Refractory Malignant Hypertension: Therapeutic Options

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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

<table>
<thead>
<tr>
<th></th>
<th>Age 1-13 yo</th>
<th>Age ≥ 13 yo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;90th %tile</td>
<td>BP &lt;120/&lt;80 mmHg</td>
</tr>
<tr>
<td>Elevated BP</td>
<td>90th to &lt;95th %ile</td>
<td>BP 120-129/&lt;80 mmHg</td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>95th to &lt;(95th %ile +12mmHg)</td>
<td>BP 130-139/80-89 mmHg</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>≥ (95th %ile + 12 mmHg)</td>
<td>BP ≥ 140/90 mmHg</td>
</tr>
</tbody>
</table>

*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 ≥ 180/120 mmHg
  - In children: not clear defined
  - The 2017 CPG statement: "Physician should be concerned about the complications when children’s BP ≥ 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 $\rightarrow$ elevated BP
  $\rightarrow$ activation of RAS/ oxidative stress/endothelial dysfunction
- Result in protein fragmentation formation (neoantigens)
  $\rightarrow$ T cell activation $\rightarrow$ inflammatory cells and cytokines
  $\rightarrow$ Causing vasoconstriction, Na/H2O retention $\rightarrow$ worsen HTN
- Vasoconstriction and pressure natriuresis lead to volume depletion
  $\rightarrow$ + feedback to the RAS
  $\rightarrow$ 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

<table>
<thead>
<tr>
<th>History</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria, edema</td>
<td>Acute or chronic GN</td>
</tr>
<tr>
<td>Recurrent UTI</td>
<td>Reflux nephropathy</td>
</tr>
<tr>
<td>Short stature, anemia</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Obesity, acne</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Palpitation, weight loss</td>
<td>Pheochromocytoma, hyperthyroidism</td>
</tr>
<tr>
<td>Medication use</td>
<td>Medication-induced</td>
</tr>
</tbody>
</table>
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 of 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 95\textsuperscript{th} percentile until 24-48 hour.
Management HTN crisis in specific settings

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