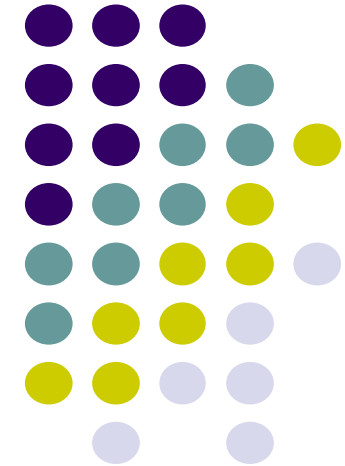
Refractory Malignant Hypertension: Therapeutic Options



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46th Pediatric Nephrology Seminar: New Advances and Old Controversies

Disclosures:

I have no actual or potential conflict of interest in relation to this program/presentation.

Scope

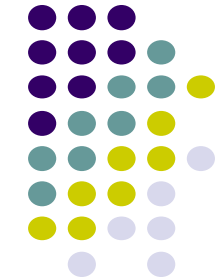
1. Definition of malignant hypertension or hypertensive emergency
2. Recognition the symptoms and signs of hypertensive emergency
3. Approach patients with hypertensive emergency management
4. Know the common cause of uncontrolled hypertension (resistant hypertension)

Updated Definition of Childhood HTN

	Age 1-13 yo	Age ≥ 13 yo
Normal	<90th %tile	BP <120/<80 mmHg
Elevated BP	90th to <95th %ile	BP 120-129/<80mmHg
Stage 1 HTN	95th to <(95th %ile +12mmHg)	BP 130-139/80-89 mmHg
Stage 2 HTN	≥ (95th %ile + 12 mmHg)	BP ≥ 140/90 mmHg

Pediatrics 2017

Malignant Hypertension VS HTN Emergency / HTN Crisis



- Malignant/Accelerated hypertension: Severe HTN associated with bilateral retinal hemorrhages and/or exudates +/- papilledema
- HTN Crisis: Severe HTN that can cause life threatening and a rapid end-organ damage
  - Includes acute encephalopathy, acute retinopathy, acute kidney injury, congestive heart failure or pulmonary edema
  - In adult: BP $\geq$ 180/120 mmHg
  - In children: not clear defined
  - The 2017 CPG statement: "Physician should be concerned about the complications when children's BP $\geq$ 30 mmHg above the 95th percentile.

HTN Crisis

- Symptoms are not related with level of BP but rather the rate of increased BP that may cause end organ damage.

- Some cases may develop complications at lower levels of BP
  - Patients at risk of bleeding
  - Patients at risk of neurological complication

HTN Crisis

HTN Emergency

- Associated with end-organ damage.

HTN Urgency

- No demonstrable end-organ damage,

Etiology

- Generally, HTN crisis in the pediatric patients are often attributed to secondary causes of HTN, specifically to renal causes

- HTN crisis may be more common in ESRD (volume-related, uremic toxin, hyperPTH) and post renal transplant (vascular disease, obstruction, calcineurin toxicity, TMA)

Pathogenesis

- Depends upon the nature of underlying condition
- Initial stimulus → elevated BP

  → activation of RAS/ oxidative stress/endothelial dysfunction
- Result in protein fragmentation formation (neoantigens)

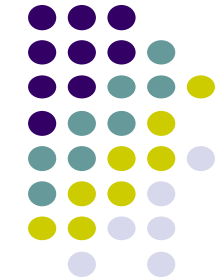
  → T cell activation → inflammatory cells and cytokines

  → Causing vasoconstriction, Na/H2O retention → worsen HTN
- Vasoconstriction and pressure natriuresis lead to volume depletion

  → + feedback to the RAS

  → causing the vicious cycle of increased vasoconstriction, oxidative stress, inflammation and progressive cytotoxic effects on vascular wall and endothelial damage and tissue ischemia

Clinical presentation



- Wide spectrum of presentation despite similarly degree of high BP
- No/mild symptoms
  - headache, nausea vomiting (HTN Urgency)
- Severe life threatening (HTN emergency)
  - CNS – HTN encephalopathy, cerebral infarction/hemorrhage
  - Ophthalmology: bilateral retinal hemorrhage, papilledema
  - Kidney: AKI, TMA
  - Cardiopulmonary system: acute heart failure, and pulmonary edema

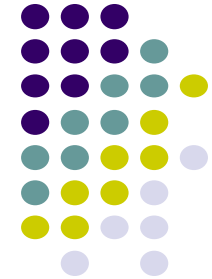
Evaluation

- Recognition of HTN urgency and emergency
- Evaluation of end-organ damage to guide initial management
- Quick evaluation to determine possible cause of HTN
- Immediate treatment, especially in cases of HTN with end organ damage should be started.

Evaluation for HTN: History

History	Diagnosis
Hematuria, edema	Acute or chronic GN
Recurrent UTI	Reflux nephropathy
Short stature, anemia	Chronic renal failure
Obesity, acne	Cushing syndrome
Palpitation, weight loss	Pheochromocytoma, hyperthyroidism
Medication use	Medication-induced

Evaluation for HTN: PE



- Edema → AGN, CKD
- Poor growth, anemia →CKD
- Leg <arm BP, femoral pulse →Coarctation of aorta
- Tachycardia/sweating →Hyperthyroid, CATs producing tumor
- Abdominal mass →Wilms tumor, neuroblastoma, ARPKD
- Frank bruit, café-au-lait spots→ RAS
- Ambiguous genitalia, virilization→ CAH

Evaluation f HTN

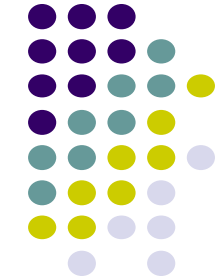
Blood and Urine tests

- CBC
- Renal function, electrolytes
- Plasma renin activity, cortisol, thyroid function
- Fractionated plasma metanephrines
- Pregnancy test (female)
- Urinalysis, urine protein, creatinine
- Urine toxicology screening

Radiology/Consultation

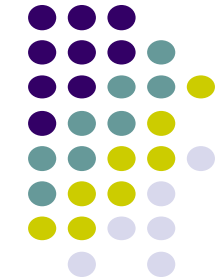
- Renal US with Doppler
- CXR (pulmonary symptoms)
- Echocardiogram
- Head CT / MRI (if encephalopathy)
- CTA/MRA if suspected RAS
- Fundoscopic examination

Hypertensive Emergencies



- Need IV short acting medication and titrate to response
- Slowly decrease BP no more than 25% of initial BP in the first 2-8 hours
  - A more rapid reduction may lead to cerebral hypoperfusion to infarction
- Slowly reduction not to achieve 95th percentile until 24-48 hour.

Management HTN crisis in specific settings



- Acute glomerulonephritis: Diuretics
- Acute kidney injury: Loop diuretics/UF if needed
  Fenoldopam
- Renal artery stenosis: ACEI/ARB, beta blockers (BB)
- Pheochromocytoma: Phentolamine, then BB and CCI
- Coarctation of aorta: Esmolol

Drug	Route	Dose	Onset of action	Side effects, comments
Diazoxide	Intravenous bolus	1–3 mg/kg every 5–15 min	Within minutes	Risk of hypotension in large doses
Hydralazine	Intravenous bolus	0.2–0.6 mg/kg	5–20 min	Reflex tachycardia, headache, fluid retention
Minoxidil	Orally	0.1–0.2 mg/kg per dose	5–10 min	Fluid retention
Nitroglycerine	Intravenous infusion	0.1–2 μg/kg per min	1–2 min	Methemoglobinemia, vasodilating effect primarily on the venous side—efficient in heart failure, limited efficacy in children
Nitroprusside	Intravenous infusion	0.5–8 μg/kg per min	Within seconds	Thiocyanate toxicity, inactivated by light
Phentolamine	Intravenous bolus	0.1–5 mg/kg	1–2 min	Tachycardia. Used only in pheochromocytoma
Phenoxybenzamine	Orally	0.2–1.2 mg/kg, daily	Several hours	Tachycardia. Used only in pheochromocytoma
Doxazosin	Orally	1–2 mg per dose, daily	2–6 h	Orthostatic hypotension, dizziness
Prazosin	Orally	0.02–0.04 mg/kg, three times daily	30–90 min	Dizziness, headache
Esmolol	Intravenous infusion	100–500 μg/kg per min	Within seconds	Contraindication in asthma, may cause bradycardia
Labetalol	Intravenous infusion	0.25–3 mg/kg per hour	5–10 min	Contraindication in asthma, heart failure, bradycardia
Urapidil	Intravenous infusion	Initial dose 0.5–4.0 mg/kg per hour Maintenance dose 0.2–2.0 mg/kg per hour	1–5 min	May cause sedation, palpitation, nausea
Clonidine	Intravenous bolus	2–6 μg/kg per dose	Within 10 min	Dry mouth, sedation, rebound hypertension
	Orally	2–10 μg/kg per dose every 6–8 h	2–4 h	Dry mouth, sedation, rebound hypertension
Enalaprilat	Intravenous bolus	0.005–0.01 mg/kg per dose	15 min	Contraindication in suspected bilateral renal artery stenosis
Captopril	Orally	0.1–0.2 mg/kg per dose 0.01–0.1 in neonates	10–20 min	Contraindication in suspected bilateral renal artery stenosis
Clevidipine	Intravenous infusion	1–7 μg/kg per min	Within 5 min	Reflex tachycardia
Isradipine (L-type of CCB)	Orally	0.05–0.1 mg/kg per dose	1 h	Higher doses may cause BP drop of > 25%
Nicardipine	Intravenous infusion	1–3 μg/kg per min	Within minutes	Reflex tachycardia
Nifedipine	Orally or sublingually	0.25 mg/kg per dose	20–30 min	May cause unpredictable hypotension, reflex tachycardia
Furosemide	Intravenous bolus	0.5–5 mg/kg per dose	Within minutes	Hypokalemia. Useful in volume hypertension
Fenoldopam	Intravenous infusion	0.2–0.8 μg/kg per min	Within 5 min	Tachycardia, flushing, headache

Case 1

- A 10 year old male presents with acute abdomen and found to have BP 140/90 mmHg
- He was finally diagnosed with acute appendicitis and appendectomy was performed.
- Postoperative he still had elevated BP 125-140/85-90 mmHg. Wt 70 kg, Ht 160 cm. (P90), unremarkable otherwise

- What will you do next?

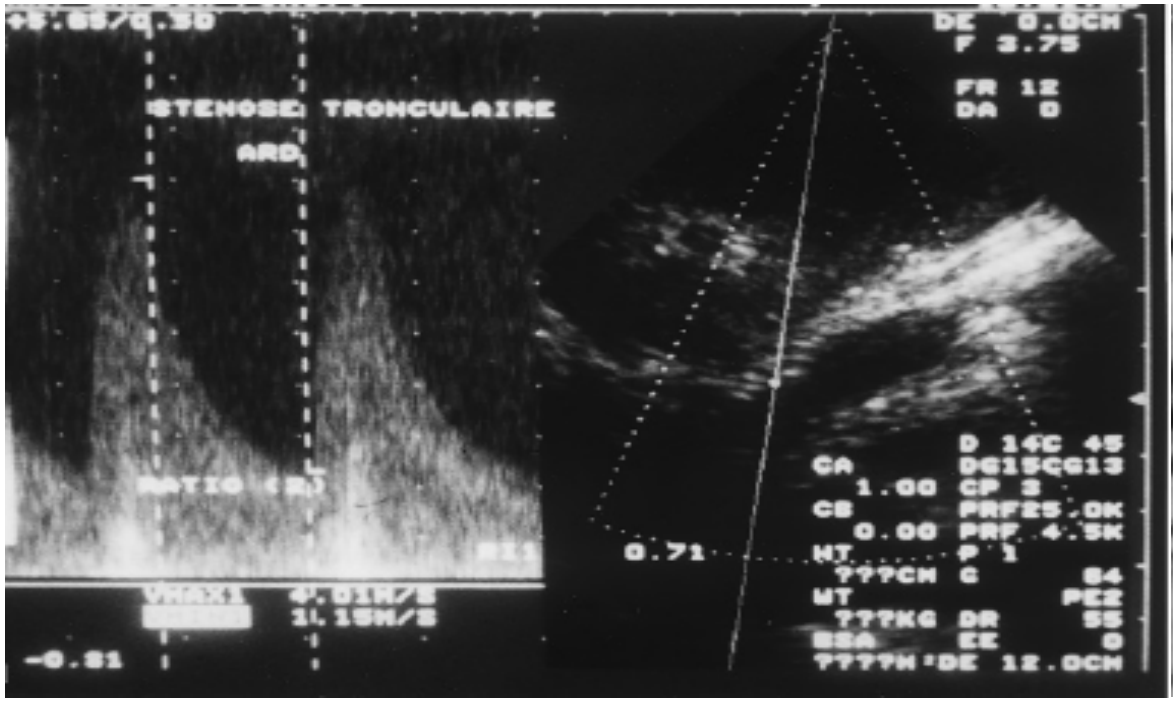
Case 2

- 11 year old female presented with severe headache and respiratory distress
- BP 160/90 mmHg, P 112/min, R 24/min,
- 4 extremities BP: 160/90 | 165/95
  170/100 | 170/100
- No edema, normal heart, lungs, no abdominal mass nor bruit
- What will you do next?

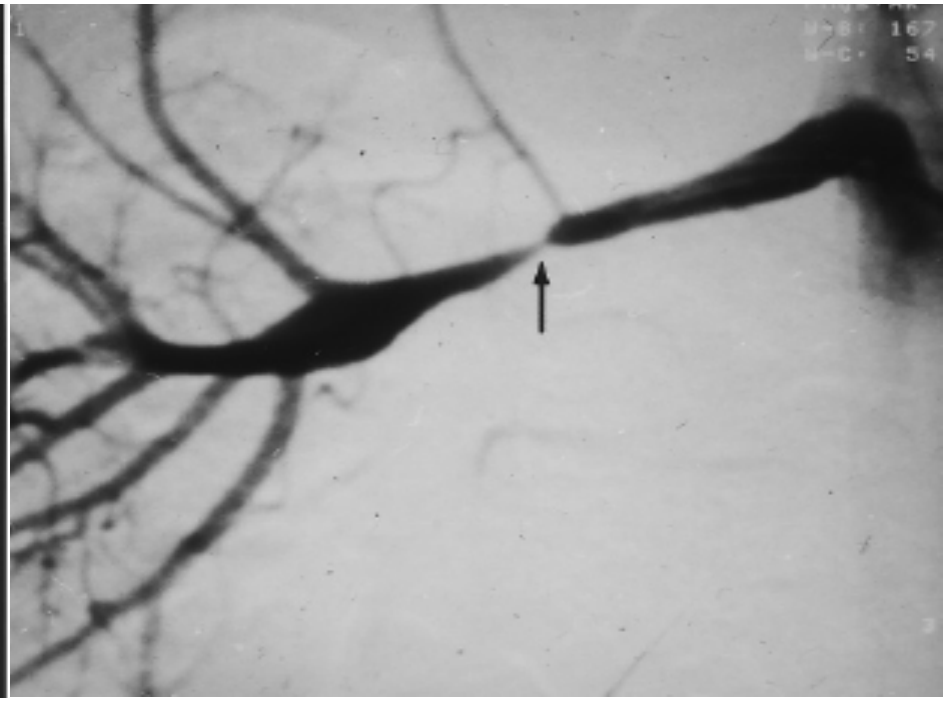
Case 2

- UA: no protein, blood, pyuria
- Normal CBC, BUN, Cr, electrolytes
- EKG, Echocardiogram: Concentric LVH
- Eye exam: narrowing of arteriole

Renal Artery Stenosis

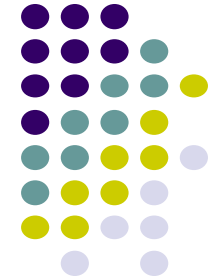


Doppler U/S: high peak velocity right renal artery



Stenosis of right main renal artery

Renovascular hypertension: Treatment



- Interventional balloon angioplasty
- ACEI provides the best control, but prolonged use lead to loss of function in the affected kidney
- Some patients with bilateral RAS may develop acute renal failure at the onset of ACEI .
- In the late phase, HTN persists despite removal of the stenosis or ischemic injury due to damage to the contralateral kidney.

Case 2 Management

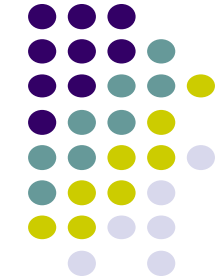
- D1 : labetalol, captopril

  BP 150/90 →130/70 mmHg
- D5 : labetalol, enalapril

  BP 110/70 - 120/80 mmHg
- Post balloon angioplasty :

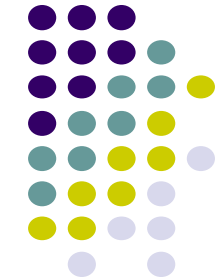
  BP 110/70 - 120/80 mmHg
- Taper enalapril, labetalol in 3 months

Resistant HTN



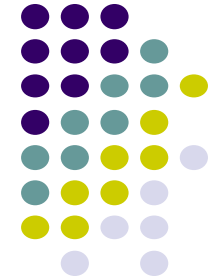
- Resistant hypertension: HTN not controlled with at least 3 antihypertensives medications
  - RAS blockers/Calcium channel blockers/Diuretics

Causes of Resistant Hypertension



- Noncompliance with regimen
- Inaccurate blood pressure measurement
- White coat hypertension (consider ABPM)
- Incorrect diagnosis/progression of disease
- Treatment program not optimized eg Thiazide diuretics are ineffective at GFR<30 – use loop diuretics instead
- Co-morbid condition eg anxiety, chronic pain, drug abuse

New/Experimental Therapies



- Renal nerve denervation
- Stimulation of carotid sinus baroreceptors
- Central arteriovenous anastomosis

Conclusions

- Malignant hypertension / hypertensive crisis is not common, but it is a potentially life threatening condition.
- Symptoms are not related to the level of BP, but rather the rate of increased BP and underlying disease
- Early recognition and management can prevent/minimize end organ damage.


THANK YOU