Vascular disease and the kidney

- Hypertension

- Non-inflammatory renal vessel diseases (thrombotic microangiopathies)

HTN and the kidney

- What is HTN? Why is it important?

- What causes HTN?

- What is the role of the kidney in regulating BP? Which renal diseases cause HTN?

- What effects does HTN have on the kidney?
What is HTN?

Definition: the level of blood pressure associated with significant morbidity and mortality
**Definition of HTN (DHHS/NIH)**

<table>
<thead>
<tr>
<th></th>
<th>Diastolic BP</th>
<th>Systolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>&lt; 80 mm Hg</td>
<td>&lt; 120 mm Hg</td>
</tr>
<tr>
<td><strong>Pre-hypertension</strong></td>
<td>80-89</td>
<td>120-139</td>
</tr>
<tr>
<td><strong>Hypertension stage 1</strong></td>
<td>90-99</td>
<td>140-159</td>
</tr>
<tr>
<td><strong>Hypertension stage 2</strong></td>
<td>≥ 100</td>
<td>≥ 160</td>
</tr>
</tbody>
</table>

**Why is HTN important?**
Why is HTN important?

- It’s common!
- It’s a risk factor for cardiovascular and renal disease
- It’s treatable
Hypertension Affects Approximately 31% of Adults

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

*Hypertension defined as a BP of ≥ 140/90 mm Hg or reported use of antihypertensives.

Error bars indicate 95% confidence intervals. Data are weighted to the US population. Adapted from Hajjar I, Kotchen TA. JAMA. 2003;290:199-206.
Why is HTN important?

B. It’s a major risk factor for other disease

- Cardiovascular disease (myocardial infarction, stroke)
- Chronic, irreversible renal failure (end-stage renal disease)

“High-Normal” BP is Not Benign

Renal manifestations of essential HTN

- Microalbuminuria in up to 37%
- Rarely, heavy proteinuria/nephrotic syndrome
- Elevated creatinine < 1%

NB: The high prevalence of HTN makes it the second leading cause (after diabetes) of end-stage renal disease in the U.S.

Incident counts & adjusted rates of ESRD, by primary diagnosis

Incident ESRD patients; rates adjusted for age, gender, & race. Source: USRDS
# 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>

**D A S H** = Dietary Approaches to Stop Hypertension.

Chobanian AV et al., JNC 7: Complete Report.

Available at: [http://hyper.ahajournals.org/cgi/content/full/43/4/1256](http://hyper.ahajournals.org/cgi/content/full/43/4/1256)

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*Walking the dog*
My Doctor said "Only 1 glass of alcohol a day". I can live with that.
What causes HTN?

Primary ("essential") (90 - 95%)

Secondary (5 - 10%)

- Renal parenchymal disease
- Renal large vessel disease
- Pregnancy
- Endocrine disorders, pheochromocytoma
- Coarctation of aorta
- Aortic insufficiency
- Miscellaneous (drugs, neurogenic)

What is the role of the kidney in HTN?
Determinants of blood pressure

\[ B P = \text{Cardiac output} \times \text{peripheral (arteriolar) resistance} \]
Role of kidney in regulating blood pressure

Regulates total body water/sodium content

\[ \text{BP} = \text{Cardiac output} \times \text{Peripheral resistance} \]

- Renin-angiotensin system
- Vasodilator substances

Which kidney diseases cause HTN?
Which kidney diseases cause HTN?

- Most chronic renal parenchymal diseases (e.g. FSGS, IgAN, MPGN)

- Large renal artery disease (i.e. renovascular HTN)

Secondary hypertension due to renal vascular disease

Causes

- Renal artery atherosclerosis
- Fibromuscular dysplasia
- Congenital anomalies
- Takayasu's aortitis
- Radiation
- Tumor
- Post-op stricture
Renal artery stenosis

Renal artery atherosclerosis
atherosclerosis

Changes occurring in renovascular hypertension

- Contralateral kidney
- Stenotic kidney
- Suppressed renin
- Pressure natriuresis
- Ischemia
- Renin ↑
- Angiotensin II
- Vasoconstriction
- Intrarenal hemodynamic changes
- Sodium retention

(b)
What effects does HTN have on the kidney?

Renal pathology of HTN:
Granular surface
Renal pathology of HTN:
Thinned renal cortex

Hypertensive arteriolosclerosis

Arteriolar sclerosis and hyalinosis
Renal pathology of HTN: arterionephroclerosis

**Gross:**
shrunken, finely granular kidneys

**Micro:**
1. Arteriolosclerosis
2. Secondary glomerulosclerosis (FSGS and global sclerosis)
3. Tubular atrophy and interstitial fibrosis
Q: In unilateral renal artery stenosis, which kidney is more likely to show hypertensive nephrosclerosis?

Renal disease caused by HTN

- Essential HTN
  - <1% develop ESRD
  - A small no. develop proteinuria

- Accelerated (malignant) HTN
  - Acute renal failure in most
  - Hemolytic anemia
  - Headache, Stroke, retinal damage
  - 50% mortality is untreated
Malignant HTN: "flea-bitten" kidney (hemorrhages)

- Petechial hemorrhages
- Capsule may be smooth if de novo (90%)
- Granular if previous HTN (10%)
Malignant HTN: arteriole with concentric intimal hyperplasia and entrapped RBCs

Malignant HTN: artery with fibrinoid necrosis
Malignant HTN: artery with fibrin thrombus

Malignant HTN: glomerular fibrin thrombi
Peripheral blood smear in malignant HTN

- Schistocytes (fragmented RBCS)

- Thrombi in arterioles/capillaries (Thrombotic microangiopathy)

- Hemolytic anemia
- Thrombocytopenia
- Acute renal failure
Thrombotic microangiopathies: etiologies

- Tumor emboli
- Antiphospholipid antibody (+/- SLE)
- Pregnancy/puerperium (pre-eclampsia/HUS)
- Dysfunction of organs
- Thrombocytopenia
- Fragmentation of red blood cells

- Malignant HTN
- Acute scleroderma renal crisis
- Bone marrow transplant
- Allograft rejection
- Drugs

Wolf G. NDT 2004
Case

- 45 yo WF admitted for skin rash and ARF
- History of 3 spontaneous abortions
- BP 170/84, UE and LE rash; Chest neg, no edema.
- BUN 97 mg/dl  Creatinine 4.0 mg/dl Palb 3.5
- WBC 11.2K Hct 37% plts 114 K , Pt 14  PTT 49
  U/A 1+ prot +rbc no casts
- ANA + 1: 40; Hep BV,HCV neg, HIV-, ANCA – ,
  CH50 and C3 nl
- Anticardiolipin antibody strong positive

Antiphospholipid Antibodies

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

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

Livedo reticularis in APLA syndrome
Livedo reticularis in APLA syndrome

APL syndrome: Glomeruli show ischemic changes (global wrinkling of glomerular basement membranes, tuft retraction, and cystic dilation of Bowman’s space)
APL syndrome: Arteries show widespread luminal narrowing with extensive endothelial swelling and mucoid intimal fibrosis.

APL syndrome: Arteries show focal entrapped RBCs and fibrin (red).
**Diagnosis**

- Primary antiphospholipid antibody syndrome with features of arteriolar and glomerular thromboses
Case

- 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, P 130 /min, T 101, Cor-Chest -, Abd diffuse mild tender, 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
From the Centers for Disease Control and Prevention
Leading From the Morbidity and Mortality Weekly Report
Atlanta, Ga

Preliminary Report: Foodborne Outbreak of *Escherichia coli* O157:H7 Infections From Hamburgers—Western United States, 1993
Multi-State Outbreak of *E. coli* O157:H7 Infections From Fresh Spinach, October 6, 2006

- 199 persons infected with the outbreak strain of *E. coli* O157:H7 reported to CDC from 26 states.

Childhood HUS

- *E. coli* shigatoxin-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
- 5-10% develop renal involvement
Role of Shiga Toxin

- Epidemic and sporadic HUS
- E. Coli 0157:H7 produce both STX1 and STX2
- Causes Hem. Colitis & is cytopathic to green monkey kidney cells
- STx – E coli in stool for wks

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, spinach
- Person to person – day care centers
**Verotoxin**

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

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**Shiga Toxin and Cell Injury**

- Binding of Shiga toxin to glycolipid receptors
- Cell membrane
- Endocytosis of a subunit of Shiga toxin and conversion to H-glycolipid
- Elimination of H adenosine from 28S ribosomal RNA
- Inhibition of protein synthesis elongation
- Cell death

*Mooke, NEJM 2002*
Shigatoxin-1 and Endothelium

- Binds to Gb3 on glomerular endothelium
- Gb3 expression equal in children vs. adults
- Mechanism for childhood susceptibility remains undetermined


Case 4: E.coli-associated HUS

- Pathologic findings
Colonic hemorrhagic necrosis

Fibrin thrombi in TMA
thrombi in glomerular capillaries

Severe HUS: cortical necrosis
Course ARF Childhood HUS

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

Higher Risk HUS

- Antibiotics
- Bloody diarrhea
- Fever, vomiting
- Leukocytosis
- < 5 yo
- females
Residual Renal Disease in Childhood HUS

- 3-18% ESRD
- 10-40% low GFR, proteinuria, CRF, HBP
- Duration of anuria predicts poor renal outcome
  - < 10 days → 7.5%
  - > 16 days → 42.5%
Thrombotic thrombocytopenic purpura (TTP)

- CNS signs predominate
- Deficiencies of vWF cleaving metalloproteinase (ADAMTS13)
  - Hereditary (rare)
  - Acquired (autoantibodies)