IV hypertonic saline
   - patients are often over-nourished and over-hydrated, given lack of movement, poikilothermia and mechanical ventilation

HD 6-8:

6. Type 1 vasospasm, coma, declining EEG or BIS, within 24 hours of salt wasting. Self limited.
   - Prophylaxis with sapropterin (5 mg/kg/day), vitamin C and 0.5 g/kg/day arginine if available
   - Nimodipine prophylaxis x 14 days as alternative
   - Baseline TCDs on HD 4-HD5, then daily on HD 6-8 and HD13-15

HD 5-14:

7. Progression of rabies in second week correlate with increasing lactic acidosis in CSF, possibly related to metabolism of excipients in IV sedatives
   - Taper sedation after 7 days, particularly to maintain EEG or BIS activity.

8. Complications of rabies associated with increased branched chain amino acids and glycine
    - Use low-dose insulin (1U/h) with sufficient nutrition to maintain euglycemia.
9. Bat rabies: immune-potentiated cerebral edema
    - Monitor serum rabies titers at least twice weekly
    - Use ribavirin or mycophenolate or methylprednisolone once serological response > 1 IU/ml
10. Dog rabies: third degree conduction block
    - Pacing effective
    - Consider xanthines
    - Atropine ineffective after 7 days from vagal denervation
    - Isoproterenol dilates intracranial arteries, increasing ICP (relative contraindication)
11. Diabetes insipidus
    - Tends to be episodic or cyclical
    - Vasopressin drip, cc/cc replacement over physiological losses; DDAVP may be too long-lasting but is effective.
12. Increased inflammatory markers (CRP, WBC with left shift, high platelets)
    - Confounded by poikilothermia
    - Correlates with detection of rabies antibody in serum
    - Correlates with "ratty appearance" to rabies DFA from skin biopsy
    - Empirical use of antibiotics should be limited to 3 days without culture evidence

HD 13-15:

13. Type 2 vasospasm (catastrophic). Ominous when associated with loss of EEG activity, autonomic instability, onset of DI, renal failure. Appears dependent on severity of antecedent Type 1 vasospasm.
    - Therapeutics unclear. Consider induced hypertension.

HD 15+:

Associated either with clinical recovery or progression to death.

14. Death in rabies associated with presumed ketogenesis (acetone > increased CSF isopropanol, presumed via alcohol dehydrogenase).
    - Use low-dose insulin (1U/h) with sufficient nutrition to maintain euglycemia.
15. Type 2 vasospasm is followed by pressure-passive, chaotic arterial velocities by TCD. In long term, may see laminar necrosis by MRI.
    - Chaotic TCD flow appears anecdotally improved by use of xanthines.
16. Futility defined as diabetes insipidus, isoelectric EEG, CSF lactate >4 mM and CSF protein > 250 mg/dl