Milwaukee Protocol, version 7.1G (cat vector rabies, no vaccination)

This protocol targets cat vector, usually vampire bat rabies (Amazonian Countries) in patients with normal immunity who did not receive rabies vaccine or immunoglobulin (RIG or IVIG). Transmission may also involve insect bat or canine rabies variants. These are all consolidated in this one protocol given low numbers.

Passage of rabies virus through the cat appears to attenuate the rabies virus. This results in slower progression of disease, often with development of an immune response by time of presentation. The early immune response should lead to many survivors, but will also lead to early development of complications relative to the normal sequence, notably early cerebral edema. It is key to monitor serology from time of admission and often, preferably by bedside point-of-care or a local laboratory.

Patients with rabies with a cat vector who received rabies vaccine should be referred to protocols 7B (dog), 7D (vampire bat) or 7F (insect bat).

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Hospital day (HD)	Risk	Therapy	Testing	Comments
HD 0	Cardiac arrest (dysautonomia) in 27% over the first 7 days	Minimize stimulation. Rabies causes extensive sensory and motor denervation over 10 days. The neurological exam is not useful and can stimulate a cardiac arrest. Pupillary exam remains useful. Sedation: <u>If alert and no dysautonomia:</u> haloperidol (5 mg hourly x 3 doses, the 5 mg daily in divided doses; 0.1 mg/kg hourly x 3, the 0.1 mg/k daily) <u>If bradycardia or tachyarrhythmia:</u> ketamine (0.5-1.0 mg/kg/h) + 1:1 midazolam. Titrate sedation to prevent dysautonomia with nursing cares.	<u>For Diagnosis:</u> Saliva for PCR Skin biopsy for PCR (or antigen) Serum for antibody CSF for antibody (Corneal impressions NOT recommended) Results of testing can be delayed. It may be necessary to sedate or treat before diagnosis is confirmed. Sedation for 7 days is less dangerous than untreated rabies. EEG or BIS monitoring Rabies mimics include NMDAR autoimmune encephalitis, scorpion sting, elapid snake venom, Guillain Barre syndrome, and orofacial seizures.	Prediction is most accurate based on hospitalization for objective signs (not symptoms). First day =0 Vaccination may accelerate immune responses leading to adverse neurological outcomes. RIG or IVIG delays development of CSF antibodies, essential for survival [Figure 1]. Sedation is tapered on HD 8 when vagal function ceases. During taper, consider addition of clonidine or dexmedetomidine rather than increases in benzodiazepines or ketamine. <u>IMPORTANT</u>: vagus nerve function and risk of arrest may persist past HD 7 in patients receiving favipiravir. Haloperidol reduces sensory input and is one of 2 drugs published for palliation of rabies. We DO NOT recommend burst suppression. Ketamine and amantadine are given as neuroprotectants based on quinolinic acid in CSF (excitotoxin) and original use in the successful protocol. Ketamine is anti-nociceptive and avoids altering the pupillary response by opiates. Barbiturates are immunosuppressive and should be avoided. Propofol appears safe but may cause isoelectric EEG in rabies. Ventilate using normal parameters. Rabies patients maintain vascular responsiveness to changes in pCO2. Avoid hypocarbia. Please time tracheostomy between HD 8 and HD 12 to avoid periods of known vasospasm and high risk of dysautonomia in the first 7 hospital days. Antipyretics have no effect in rabies. Ambient temperatures may have major effects on heart rate and blood pressure.
HD 0	Immune response is often favorable in cat-transmitted rabies. In serum and CSF, 57-60%	Inquire IMMEDIATELY about the possibility of investigational or compassionate use of	<u>Monitoring:</u> Saliva and serum/CSF are tested twice weekly. *This is ESSENTIAL for*	CSF antibody is necessary for survival. Antibody must be detected by HD 7 (in the absence of experimental therapy) for survival. The serological response to cat-transmitted rabies is regularly detected early. There is plenty of virus

	had immune response by 7 days. (Figure 1)	rabies antivirals, biologics, or gene therapies. These require time for approvals and logistics. Do NOT administer rabies vaccine or immunoglobulin products. Consider administration of interferon-beta.	*predicting survival/futility and complications and is especially important for cat-transmitted rabies in the first week of hospitalization*	antigen in the skin by HD0, so vaccination serves no purpose. Chlorhexidine oral care interferes with PCR for rabies virus. Freeze saliva. CSF should be sent for cells and protein (criteria for futility) and lactate if available. Favipiravir (ebola oral dosing regimen) modifies the clinical course of rabies (less denervation) but its bioavailability in the brain is uncertain. Some countries have favipiravir available (China, Russia, Japan). There are theoretical reasons to administer BOTH IFN-beta and favipiravir together: interferons reduce the purine precursor pool to enhance inhibition by favipiravir. Rabies is inhibited by type I interferons (IFN-alpha and IFN-beta). IFN-alpha can be neurotoxic, but IFN-beta is used in multiple sclerosis. We have anecdotal evidence for a reduction in salivary viral load after IFN-beta. We have not seen adverse effects. We have only used Avonex 30 mcg IM once weekly. Ribavrin is immunosuppressive. It is an inosine monophosphate dehydrogenase (IMPDH) inhibitor, similar to mycophenolate. [see cerebral edema, next]
HD 0-16	Cerebral edema is likely to exceed the 40% encountered in bat rabies and may approach 100% (Figure 1)	<u>Prevention:</u> Maintain head of bed elevated 30 degrees; Serum sodium > 140; Fludrocortisone; isotonic saline in IVs Consider administration of ribavirin (1000 mg/day in 2 divided doses (adult); 15 mg/kd/day in 2 divided doses x 2 wks; round to nearest	Daily serum sodiums Intracranial pressure monitoring OR daily optic nerve sheath diameter (ONSD) OR transcranial doppler ultrasounds (TCD) to detect cerebral edema. <u>If ONSD or TCD are not available:</u> Twice weekly CT or MRI x 2 weeks (until immune response matures)	Rabies immune response is rapid in cat-transmitted rabies and predicts complications. Titers can be excessive (>100 IU/ml) [Figure 1]. Bedside or local monitoring (RAPINA cartridges, Platelia II ELISA serology at a local veterinary or medical institute will improve timely care and can be validated at (slower) rabies reference laboratories. Cerebral edema is associated with the immune response. The mechanism is uncertain. There is no evidence for vasogenic edema: the blood-brain-barrier (as evidenced by contrast enhancement) appears to be intact, so the benefit of corticosteroids rests on immune modulation. The cerebral edema appears to last for several weeks. Dexamethasone (30-40 mg/day adults; 6 mg/kg/d child x 5 days) and IVIG (1 g/kg) appear to slow the immune response when given very but have not

		200 mg, child x 2 wks) or mycophenolate mofetil (500 mg twice daily orally, adult x 2 weeks; 600 mg/m^2/dose twice daily orally, child x 2 weeks) <u>Treatment:</u> Extraventricular drain if possible. Avoid diuretics and mannitol. Consider hypernatremia (with prophylaxis against DVTs). **Consider therapeutic hypothermia.**	Monitor hemoglobin or hematocrit weekly if ribavirin is used.	shown clear benefit against later demyelination. [See alternative therapies.] Rabies patients may have cerebral salt-wasting and may progress to diabetes insipidus as a complication. Avoid diuretics and mannitol given the fluid and electrolyte challenges. Ribavirin is immunosuppressive and was used in our initial survivor. It can be used pre-emptively. It is an inosine monophosphate dehydrogenase (IMPDH) inhibitor, similar to mycophenolate. Ribavirin and mycophenolate also decrease BH_4 by reducing guanosine pools. This may predispose to cerebral artery spasm [see HD 4-6.] Mycophenolate has been studied for multiple sclerosis. Ribavirin accumulates in red blood cells and will lead to hemolysis. Bioavailability in the brain is low. Insertion of the EVD has been associated with transient PCR positivity of the CSF. Neither MRI nor CT adequately detects early intracranial hypertension. MRI in rabies is not associated with restricted diffusion or contrast enhancement. When these are noted, there has been a complication (arrest) or the diagnosis is not rabies. Bedside testing (ONSD by ultrasound, or TCD ultrasound) detect increases in intracranial pressure associated with the immune response, allowing intervention when serologies lag or transport is risky. Hypothermia should not be considered up front (when we need an immune response) but makes sense to modulate inflammation and the adaptive immune response and is neuroprotective. We only have experience with one patient receiving hypothermia after a cardiac arrest.
HD 0-16	Sepsis syndrome			The rabies immune response is associated with increased CRP, WBC with left shift and high platelets. Empirical use of antibiotics should be restricted to 3 days.
HD 0-16	Low risk of nosocomial transmission	Isolation		There has never been a laboratory-confirmed case of human to human rabies transmission (other than by corneal or solid organ transplantation) during medical

				care or autopsy. Blood and urine cannot transmit rabies. Patients can be removed from isolation when saliva is negative by PCR on 3 occasions in the presence of neutralizing antibody > 0.5 IU/ml by RFFIT, FAVN or other test for neutralizing antibodies
HD 4	Salt-wasting syndrome on HD 5	Begin fludrocortisone 100 mcg child or 200 mcg adult or other mineralocorticoid; use lactate or normal saline fluids Minimize vasopressors and diuretics; use fluids to maintain blood pressure For hyponatremia, enteric sodium (23%; 1 g in 5 ml water) is more efficacious than 3% IV hypertonic saline	Daily serum sodium and glucose Consider BNP or NT-pro-BNP monitoring Consider serum uric acid and urinary sodium Serum and CSF neutralizing antibody (HD4)	*Avoidance of hyponatremia appears to prevent vasospasm in human rabies. [See HD 6-8]* A physiological dose of hydrocortisone (1X dosing) may be used if no pure mineralocorticoid: 15 mg/day divided Q8-12h in aduls; 8 mg/m2/day divided Q8h in children. HC risks immunosuppression at higher doses. Central venous pressure appears inaccurate in rabies. Monitoring inferior vena cava collapse by bedside ultrasound is preferred. Rabies is associated with tetrahydrobiopterin (BH_4) deficiency that causes adrenaline deficiency as well as nitric oxide (NO) deficiency. Vasopressor agonism is not opposed by NO dilation, leading to profound ileus.
HD 4	Neuroprotection during rabies	Begin low-dose insulin infusion (0.5 U/h regular insulin in adults; 0.005 U/kg/h in children) and gastric or jejunal feeds. Amantadine, Vitamin C (500 mg) and vitamin B complex are recommended.	Daily serum glucose and glucose Urine dipsticks for ketones, daily	This is NOT tight glucose control, rather prevention of catabolism. Reduce but maintain some insulin before hypoglycemia occurs. Complications in rabies are associated with CSF markers of gluconeogenesis and ketogenesis. Promotion of anabolism (with adequate caloric intake) appears to improve survival curves by about one week. Insulin may minimize toxic alcohol metabolites and lactic acidosis associated with benzodiazepine sedatives. Amantadine (alone with ketamine and midazolam) were part of the original successful protocol. There is biochemical evidence for high quinolinic acid in CSF during rabies (excitotoxicity). Ketamine, midazolam and amantadine are neuroprotectants.

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				Vitamin C recycles BH_2 to BH_4. B vitamins may minimize demyelination.
HD 4	Thrombosis of cerebral veins or sinuses	DVT prophylaxis		
HD 6-8	Generalized intracranial vasospasm leading to coma	(fludrocortisone and Na > 140 meq/L)	Optional transcranial doppler ultrasound (needs baseline study)	Prophylaxis for vasospasm can also be considered using (a) sapropterin (5 mg/kg/day), vitamin C (500 mg) and 0.5 g/kg/day of arginine or citrulline, or (b) nimodipine at ½ to 1/3 the standard dose x 14 days. Vasospasm is associated with onset of coma and mild dysautonomia and pupillary changes. This is evident by transcranial doppler ultrasound and lasts about 1 day, then resolves. Vasospasm is followed by a gradual increase in intracranial pressure and changes in metabolism (see insulin- above). TCDs are often normal in patients who appear brain-dead by exam.
HD 7	Survival is associated with detection of neutralizing antibody by HD 7		<u>Key test timing:</u> Serum and CSF for rabies neutralizing antibody (HD 7)	Lack of detection of neutralizing antibody in CSF by HD 7 indicates medical futility of further care unless you are using an antiviral or other biological. This lab test is essential to unnecessary prolongation of medical care.
HD 8	Risk of cardiac arrest abates (unless you use favipiravir or other biological)	Rapidly taper sedation		There is generally a “honeymoon” of medical stability between HD 8-12 that may be useful for tracheostomy and use of diuretics.
HD 10	Total paralysis by HD 10		Serum and CSF for rabies neutralizing antibody (HD10)	Paralysis reverses (distal to proximal) with virus clearance and often includes orofacial dyskinesias (myokymia) during progression and recovery. These are not seizures.
HD 12-15	Severe generalized intracranial vasospasm; diabetes insipidus		Optional transcranial doppler ultrasound (needs baseline study)	In the absence of neutralizing antibody, the patient develops dysautonomia, drop in intracranial pressure and blood flow (high resistance), with flattening of EEG and pupillary dilation, followed in 24 hours by diabetes insipidus.
HD 15 -21	Medical futility vs recovery		Criteria for futility (HD >10): diabetes insipidus, isoelectric EEG, CSF lactate > 4	Following “type II” vasospasm, low resistance, chaotic blood flow then supervenes leading to cerebral edema and death. There is no recovery. *Virology studies should ALWAYS be completed even if the patient dies. This allows retrospective*

			mM, CSF protein > 250 mg/dL	*interpretation of care decisions and the opportunity to detect new complications and improve future care.* In the presence of CSF neutralizing antibody (>0.3 IU/ml in our experience), the patient regains pupillary activity, cough and diaphragmatic activity, and re-innervates distal to proximal motor reflexes, then function. Sensation and vestibular function lag. Myokimia re-appears. Dysautonomia occurs with cares and must be tolerated. There are a few days of profuse sialorrhea, bronchial and gastric secretions. There is a subtle SIADH. A few patients develop profound cachexia before recovering. The patients do not regulate temperature well and heart rate (and blood pressure) varies by body temperature; the patients require bundling.
Autopsy				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. 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.

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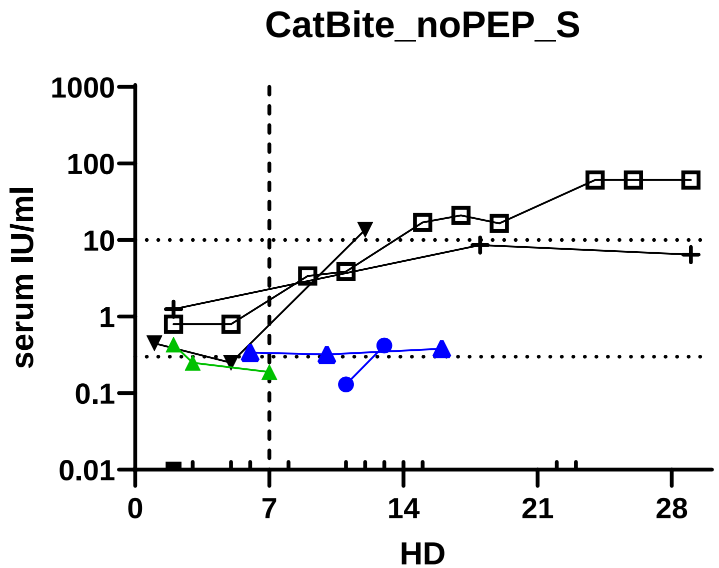
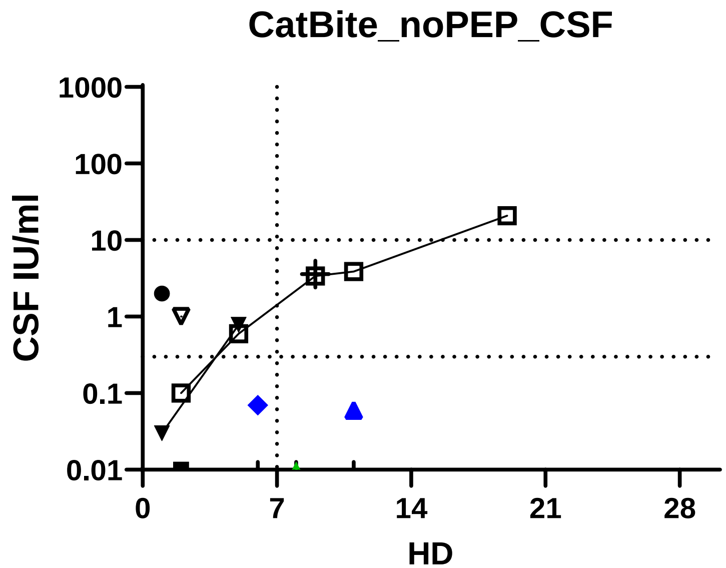
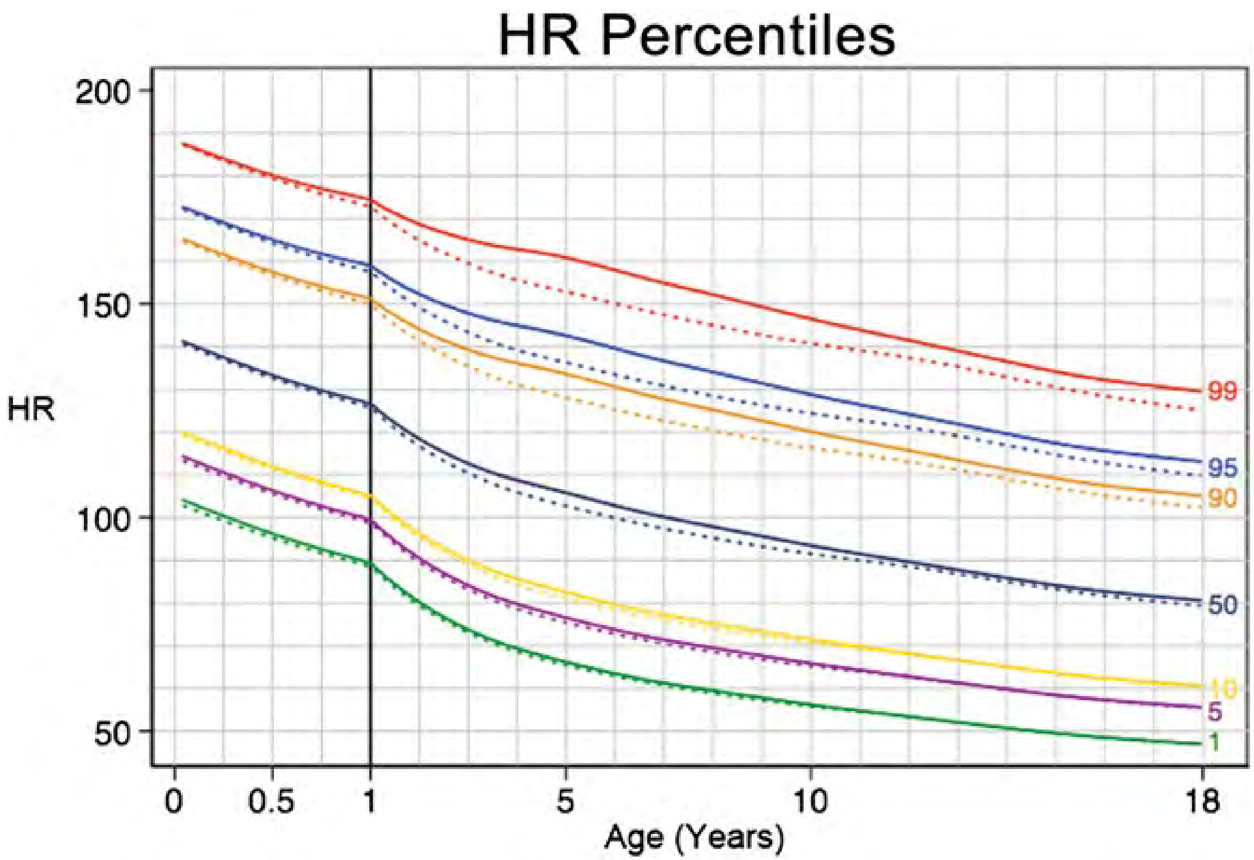
Figure 1. Immune response to cat-transmitted rabies without immunomodulation (vaccine, RIG, immunocompromise) in serum and CSF in our series and the literature. For comparison, two ungulate-transmitted rabies (blue) and one dog-transmitted rabies, presumed from an insectivorous bat (green), are shown. In serum, 3 of 5 (60%) were detected by 7 days. In CSF, 4 of 7 (56%) were detected by 7 days. Horizontal lines show antibody titers associated with survival and good neurological outcome. There were 2 of 7 (29%) survivors.





APPENDIX

Heart rate norms. 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.



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Blood pressure norms (adults)

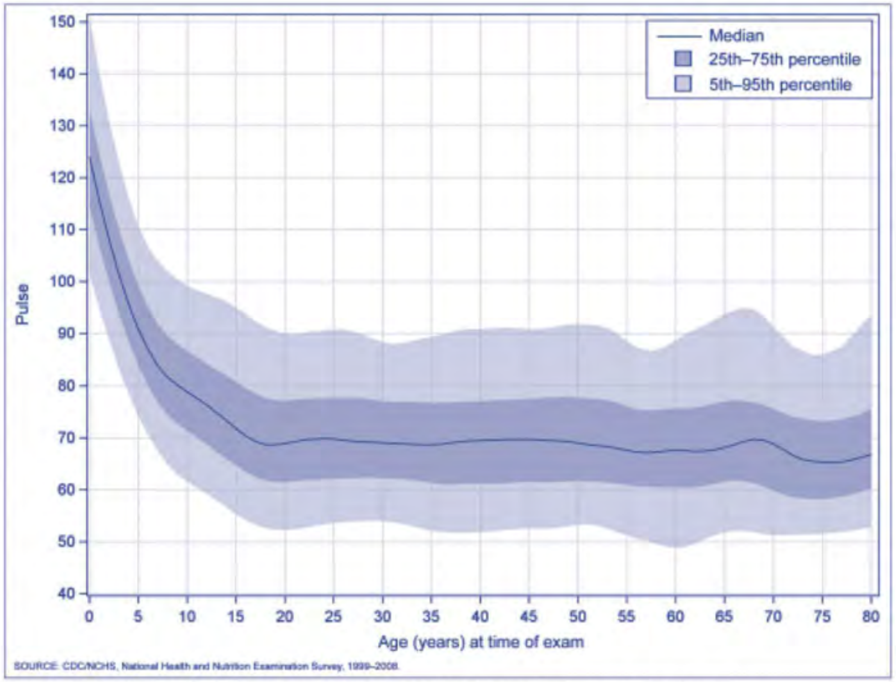

Figure 1. Resting pulse rates for U.S. males, by age: National Health and Nutrition Examination Survey, 1999–2008

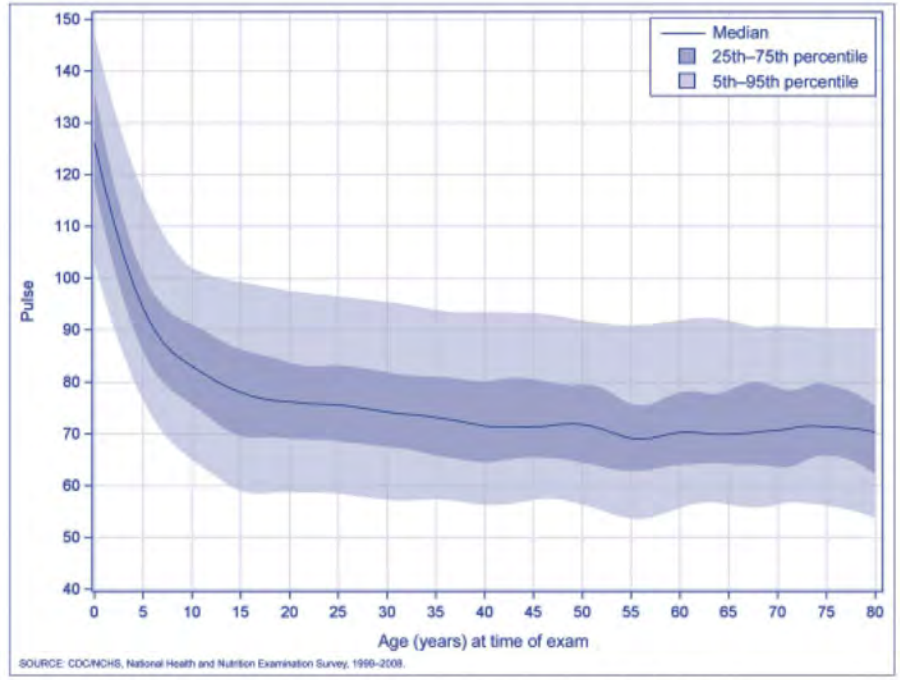

Figure 2. Resting pulse rates for females, by age: National Health and Nutrition Examination Survey, 1999–2008

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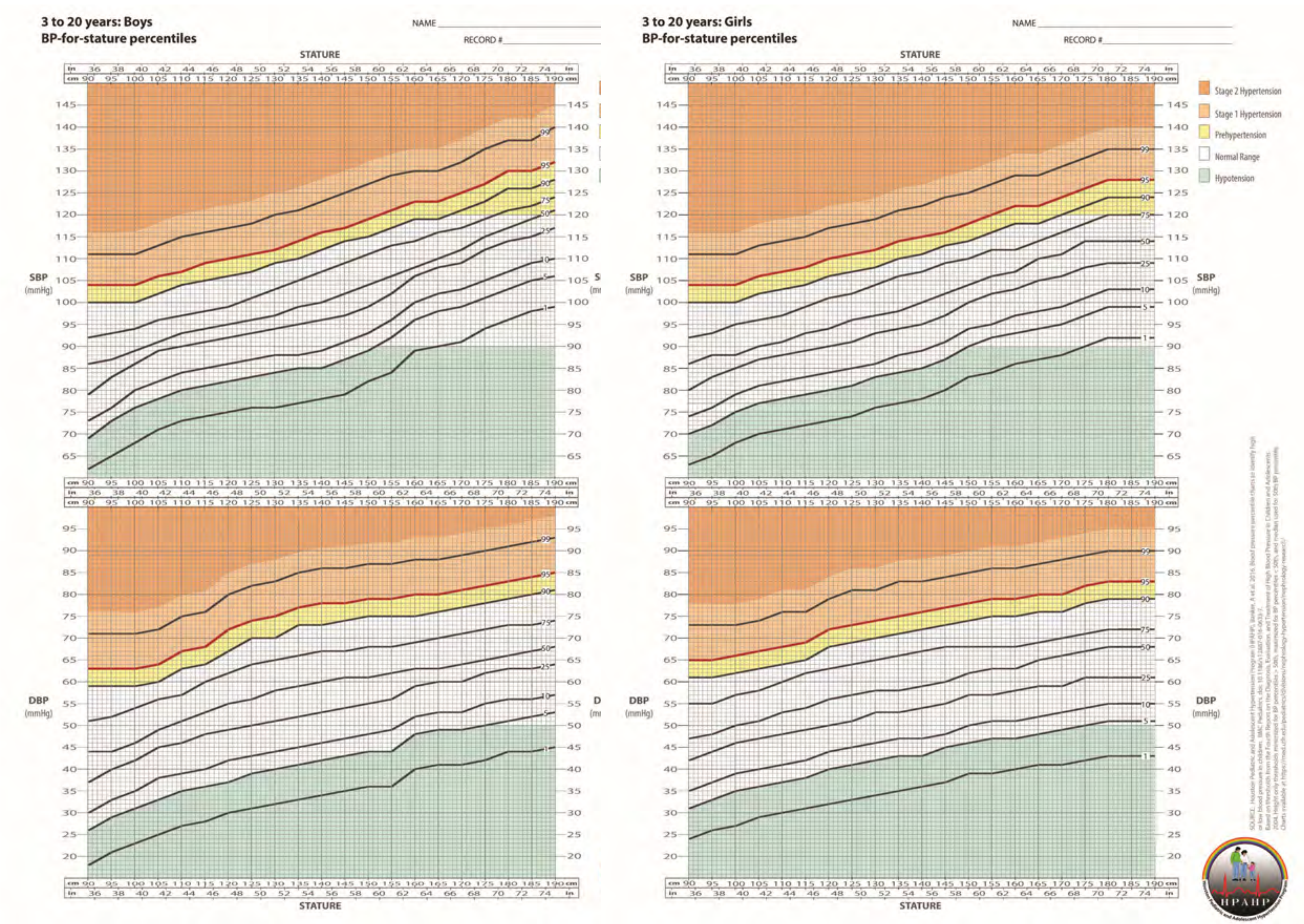
Blood pressue norms (child)



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Optic nerve sheath diameter norms (adult)

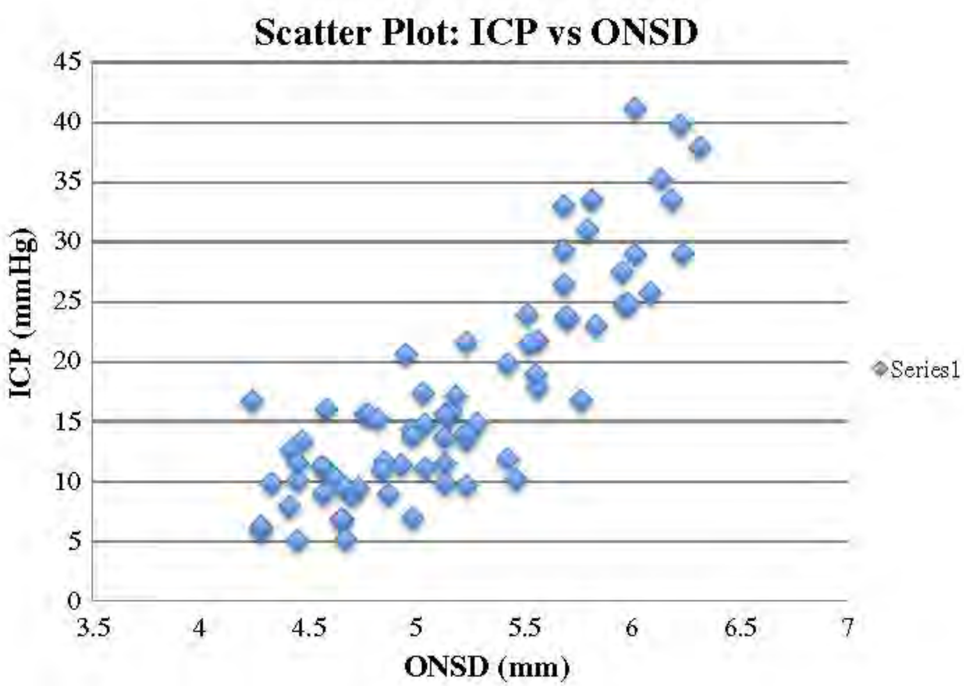

Fig. 1. Scatter Plot 1: ICP vs ONSD. Scatter plot of 75 measurements of ICP in the X axis against the ONSD value in the Y axis. Generally this scatter plot shows a linear relationship. However towards the extreme end of ICP value, the ONSD value started to reach a plateau phase. This is due to maximal 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.

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Optic nerve sheath diameter norms (child)

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

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Transcranial doppler ultrasound norms (child): mean flow (time-averaged mean max) and resistive index, middle cerebral artery

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.

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

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Transcranial doppler ultrasound norms (adult)

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 ± 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 ± 0.16	0.80 ± 0.14	0.85 ± 0.16	1.02 ± 0.18
RI	0.56 ± 0.07	0.53 ± 0.05	0.56 ± 0.07	0.62 ± 0.06
MCA				
PI	0.86 ± 0.15	0.83 ± 0.14	0.82 ± 0.13	0.96 ± 0.17
RI	0.56 ± 0.06	0.54 ± 0.05	0.55 ± 0.05	0.60 ± 0.06
PCA				
PI	0.81 ± 0.15	0.76 ± 0.12	0.79 ± 0.12	0.94 ± 0.16
RI	0.54 ± 0.07	0.52 ± 0.06	0.53 ± 0.05	0.60 ± 0.09

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

[a]Mean ± 2 SD.