

Protocol

1. DO NOT administer rabies vaccine or immunoglobulin to a patient with rabies. This practice has never worked and may cause adverse outcomes.
 - RIG delays development of rabies antibodies in CSF, essential for survival.
 - Preliminary evidence favors detrimental survival times after rabies vaccine in bat rabies.
 - We have administered beta-interferon to a few rabies patients with poor prognostic epidemiology, with evidence for a beneficial peripheral effect on viral load. This can be considered in particular for dog rabies, where CSF responses are often poor. It appears to stabilize peripheral rabies disease and “buy” an additional week for serological response to develop.
2. Maintain patient in isolation.
 - There has never been a laboratory-documented case of human-human transmission of rabies (other than by transplantation of corneas or solid organs).
 - 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/or tetanus within critical care units.
4. Treatment requires access to a rabies reference lab
 - Transport needs to be prioritized. There can be delays in transporting samples to rabies reference laboratories and in their analysis and reporting that compromise patient care. Reporting should be done by telephone or email as quickly as possible in addition to through standard reporting channels.
 - Depending on logistics of transport, treatment with the Milwaukee Protocol may need to begin if patient is approaching day 5 without a diagnosis. Sedation for 7 days is less dangerous than untreated rabies.
 - Consider use of Bio-Rad Platelia Rabies II Kit (human) #355-1180 for rabies anti-glycoprotein antibody, that is ELISA based and for which comparative studies and precedent for use in humans exist. This can be done locally with fast turnaround and reference laboratory backup confirmation.
 - Consider use of ADTEC Corporation RAPINA lateral flow assay, a single use bedside test for determining rabies anti-glycoprotein antibody. See Vaccine (2012) 30: 3891-96
 - Reporting of results needs to be rapid to be useful in a rapidly progressive encephalitis. Arrange for results to be reported by phone, email or text to a designated member of the treatment team in addition to standard reporting practices that take longer.
 - By the same token, send permission to the rabies reference lab to quickly share results with us when they are reported to the local treatment team. [In particular, CDC Atlanta has recently required this permission before communicating results.]
5. Treatment also requires access to a rehabilitation facility
6. Involve us early and daily. There is a lot to learn and to interpret. Treatment generally requires 2 lines of communication:

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- A small group of physicians, lab officials and outside consultants with confidential communications. This has been done by email and by text-messaging applications such as WhatsApp.
- A larger group of public health and laboratory authorities charged with epidemiology, public health response, logistics and drug procurement, and public relations. This has been done by conference calls and email.

7. Count hospital days (HD) starting at HD 0 from the first day of admission to inpatient care. This is more accurate than counting days of prodromal symptoms for predicting complications.
8. Some patients may experience delays in seeking hospitalization. We generally count hospital days in these patients from the day of OBJECTIVE NEUROLOGICAL SIGNS (e.g., severe agitation, paralysis, movement disorder, tachyarrhythmias or bradycardia, priapism) that would normally lead to hospitalization. Subjective symptoms (insomnia, pain, paresthesias) show longer prodromes and are not reliable in predicting the hospital course of patients, so are NOT used when establishing HD 0. When do you institute the Milwaukee Protocol? The intent if the Milwaukee protocol is to prevent fatal dysautonomia (20% of rabies patients die from dysautonomia) during HD 0 to 7. Particularly in paralytic rabies and bat rabies, the prodrome of paresthesias or pain may occur over 1-2 weeks in otherwise interactive patients. We observe these patients and begin the protocol when significant dysautonomia (tachyarrhythmias, bradycardia) or paresis develops.
9. Aggressive sedation is essential in the first week of hospitalization:
 - Minimize stimulation. DO NOT perform interval neurological examinations.
 - Increase sedation until there are no autonomic responses to stimuli associated with medical care. We do not care about abnormal movements. Seizures are very rare in uncomplicated rabies (e.g. arrest) and should suggest an alternative diagnosis.
 - There is always some tachycardia and fluctuation in rabies. We must tolerate some. By significant dysautonomia that we need to treat with sedation, we refer to heart rates and blood pressures above or below the 99th percentiles for age or height (e.g. P >150 or < 60; BPsys >120 or < 75 in children. For adults, we refer to heart rates and blood pressures above or below the 95th percentiles -- for lack of more extreme normative data (e.g. BPsys > 152 or < 100; see appendix).
 - 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. You may require doses up to 3.5 mg/kg/h
 - Ketamine is best balanced by a benzodiazepine, typically midazolam, sufficient to minimize vascular reactivity during endotracheal suction or turning. You may require doses up to 4.0 mg/kg/h. Midazolam carries a high preservative load that may cause hippuric acidosis.
 - Sedation is directed at cardiac dysautonomia, not abnormal movements which are common.
 - Consider use of haloperidol to minimize sedation with ketamine and midazolam. Haloperidol is known to be palliative in human rabies. We have increasingly found haloperidol to be of use when patients remain agitated despite generous use of ketamine and midazolam. We are now considering whether early, regular use might minimize more dangerous sedation.
 - Propofol tends to over-sedate rabies patients (to isoelectric EEG) but can be used carefully with EEG or BIS monitoring

- 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 been used but not enough for us to comment. Ketamine is a potent analgesic that suffices. opiates confound the pupillary exam; Opiates may be useful with severe agitation, but we found that haloperidol worked better.
 - Paralysis of the patient is almost never indicated. When considered, often sedation has been inadequate. The natural history of rabies is for full paralysis and loss of sensation by HD10.
 - 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.
10. Reduce sedation aggressively starting HD8. Attempt to wean every 12hours. Sedation should be off by HD12 if possible.
- The vagus nerve is no longer functional at this point; atropine ceases to be effective.
 - Tolerate abnormal movements, particularly of the face. These are not seizures, are common during recovery, and do not respond to usual sedatives.
 - Consider addition of clonidine or dexmedetomidine rather than reversing toward increases in benzodiazepines or ketamine when additional sedation is needed.
 - DO NOT aggressively taper if there is cerebral edema.
11. 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 in the second week. Rabies virus incapacitates the myenteric plexus in the gut.
- We have seen normal central venous pressures in patients with low volume as determined by echocardiography.
12. 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.
 - When fludrocortisone is not available, consider a physiological dose of hydrocortisone (1X not 3X stress dosing; 15 mg/day divided Q8-12h in adults; 8 mg/m²/day divided Q8h in children). Hydrocortisone risks mild immunosuppression at higher doses.
 - 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. Neuroimaging is insensitive to the increased intracranial pressure. Optic nerve sheath diameter by ultrasound is helpful when direct monitoring of intracranial pressure is unavailable.

- Use of inotropes: with use of fludrocortisone and normal saline solutions, use of inotropes is infrequent during treatment of rabies.
 - Inotropes are considered during periods of vasospasm (HD 5-8 and 12-15).
 - There may be mild adrenal medullary insufficiency of adrenaline caused by the rabies virus.
 - Vasoconstrictors are not counter-balanced by NO-mediated vasodilation (from BH4 deficiency) and so will exacerbate ileus. When possible, we suggest titrating vasoconstrictors based on transcranial dopplers to normal velocities for age (median or higher) rather than using population norms for targeting blood pressure. This often results in less inotropes with an objective measure of cerebral perfusion. A target MAP can then be individualized for the specific patient.
 - There is no cardiomyopathy in rabies, so B1 agonists are rarely indicated. (There are rare instances of myocardial stunning on presentation from extreme dysautonomia.)
 - There may be mild pulmonary hypertension caused by loss of NO-mediated vasodilation of the pulmonary bed. CVP may appear normal with hypovolemia as detected by echocardiography of the inferior vena cava.
- 13. Ventilate using normal parameters. Rabies patients maintain CNS responsiveness to changes in pCO₂. Avoid hypocarbia.
 - The tetrahydrobiopterin (BH₄) deficiency repeated measure in human rabies is predicted to abrogate low-pressure autoregulation of cerebral perfusion pressure. It may also contribute to modest pulmonary hypertension and modest adrenal medullary insufficiency (low adrenaline).
 - Tracheostomy is often considered given prolonged intubation (about 3 weeks). Please time tracheostomy between day 8 and 12 to avoid periods of known vasospasm and high risk of dysautonomia in the first 7 hospital days.
- 14. This is key: Administer low-dose insulin drip (0.5 U/h regular insulin in adults; 0.010 U/kg/h in children) with sufficient enteral and intravenous nutrition to maintain euglycemia.
 - Complications in rabies are associated with biochemical markers of catabolism (gluconeogenesis and Ketogenesis measured in CSF). Promotion of anabolism appears to improve the survival curve by about a week.
 - Insulin may also minimize toxic alcohol metabolites and lactic acidosis associated with propylene glycol stabilizers in benzodiazepine sedatives.
- 15. Prophylaxis against DVT is recommended.
- 16. Precautions against pressure ulcers are recommended.
- 17. General targets:
 - Maintain head of bed elevated 30 degrees
 - mean arterial pressure > 80 mm (adult). Generally, central venous pressure 8-12 mm Hg
 - O₂ saturation > 94%
 - PaCO₂ 35-40 mm Hg. Avoid low PaCO₂.
 - Hemoglobin > 10 mg% (historical observation)

- Serum sodium 145-155 mEq/L. Avoid Na < 140.
 - Serum glucose 70-110 mg% with low dose insulin infusion. This IS NOT intended to be tight control.
 - 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
18. Maintain core temperature 35-37C. Patients are poikilothermic.
- Antipyretics generally have no effect in rabies
 - Ambient temperature has a major effect in rabies.
 - Patient temperature affects heart rate and blood pressure
19. Hypothermia is NOT RECOMMENDED because it slows the immune response.
- Therapeutic hypothermia may be helpful in vaccinated patients and in bat rabies once the immune response is detected, particularly if cerebral edema is evident.
20. 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 is neuroprotective by this mechanism.
21. Ribavirin is NOT RECOMMENDED because of its immunosuppressive effects.
22. Vasospasm and clinical exacerbations are regularly encountered on days 6-8 and 13-15 of first hospitalization.
- Early, effective use of fludrocortisone appears to minimize vasospasm. These are effectively monitored by transcranial Doppler and can be evident by EEG or BIS monitor.
 - Vitamin C (250 mg daily for child and 500 mg for adult, IV or enterally)
 - DO NOT use nimodipine and sapropterin together. If fludrocortisone is not used, then use sapropterin (Kuvan (Merck) 5 mg/kg/day enterally) with vitamin C (250-500 mg total/day IV or PO), and L-arginine (0.5 gm./kg/day IV or enterally). Sapropterin is preferred over nimodipine when available because of proven deficiency in rabies and the potential for autoregulation when used early (before HD6). Sapropterin should also maintain blood pressure better by improving adrenaline synthesis in the adrenal medulla.
 - DO NOT use nimodipine and sapropterin together. If fludrocortisone and sapropterin are not used, then nimodipine is recommended at half to full dose for prophylaxis against vasospasm Reduce dose as needed to avoid hypotension and systemic steal syndrome, because autoregulation at low blood pressures is impaired by tetrahydrobiopterin and NO deficiency.

Laboratory monitoring:

1. Serum sodium twice daily.
 - Obtain urine sodium when serum sodium abnormal or difficult to control
 - Consider serum/urine uric acid as second 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 in the second and third week twice weekly to detect cerebral edema until CSF titers stabilize.
 - MRI in rabies is not associated with restricted diffusion nor contrast enhancement. When these are noted, there has either been a significant complication (e.g. arrest) or the diagnosis is not rabies.
 - MRI and CT are poorly sensitive for increased intracranial pressure that is regularly present before serological response.) MRI detects the immune response by subtle edema in the basal ganglia and thalamus.
 - IN BAT RABIES, IMAGING IS PARTICULARLY CRITICAL DURING THE SECOND WEEK TO DETECT CEREBRAL EDEMA when serologies or optic nerve sheath diameter (ONSD) are unavailable.
6. Transcranial Doppler ultrasound (TCD) daily on days 4-8 and days 12-15 after first hospitalization to monitor for degree of vasospasm. Values are best reported as TAMv or TAMx and resistive index (RI) in the middle cerebral arteries (MCA). The only values that are highly reliable are from the MCAs, so restricting the study to these arteries may reduce the time commitment and permit more days of observation by the radiologists. The Lindegaard ratio (ratio of MCA to internal carotid) is generally not of value in human rabies.
 - TCDs on days 9-11 may detect progressive cerebral edema by high RI when no intracranial pressure monitoring is undertaken.
 - TCDs are often normal in patients who appear brain dead by exam.
7. We have gained experience with ultrasound of the globe of the eye to estimate intracranial pressure when MRI or CT is not available. This is a very quick bedside test that can be performed daily. Optic nerve sheath diameter (ONSD) is rapidly dynamic. It may be most helpful when a baseline is established early on for comparison.
8. Dog rabies: ECG daily HD 5-14 to measure PR interval and assess for heart block

Virological Monitoring (clinical samples) with transport twice weekly to the reference laboratory

9. Saliva (0.5-1.0 ml, frozen for PCR) every other day (twice weekly minimum) until 3 negatives obtained sequentially.
 - Avoid collection after chlorhexidine mouth care.
 - more frequent testing removes patient from isolation faster

10. Serum (2 ml, frozen for serology) every other day (twice weekly minimum) for first 2 weeks, then 1-2 times weekly.
 - More frequent testing better anticipates complications related to immune response.
11. CSF (2 ml, frozen for serology) twice weekly. Consider ventricular or lumbar drain.
12. CSF twice weekly for cells, chemistry including lactate
13. After a number of incidents, we now strongly recommend:
 - splitting samples to maintain local backup samples (frozen -20/c or -80C) to avoid loss or thawing of samples during transport.
 - local use of Bio-Rad Platelia rabies II or ADTEC lateral flow assays for more timely reporting and patient management. Rabies titers are essential to rabies management.
14. Virology reports should ALWAYS be completed even if the patient dies. This allows retrospective interpretation of care decisions and the opportunity to detect new complications and improve future care.
15. There are many ICU complications that result in death during rabies care. The autopsy will identify new complications in 25% of patients. It may show virus clearance (evidenced by lack of virus cultivation and spotty rather than homogeneous detection of virus antigen and RNA in tissues). This finding of virus clearance is often of consolation to family members and the medical staff.
16. There are needle biopsy alternatives to standard autopsy when the standard form is prohibited by cultural or religious norms. **THERE HAS NEVER BEEN TRANSMISSION OF RABIES DURING AN AUTOPSY.**

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): Dysautonomia

- Dehydration, electrolyte disturbances, ketosis.
 - volume replacement, isotonic fluids, low-dose insulin drip
- 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 (bolts or electrodes).
- Sudden death from asystole or tachyarrhythmias.
 - minimize stimulation and neurological exams
 - sufficient sedation to avoid changes in heart rate with nursing care
 - consider pacer at bedside
 - asystole responds to increased sedation
- Cardiac stunning from catecholamine storm
 - consider milrinone and beta-blockers

HD 5: Salt wasting

- Salt wasting, hyponatremia and dehydration
 - fludrocortisone prophylaxis. Hydrocortisone at 1X physiological if fludrocortisone is not available.
 - CVP monitoring
 - frequent measures of serum sodium
 - hypertonic saline replacement; watch free water from medications
 - enteric sodium (23%; 1 g in 5 ml water) 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 (within 1 day of hyponatremia): Cerebral artery spasm, generalized

- Type 1 vasospasm, coma, declining EEG or BIS, within 24 hours of salt wasting. Self limited.
 - Prophylaxis with fludrocortisone, serum sodium > 145, normal CVP.
 - AND: Prophylaxis with sapropterin (5 mg/kg/day), vitamin C and 0.5 g/kg/day arginine if available
 - OR, nimodipine prophylaxis x 14 days. Reduce nimodipine dose to avoid hypotension; often ½ or 1/3 the standard dose is used.
 - Baseline TCDs on HD 4-HD5, then daily on HD 6-8 and HD13-15

HD 5-14: Neurometabolic effects of catabolism; bat/dog rabies-specific complications

- Progression of rabies in second week correlate with increasing lactic acidosis in CSF, possibly related to metabolism of excipients in IV sedatives or to the immune response by astrocytes or to decreased lactate consumption by neurons
 - Taper sedation aggressively after 7 days, particularly to maintain EEG or BIS activity. Target removal of all sedation by HD 12.
- Complications of rabies associated with increased branched chain amino acids and glycine
 - Use low-dose insulin (0.5 U/h in adults, 0.010 U/kg/h in children) with sufficient nutrition to maintain euglycemia.
- Bat rabies: immune-potentiated cerebral edema
 - Monitor serum rabies titers at least twice weekly
 - Monitor by MRI or CT twice weekly in the second or third weeks
Dexamethasone 30-40 mg/day in adults or 6 mg/kg/day in children a 5-day pulse ONCE SEROLOGICAL RESPONSE > 1 IU/ML. (We have not had as good an effect with methylprednisolone 30 mg/kg/day.)
 - IF PATIENT RECEIVED RABIES VACCINE, then risk for cerebral edema is much higher. Administer intravenous immune globulin (IVIG) 1 g/kg over 12-24 hours AT TIME OF DEXAMETHASONE PULSE.
 - Follow dexamethasone pulse with 4 weeks of a taper of prednisone or prednisolone starting at 60 mg/day in adults or 2 mg/kg/day in children.
- Dog rabies: third degree conduction block
 - Pacing effective
 - Consider xanthines (adenosine inhibitors). Caffeine base 2.5 mg/kg daily (approximately 1-1.5 cc/kg of espresso coffee).
 - Atropine ineffective after 7 days from vagal denervation
 - CAUTION: Isoproterenol dilates intracranial arteries, increasing ICP (relative contraindication)
- Diabetes insipidus
 - Tends to be episodic or cyclical. True DI is biphasic, so be prepared.
 - Vasopressin drip, cc/cc replacement over physiological losses; DDAVP may be too long-lasting but is effective.
- 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” (clearance) by rabies DFA from skin biopsy
 - Empirical use of antibiotics should be limited to 3 days without culture evidence

HD 12-15: Cerebral artery spasm, generalized

- Type 2 vasospasm (often catastrophic) is encountered when the immune response has not appeared. Vasospasm is ominous when associated with loss of EEG activity, autonomic

instability, onset of DI, renal failure. Vasospasm appears dependent on the lack of an immune response and the severity of antecedent Type 1 vasospasm.

1. This is avoided when the immune response arrives early (before day 10). This is also avoided when the hyponatremia and vasospasm around HD 6-8 were prevented.
2. Therapeutics unclear. Consider induced hypertension/hypervolemia.
3. This may be an optimal period for induced hypothermia (days 12-14) as a neuroprotective strategy, because the immune response is already present

HD 15+: Recovery

Associated either with clinical recovery or progression to death.

- Death in rabies associated with presumed ketogenesis (acetone > increased CSF isopropanol, presumed via alcohol dehydrogenase).
 - Use low-dose insulin (0.5 U/h in adults or 0.010 U/kg/min in children) with sufficient nutrition to maintain euglycemia.
- 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 (see #10).
- Futility defined as diabetes insipidus, isoelectric EEG, CSF lactate >4 mM and CSF protein > 250 mg/dl after HD10.

It is NOT clear that these criteria still apply with later versions of the protocol using mineralocorticoid and insulin that have pushed survival out further.

Vaccine recipients, HD 15+ Progressive white matter damage

- We have seen late onset progression of white matter disease associated with loss of interaction and severe spasticity. Neuroimaging is reminiscent of interferonopathies, classically associated with Aicardi-Goutières disease. This has NOT yet been confirmed by cytokine assay or histology, so is speculative.
 - Dexamethasone 6 mg/kg/day in a 5-day pulse ONCE SEROLOGICAL RESPONSE > 1 IU/ML. (We have not had as good an effect with methylprednisolone 30 mg/kg/day.)
 - AND intravenous immune globulin (IVIG) 1 g/kg over 12-24 hours AT TIME OF DEXAMETHASONE PULSE. Follow pulse with 4 weeks of a taper of prednisone or prednisolone starting at 2 mg/kg/day.
 - We have been considering use of simvastatin in this setting starting at the time of dexamethasone and IVIG. Simvastatin is (a) anti-inflammatory (b) increases tetrahydrobiopterin synthesis (c) protects against neuronal and volume loss and (d) may promote myelination in other diseases.

APPENDIX

Heart rate

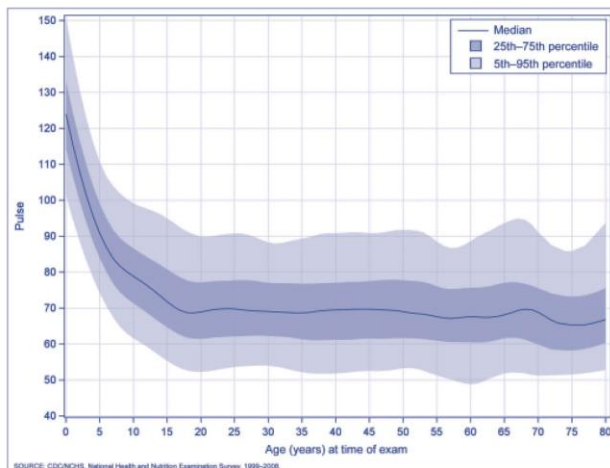
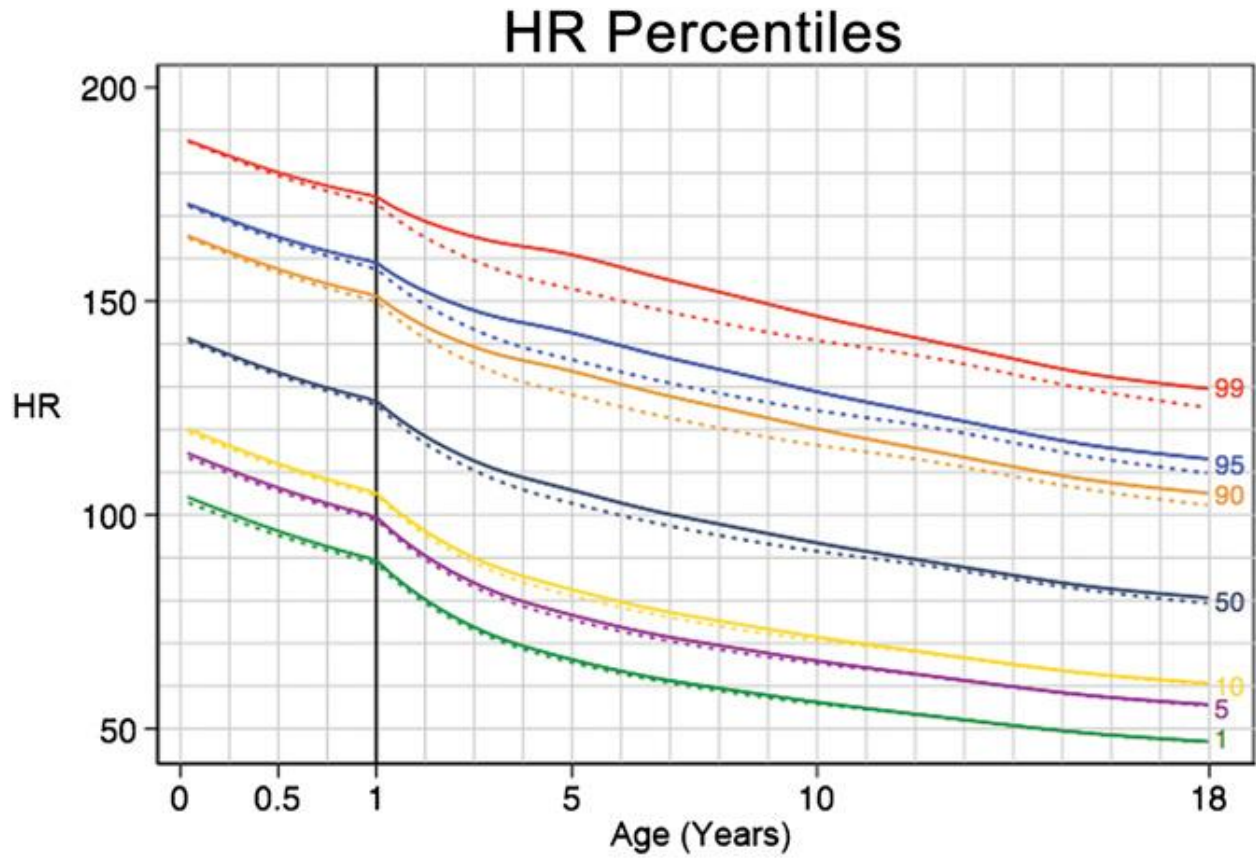


Figure 1. Resting pulse rates for U.S. males, by age: National Health and Nutrition Examination Survey, 1999-2008

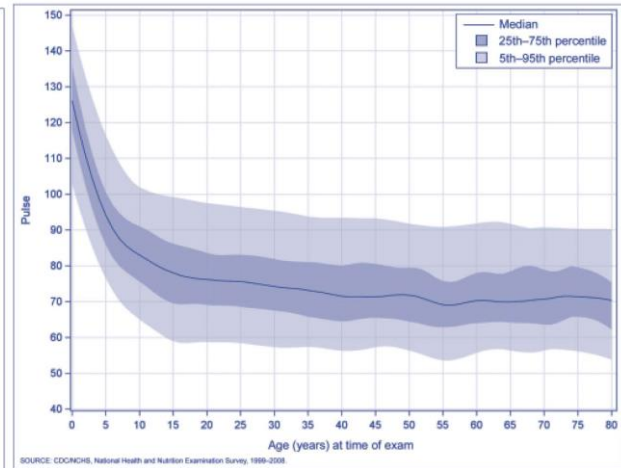
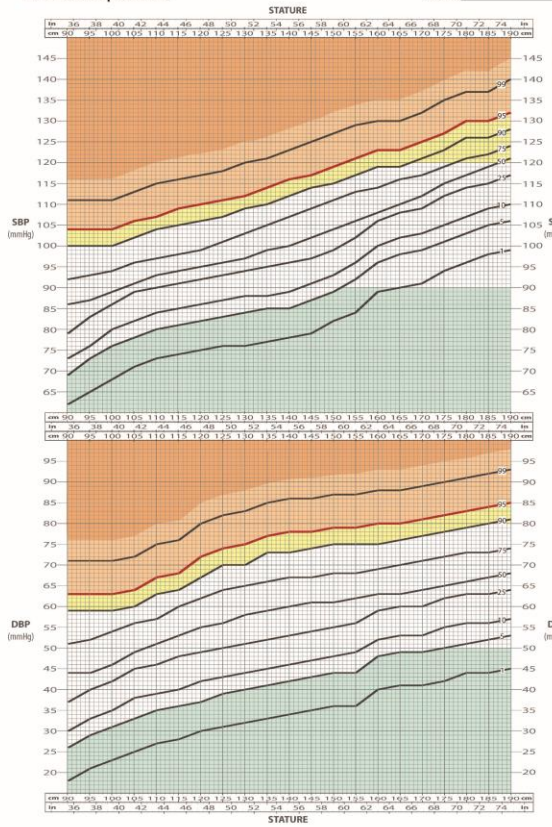


Figure 2. Resting pulse rates for females, by age: National Health and Nutrition Examination Survey, 1999-2008

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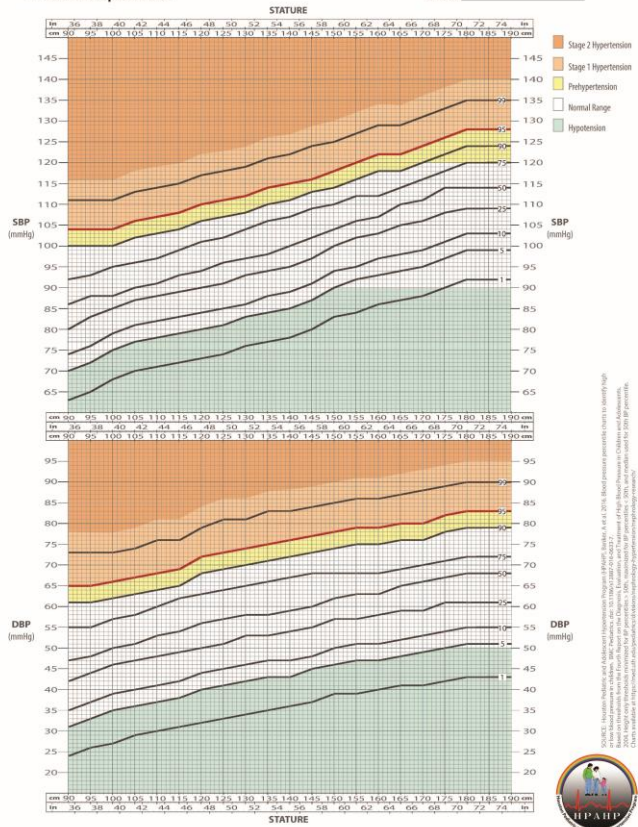
3 to 20 years: Boys BP-for-stature percentiles

NAME _____
RECORD # _____



3 to 20 years: Girls BP-for-stature percentiles

NAME _____
RECORD # _____



- Stage 2 Hypertension
- Stage 1 Hypertension
- Prehypertension
- Normal Range
- Hypotension

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Characteristic	Total percentile					Normal percentile					Treated percentile					Untreated percentile				
	5th	25th	50th	75th	95th	5th	25th	50th	75th	95th	5th	25th	50th	75th	95th	5th	25th	50th	75th	95th
All races or ethnicities																				
18 years and over, age-adjusted	102	113	121	131	152	101	111	118	125	134	105	119	130	141	168	125	139	144	152	172
18-39 years	101	111	117	125	138	101	110	116	123	132	107	119	125	133	148	124	134	141	144	152
40-59 years	103	114	122	132	151	102	112	118	125	135	104	118	127	139	161	124	137	143	151	171
60 years and over	103	119	131	144	169	99	113	122	130	137	105	120	133	146	172	140	145	151	160	181
Non-Hispanic white																				
18 years and over, age-adjusted	102	113	121	131	151	101	111	118	125	134	105	119	129	140	166	125	139	144	152	171
18-39 years	101	111	117	125	137	100	110	116	123	133	109	119	125	133	143	124	134	141	144	150
40-59 years	103	114	121	131	148	102	112	118	125	134	104	117	126	136	155	124	137	142	150	169
60 years and over	102	118	130	143	167	98	113	122	130	137	105	120	132	145	170	140	145	150	159	177
Non-Hispanic black																				
18 years and over, age-adjusted	104	115	123	135	159	103	112	119	126	135	106	121	132	148	175	125	140	145	154	176
18-39 years	104	113	120	128	142	103	112	119	125	134	100	119	128	135	155	120	135	141	146	155
40-59 years	103	117	126	139	165	101	113	119	127	136	103	120	132	149	174	125	140	145	157	178
60 years and over	106	121	134	148	178	100	111	122	132	137	110	122	135	148	179	138	144	152	164	191
Mexican American																				
18 years and over, age-adjusted	102	112	118	128	145	102	111	117	124	133	101	121	131	145	169	125	139	143	150	175
18-39 years	102	111	117	125	137	102	111	116	123	132	*	114	124	134	*	123	135	141	145	151
40-59 years	102	112	121	131	150	102	111	118	126	136	96	119	130	138	161	124	138	145	151	180
60 years and over	106	120	132	145	173	105	114	122	130	137	106	124	136	148	178	*	144	150	160	187

Table 10. Selected percentiles of systolic blood pressure (mm Hg) for women aged 18 and over, by hypertension status, race or ethnicity, and age: United States, National Health and Nutrition Examination Survey, 2001-2008

Characteristic	Hypertension status																			
	Total percentile					Normal percentile					Treated percentile					Untreated percentile				
	5th	25th	50th	75th	95th	5th	25th	50th	75th	95th	5th	25th	50th	75th	95th	5th	25th	50th	75th	95th
All races or ethnicities																				
18 years and over, age-adjusted	96	107	117	131	160	95	104	112	120	132	104	120	133	148	177	130	142	149	160	185
18-39 years	94	103	109	116	128	94	102	109	115	126	99	114	123	130	148	114	131	142	146	157
40-59 years	97	109	119	131	153	96	107	115	124	134	101	115	127	140	164	127	141	146	154	176
60 years and over	107	122	135	151	181	102	114	122	130	137	109	125	138	155	183	140	145	153	167	194
Non-Hispanic white																				
18 years and over, age-adjusted	96	108	117	131	160	95	105	112	121	132	105	119	133	147	175	130	142	148	160	184
18-39 years	94	102	109	115	127	94	102	108	115	125	93	112	120	127	132	*	128	140	145	*
40-59 years	97	109	119	130	150	95	107	115	123	133	100	115	125	137	160	125	140	144	152	172
60 years and over	107	122	135	150	180	102	114	122	130	137	108	125	137	154	182	140	145	153	166	192
Non-Hispanic black																				
18 years and over, age-adjusted	98	110	120	135	167	97	106	114	121	134	103	120	133	150	183	128	143	150	159	188
18-39 years	97	105	113	120	138	97	104	112	118	131	100	117	128	139	157	116	130	141	151	*
40-59 years	101	113	124	139	167	98	108	117	126	136	102	117	130	145	174	134	144	150	159	184
60 years and over	108	126	139	158	193	104	118	125	130	137	107	126	141	159	192	140	149	156	175	207
Mexican American																				
18 years and over, age-adjusted	96	105	113	124	155	95	104	110	117	131	106	121	136	154	180	138	143	150	164	184
18-39 years	94	103	108	115	127	94	103	108	114	124	*	113	119	130	*	138	142	144	*	
40-59 years	99	110	118	130	159	98	109	115	124	133	103	119	132	146	172	131	144	150	165	181
60 years and over	107	123	138	154	184	101	112	122	131	137	112	127	140	160	194	141	146	152	165	192

* Statistic was deemed unreliable based on sample size criteria.

Table 6 ONSD cut-off values in children >1 year old and children with a closed AF

ICP threshold (in mmHg)	ONSD cut-off in children over 1 year old (in mm)	ONSD cut-off in children with a closed AF (in mm)
≥20	5.75	5.81
≥15	5.49	5.50
≥10	5.20	5.20
≥5	5.10	5.00

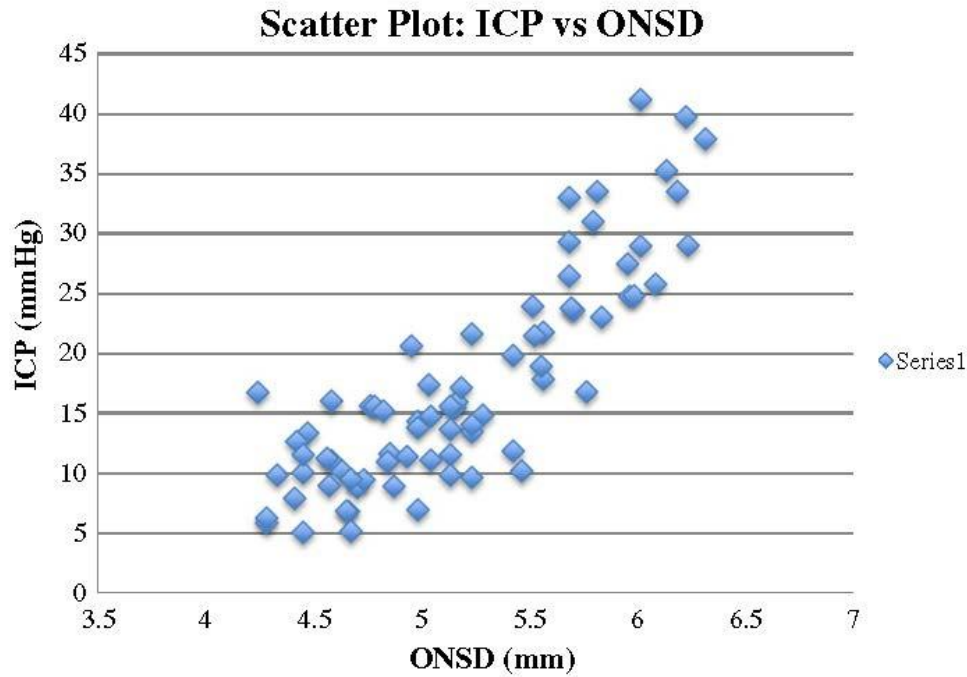


Fig. 1. Scatter Plot 1: ICP vs ONSD. Scatter plot of 75 measurements of ICP in the X axis against the ONSD value in the Y axis. Generally this scatter plot shows a linear relationship. However towards the extreme end of ICP value, the ONSD value started to reach a plateau phase. This is due to maximal dilatation of the optic nerve sheath despite elevation of ICP. Prior studies suggested that with increasing ICPs there might be a maximum nerve sheath diameter that would create an asymptotic relationship. A scatterplot of ICP as a function of ONSD demonstrates this relationship with the maximum ONSD in this population of 6.31 mm.

Table 3 Mean (SD) flow velocities in basal cerebral arteries (in cm/second) in a cross sectional study of healthy children (n=112)

Age	n	Middle cerebral artery	Internal carotid artery	Anterior cerebral artery	Posterior cerebral artery		Basilar artery
					P1*	P2†	
Systolic peak flow velocity:							
0-10 days	18	46 (10)	47 (9)	35 (8)	—	—	—
11-90 days	14	75 (15)	77 (19)	58 (15)	—	—	—
3-11.9 months	13	114 (20)	104 (12)	77 (15)	—	—	—
1-2.9 years	9	124 (10)	118 (24)	81 (19)	67 (18)	69 (9)	71 (6)
3-5.9 years	18	147 (17)	144 (19)	104 (22)	84 (20)	81 (16)	88 (9)
6-9.9 years	20	143 (13)	140 (14)	100 (20)	82 (11)	75 (10)	85 (17)
10-18 years	20	129 (17)	125 (18)	92 (19)	75 (16)	66 (10)	68 (11)
Mean flow velocity‡:							
0-10 days	18	24 (7)	25 (6)	19 (6)	—	—	—
11-90 days	14	42 (10)	43 (12)	33 (11)	—	—	—
3-11.9 months	13	74 (14)	67 (10)	50 (11)	—	—	—
1-2.9 years	9	85 (10)	81 (8)	55 (13)	50 (17)	50 (12)	51 (6)
3-5.9 years	18	94 (10)	93 (9)	71 (15)	56 (13)	48 (11)	58 (6)
6-9.9 years	20	97 (9)	93 (9)	65 (13)	57 (9)	51 (9)	58 (9)
10-18 years	20	81 (11)	79 (12)	56 (14)	50 (10)	45 (9)	46 (8)
End diastolic peak flow velocity:							
0-10 days	18	12 (7)	12 (6)	10 (6)	—	—	—
11-90 days	14	24 (8)	24 (8)	19 (9)	—	—	—
3-11.9 months	13	46 (9)	40 (8)	33 (7)	—	—	—
1-2.9 years	9	65 (11)	58 (5)	40 (11)	36 (13)	35 (7)	35 (6)
3-5.9 years	18	65 (9)	66 (8)	48 (9)	40 (12)	35 (9)	41 (5)
6-9.9 years	20	72 (9)	68 (10)	51 (10)	42 (7)	38 (7)	44 (8)
10-18 years	20	60 (8)	59 (9)	46 (11)	39 (8)	33 (7)	36 (7)

*Precommunicating part of posterior cerebral artery.
 †Postcommunicating part of posterior cerebral artery.
 ‡Mean flow velocity=time-mean of the maximal velocity envelope curve.

7. Appendices

Appendix IVe. Resistance index RI = (vs—vd)/vs—mean values

Age	MCA	ICA	SIPH	ACA	PCA 1	PCA 2	BAS
0-10 days	0.71	0.71*	—	0.64+	—	—	—
11-90 days	0.63	0.71*	—	0.60+	—	—	—
3-11.9 months	0.58	0.67*	—	0.60+	—	—	—
1-2.9 years	0.47	0.52	0.57	0.55	0.55	0.52	0.55
3-5.9 years	0.55	0.60	0.63	0.57	0.58	0.59	0.60
6-9.9 years	0.50	0.55	0.55	0.57	0.55	0.52	0.55
10-16.9 years	0.53	0.58	0.58	0.58	0.55	0.57	0.57

Standard deviations: 0-10 days : 0.11
 -11-90 days : 0.07-0.10
 3-11.9 months : 0.05-0.07
 > 1 year : 0.04-0.06

TABLE 1 Normal Reference Values of Blood Flow Velocities in the Basal Cerebral Arteries in Different Age Groups					
Blood Flow Velocity (cm/sec)	n	Subjects			
		All	20–40 Years Old	41–60 Years Old	>60 Years Old
ACA	313				
Peak		79 (37–121)	82 (40–124)	80 (36–124)	72 (52–102)
Mean		53 (33–83)	56 (42–84)	53 (37–85)	44 (22–66)
End-diastolic		35 (13–57)	38 (16–60)	35 (13–57)	28 (12–44)
MCA	335				
Peak		110 (54–166)	120 (64–176)	109 (65–175)	92 (58–126)
Mean		73 (33–133)	81 (41–121)	73 (35–111)	59 (37–81)
End-diastolic		49 (21–77)	55 (29–81)	49 (23–75)	37 (21–53)
PCA	336				
Peak		71 (39–103)	75 (43–107)	74 (40–108)	62 (38–86)
Mean		49 (25–73)	52 (28–76)	51 (25–75)	40 (22–58)
End-diastolic		33 (15–51)	36 (20–52)	34 (18–50)	26 (14–38)

ACA = anterior cerebral artery, MCA = middle cerebral artery, PCA = posterior cerebral artery. Range of velocities (calculated as mean \pm 2 SD) is given in parentheses.

TABLE 2 Normal Reference Values of Impedance Indexes in the Basal Cerebral Arteries in Different Age Groups				
Impedance Index ^a	Subjects			
	All	20–40 Years Old	41–60 Years Old	>60 Years Old
ACA				
PI	0.87 \pm 0.16	0.80 \pm 0.14	0.85 \pm 0.16	1.02 \pm 0.18
RI	0.56 \pm 0.07	0.53 \pm 0.05	0.56 \pm 0.07	0.62 \pm 0.06
MCA				
PI	0.86 \pm 0.15	0.83 \pm 0.14	0.82 \pm 0.13	0.96 \pm 0.17
RI	0.56 \pm 0.06	0.54 \pm 0.05	0.55 \pm 0.05	0.60 \pm 0.06
PCA				
PI	0.81 \pm 0.15	0.76 \pm 0.12	0.79 \pm 0.12	0.94 \pm 0.16
RI	0.54 \pm 0.07	0.52 \pm 0.06	0.53 \pm 0.05	0.60 \pm 0.09

ACA = anterior cerebral artery, PI = pulsatility index, RI = resistivity index, MCA = middle cerebral artery, PCA = posterior cerebral artery.

^aMean \pm 2 SD.