Case 1

- A 28 yo B M presents with acute low back pain following weekend basketball game.
- Has no other complaints; states he was told of HBP during college sports Px but never followed up on this.
- You treat the acute low back pain and ask the patient to return for a more thorough evaluation of CV status.
- BP: 148/90 mm Hg (first reading)
  - 146/88 mm Hg (second reading - end exam)
  
  - Height: 6’0”; weight: 218 lb; BMI: 29.6 kg/m²
- BP on return visit when patient feels well is 150/92 and repeat is 148/90 mm Hg.
- Family Hx is significant for HBP in both parents.
- Laboratory findings: BUN 13 mg/dl creatinine 0.9 mg/dL;
  
  - Fasting glucose: 96 mg/dl
  - U/A 2+ prot, 0 heme
  - Cholesterol 170 mg/dL, LDL-C: 102 mg/dL, HDL 48 mg/dL, TG 100 mg/dL
  - CXray wnl, EKG borderline LVH.
Non-Hispanic White Non-Hispanic Black Mexican American

Hypertension* Prevalence (%) 18-39 40-59 ≥60

Women (age, years) 0 20 40 60 80 100

Hypertension* Prevalence (%) 18-39 40-59 ≥60

Men (age, years) 0 20 40 60 80 100

Note: Error bars indicate 95% confidence intervals. Data are weighted to the US population. Hypertension defined as a BP of ≥140/90 mm Hg or reported use of antihypertensives.

Adapted from Hajjar I, Kotchen TA. JAMA. 2003;290:199-206.

The Most Common Causes of ESRD


Case 1

- Lifestyle modifications alone may be sufficient for a 28 yo patient with mild hypertension and no other CV risk factors.
- If lifestyle modifications do not achieve goal BP within 3-6 months, pharmacologic therapy can be prescribed (speaker’s opinion)
- Excellent clinical trial outcome data prove that lowering BP with several classes of drugs, including ACEIs, ARBs, β-blockers, CCBs, and thiazide-type diuretics, will reduce the complications of hypertension

JNC 7: Lifestyle Modifications to Prevent and Manage Hypertension

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>5-20 mm Hg/10 kg</td>
</tr>
<tr>
<td>DASH diet</td>
<td>8-14 mm Hg</td>
</tr>
<tr>
<td>Sodium reduction</td>
<td>2-8 mm Hg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>4-9 mm Hg</td>
</tr>
<tr>
<td>Moderate alcohol consumption</td>
<td>2-4 mm Hg</td>
</tr>
</tbody>
</table>

DASH = Dietary Approaches to Stop Hypertension.
Chobanian AV et al. JNC 7: Complete Report. Available at: http://hyper.ahajournals.org/cgi/content/full/42/6/1206.

Walking the dog

Case 1

- Patient education is:
  - An integral component of successful management of hypertension
  - Critical to establish adherence to a treatment regimen
- Emphasize to patients that lifestyle modifications and medications not only lower BP numbers but also reduce the incidence of CV events

Chobanian AV et al. JNC 7: Complete Report. Available at: http://hyper.ahajournals.org/cgi/content/full/42/6/1206.
Pathology of hypertensive kidney disease (arterionephrosclerosis)

Clinical features of hypertensive arterionephrosclerosis

Most patients are asymptomatic
A minority develop chronic renal failure, with/without proteinuria

Arterionephrosclerosis:
Bilateral, small kidneys, granular surface

Hypertension and the kidney
Renal disease causes hypertension

Hypertension causes renal disease

Uniform thinning of cortex
Case 2:

- 60 yo BM with severe hypertension presents to ER with severe headache over last few weeks, and chest pain and SOB of 2 hrs duration.
- He is found in the ER to have a BP of 190/130 mm HG, P84, R 18/min, blurring of disc margins on eye exam, S4G, Rales at both bases, and no edema.
- Lab: BUN 38 mg/dl, creatinine 2.4 mg/dl, U/A 2+ prot, 2+ heme 10-15 rbc no casts. CXray cardiomegaly. EKG shows LVH + evidence of an acute inferior MI.
- BP is controlled with IV labetalol, he is given ASA and plavix, and of bare-metal cardiac stent is placed in his R coronary artery.
- Over next few days BP is controlled with a beta blocker, ACE inhibitor and diuretic. He feels much improved, but BUN and creatinine only change slightly.
- USG shows 10 cm echogenic kidneys.

Case 2

- What are the consequences of severe (accelerated, malignant) HBP?
- What is likely to happen to his kidney function if he stops his BP medications after hospital discharge?
- What is likely to happen to his kidney function if he stays on BP medications?
- How many BP medications will it take to control his hypertension?
- If this patient had died from his myocardial infarct, what would his kidneys likely show at autopsy?
**Many Patients in the US Are Not at JNC-Recommended BP Goals**

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Goal BP (mm Hg)</th>
<th>% Not at Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hypertensives</td>
<td>&lt;140/90</td>
<td>57% 26%</td>
</tr>
<tr>
<td>African American</td>
<td>&lt;140/90</td>
<td>60% 32%</td>
</tr>
<tr>
<td>Mexican American/Hispanic</td>
<td>&lt;140/90</td>
<td>63% 30%</td>
</tr>
<tr>
<td>Older patients (≥60 yr)</td>
<td>&lt;140/90</td>
<td>71% 9%</td>
</tr>
<tr>
<td>Symptomatic CHD</td>
<td>&lt;140/90</td>
<td>47% 4%</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>&lt;130/85</td>
<td>81% 24%</td>
</tr>
</tbody>
</table>


**Syst-Eur: Adjusted Relative Hazards for Active Therapy vs Placebo**

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>SBP (mm Hg)</th>
<th>Diabetic Patients (N=402)</th>
<th>Nondiabetic Patients (N=402)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality from CV causes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CV events</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac events</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment better</td>
<td>Treatment better</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo better</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted relative hazard</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.45</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p&lt;0.04</td>
<td>p&lt;0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.91</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.22</td>
<td>p&lt;0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.37</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.70</td>
<td>2.00</td>
</tr>
</tbody>
</table>

**MRFIT: Effect of Systolic BP and Diastolic BP on Age-Adjusted CHD Mortality**

<table>
<thead>
<tr>
<th>BP (mm Hg)</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHD death rate per 10,000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.69</td>
</tr>
</tbody>
</table>

**Summary of Studies on Nephropathy Progression**

<table>
<thead>
<tr>
<th>Study</th>
<th>SBP (mm Hg)</th>
<th>N = 18,790.</th>
<th>HOT = Hypertension Optimal Treatment.</th>
<th>No. at risk</th>
<th>Months of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan</td>
<td>130-134</td>
<td>138</td>
<td></td>
<td>579</td>
<td>0-64</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>142-146</td>
<td>150</td>
<td></td>
<td>565</td>
<td>0-64</td>
</tr>
<tr>
<td>Placebo</td>
<td>154</td>
<td>170-180</td>
<td></td>
<td>586</td>
<td>0-64</td>
</tr>
</tbody>
</table>

**IDNT: Renal Outcome End Point—Time to Doubling of Serum Creatinine, ESRD, or Death**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at risk</th>
<th>Months of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irbesartan</td>
<td>579</td>
<td>0-64</td>
</tr>
<tr>
<td>Amlodipine</td>
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</tr>
<tr>
<td>Placebo</td>
<td>586</td>
<td>0-64</td>
</tr>
</tbody>
</table>

Case 2: Pathology of malignant (accelerated) hypertension

Malignant nephrosclerosis

Normal size kidney*
Smooth surface*
Petechial Hemorrhages

(*Unless underlying essential HTN)
Severe endothelial injury leads to thrombotic microangiopathy

1. Acute renal failure
2. Microangiopathic anemia
3. Thrombocytopenia

Arteriole with fibrin thrombus

Schistocytes in hemolytic anemia
**Case 3**

- 68 yo WM retired construction worker transferred for eval vasculitis and ARF.
- Excellent health – golfer and bowler.
- 5/95 loss of appetite, fevers, temps to 102, rash on back, cough Adm Hosp
- Mild ↑ LFTs B13/Cr 1.1 WBC 2.9 Hc3 33, plts 49 K. CH50 borderline, C4 low No dx disch
- 2 days later readm for temps Hosp x 10 days Cr
- to 3.6 mg/dl, aDNA -, ANA + 1:400, ESR 68-145, U/A 2+ prot, 2+ heme, several rbc ? Rbc casts?
- Urinary protein 784 mg/d
- WBC 10.0, Hct 35%, plts 142,000 LFTs wnl

---

**Case 3**

- Transfer to CUMC Px WD,WN, NAD, BP 170/84, Cor-Chest neg, Abd 2 Fb L, no edema, no rash.
- BUN 97 mg/dl Creatinine 4.0 mg/dl Palb 3.5, ALT 60 other LFTs nl
- WBC 11.2K Hct 37% plts 114 K , Pt 14 PTT 49 U/A 1+ prot +rbc no casts ANA + 1: 40 Hep B,C neg, ANCA – , CH50 and C3 nl, C4 low cryos neg,
Case 3

- What other tests should be done?
- Will a biopsy influence therapy here?
- What is a renal biopsy likely to show?
- What treatment options are available and what do we expect for outcome?
Case 3: Antiphospholipid antibody syndrome

Pathologic findings

Glomeruli show ischemic changes (global wrinkling of glomerular basement membranes, tuft retraction, and cystic dilation of Bowman’s space)
Glomeruli show segmental intracapillary fibrin.

Arteries show widespread luminal narrowing with extensive subendothelial hyalinosis, endothelial swelling, focal myocyte dropout, focal mucoid intimal fibroplasia, and focal intramural fibrin with entrapped red blood cells.

Recanalized artery (healed thrombus).
Case 4

- A 4 yo girl presents with diarrhea and acute renal failure.
- Pt was in good health until 3 days PTA when went to neighbor’s Bar-B-Q and had a hamburger. Over 24 hrs developed abdominal cramps, N/V, and bloody diarrhea. He became lethargic took in less fluids and his parents brought him to ER.
- BP 70/45 mm Hg, P130 /min, T 101, R22/min Cor-
-Chest -, Abd diffuse mild tender , no rebound, increased BS, ext- no edema, + petechiae on legs.
- WBC 12.2K, Hct 28%, plts 52K, smear with schistocytes.
- BUN 45 mg/dl, creatinine 3.1 mg/dl.
- U/A 2+ prot. 3+ heme, +rbc TNTC, + rbc casts.

Renal disease is progressive and creatinine increases to 6 mg/dl leading to institution of dialysis.

Would you do a biopsy?

If yes what would it show?

What is the diagnosis here?

How else could you make the diagnosis?

Childhood HUS
- STx Associated
- 2.1 per 100,000 /yr peak < 5 yo
- Warm summer months
- Onset GI sx, cramps, diarrhea, n/v, fever
- 70% bloody diarrhea w/i 2 days
- E.coli 0157 3-7%sporadic, 20%epidemic
- STx – E coli in stool for wks

Role of Shiga Toxin
- Epidemics with hemorrhagic colitis +/- HUS
- Epidemics in fast food outlets
  E. coli 0157:H7
- Sporadic HUS same
- A filterable agent in stool causes Hem. Colitis & cytopathic to green monkey kidney cells (verotoxin)
  E. Coli 0157:H7 produce both STX1 and STX2
- Transmission of E. Coli - STX
  E. coli in cattle (& other animals) – manure, water troughs, farms
  Transmit by food or water
  Usually beef contaminated at slaughter
  Also raw milk, fruit & veg, apple cider, apple juice
  Person to person – day care centers
Case 4: E.coli-associated HUS

Pathologic findings

- Fibrin thrombi in TMA
- Thrombi in glomerular capillaries
- Cortical necrosis
- Colon: hemorrhagic necrosis
- Shigatoxin-1 and Endothelium
  - Binds to Gb3 on glomerular endothelium
  - Gb3 expression equal in children vs. adults
  - Mechanism for childhood susceptibility remains undetermined

Ergonul, Clayton, Fogo, Kohan, 2003
Verotoxin

- A subunit binds 60S ribosomes, inhibit protein synthesis
- 5 B subunits binds glycolipid receptors (gb3) on surface of colonic epithelium, endothelium, and WBCs

Course ARF Childhood HUS

- 50% dialysis
- 75% transfusions
- 25% Neuro sx (CVA, sz, coma)
- 3-5% die in acute phase
- Long term renal dysfunction common

Shiga Toxin and Cell Injury

Residual Renal Disease in Childhood HUS

- 3-18% ESRD
- 10-40% low GFR, proteinuria, CRF, HBP
- Duration anuria predicts dysfunction
  - 7.5% anuria < 10 days low GFR
  - 42.5% anuria > 16 days low GFR

Higher Risk HUS

- Antibiotics
- Bloody diarrhea
- Fever, vomiting
- Leukocytosis
- < 5 yo
- females
Thrombotic thrombocytopenic purpura (TTP)

- Familial or acquired
- Single episode, or relapsing
- F:M 3:2
- Peak in 3rd decade
- CNS, other extrarenal signs often predominate (e.g. fever; purpura; heart failure; lung edema; elevated LDH)
- Acute renal failure; microangiopathic hemolytic anemia; thrombocytopenia

**ADAMTS13**

- A disintegrin and metalloprotease, with TSP-1-like domains (aka vWF-clearing protease)
- Protease, normally degrades vWF multimers
- Deficiency → platelets GPIIb ↔ vWF multimers
- Mutations or autoAb

**Definition of TTP Based on ADAMTS13 Deficiency**

- Low ADAMTS13 activity
- Evidence of biological effects of low ADAMTS13 activity
  - ↓ proteolysis of VWF (ultra-large multimers)
- Causes
  - Genetic mutations of ADAMTS13
  - Inhibitors of ADAMTS13
  - Others?
- Propensity to microvascular thrombosis, presenting with:
  - VWF-rich thrombi in arterioles and capillaries
  - Thrombocytopenia
  - Microangiopathic hemolysis
  - Dysfunction of organs