Case 1

- A 28 yo AA M presents with acute low back pain following weekend basketball game.
- Has no other complaints; states he was told of HBP during college sports but never followed up.
- BP: 148/90 mm Hg (first reading)
  - 146/88 mm Hg (second reading - end exam)
- Height: 6'0''; weight: 218 lb
- You treat the acute low back pain and ask the patient to return.
- BP on return when he feels well is from 150/92 to 148/90 mm Hg.
- Family history significant for HBP in both parents.
- Laboratory: BUN 13 mg/dl, creatinine 0.9 mg/dl; Fasting glucose: 96 mg/dl.
  - UA 2+ prot; O hematoxyline
  - CXR normal, EKG borderline LVH.

Hypertension Affects Approximately 65 Million Americans: 28% of

<table>
<thead>
<tr>
<th>Adults</th>
<th>Non-Hispanic White</th>
<th>Non-Hispanic Black</th>
<th>Mexican American</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population With Hypertension (%)</td>
<td>27%</td>
<td>38%</td>
<td>29%</td>
</tr>
</tbody>
</table>


Prevalence of Hypertension Increases With Age: NHANES 1999-2000 Data

1 in 3 have high blood pressure, study finds

USA TODAY

Heart attack, stroke risk rises

Error bars indicate 95% confidence intervals. Data are weighted to the US population. Adapted from Hajjar I, Kotchen TA. JAMA. 2003;290:199-206.
### 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://jama.ahajournals.org/cgi/content/full/42/6/1206](http://jama.ahajournals.org/cgi/content/full/42/6/1206).

### Case 1

- Lifestyle modifications alone may be sufficient for a 28 yo patient with mild hypertension and no other CV risk factors.
- If do not achieve goal BP within 3-6 months, pharmacologic therapy can be prescribed.
- Excellent 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.
- WHAT IS HAPPENING IN THE
Case 1

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- WHAT IS HAPPENING IN THE KIDNEYS?

Pathology of hypertensive kidney disease (arterionephrosclerosis)

Hypertension and the kidney

Renal disease causes hypertension

Hypertension causes renal disease

Clinical features of hypertensive arterioneerphrosclerosis

Most patients are asymptomatic

A minority develop chronic renal failure, with/without proteinuria
Arterionephrosclerosis:
Bilateral, small kidneys, granular surface

Arterionephrosclerosis

- Arteriolosclerosis/hyalinosis
- Segmental and global glomerulosclerosis
- Patchy tubular atrophy and interstitial fibrosis

Arterionephrosclerosis

- Arteriolar sclerosis and hyalinosis: Insudated plasma proteins and degenerating medial myocytes

Case 2:
- 60 yo AA M with Hypertension presents to ER with severe head aches over few weeks, and chest pain and SOB of 2 hrs duration.
- He has a BP of 190/130 mm HG, P84, R18/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

NHANES (1999-2000)

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Goal BP Systolic (mm Hg)</th>
<th>% Not at Goal*</th>
<th>Diastolic BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hypertensives</td>
<td>&lt;140/90</td>
<td>57%</td>
<td>26%</td>
</tr>
<tr>
<td>African American</td>
<td>&lt;140/90</td>
<td>60%</td>
<td>32%</td>
</tr>
<tr>
<td>Mexican American/Hispanic</td>
<td>&lt;140/90</td>
<td>63%</td>
<td>30%</td>
</tr>
<tr>
<td>Older patients (≥60 yr)</td>
<td>&lt;140/90</td>
<td>71%</td>
<td>9%</td>
</tr>
<tr>
<td>Symptomatic CHD</td>
<td>&lt;140/90</td>
<td>47%</td>
<td>4%</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>&lt;130/80†</td>
<td>81%</td>
<td>24%</td>
</tr>
</tbody>
</table>

NHA NES (1999-2000)

Many Patients in the US Are Not at JNC-Recommended BP Goals

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

HOT Study: Fewer Major CV Events in Patients With Diabetes Randomized to Lower BP Goal

Summary of Studies on Nephropathy Progression

IDNT: Renal Outcome End Point—Time to Doubling of Serum Creatinine, ESRD, or Death
**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
**Case 3**

- **68 yo WM** retired construction worker transferred for eval vasculitis and ARF.
- Excellent health – golfer and bowler.
- 5/95 loss of appetite, temps to 102, rash on back, cough Adm Hosp
- B13 mg/dl Cr 1.1 mg/dl WBC 2.9 Hct 33, plts 49 K. Rx antibiotics 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, Z+ heme, several rbc ? rbc casts?
- Urinary protein 784 mg /day
- WBC 10.0, Hct 35%, plts 142,000

**Underlying Conditions with Antiphospholipid Antibodies**

- Systemic Lupus Erythematosus
- "Lupus-Like" Syndrome
- Primary Anti-phospholipid Syndrome

**Antiphospholipid Antibodies**

- Family of Antibodies (IgG, IgM, IgA) against negatively charged phospholipids
- Lupus Anticoagulant - Aba that prolong lipid dependant coag tests, interfere with phospholipid of the prothrombin activator complex.
- Anticardiolipin antibodies - Aba that bind to cardiolipin (phospholipid antigen used in tests for syphilis)
- False + VDRL
- Procoagulant Effect in vivo

**Endothelial pro- and anticoagulants**

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Procoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue factor</td>
<td>Factor V</td>
</tr>
<tr>
<td>Factor Xa, Xa</td>
<td>tPA Inhibitor</td>
</tr>
<tr>
<td>von Willebrand factor cleaving metalloproteinase (ADAMTS13)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Manifestations Related to Anticardiolipin Antibodies

- Recurrent arterial and venous thromboses
- Placental thromboses and spontaneous abortions
- Livedo reticularis
- CNS complications
- Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Extrarenal Manifestations of APLS (65%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS disease</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Livedo reticularis</td>
</tr>
<tr>
<td>Adrenal disease</td>
</tr>
<tr>
<td>Other (aortic thrombosis with RAS, bowel infarction, miscarriage)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

Serologies and Lab Data

- Prolonged PTT 12/26 (46%)
- Thrombocytopenia 9/23 (38%)
- +ANA 15/26 (56%)
- +AntiDNA 2/24 (8.3%)
- Low complement 7/24 (29%)
- False positive VDRL 6/11 (55%)

Clinical Presentation at Biopsy

- Hypertension 16/26 (62%)
- Active urine sediment 10/26 (38%)
- Serum creatinine (mg/dl) 2.0 +/- 0.22
- Proteinuria (g/day) 4.4 +/- 0.87
- Nephrotic Syndrome 15/26 (58%)
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)

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

- Glomeruli show segmental intracapillary fibrin
**Case 4**

- A 4 yo girl presents with diarrhea and acute renal failure.
- She 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. She became lethargic took in less fluids and her parents brought her to ER.
- BP 70/45 mm Hg, P130 /min, T 101, Cor- Chest -, Abd diffuse mid tender, increased BS, ext- no edema, + petechiae on legs.
- WBC 12.2K, Hct 28%, pts 52K, smear with schistocytes.
- BUN 45 mg/dl, creatinine 3.1 mg/dl.
- U/A 2+ prot: 3+ heme, +rbc TNTC, + rbc casts.
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

**Shiga Toxin and Cell Injury**

Moake, NEJM 2002

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

**Higher Risk HUS**
- Antibiotics
- Bloody diarrhea
- Fever, vomiting
- Leukocytosis
- < 5 yo
- females

**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
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

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

ADAMTS 13

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

Criteria for Inclusion of TTP Cases

- Presence of thrombocytopenia & microangiopathic hemolysis
- No plausible causes
- No features suggestive of typical or atypical HUS
- Age > 10 yr

127 Cases in 4 yrs – All severe ADAMTS 13 deficient


ADAMTS and TTP

Levy et al, Nature 2002
**ADAMTS13**

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

- HUS (shiga toxin)
- Allograft rejection
- Factor H mutations
- Others
- Anti-phospholipid Antibody syndrome
- Thrombotic microangiopathy
- Metastatic cancer
- Thrombocytopenia
- Micropigopathic hemolysis
- Dysfunction of vital organs