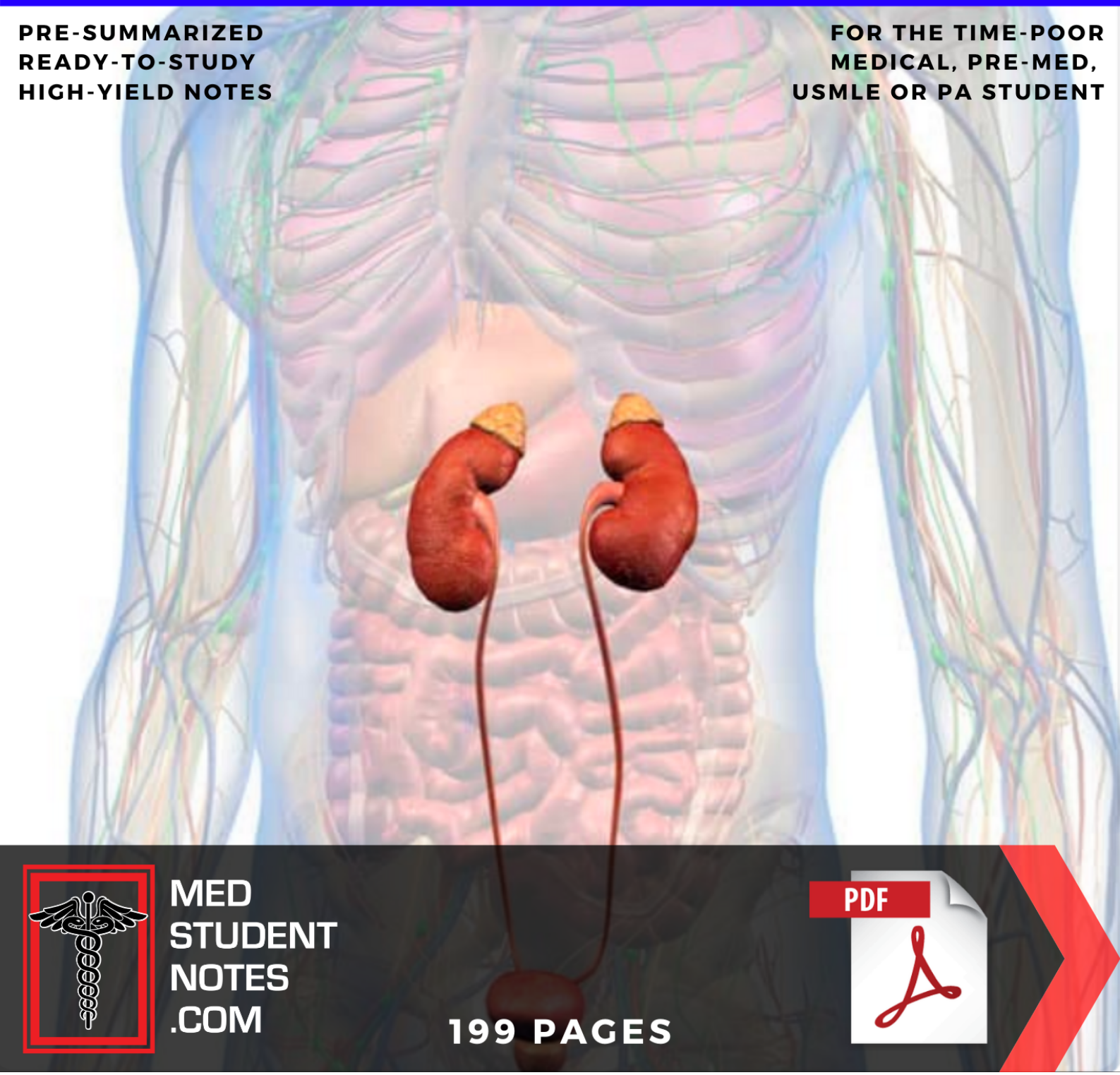
ANATOMY, PHYSIOLOGY & PATHOLOGY NOTES OF THE

GENITOURINARY SYSTEM

SECOND EDITION

PRE-SUMMARIZED
READY-TO-STUDY
HIGH-YIELD NOTES

FOR THE TIME-POOR
MEDICAL, PRE-MED,
USMLE OR PA STUDENT



MED STUDENT NOTES .COM

199 PAGES

PDF

A Welcome Letter From The Team At:

MEDSTUDENTNOTES.COM

Congratulations on your purchase!!

Studying medicine or any health-related degree can be stressful; believe us, we know from experience! (Yes, we are a team of doctors, so we've been there, done that! Now we want to pay it forward by building the greatest educational resource for our junior medical student upstarts). Our goal is not to make a profit; we simply aim to cover our costs, which is why our notes and resources are so very affordable! (…and always will be! ☺)

Here are just a few things you need to know to get the most out of your purchased notes:

1. **Your notes are yours for life! (Yay!)** We do not charge any recurring subscriptions or hidden fees etc. Also, any updates we make to your purchased notes in the future are provided free of charge and you will receive an email notification if/when this occurs.

2. **Our hosting website charges us a fee each time a file is downloaded, so we allocate a download allowance (per file) for each of your purchases.** Don't worry if you exceed this though -- you will simply get a notification and be prompted to request a download extension from us at admin@medstudentnotes.com .

3. **Therefore, we encourage you to SAVE your files onto your personal computer (or hard drive/device) for future access.** Once saved to one of your devices, it is very easy to transfer your files to all of your personal/mobile devices without the need to re-download all of your files.

4. **All of our study notes are delivered in PDF format.** This is the most reliable and universal computer format available. We have double checked all of our files and they all functional and virus free. **Please do not open any medstudentnotes documents shared to you by another person as we cannot guarantee those files will be virus-free.**

5. **If you are having trouble downloading your files or your files are not displaying properly on your device, please consider the following remedies:**
    a. **Try updating your PDF viewer** software to the latest version

    b. **If you are using a mac, try opening the files with 'Preview'** instead of Adobe.

    c. **Try an alternative PDF viewer software**. For a list of free PDF readers, click this link: https://blog.hubspot.com/marketing/best-free-pdf-reader

d. If you are attempting to download on a phone or tablet, **we suggest downloading first onto a computer, then transferring files to your mobile devices.** This is because some files are quite large - sometimes over 100MB - and might be too much for a mobile device to handle.

e. **If none of these solutions work for you**, please let us know by emailing us at admin@medstudentnotes.com

6. **If you have any further queries,** feel free to check out our FAQ page: https://www.medstudentnotes.com/pages/faqs or email us at admin@medstudentnotes.com

7. **Please ensure you use the SAME Email address for any future purchases.** That way, all of your files will be visible in the one place on your account page. (Accounts are free and optional; if you do not wish to create an account, you can simply open and save your files directly from your order-confirmation email).

8. **Feel free to use the discount code "TAKE20OFF"** for 20% off any future purchases you make with us. This code MUST be applied PRIOR to submitting payment for the discount to take effect.

9. **We understand the desire to share your purchased notes with your friends, HOWEVER, we encourage you to instead consider signing up to our free Affiliates program . That way you can share your unique referral code with your friends, they get 15% off their purchase, and YOU earn 30% commission on any sales you refer to us.**

   For more info, visit: https://affiliates.medstudentnotes.com/?ref=r2cuusbruqt

From everyone here at MedStudentNotes.com, thankyou once again for your purchase! We wish you every success in your studies and career ahead!! ☺

Table Of Contents:

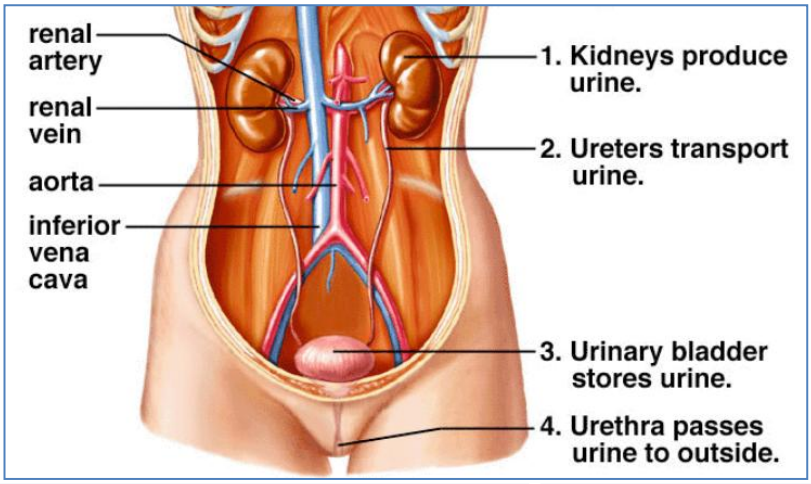
What's included: Ready-to-study anatomy, physiology and pathology notes of the genitourinary system presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your iPad or tablet PC.

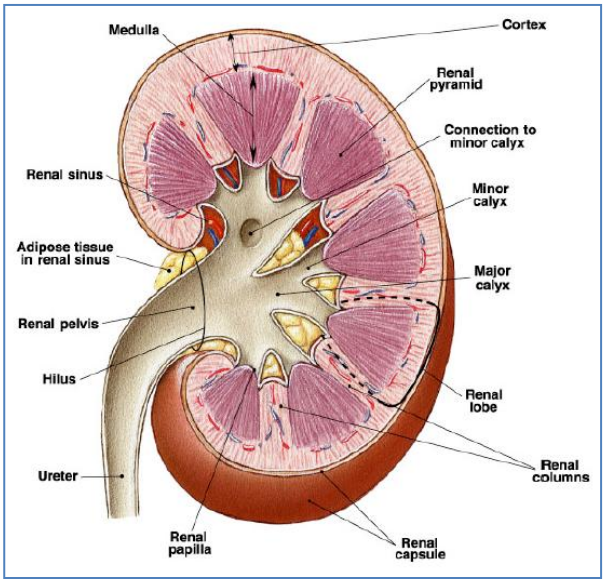
Free Bonus: 'Nephrology' and 'Urology' chapters of Toronto Notes for reference and further detailed reading.

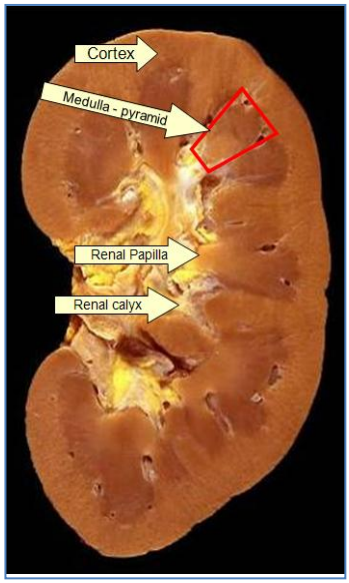
File List:

Macroscopic Anatomy of Kidneys:

- **Renal Capsule:** Thin skin of Fibrous Tissue covering the Kidney.
- **(Outer) Cortex:** The Filtering Apparatus (Glomeruli)
- **(Inner) Medulla:** Contains Major Blood Vessels + Collecting Ducts
- **Renal Pyramids:** Formed by straight parallel segments of Nephrons.
- **Renal Lobes:** Renal Pyramid + Renal Cortex Above.
- **Renal Papilla:** Where Collecting Ducts of the Pyramids empty into the renal pelvis.
- **Renal Pelvis / Hilum:** Convergence of all Calyces & Connecting Ducts → Ureter.

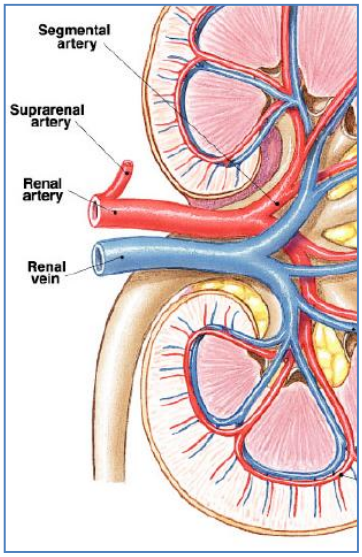


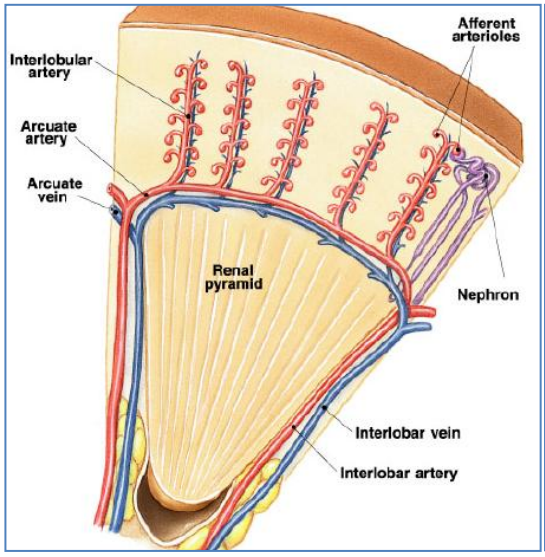


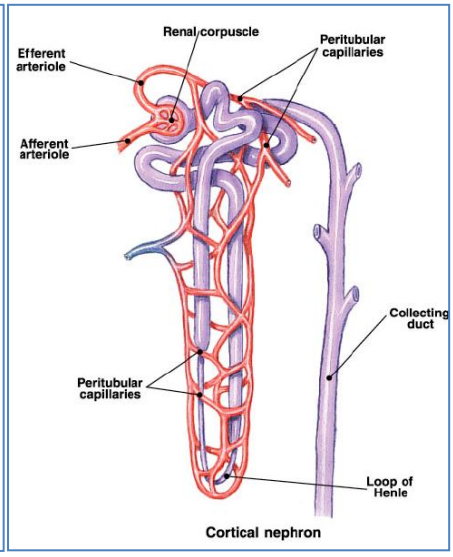


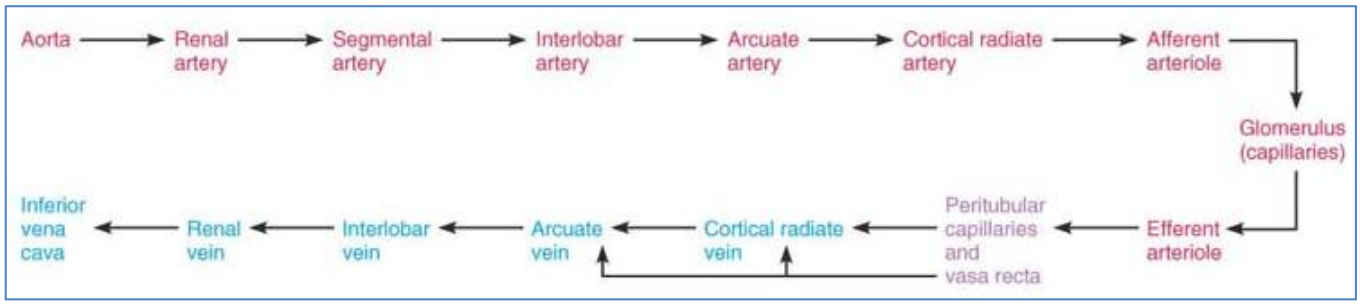
Microscopic Anatomy of Kidneys:

- **Microvascular Supply:**
  - **Interlobar Arteries & Veins:**
    - Run up from the Medulla *Through* the Renal Columns
    - Each form an arc with Interlob*ular* Arteries/Veins.
    - 'horseshoe bends'
  - **Interlobular → Arcuate Arteries/Veins:**
    - Projections of the Interlo*bar* Arteries/Veins into the Cortex.
    - 'little dead-end streets'
  - **Afferent Arterioles:**
    - Carry blood from Interlobar Arteries → Corpuscle of the Nephron
    - 'driveways off little dead-end streets'
  - **Renal Corpuscle:**
    - ***The Glomerular Capillaries + Glomerular Capsule***
    - *Glomerular Capsule* = Little deeply-concaved membrane in which a convoluted mass of *Glomerular Capillaries* are bundled.
    - **NB:** Glomerular Capillaries are *Highly Fenestrated* → 'Leaky' → Aids in filtration.
    - Place of filtration
  - **Efferent Arterioles:**
    - Carry blood away from the Corpuscles → Peritubular Capillaries
  - **Peritubular Capillaries:**
    - Supply the rest of the Nephron (Renal Tubules & Ascending/Descending Limbs)
  - **Venules**:
    - Drain filtered blood back to Inferior Vena Cava.
    - Peritubular Capillaries→ Interlobular Venules → Arcuate Veins → Interlobar Veins → Segmental Veins →Renal Vein → IVC.

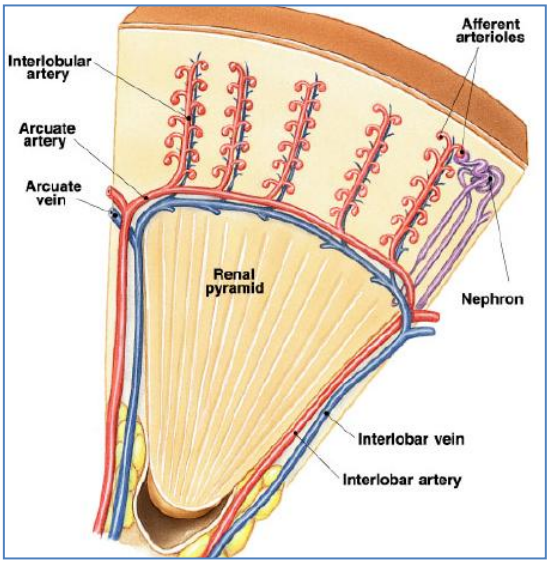


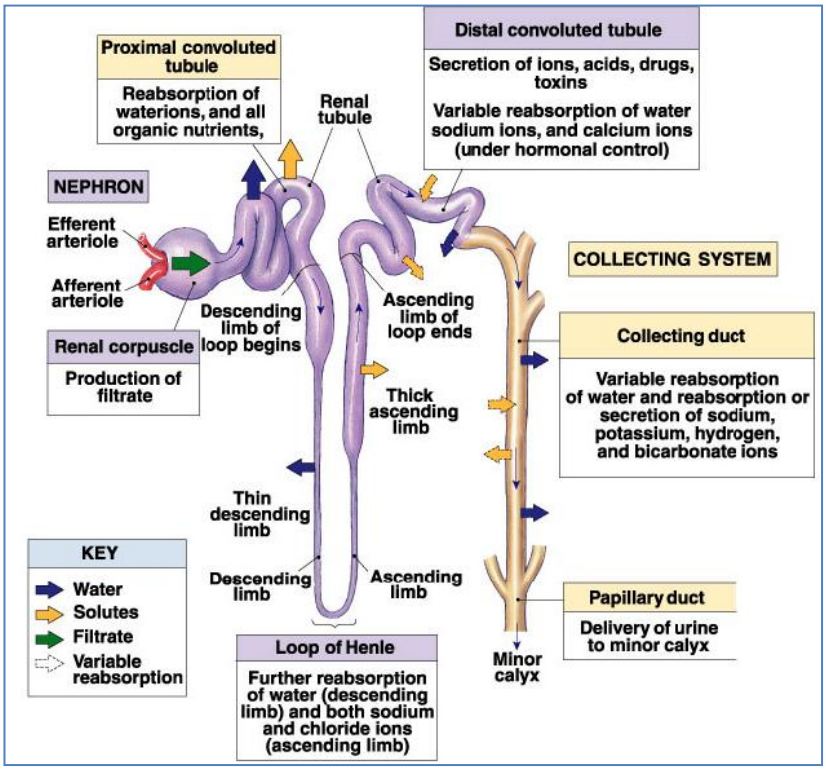


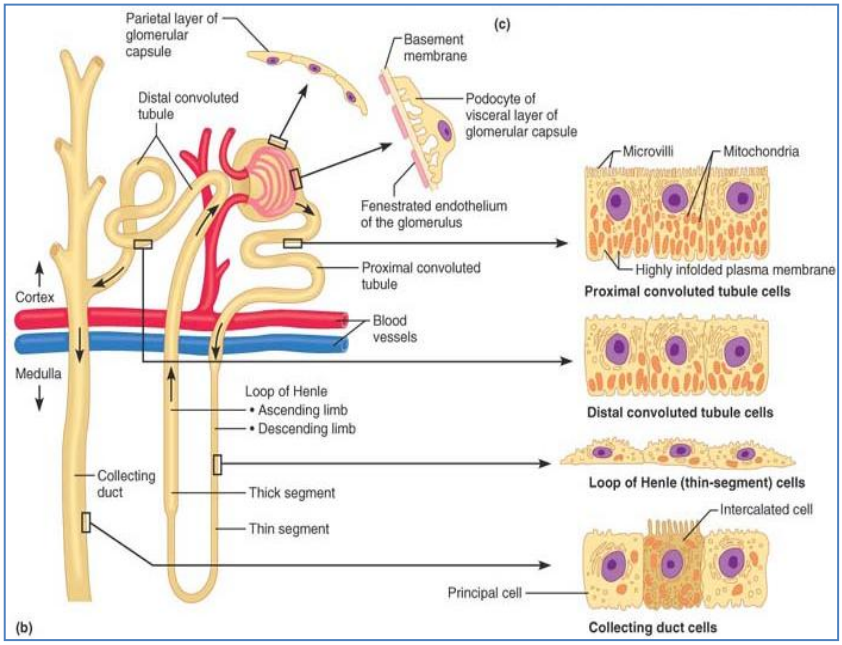


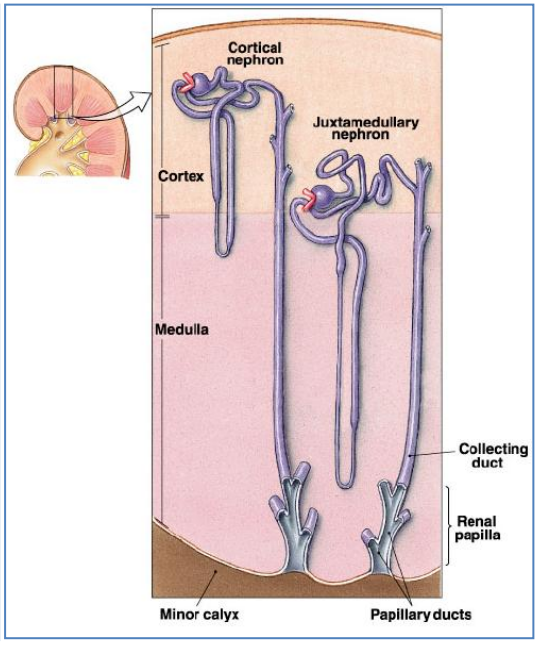


- **The Nephron:**
  - **The Nephron:**
    - ***The Glomerular Capillaries + Glomerular Capsule***
      - ***Histology:*** **Fenestrated Endothelium** for Mass Filtration
    - **Proximal Convoluted Tubule:**
      - ***Histology:*** **Simple Cuboidal Epithelia w. Microvilli** for bulk Reabsorption.
    - **Loop of Henle:**
      - **Descending Limb (Thick & Thin):**
        - ***Histology:*** **Simple Squamous Epithelia** → H_2O Reabsorption only.
      - **Ascending Limb (Thin & Thick):**
        - ***Histology:*** **Simple Cuboidal Epithelia** → Resorption of **Ions**.
    - **Distal Convoluted Tubule:**
      - Secretion of Ions, Acids, Drugs & toxins
      - Variable Reabsorption of Water, Na^+ & Ca^+ ions (under endocrine control)
      - ***Histology:*** **Simple Cuboidal Epithelia (No Microvilli)** → Resorption of Ions.
    - **Collecting System:**
      - Variable Reabsorption of Water
      - ***Histology:*** **Simple Cuboidal – Columnar** for resorption of H_2O, Urea & other Ions.

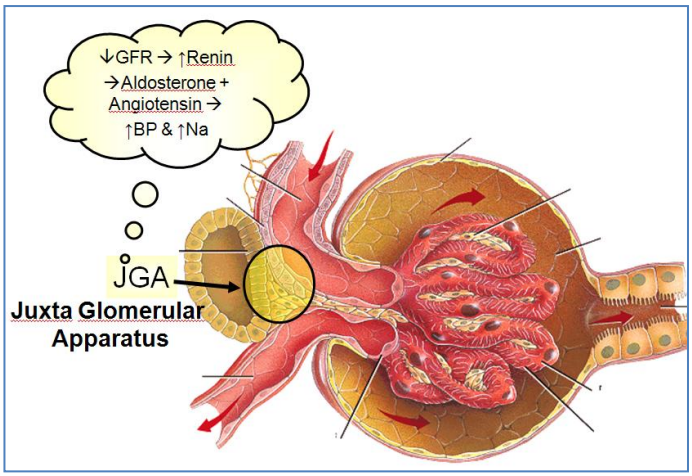




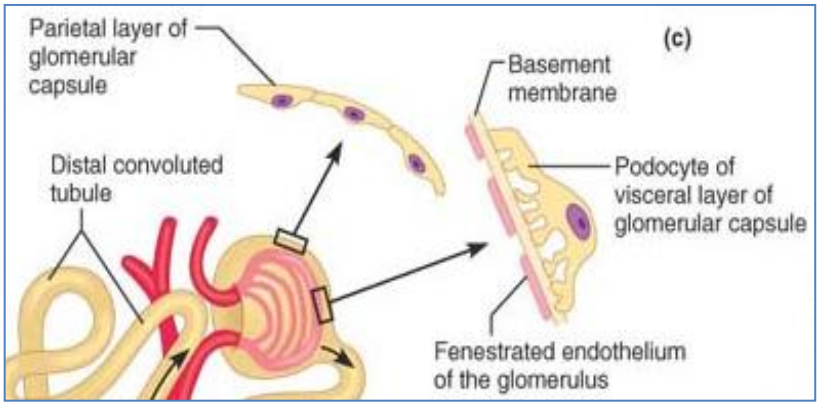


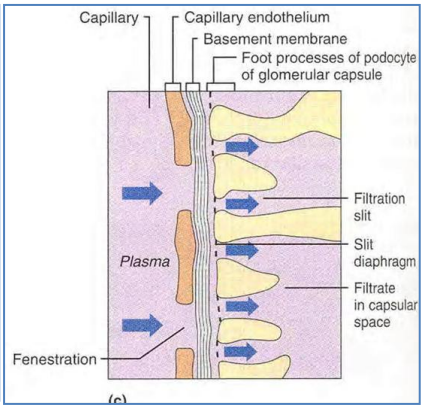


- **Physiology:**
  - **7 Functions of the Kidney:**
    - **Fluid Conservation**
    - **Electrolyte Balance (Particularly Na^+, K^+, PO_4^- & HCO_3^-)**
    - **Waste Disposal (Urea, Creatinine, Urobilin/Bilirubin)**
    - **Acid-Base Homeostasis (H^+ Resorption/Excretion…OR HCO_3^- Resorption/Excretion)**
    - **Blood Pressure Regulation (Fluid Volume + Hormonal [Renin/Angiotensin])**
    - **Haematopoiesis (Erythropoietin EPO)**
    - **Vitamin D Activation**
  - **Hormones:**
    - **Renin:**
      - **Released by** Juxta-Glomerular Apparatus in response to Renal Hypoperfusion
      - **Causes** → Conversion of Angiotensin-I to Angiotensin-II,
        - →& Vasodilates Afferent Arteriole to ↑Kidney Perfusion
    - **Angiotensin-II:**
      - **Released by** Lungs in response to Renin
      - **Causes** → Systemic Vasoconstriction → ↑BP
        - →& Constriction of the Efferent Arteriole to ↑GFR
        - → & Adrenal Release of Aldosterone
    - **Aldosterone:**
      - **Released by** Adrenal Glands in response to AT-II, HyperKalaemia, & HypoNatraemia.
      - **Causes** → ↑Na^+ Reabsorption (& K^+ Excretion) (& H_2O Reabsorption)
    - **Anti-Diuretic Hormone (ADH):**
      - **Released by** Posterior Pituitary Gland in response to ↑Plasma-Osmolality (Dehydration)
      - **Causes** → ↑Water Resorption from the Collecting Ducts → ↑Plasma Volume & ↓Urine



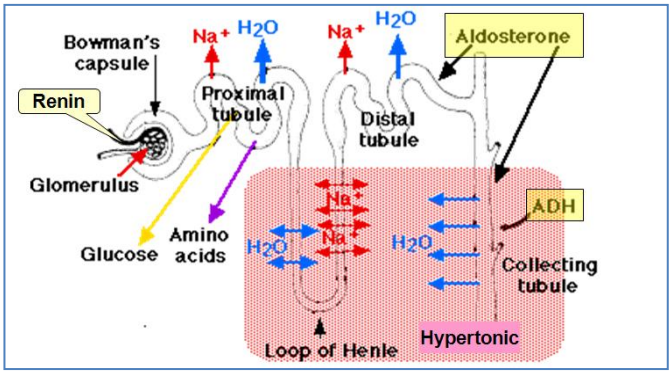
- **Step 1 – Glomerular Filtration:**
  - **Filtration of Large Volumes of Blood:**
    - Filtration is *Passive & Non-Selective* (Fluids & Solutes are forced through via Hydrostatic Pressure)
  - **Filtration Through 3 Layers of Capillary (Glomerular) Membrane:**
    - Endothelium
    - Basement Membrane
    - "Podocytes" of Visceral Layer of Glomerular Capsule (NB: "Podocyte" = "Cells with Feet")





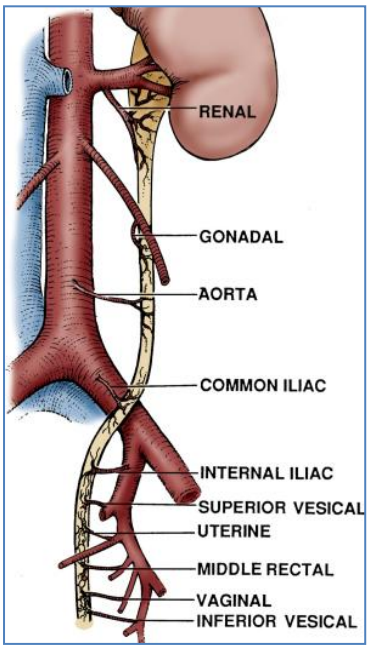
NB: Visceral Membrane of Glomerular Capsule is *IMPEREABLE TO PROTEINS* –
ie. If Proteins/Cells appear in urine →Means Membrane is Damaged

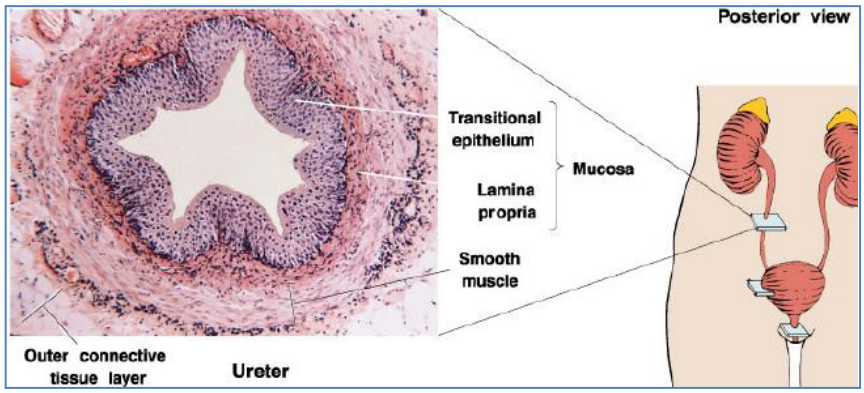
- **Step 2 – Tubular Reabsorption:**
  - Normally, 99% of Fltrate is Reabsorbed
  - **-Is Highly Selective:**
    - Some Substances (Eg. Glucose) are Almost Completely Reabsorbed.
    - Some Substances (Eg. $NaCl^-$) are Variable.
    - Some Substances (Eg. Urea) are Not Reabsorbed at All.
  - **-Is Passive & Active:**
    - **Passive:**
      - Eg. Water – Via Osmosis
    - **Active:**
      - Ie. Moving Solutes Against an Electrochemical Gradient. (Either Primary/Secondary)
      - Eg. Na^+ - (By Na^+/K^+-ATPase)
- **Step 3 – Tubular Secretion:**
  - **Important For:**
    - Disposing of Substances That Weren't Filtered (or Weren't Filtered Enough)
      - Eg. Drugs (eg. Penecillin)
    - Eliminating 'Bad' Substances that have been Passively Reabsorbed
      - Eg. Urea, Uric Acid, etc.
    - Removing Excess K^+ ions.
    - Controlling Blood pH
  - **Proximal Tubules:**
    - Site of Secretion of ***Organic Acids/Bases*** (Bile Salts, Oxalate, Uric Acid, etc)



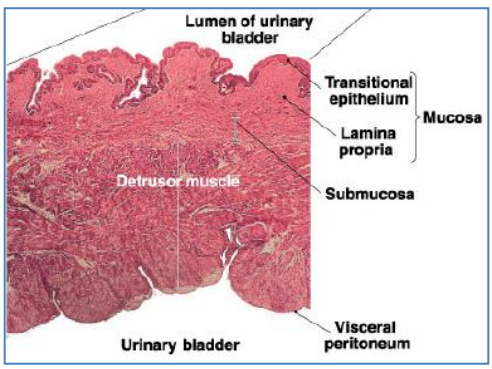
Functional Anatomy:

- **Ureters**
  - Carry Urine from Renal Pelvis → Bladder
  - 30-35cm Long
  - **Muscular Tubes:**
    - Peristaltic Contractions – help urine flow
  - **Histology:**
    - Mucosa = Transitional Epithelium
    - Smooth Muscle Outer Layer
  - **Abdominal Part** – Runs just anterior to Psoas Major
  - **Pelvic Part** – From below Bifurcation of Common Iliac Artery
  - **3 Sites of Constriction:** - (where calculi can be caught)
    - 1. Junction with Renal Pelvis (Hilum)
    - 2. Entry to Bony Pelvis (Over the Pelvic Brim)
    - 3. Entry to Bladder
  - **Blood Supply:**
    - Upper Ureter – Branch of Renal Artery
    - Middle Ureter – Branches of Gonadal (Ovarian/Testicular), Aorta & Common Iliac Arteries.
    - Lower Ureter – Branches of Internal Iliac

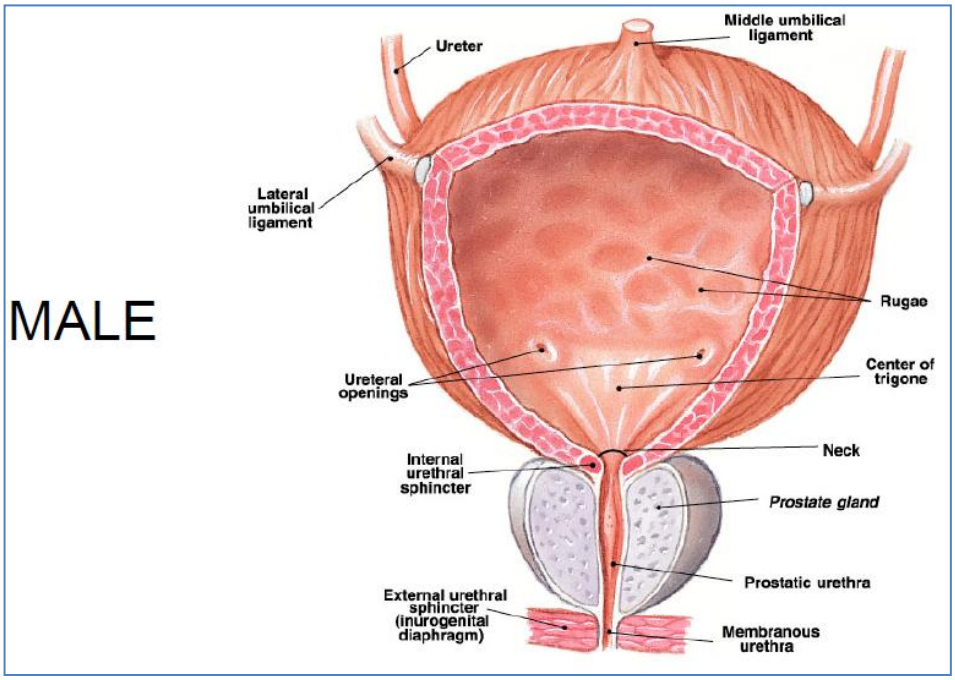




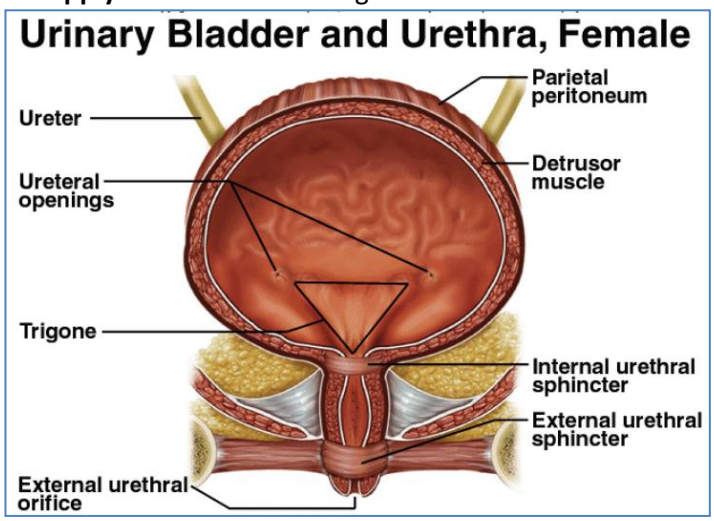
- **Bladder:**
  - **General Info:**
    - Muscular-Walled Sac (**Detrusor Muscle)**
    - Inferior to Peritoneum
    - Ureter Openings – Just Below Pubic Tubercles.
    - **Trigone:**
      - Smooth Triangular Area on lower-posterior bladder wall
      - Triangle defined by openings of Ureters (top) & Urethra (bottom)
    - **Apex** at bottom
    - **Neck** – Entry to Urethra
      - Guarded by **Internal Urethral Sphincter**
    - **Body**
    - **Fundus –** Above Ureteral Openings.
  - **Histology:**
    - Mucosa = Transitional Epithelium
    - Muscular Layer = Detrusor Muscle
    - Visceral Peritoneum
  - **Male:**
    - **Rectovesical Pouch** – Space between Bladder & Rectum



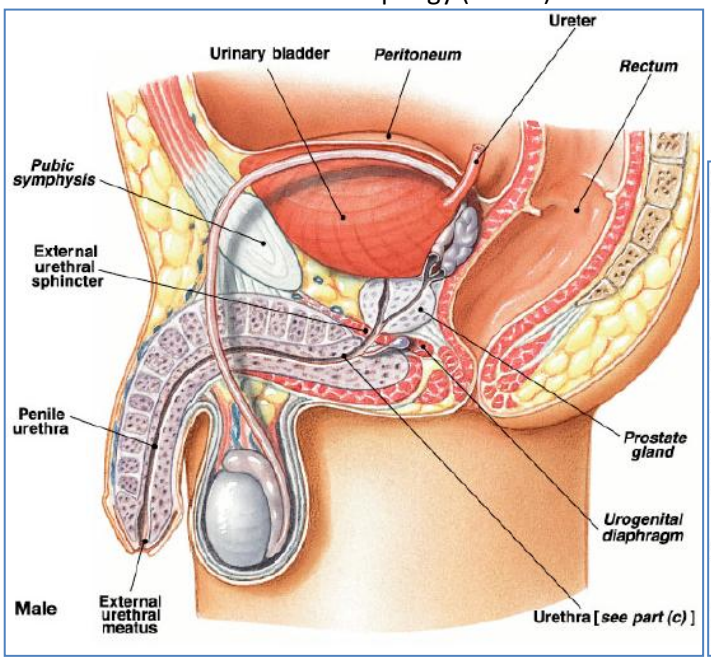
- **Blood Supply** – Internal Iliac Artery

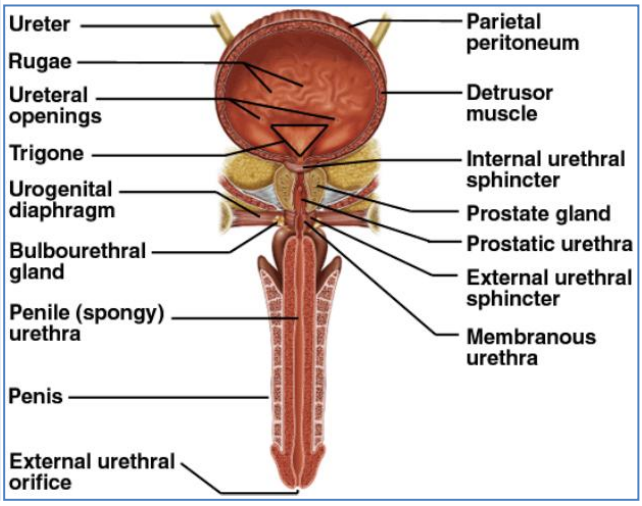


- **Female:**
  - **VesicoUterine Pouch** – Space between Bladder & Uterus
  - **Blood Supply** – Internal Iliac & Vaginal Arteries.

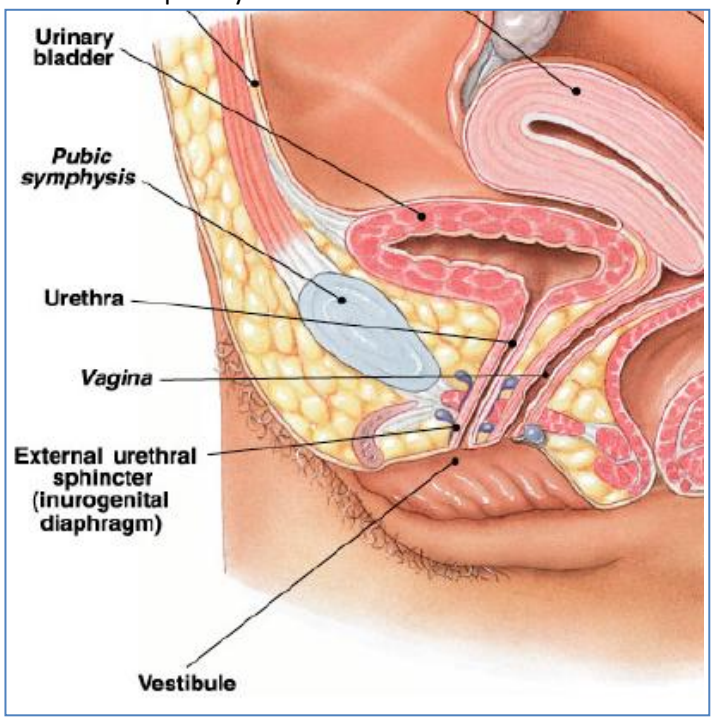


- **Urethra:**
  - **Male:**
    - 20cm Long
    - Integrated with Repro. System
    - **3 Parts + Histology:**
      - Prostatic Urethra - Transitional Epithelium
      - Membranous Urethra - Pseudostratified Columnar Epithelium
      - Spongy (Penile) Urethra - Pseudostratified Columnar Epithelium





  - **Female:**
    - 2-3cm Long
    - **Histology:**
      - Mostly Pseudostratified Columnar Epithelium
      - Stratified Squamous (external orifice)
    - Separate from Repro. System

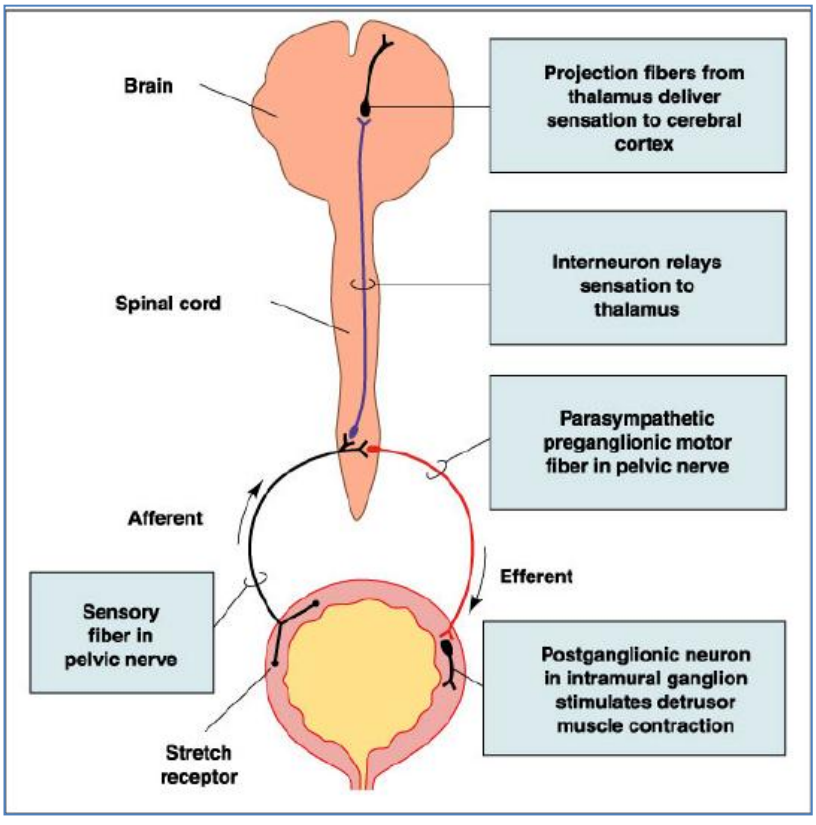


Lymphatic Drainage of Urinary System:

- Mostly *Lumbar* Nodes

Micturition Reflex (Urination):

- Voluntary (in Health Adults)
- Involuntary (In Infants + Neurological Injury) → Urinary Incontinence
- A *'Learned'* Process (develops @ 2-3yrs)
- **2 Phases:**
  - Collection Phase
  - Micturition Phase
- **Reflex Process:**
  - Facilitated / Inhibited by Higher Brain Centres
  - The *Phase* of the system - dependent on:
    - 1. A Conscious Signal from the brain and
    - 2. The *Firing Rate* of sensory fibres from the bladder and urethra.
  - **Empty Bladder:** Afferent Firing Rate ↓→ excitation of the outlet (the sphincter and urethra), and relaxation of the bladder.
  - **Full Bladder:** Afferent Firing Rate ↑ → Urinary Urge.
    - **Voluntary Urination:** Person Consciously Initiates peeing → Bladder contracts +Sphincters relax.
    - Urination Continues until Bladder is Empty → Bladder Relaxes + Sphincters Contract →Collection Phase

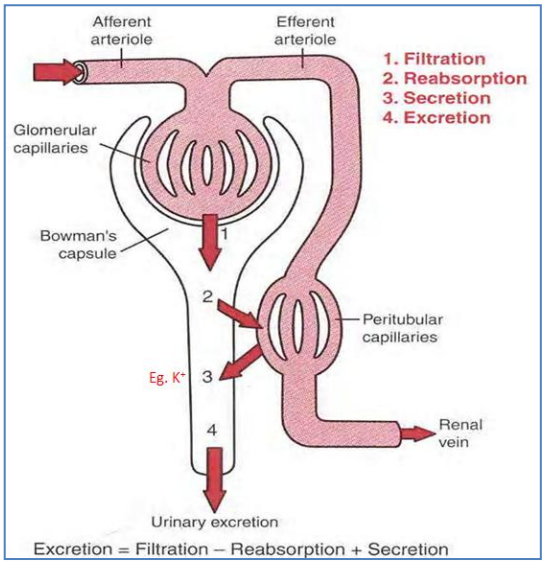


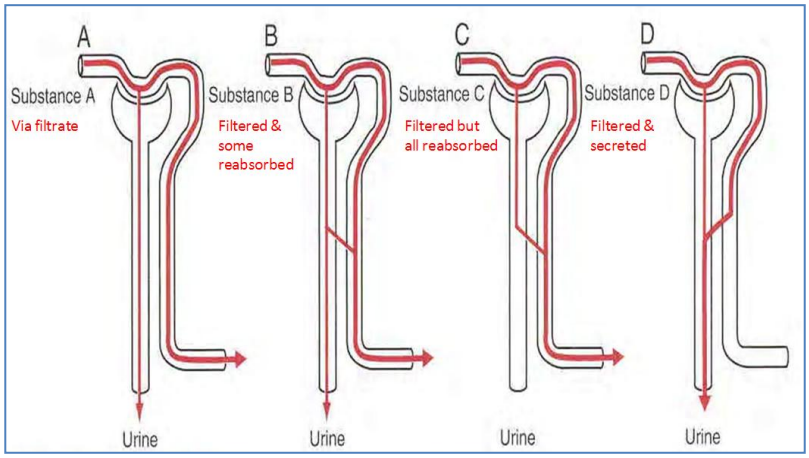
Urine Production and Excretion

3 Processes of Urine Formation:

- **1. Glomerular Filtration:**
  - Filtration of Blood
- **2. Tubular Reabsorption:**
  - Reabsorption of Certain Filtered Substances (In Renal Tubules) → Back into Blood
- **3. Tubular Secretion:**
  - Active Secretion of Substances From Peritubular Capillaries (Blood) → Into Renal Tubules.

Urine Excretion = Filtrate – Reabsorbed + Secreted



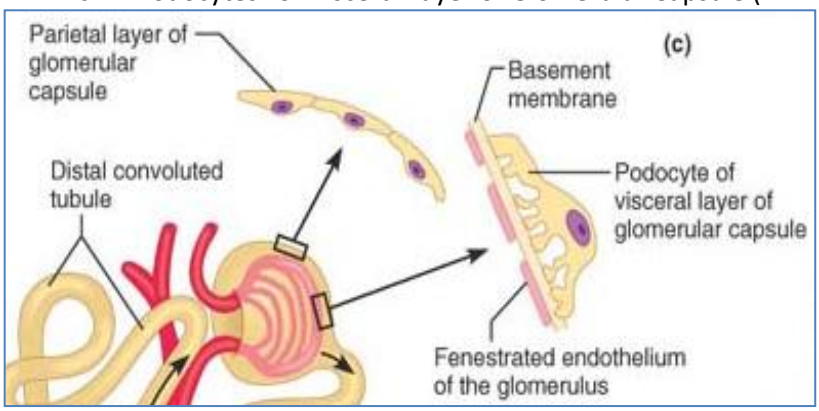


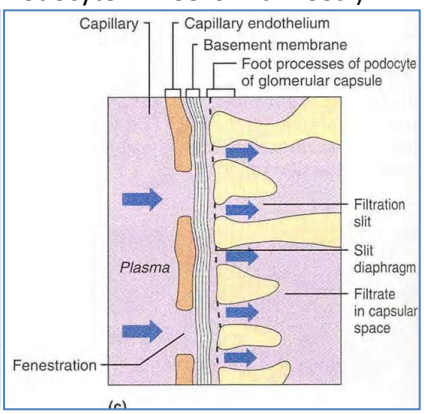
- **NB: Different Substances are Filtered, Reabsorbed & Secreted Differently:**

Urine Production

Step 1 – Glomerular Filtration:

- **Filtration of Large Volumes of Blood:**
  - Through Glomerular Capillaries → Glomerular (Bowman's) Space.
  - Filtration is *Passive & Non-Selective* (Fluids & Solutes are forced through via Hydrostatic Pressure)
    - Ie. Forming Filtrate Doesn't Require Energy (ie. Simply a Mechanical Filter)
- **Filtration Through 3 Layers of Capillary (Glomerular) Membrane:**
  - Endothelium
  - Basement Membrane
  - "Podocytes" of Visceral Layer of Glomerular Capsule (NB: "Podocyte" = "Cells with Feet")





NB: Visceral Membrane of Glomerular Capsule is Relatively *IMPEREABLE TO PROTEINS* –
ie. If Proteins/Cells appear in urine →Means Membrane is Damaged

- **Filtrate:**
  - Ie. The Glomerular *FILTRATE* = Similar to Plasma (But *Without* the Proteins)
- **Permeability of Glomerular Membrane:**
  - Filterability of Solutes – Based on Size.
  - Small Chemicals are often bound to Plasma Proteins (Ca^+, FA's, Drugs) – Hence not freely filtered.

- **Glomerular Filtration Rate:** = Total Filtrate Formed/Per Minute
  - **Determined by Net *Hydrostatic Pressure* and Net *Colloid-Osmotic Pressure*** Across Membrane.
    - **Capillary Hydrostatic Pressure:**
      - The force the blood exerts against the capillary wall.
      - Tends to force fluids through the capillary
      - *Net Hydrostatc Pressure = Capillary Pressure – Interstitial Pressure.*
    - **Colloid Osmotic Pressure:**
      - Opposes hydrostatic pressure
      - Due to non-diffusible molecules (In Plasma) drawing fluid into capillaries.
      - *Net Osmotic Pressure = Capillary Osmotic Pressure – Interstitial Osmotic Pressure.*
  - **Also Determined By:**
    - **Total Surface Area for Filtration**
    - **Membrane Permeability**

  - Kidneys receive ≈1/4 of Cardiac Output (1L of Blood/min)...
    - Of that ≈125mL of Filtrate is Generated/Min → 180L of Filtrate/Day (From only 3L of Plasma)
    - →Hence, The Blood Is Extremely well Filtered.
    - NB: Most of Filtrate is Reabsorbed into Blood (Via Renal Tubules)

- **Control of GFR:**
  - **Sympathetic NS:** (Fight/Flight)
    - Constriction of Afferent & Efferent Arterioles.
    - →↓Renal Blood Flow
    - →↓GFR
  - **Hormones & Autocrine Secretions:**
    - **Causing Arteriole *CONSTRICTION*:**
      - (ADRENALINE, ENDOTHELIN...others)
        - →↓Renal Blood Flow
        - →↓GFR
    - **Causing Arteriole *DILATION*:**
      - (NITRIC OXIDE, PROSTAGLANDINS, BRADYKININ...others)
        - →↑Renal Blood Flow
        - →↑GFR
  - **Angiotensin II:**
    - Constriction of *EFFERENT ARTERIOLES*
      - →↓Renal Blood Flow
      - BUT – Maintains GFR (By keeping Glomerular Hydrostatic Pressure Up)

- **Control of Renal Blood Flow:**
  - **Autoregulation (Local):** (The first of the body's regulators of Mean Arterial Pressure)
    - Automatic Adjustment of Blood Flow to a Capillary Bed Relative to the Tissue's Requirements
      - Maintains Normal Renal Function (GFR) Despite Changes in Arterial Pressure.
    - **How?...Juxtaglomerular Apparatus is Sensitive to:**
      - **Metabolic Controls: → Vasodilation:**
        - Low Oxygen / Nutrient levels
        - Nitric Oxide
        - Endothelin
      - **Myogenic Control: → Vasoconstriction:**
        - Sheer Stress: Vascular Smooth Muscle Contracts When Stretched

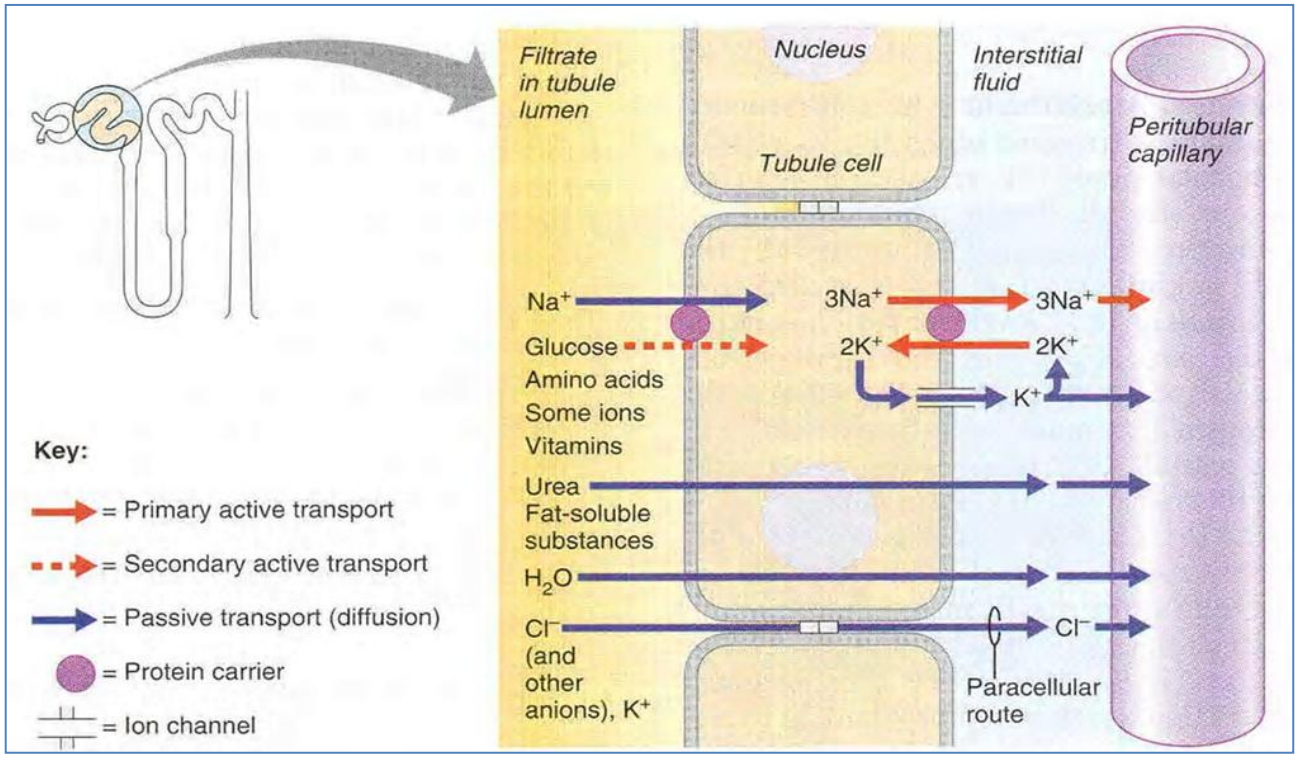
Step 2 – Tubular Reabsorption:

- Normally, 99% of Fltrate is Reabsorbed
- **-Is Highly Selective:**
  - Some Substances (Eg. Glucose) are Almost Completely Reabsorbed.
  - Some Substances (Eg. $NaCl^-$) are Variable.
  - Some Substances (Eg. Urea) are Not Reabsorbed at All.

- **-Is Passive & Active:**
  - **Passive:**
    - Eg. Water – Via Osmosis
  - **Active:**
    - Ie. Moving Solutes Against an Electrochemical Gradient. (Either Primary/Secondary)
    - Eg. Na^+ - (By Na^+/K^+-ATPase)
  - NB: Remember that all Active & Passive Transporters (Excluding Channels) Reach Saturation. (Max.V)
    - Eg. Glucose doesn't normally appear in urine. However, if Filtered Load Exceeds Reabsorption, Urinary Excretion Occurs (ie. In Uncontrolled Diabetes.)

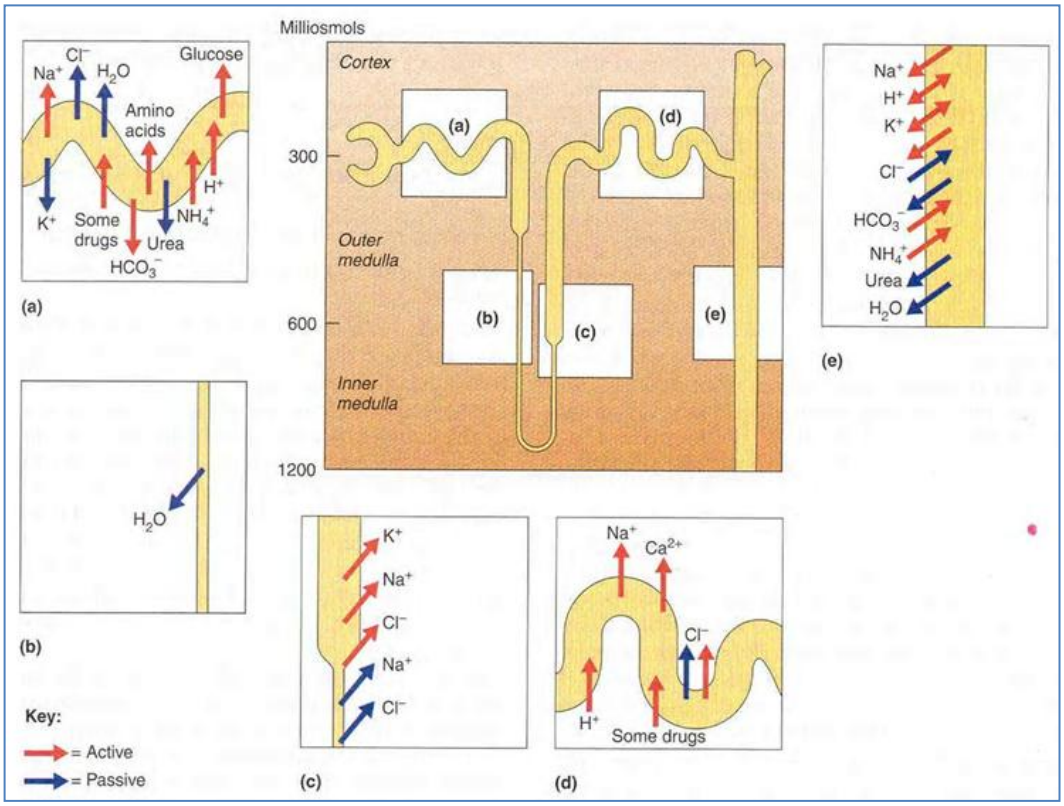
- **Solutes May Be Reabsorbed Via 1 of 2 Routes:**
  - **1.** Transcellular Pathway – Through The Cells
  - **2.** Paracellular Pathway – Between Cells

- **Active Na^+ Reabsorption:**
  - Occurs in Ascending Limb of Loop of Henle.
  - TransCellular Pathway
  - Involves 3 Steps:
    - Na^+ *Passively* Diffuses from Tubule Lumen (Down an Electrochemical Gradient)→ Tubule Cell
    - Na^+ *Actively* Transported across Basolateral Membrane → Interstitium (By Na^+/K^+-ATPase)
    - Na^+ (+Water & Other Solutes) Reabsorbed from Interstitium → Peritubular Capillaries.



Step 3 – Tubular Secretion:

- **Important For:**
  - Disposing of Substances That Weren't Filtered (or Weren't Filtered Enough)
    - Eg. Drugs (eg. Penecillin)
  - Eliminating 'Bad' Substances that have been Passively Reabsorbed
    - Eg. Urea, Uric Acid, etc.
  - Removing Excess K^+ ions.
  - Controlling Blood pH
- **Proximal Tubules:**
  - Site of Secretion of ***Organic Acids/Bases*** (Bile Salts, Oxalate, Uric Acid, etc)
- **Renal Tubules:**
  - Secretion of K^+
  - Secretion of H^+
  - Secretion of Drugs/Toxins (eg. Penecillin)

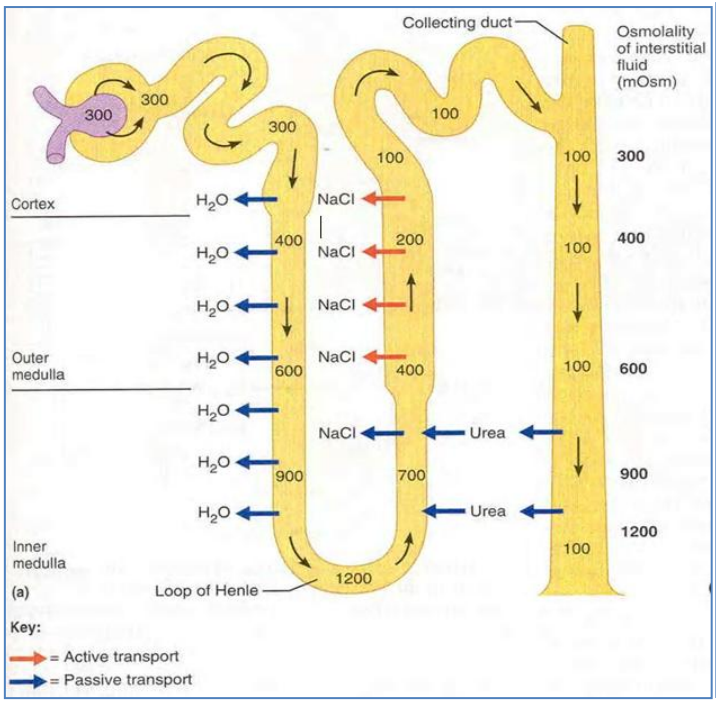


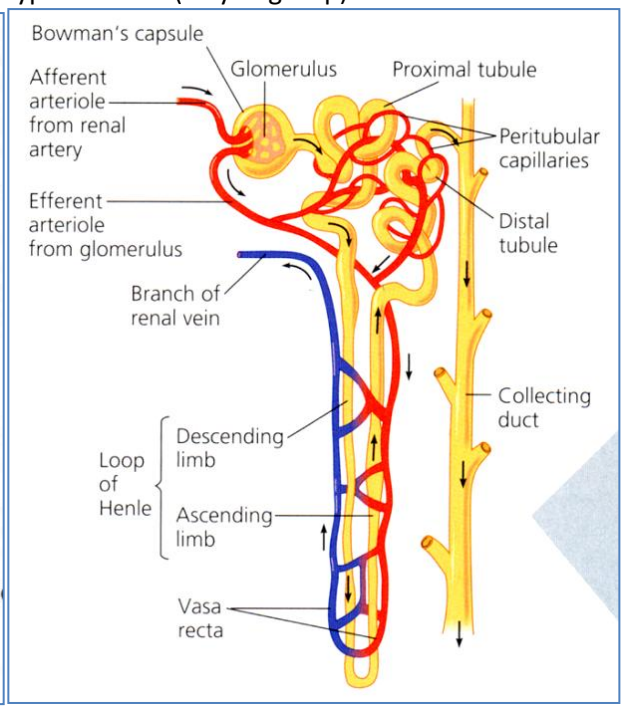
Regulating Urine Volume:

- Kidneys aim to keep Solute-Load (OSMOLALITY) in Blood at around 300mOsm (miliosmols)
- The Kidneys can Regulate the Volume & Nature of Urine Produced...
- **Water Balance:**
  - **Conserve:**
    - By Producing Low Volumes of Concentrated Urine.
  - **Excrete Excess:**
    - By Producing High Volumes of Dilute Urine.

- **The Loop Of Henle:**
  - Actively Creates a High Osmotic Conc. Of Solutes in Interstitial Space of Medulla.
  - **Descending Limb:**
    - Permeable to Water – H_2O Passively Flows into Interstitium (Then →Vasa Recta)
    - Therefore, Desc.Limb Contents Become Progressively More Hyperosmotic (Concentrated)
  - **Ascending Limb:**
    - Active Na^+ Transport From Tubule Lumen→ Tubule Cell →Interstitium (Then→Vasa Recta)
    - Therefore Asc.Limb Contents Become Progressively More Hypo-Osmotic (Diluted)

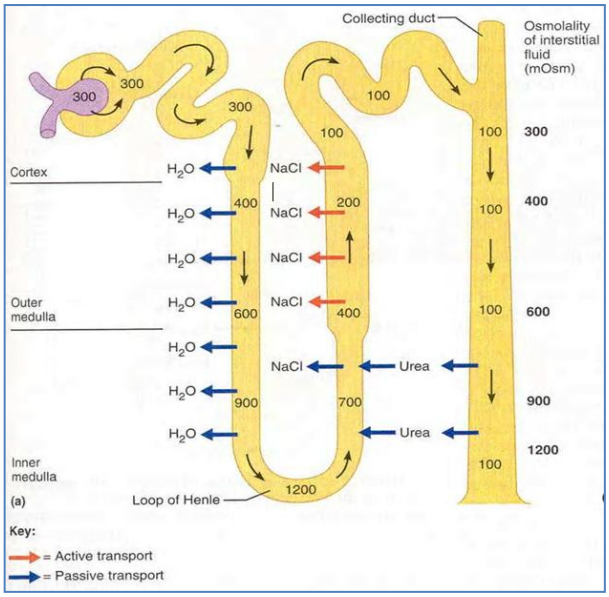
- **The 'Vasa Recta':**
  - Runs ***"Counter-Current"*** to the Loop of Henle.
    - Descending Vasa Recta = Parallel With Ascending Loop of Henle
    - Ascending Vasa Recta = Parallel With Descending Loop of Henle
  - **Descending Vasa Recta:**
    - Absorbs the *Actively-Transported* Na^+ (From Asc.Loop of Henle)
    - Absorbs the *Co-Transported* K^+ & Cl^-
    - *Loses* Some H_2O
      - -Therefore Becomes More Hyper-Osmotic (As you go down)
  - **Ascending Vasa Recta:**
    - Absorbs the H_2O (Lost through Desc.Limb of Loop of Henle)
    - *Loses* Some of the Salts/Ions into the Interstitium. (Na^+, Cl^-, K^+)
      - -Therefore Becomes More Hypo-Osmotic (As you go Up)



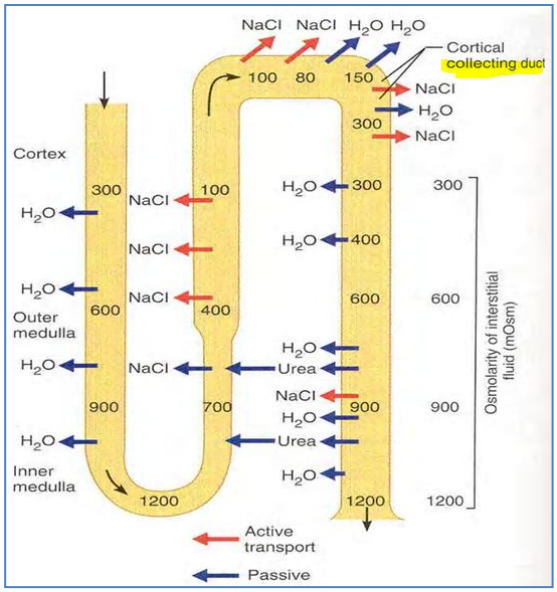


- **Anti-Diuretic Hormone (ADH)** (Aka: "Vasopressin"):
  - Made by Posterior Pituitary (In Response to Angiotensin-II)
  - Primary Regulator of Urine Volume
  - **Affects on Distal & Collecting Ducts:**
    - Distal Tubules & Collecting Ducts are Normally *Impermeable to H_2O.*
    - However, the Presence of ADH → ↑Permeability to H_2O.
      - ↑Permeability to H_2O + High [Solute] in Medulla →H_2O Reabsorption (From Collecting Duct→ Interstitium →Blood)

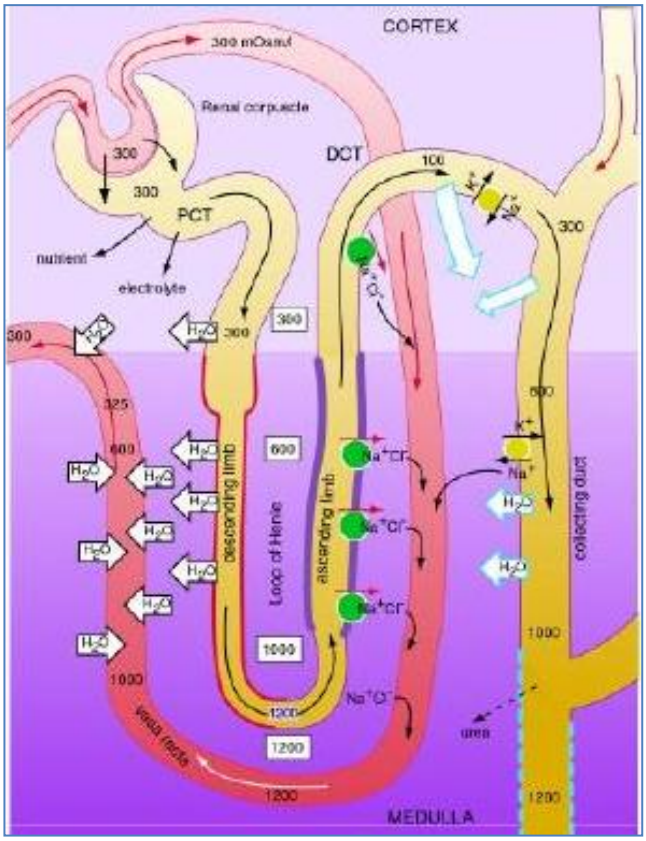
Absence of ADH



Presence of ADH

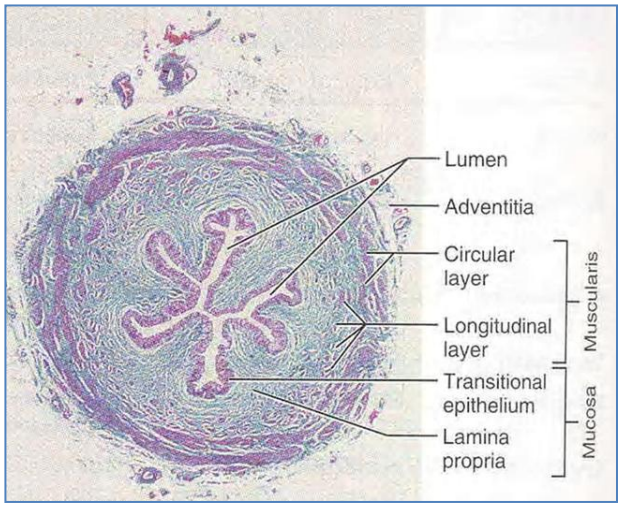


- **Aldosterone:**
  - Released from Adrenal Cortex (In Response to Angiotensin-II)
  - Activates Na^+/K^+-ATPase's in the Distal Tubules & Collecting Ducts.
  - Increases Reabsorption of Na^+ & Cl^- from Distal Tubule→Interstitium
  - – This Movement of Na^+ →↑Osmolarity of Interstitium → Facilitates H_2O Reabsorption



Excretion of Urine From Kidneys:

- Collecting Ducts → Large *Papillary Ducts* → Minor Calyces
- Stretch of Calyces Initiates *Peristaltic Contractions* → Spreads through Renal Pelvis → Ureters → Bladder.
- **The Ureters:**
    - Convey urine from Kidneys to Bladder
    - **3 Layers:**
        - Transitional Epithelium
        - Muscularis (Inner Longitudinal & Outer Circular)
        - External Fibrous Adventitia



- **The Bladder:**
    - Smooth Muscular Sac
    - Very Distensible
    - Holds ≈ 500mL of urine.
    - **3 Layers:**
        - Transitional Epithelium
        - Thick Smooth Muscle (Detrusor Muscle)
        - Fibrous Adventitia

- **The Urethra:**
    - Thin-Walled Muscular Tube.
    - Drains Urine from Bladder →Outside
    - **Sphincters:**
        - **Internal Urethral Sphincter**
            - @ Bladder-Urethra Junction
            - Prevents leakage between urinations.
        - **External Urethral Sphincter**
            - @ Urethra-Pelvic Diaphragm Junction
            - Voluntary

ELECTROLYTE BALANCE:

Significant Electrolytes:

- **Na^+** = High Extracellular Concentration
- **Cl^-** = High Extracellular Concentration
- **K^+** = High Intracellular Concentration (**NB:** too high *Extracellular* K^+ interferes with Cardiac Function = Fatal)

Why Maintain Electrolytes

- **Na^+** = Important for Heart & Nerve Function/Cellular Transport
- **K^+** = Important for Heart Function/Cellular Transport
- **Ca^+** = Important for Muscle, Heart & Nerve Function/Bone Formation
- **Mg^+** = Important for AcetylCholine Release → Important for Neural & Cardiac Function
- **HPO_4^{2-}** = Important for Bone Formation (Bone salts – primarily calcium & phosphates)

Na^+: The Primary Extracellular Electrolyte:

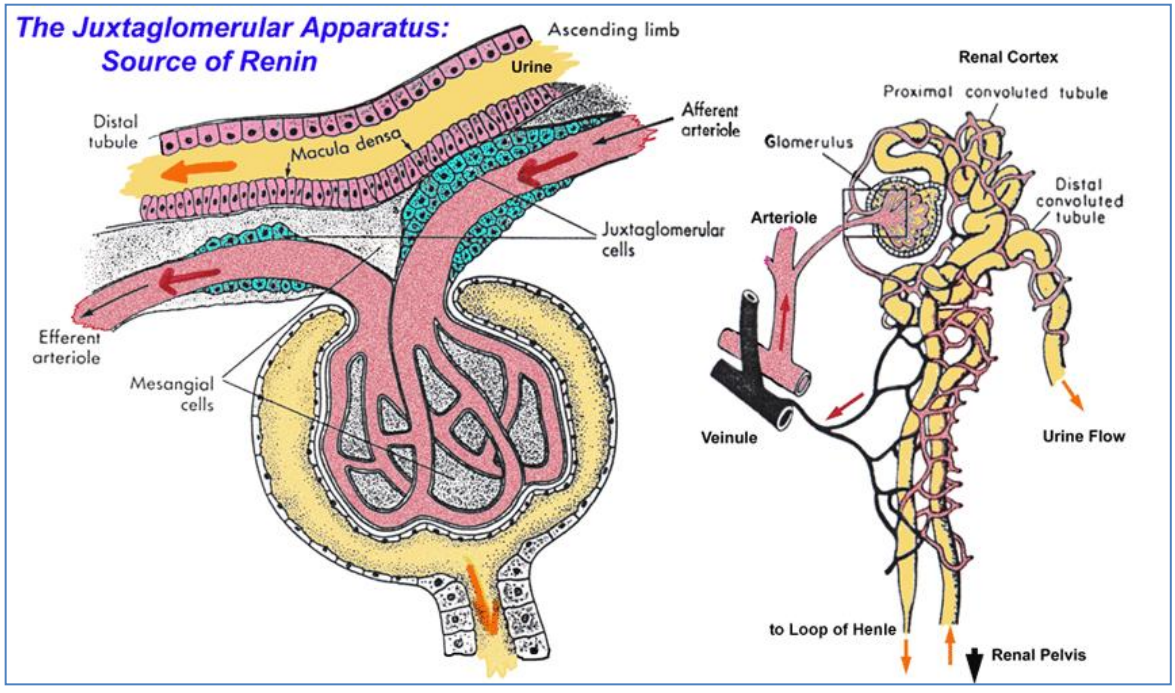
- Primary role in Fluid & Electrolyte Balance (Because Water Follows Na^+ Movement)
- Extracellular [Na^+] is normally stable, Regulated by levels of **Aldosterone.**
- **Aldosterone:**
  - Acts to Increase Na^+ Reabsorption from Distal & Collecting Ducts of the Nephron.
    - Also Indirectly increases Water Reabsorption.
  - Released from Adrenal Glands
  - **Released in response to:**
    - Angiotensin-II, Part of the Renin-Angiotensin System (Due to Renin Release by Kidneys)
  - **Works by ACTIVATING the Na/K-ATPases in the Distal & Collecting Ducts of the Nephrons:**
    - Activates Na^+/K^+-ATPase's in the Distal Tubules & Collecting Ducts.
    - Increases Reabsorption of Na^+ & Cl^- from Distal Tubule→Interstitium
    - – This Movement of Na^+ →↑Osmolarity of Interstitium → Facilitates H_2O Reabsorption

K^+: The Primary Intracellular Electrolyte:

- Primary Roles in Normal Neuromuscular Function, Membrane Potentials & Membrane Transport.
- **Deficient Intracellular K^+:**
  - Cell membrane will be more Negative than normal (Ie. *Hyperpolarised*)
  - Therefore it'll be harder to initialize an action potential as it takes more to reach threshold.
- **Excess Intracellular K^+:**
  - Cell membrane will be more Positive than normal (Ie. *Depolarised*)
  - Therefore it'll be easier to initialize an action potential as it takes less to reach threshold.
- **Affect on the Heart:**
  - The heart is particularly sensitive to K^+ Levels.
  - Both Too High & Too Low K^+ Levels will Disrupt Electrical Conduction of the Heart → Can be Fatal.
- **Regulating K^+ Levels:**
  - Relies solely on K^+ Secretion by the ***"Principal Cells"*** in the Collecting Ducts of the Kidneys.
  - **Principal Cells Detect [K^+] in the Blood:**
    - High Blood [K^+] → K^+ Secretion is Increased
    - High Blood [K^+] → K^+ Secretion is Decreased
  - **Adrenal Glands Detect [K^+] in the Blood:**
    - High Blood [K^+] DIRECTLY Stimulates **Aldosterone** Release from Adrenal Cortex.
  - **Aldosterone** → Activates Na^+/K^+-ATPase's in the Distal Tubules & Collecting Ducts:
    - This Increases Reabsorption of Na^+, Cl^- & H_2O from Distal Tubule→Interstitium
    - But ALSO causes Secretion of K^+ into the Filtrate.

The Renin-Angiotensin System (RAS): - Regulates Extracellular Fluid Volume & Systemic Blood Pressure

- **The Juxtaglomerular ("beside the glomerulus") Apparatus:**
  - The 'sensor' for the RAS.
  - A region in the Nephron containing 2 Types of Receptor Cells:
    - **1. Juxtaglomerular Cells:**
      - **Mechanoreceptors** – Detect Changes in Blood Pressure in Afferent Arteriole.
        - They are essentially enlarged Smooth-Muscle Cells
        - They contain Secretory Granules of 'Renin'.
      - **Release Renin** in response to:
        - *LOW BLOOD PRESSURE* in the *AFFARENT ARTERIOLE*. (Reduced Stretch – Maybe due to a significant drop in Systemic BP)
        - *DIRECT SYMPATHETIC STIMULATION* of JG-Cells (By Renal Sympathetic Nerves)
        - *ANGIOTENSIN-II* (Direct Stimulation of JG-Cells)
      - **Renin Release Leads To:**
        - Systemic Vasoconstriction (by Angiotensin-II) → Increase in Blood Pressure.
    - **2. Macula Densa:**
      - **Osmoreceptors** – Detect Osmolarity of Distal Tubule Contents.
        - They are a modified epithelium of the Distal Tubule.
        - They are Tall & Densely packed (Compared to the normal Simple Cuboidal)
      - **Stimulate Renin Release** from JG-Cells in response to:
        - *HIGH FILTRATE OSMOLARITY.*
        - *HIGH FILTRATE FLOW RATE* (High flow rate gives the illusion of High Osmolarity as more solutes come in contact with the cells per unit time.)
      - **Renin Release Leads To:**
        - Systemic Vasoconstriction (by Angiotensin-II)
          - Therefore Vasoconstriction of Renal Arteries
          - Therefore Decrease in GFR:
            - Decreases Filtrate Flow Rate
            - Decreases Filtrate Osmolarity (as there is more time for solute reabsorption)
      - **NB: Macula Densa Also Plays a Role in "Tubuloglomerular" Autoregulation of GFR:**
        - High Filtrate Flow/Osmolarity → Promotes Vasoconstriction of Aff. Arteriole
        - Low Filtrate Flow/Osmolarity → Promotes Vasodilation of Aff. Arteriole



Functional Anatomy of the Urinary System

Urinary System - General Functions:

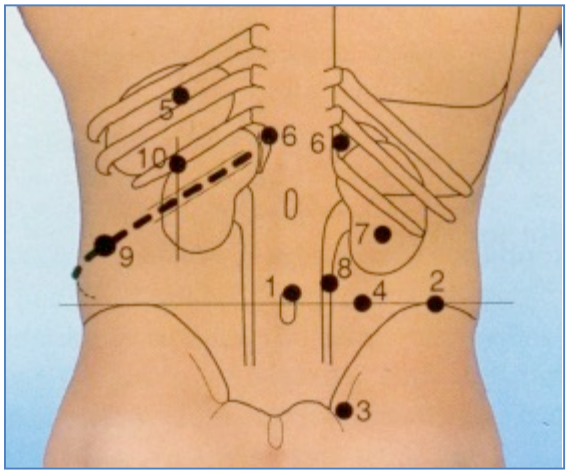
- Filter blood (Through "Ultrafiltration" – A filtration process using a porous membrane to remove particles, bacteria & viruses)
- Reabsorb Water
- Reabsorb Small Molecules
- Produce Urine
- Store & Eliminate Urine
- Maintain Blood Volume
- Maintains Blood pH
- Maintains Blood Pressure
- Reproduction (Males)

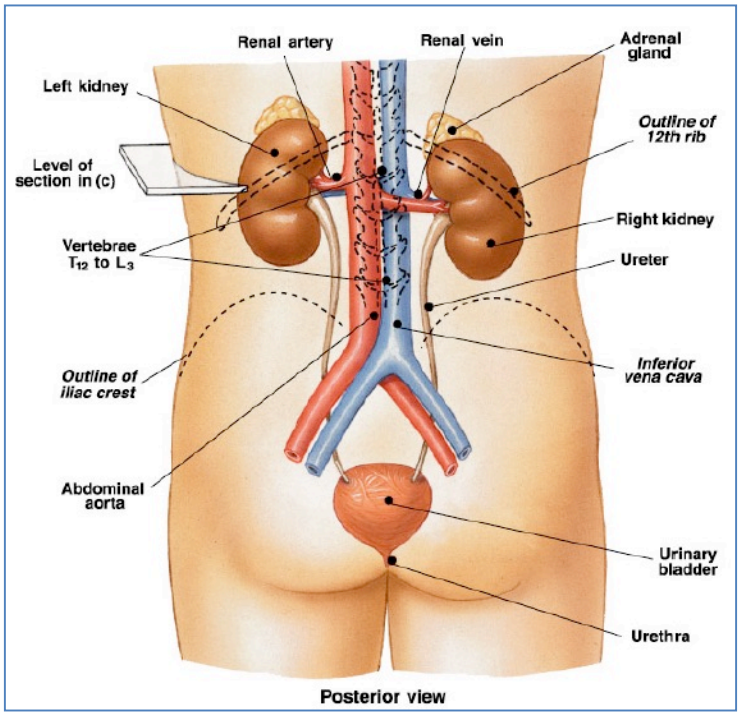
Abdominal Boundaries:

- **Superior:**
  - Thoracic Diaphragm
- **Inferior:**
  - Pelvic Diaphragm
- **Anterior:**
  - Abdominal Muscles
  - Costal Margin
- **Posterior:**
  - 'Erector' Back Muscles
  - Quadratus Lumborum
  - Iliac Crest

Surface Projections:

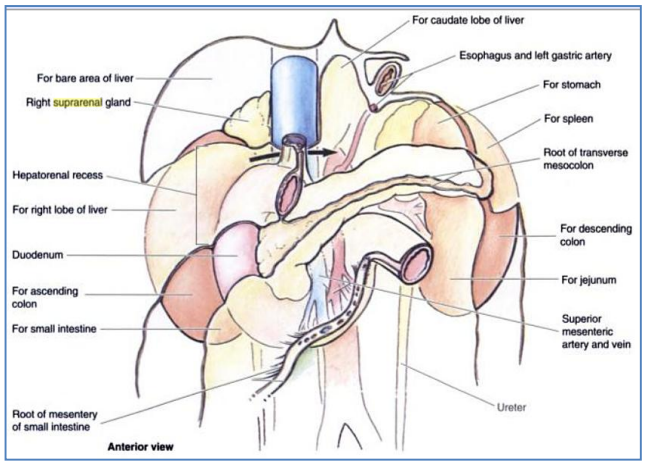
- ***Transpyloric Plane*** **(Transverse line @ T12):**
  - Hilum of L-Kidney
  - Superior Pole of R-Kidney
- ***Median Line*** **(Midline):**
  - Hilum of Kidneys ≈ 5cm from Midline
  - Slightly Splayed Outwards (further from midline at inferior pole)
  - Ureters ≈ 5cm from Midline
- **Height:**
  - Kidneys lie just deep to Ribs 11 & 12.
  - Kidneys move up/down 2-3cm during deep breathing.
  - Inferior Pole of R-Kidney = a finger's breadth superior to Iliac Crest
- **Right Vs. Left:**
  - Left = Higher than Right
  - Right = Lower (The Palpable One)
  - (by ≈2.5 cm)
  - Due to liver (invades R-Abdomen)
  - Left Renal Artery – Shorter than Right (as Aorta lies to left of midline)
  - Left Renal Vein – Longer than Right (as IVC lies to right of midline)
- **Dimensions:**
  - 12 cm Long
  - 3-4 cm Thick
  - 5-6 cm Wide

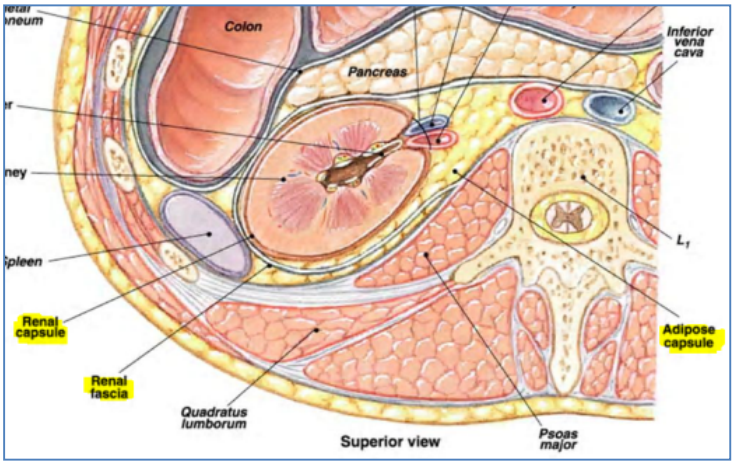




Position of Kidneys Within Abdomen:

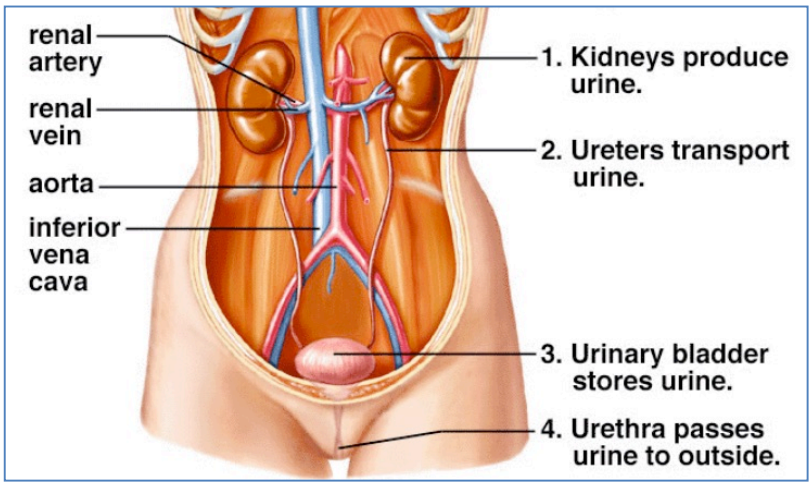
- Retroperitoneal
- Spleen on Lateral Border of L-Kidney
- Adrenal Glands on Superior Poles of Both Kidneys
- Pancreas on Anterior Margin of L-Kidney
- Duodenum on Anterior Margin of R-Kidney
- Liver on Superior Aspects of Both Kidneys
- Ascending Colon Anterior To R-Kidney
- Descending Colon Anterior To L-Kidney





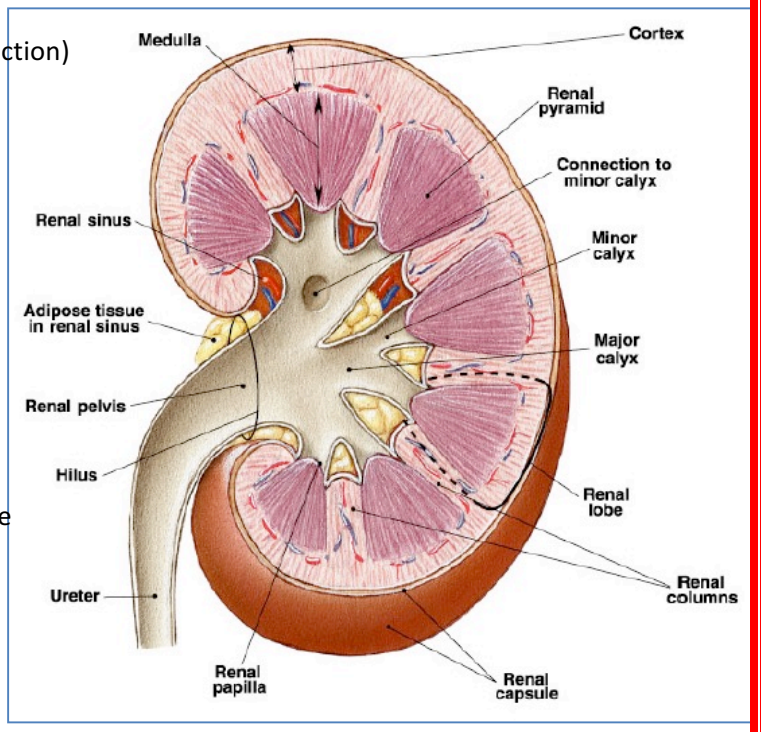
Functional Components:

- **Kidneys:**
  - Filter Blood
  - Produce Urine
  - Blood pH/Volume/Pressure Homeostasis
- **Renal Veins:**
  - Anterior
  - Drain Blood From Kidneys
- **Renal Arteries:**
  - Supply Blood to Kidneys
  - Between Vein & Hilum
- **Renal Hilums ("Opening"):**
  - Beginning of Ureters
  - Posterior
- **Ureters:**
  - Transport Urine → Bladder
- **Bladder:**
  - Stores Urine
- **Urethra:**
  - Excretion of Urine



Macroscopic Anatomy of Kidneys:

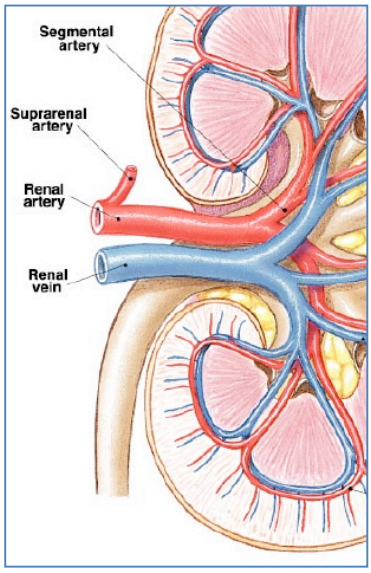
- **Encased In Fascia & Fat:**
  - (Fat – Important in Stabilisation & protection)
- **Renal Capsule:**
  - Tough, Fibrous layer surrounding the Kidney.
- **(Outer) Cortex:**
  - Contains the Filtering Apparatus:
    - Blood Vessels
    - Renal Corpuscles
    - Renal Tubules (excluding the Loop of Henle – in Medulla)
- **(Inner) Medulla:**
  - Contains the Major Blood Vessels
  - Made up of Renal Pyramids & Columns
  - Contains Collecting Ducts – Deliver Urine to Minor Calyces.
- **Renal Pyramids:**
  - Cone-shaped tissues
  - Formed by straight parallel segments of Nephrons.

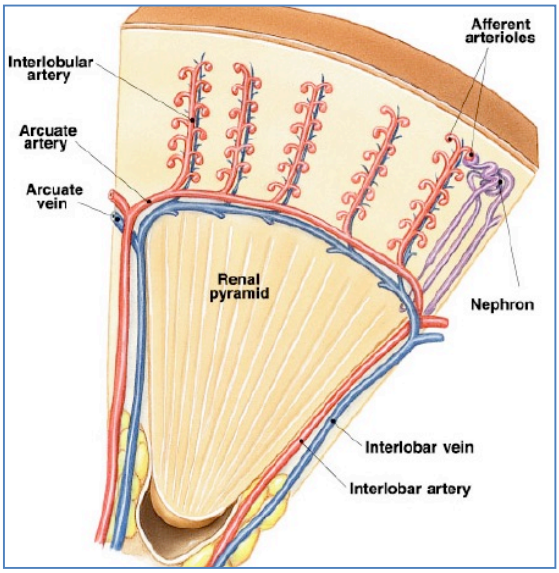


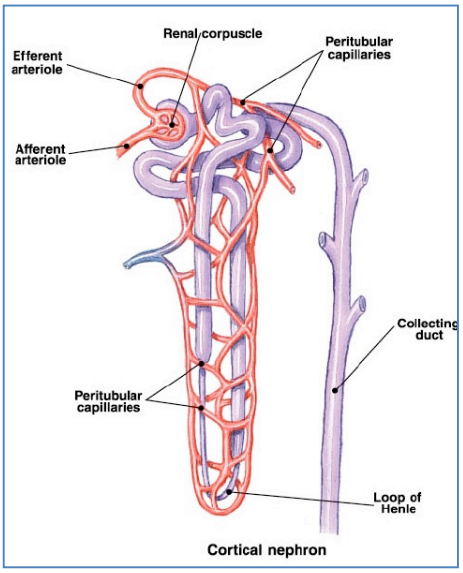
- **Renal Lobes:**
  - Portion consisting of a Renal Pyramid & the Renal Cortex Above.
- **Renal Columns:**
  - Spaces between Renal Pyramids
  - Contains Interlobar Blood Vessels
- **Renal Papilla:**
  - Where the Collecting Ducts of the Medullary Pyramids empty Urine into the renal pelvis.
- **Minor Calyx (Calyces):**
  - Transport Urine from Collecting Ducts → Major Calyces
- **Major Calyx (Calyces):**
  - Transport Urine → Renal Pelvis
- **Renal Pelvis / Hilum:**
  - Convergence of all Calyces & Connecting Ducts
  - Becomes the Ureter as it Exits the Kidney.

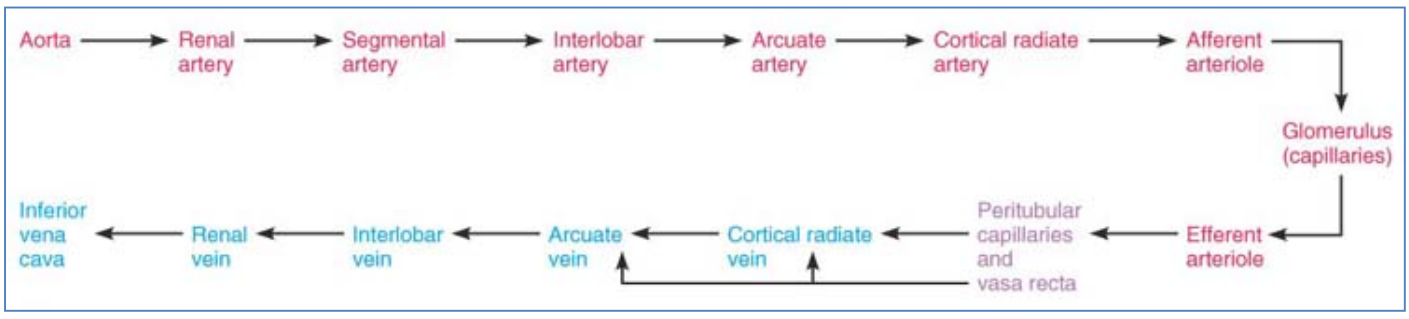
Microscopic Anatomy of Kidneys:

- **Microvascular Supply:**
  - **Interlobar Arteries & Veins:**
    - Run up from the Medulla *Through* the Renal Columns
    - Each form an arc with Interlob*ular* Arteries/Veins.
    - 'horseshoe bends'
  - **Interlobular → Arcuate Arteries/Veins:**
    - Projections of the Interlo*bar* Arteries/Veins into the Cortex.
    - 'little dead-end streets'
  - **Afferent Arterioles:**
    - Carry blood from Interlobar Arteries → Corpuscle of the Nephron
    - 'driveways off little dead-end streets'
  - **Renal Corpuscle:**
    - ***The Glomerular Capillaries + Glomerular Capsule***
    - *Glomerular Capsule* = Little deeply-concaved membrane in which a convoluted mass of *Glomerular Capillaries* are bundled.
    - **NB:** Glomerular Capillaries are *Highly Fenestrated* → 'Leaky' → Aids in filtration.
    - Place of filtration
  - **Efferent Arterioles:**
    - Carry blood away from the Corpuscles → Peritubular Capillaries
  - **Peritubular Capillaries:**
    - Supply the rest of the Nephron (Renal Tubules & Ascending/Descending Limbs)
  - **Venules**:
    - Drain filtered blood back to Inferior Vena Cava.
    - Peritubular Capillaries→ Interlobular Venules → Arcuate Veins → Interlobar Veins → Segmental Veins →Renal Vein → IVC.

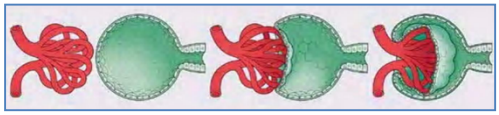




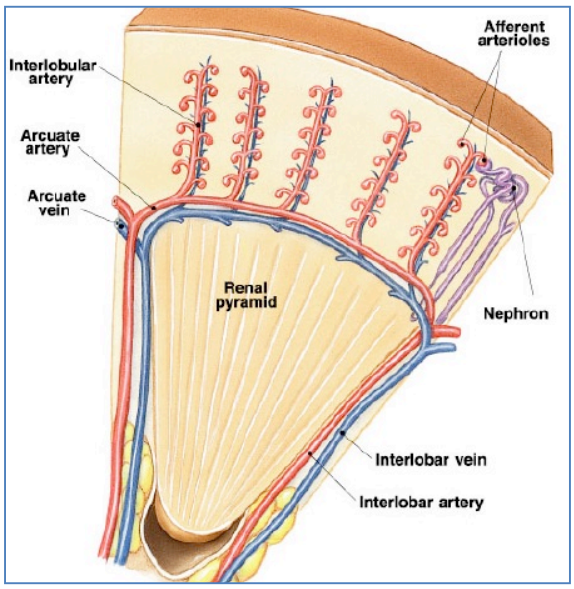


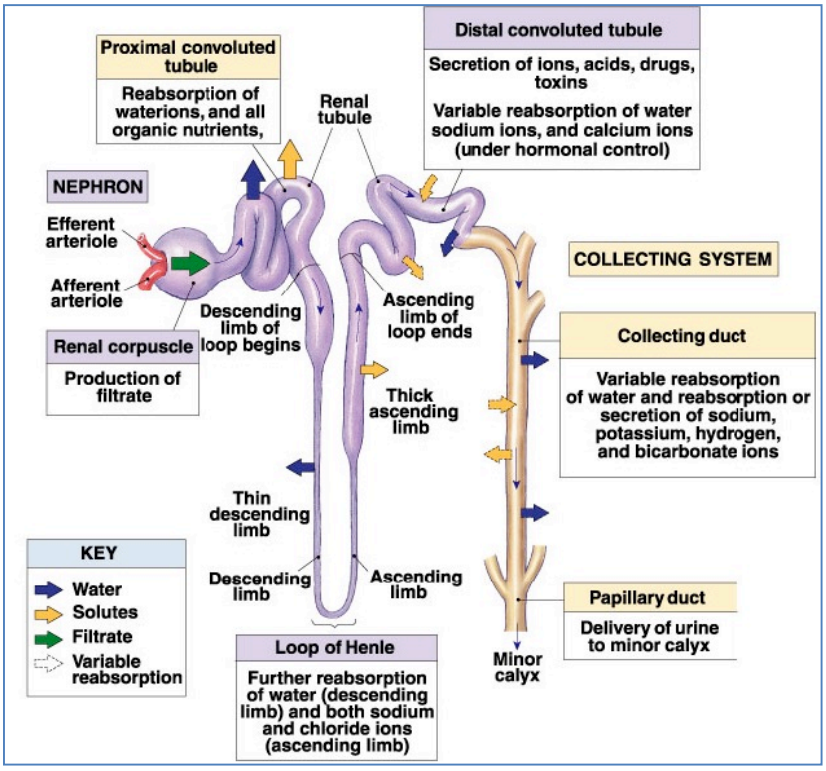


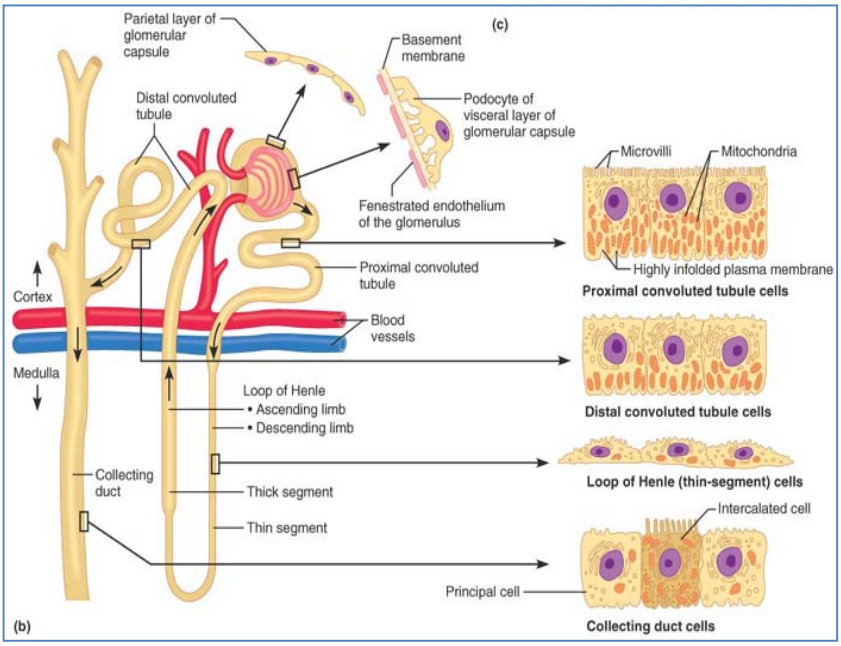
- **The Nephron:**
  - **Renal Corpuscle:**
    - ***The Glomerular Capillaries + Glomerular Capsule***
    - *Glomerular Capsule* = Little deeply-concaved membrane in which a convoluted mass of *Glomerular Capillaries* are bundled.
    - Place of filtration

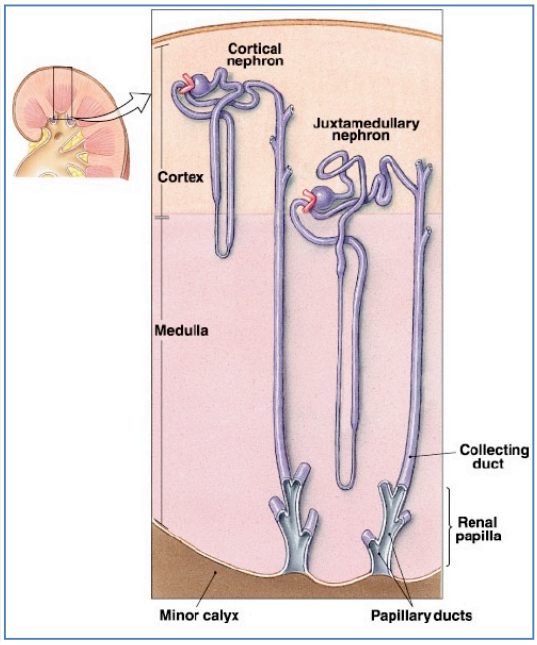


  - **Renal Tubule:**
    - **Proximal Convoluted Tubule:**
      - Reabsorption of Waterion & Organic Nutrients.
      - ***Histology:*** **Simple Cuboidal Epithelia w. Microvilli** for bulk Reabsorption.
    - **Loop of Henle:**
      - **Descending Limb (Thick & Thin):**
        - Further Water Reabsorption
        - ***Histology:*** **Simple Squamous Epithelia** → H_2O Reabsorption only.
      - **Ascending Limb (Thin & Thick):**
        - Na^+ Reabsorption
        - Cl^- Reabsorption
        - ***Histology:*** **Simple Cuboidal Epithelia** → Resorption of Ions.
    - **Distal Convoluted Tubule:**
      - Secretion of Ions, Acids, Drugs & toxins
      - Variable Reabsorption of Water, Na^+ & Ca^+ ions (under endocrine control)
      - ***Histology:*** **Simple Cuboidal Epithelia (No Microvilli)**→ Resorption of Ions.
  - **Collecting System:**
    - **Collecting Duct:**
      - Variable Reabsorption of Water
      - Reabsorption OR Secretion of Na^+, K^+, H^+ & HCO_3^-.
      - ***Histology:*** **Simple Cuboidal – Columnar Epithelia** for reabsorption of H_2O, Urea & other Ions.
    - **Papillary Duct:**
      - Carries urine to Minor Calyces.



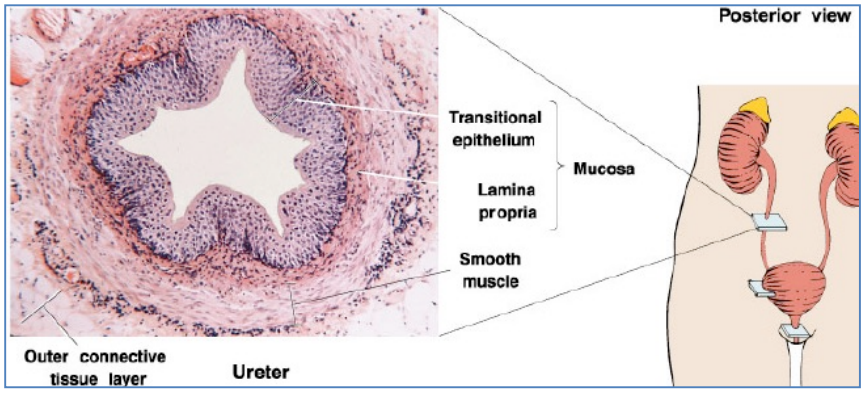


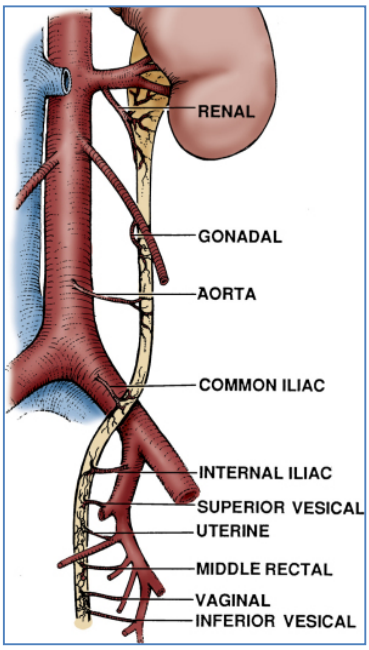




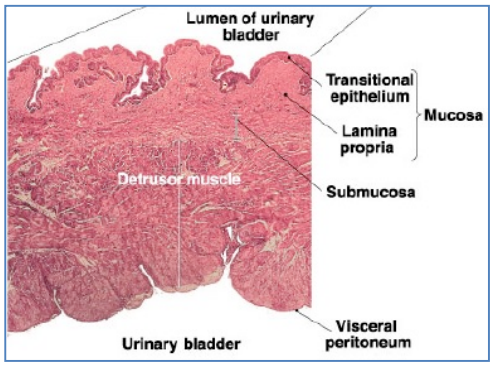
Functional Anatomy:

- **Ureters**
  - Carry Urine from Renal Pelvis → Bladder
  - 30-35cm Long
  - **Muscular Tubes:**
    - Peristaltic Contractions – help urine flow
  - **Histology:**
    - Mucosa = Transitional Epithelium
    - Smooth Muscle Outer Layer
  - **Abdominal Part** – Runs just anterior to Psoas Major
  - **Pelvic Part** – From below Bifurcation of Common Iliac Artery
  - **3 Sites of Constriction:** - (where calculi can be caught)
    - 1. Junction with Renal Pelvis (Hilum)
    - 2. Entry to Bony Pelvis (Over the Pelvic Brim)
    - 3. Entry to Bladder
  - **Blood Supply:**
    - Upper Ureter – Branch of Renal Artery
    - Middle Ureter – Branches of Gonadal (Ovarian/Testicular), Aorta & Common Iliac Arteries.
    - Lower Ureter – Branches of Internal Iliac

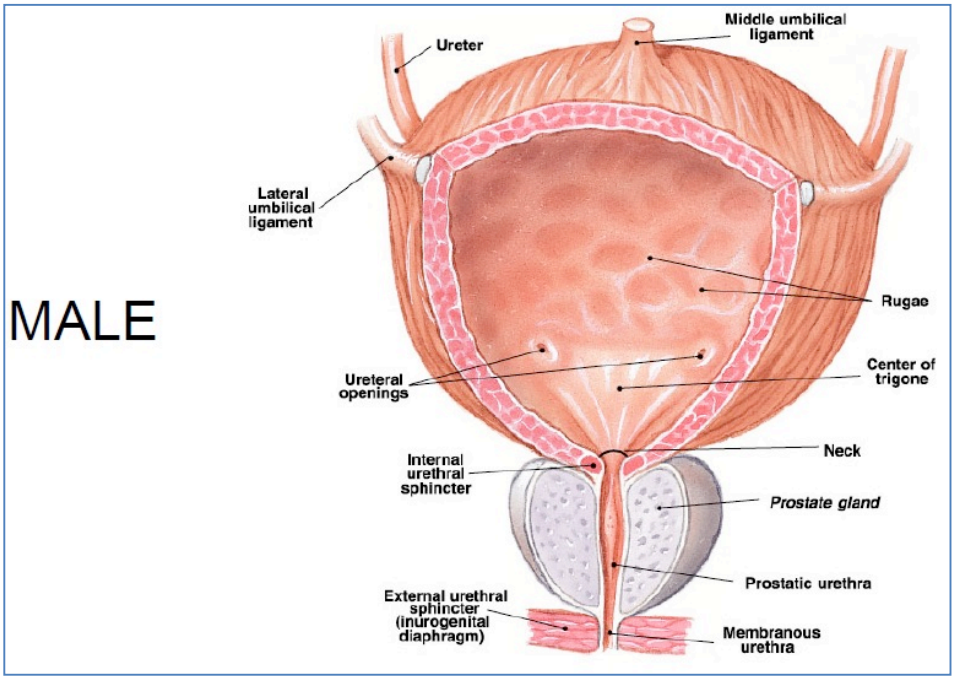




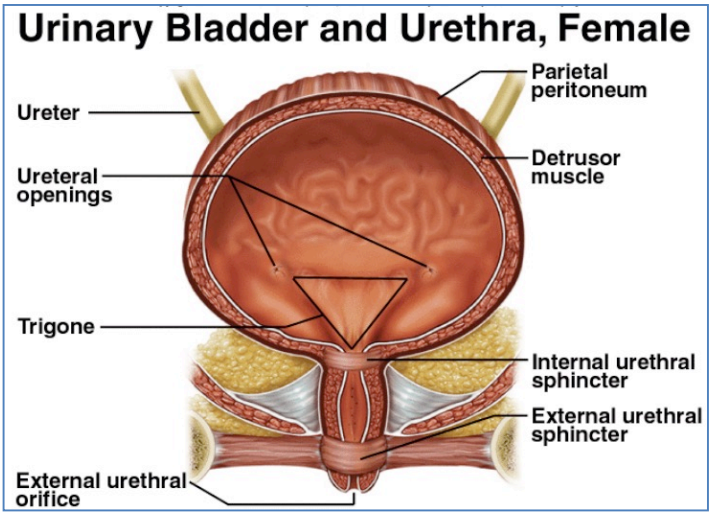
- **Bladder:**
  - **General Info:**
    - Muscular-Walled Sac (**Detrusor Muscle)**
    - Inferior to Peritoneum
    - Ureter Openings – Just Below Pubic Tubercles.
    - **Trigone:**
      - Smooth Triangular Area on lower-posterior bladder wall
      - Triangle defined by openings of Ureters (top) & Urethra (bottom)
    - **Apex** at bottom
    - **Neck** – Entry to Urethra
      - Guarded by **Internal Urethral Sphincter**
    - **Body**
    - **Fundus –** Above Ureteral Openings.



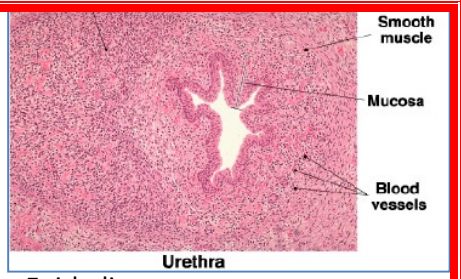
  - **Histology:**
    - Mucosa = Transitional Epithelium
    - Muscular Layer = Detrusor Muscle
    - Visceral Peritoneum
  - **Male:**
    - **Rectovesical Pouch** – Space between Bladder & Rectum
    - **Blood Supply** – Internal Iliac Artery

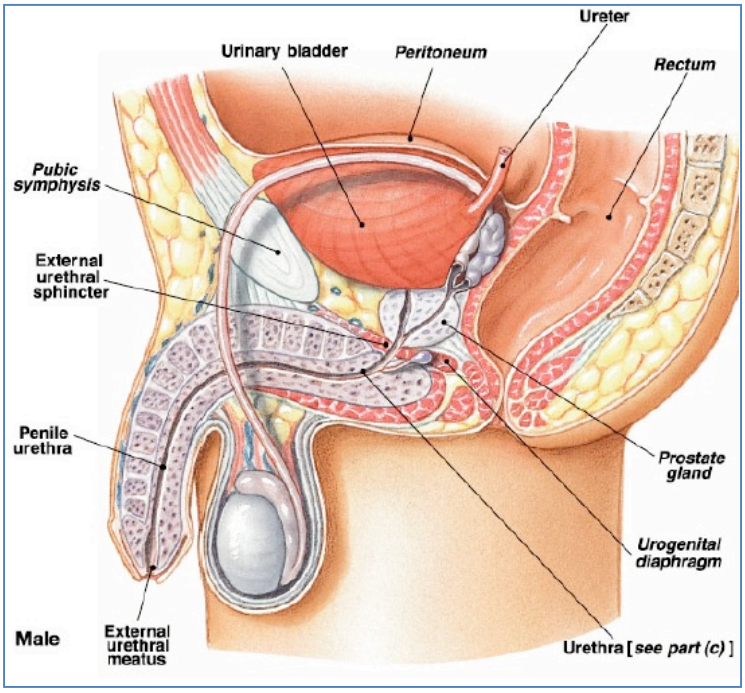


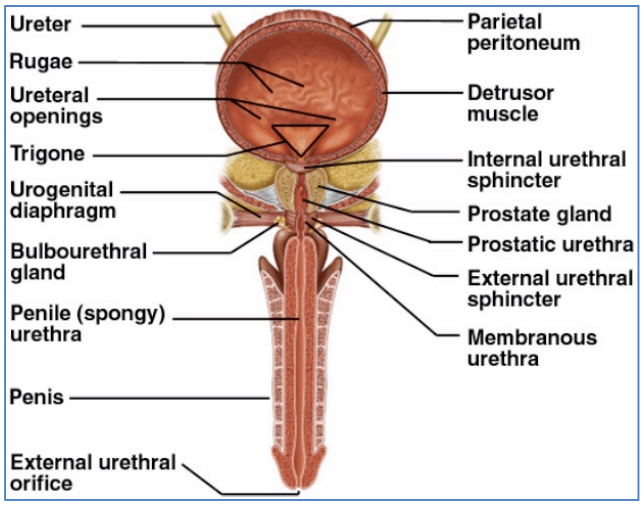
  - **Female:**
    - **VesicoUterine Pouch** – Space between Bladder & Uterus
    - **Blood Supply** – Internal Iliac & Vaginal Arteries.



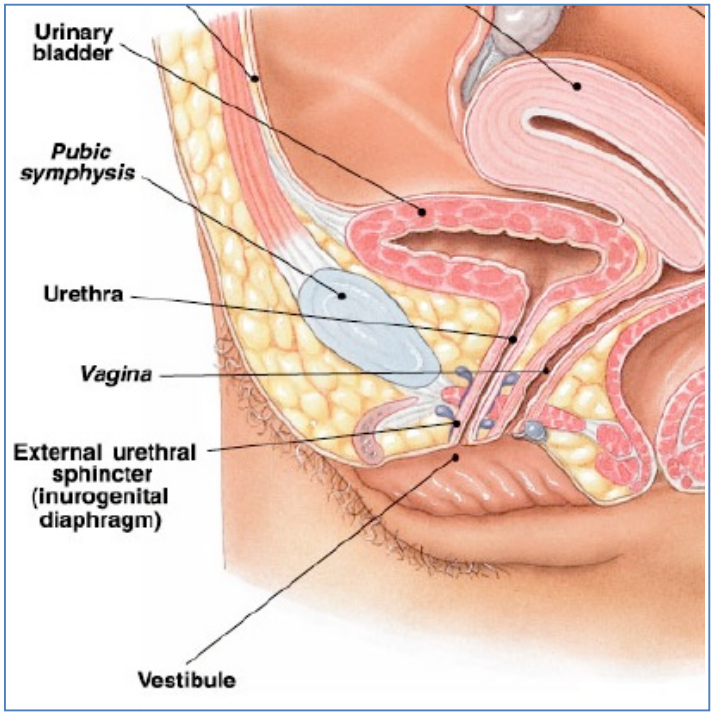
- **Urethra:**
  - **Male:**
    - 20cm Long
    - Integrated with Repro. System
    - **3 Parts + Histology:**
      - Prostatic Urethra - Transitional Epithelium
      - Membranous Urethra - Pseudostratified Columnar Epithelium
      - Spongy (Penile) Urethra - Pseudostratified Columnar Epithelium







  - **Female:**
    - 2-3cm Long
    - **Histology:**
      - Mostly Pseudostratified Columnar Epithelium
      - Stratified Squamous (external orifice)
    - Separate from Repro. System

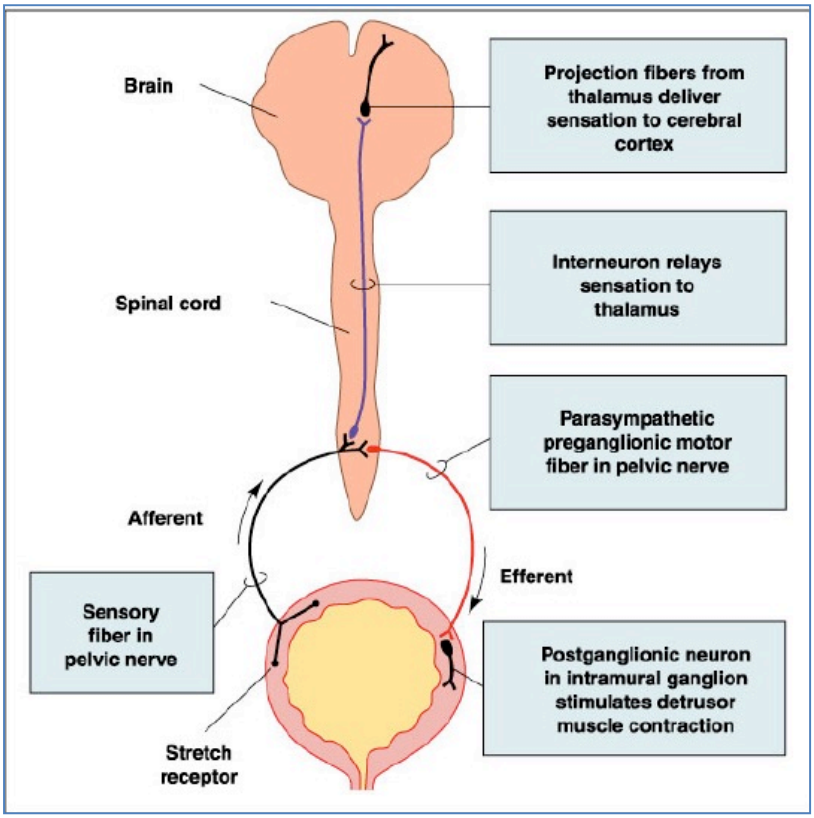


Lymphatic Drainage of Urinary System:

- Mostly *Lumbar* Nodes

Micturition Reflex (Urination):

- Voluntary (in Health Adults)
- Involuntary (In Infants + Neurological Injury) → Urinary Incontinence
- A *'Learned'* Process (develops @ 2-3yrs)
- **2 Phases:**
  - Collection Phase
  - Micturition Phase
- **Reflex Process:**
  - Facilitated / Inhibited by Higher Brain Centres
  - The *Phase* of the system - dependent on:
    - 1. A Conscious Signal from the brain and
    - 2. The *Firing Rate* of sensory fibres from the bladder and urethra.
  - **Empty Bladder:** Afferent Firing Rate ↓→ excitation of the outlet (the sphincter and urethra), and relaxation of the bladder.
  - **Full Bladder:** Afferent Firing Rate ↑ → Urinary Urge.
    - **Voluntary Urination:** Person Consciously Initiates peeing → Bladder contracts +Sphincters relax.
    - Urination Continues until Bladder is Empty → Bladder Relaxes + Sphincters Contract →Collection Phase



Role of the Kidneys in Fluid & Electrolyte Balance

Why Maintain Fluid & Electrolyte Balance?:

- Critical for Normal Cell Function
- Critical for Chemical Stability (Homeostasis) of Surrounding Fluids
- *Electrolyte Balance (Particularly **Na^+** & **K^+**) – Critical for function of Excitable Tissues
- Critical for Blood Pressure Homeostasis

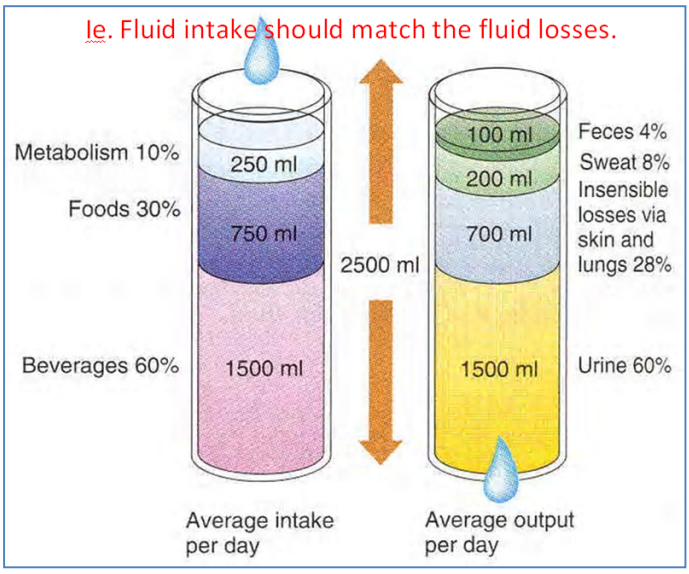
FLUID BALANCE:

Normal Adult Fluid Volume ≈ 40 Litres:

- **Extracellular** = 15 Litres
  - 3 Litres = **Plasma**
  - 12 Litres = **Interstitial Fluid**
- **Intracellular** = 25 Litres

Water Intake & Output:

- **Intake:**
  - Produced in Metabolism
  - Contained in Foods
  - Consumed Fluids
- **Output:**
  - Faeces (Obligatory)
  - Sweat (Obligatory)
  - Lungs (Obligatory)
  - Urine



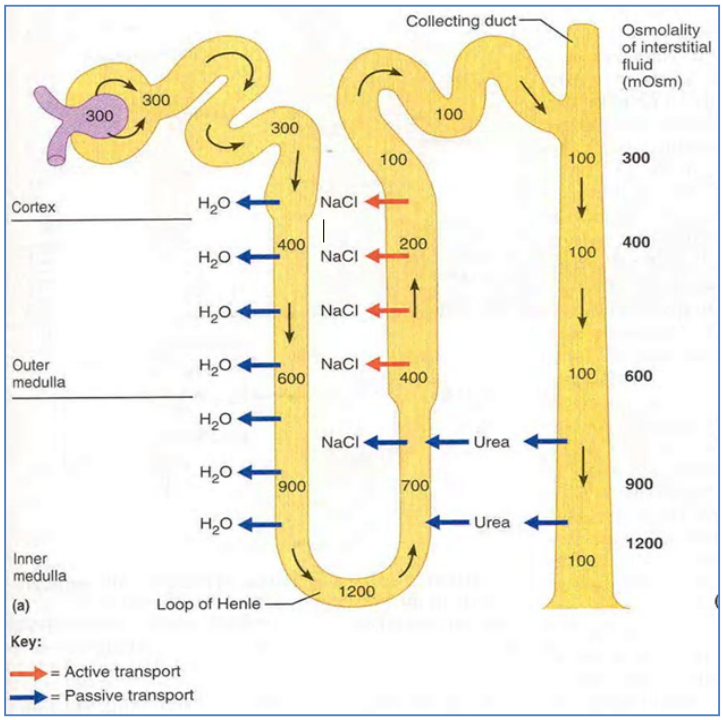
Regulation of Water Intake (Thirst):

- **Thirst Triggered by 2 Things:**
  - **1.** A 10%+ Decrease in Plasma Volume....OR
  - **2.** A 1-2% Increase in Plasma Osmolarity
- **1. Decreased Plasma Volume → Reduced Blood Flow to Salivary Glands → *"Dry Mouth"* → Triggers Thirst Centre in Hypothalamus.**
- **2. Increased Plasma Osmolarity → Directly Triggers Thirst Centre in Hypothalamus.**

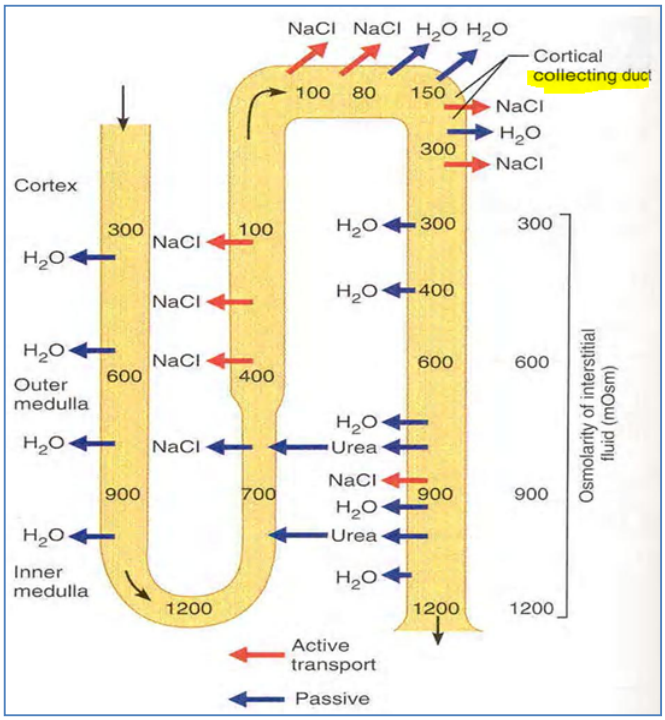
Regulation of Water Output:

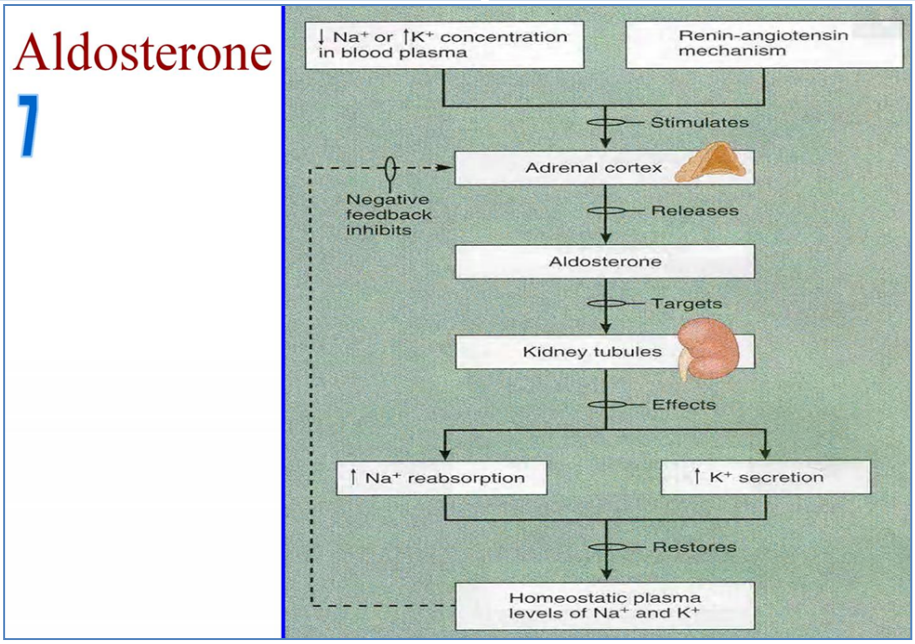
- A lot of water loss is unavoidable.
- However, the rest (lost through Urine) is Regulated by levels of **Anti-Diuretic Hormone (ADH)**
- **Anti-Diuretic Hormone (ADH):**
  - Acts to increase Blood Volume.
  - Released from the Posterior Pituitary Gland
  - **Released in response to:**
    - Stimulation of Osmoreceptors in Hypothalamus due to Increased Plasma Osmolarity
    - Stimulation of Hypothalamus by Angiotensin-II (Due to Renin Release by Kidneys)
  - **Works by INCREASING H_2O Permeability of Distal & Collecting Ducts:**
    - Distal Tubules & Collecting Ducts are Normally *Impermeable to H_2O.*
    - However, the Presence of ADH → ↑Permeability to H_2O.
    - This ↑Permeability to H_2O + High [Solute] in Medulla →H_2O Reabsorption (From Collecting Duct→ Interstitium →Blood)
- **NB: Aldosterone** (Released by Adrenal Gland in response to Angiotensin-II) Acts in conjunction with ADH by Increasing Na^+ & Cl^- Reabsorption (↑Medullary Interstitial Osmolarity) to facilitate more H_2O Reabsorption.

Absence of ADH



Presence of ADH (+Aldosterone)





Diuretic Drugs:

- Drugs that Decrease Sodium Reabsorption in the Kidneys →
  - Cause a Net Loss of Na^+ and therefore Water as well.
- **Why Use Diuretics?:**
  - Treatment of Oedema
  - Treatment of Hypertension
  - Treatment of Acute Renal Failure
  - Treatment of Cardiac Failure
- **Types of Diuretics:**
  - **Loop Diuretics:** (Most Powerful)
    - Diuretics that act on the Loop of Henle
    - **Act By:**
      - Inhibiting the Na/K/Cl-Transporter in the Thick-Ascending Loop of Henle.
      - This prevents NaCl Resorption into Interstitium (Therefore Prevents H_2O Resorption)
      - *Prevents* the Normal High Medullary NaCl Concentration that ordinarily facilitates Water Resorption (under the influence of ADH).
    - **Used Primarily For:**
      - Hypertension
      - Heart Failure
    - **Side Effects:**
      - Hypokalaemia (Due to K^+ due to Increased Na^+ delivery to Distal Tubules)
        - May require Potassium Supplements.
        - Or the coupled use of **K^+-Sparing Diuretics**.

  - **Thiazide Diuretics:**
    - Diuretics that act on the Distal Tubules
    - **Act By:**
      - Inhibiting the Na/Cl-Cotransporter.
      - This Inhibits the Reabsorption of Na^+ (and accompanying Cl^-) in the Distal Tubules.
      - Maintains a High Filtrate Osmolarity → Retaining Water in the Tubule.
    - **Used Primarily For:**
      - Acute Renal Failure
      - Cerebral Oedema

  - **Osmotic Diuretic Drugs:**
    - Inert Substances (Eg. Sugars) that are filtered by the Kidneys, but not reabsorbed.
    - Ie. They increase the Filtrate Osmolarity to Prevent Water Resorption into the Interstitium
    - **Act By:**
      - Increasing Filtrate Osmolarity – To Inhibit Passive Water Reabsorption.
      - Therefore affects the Nephron where it is Freely Permeable to Water (Proximal Tubule, Desc.Loop of Henle, & Collecting Ducts – Under the Influence of ADH).
    - **Used Primarily For:**
      - Rapid Reversal of Oedema
      - Acute Renal Failure – To maintain urine flow to prevent tubule drying/damage.
      - **Cerebral Oedema & Intraocular Pressure:**
        - Simply by increasing Plasma Osmolarity.
        - Relieves such pressures via osmosis.

ELECTROLYTE BALANCE:

Significant Electrolytes:

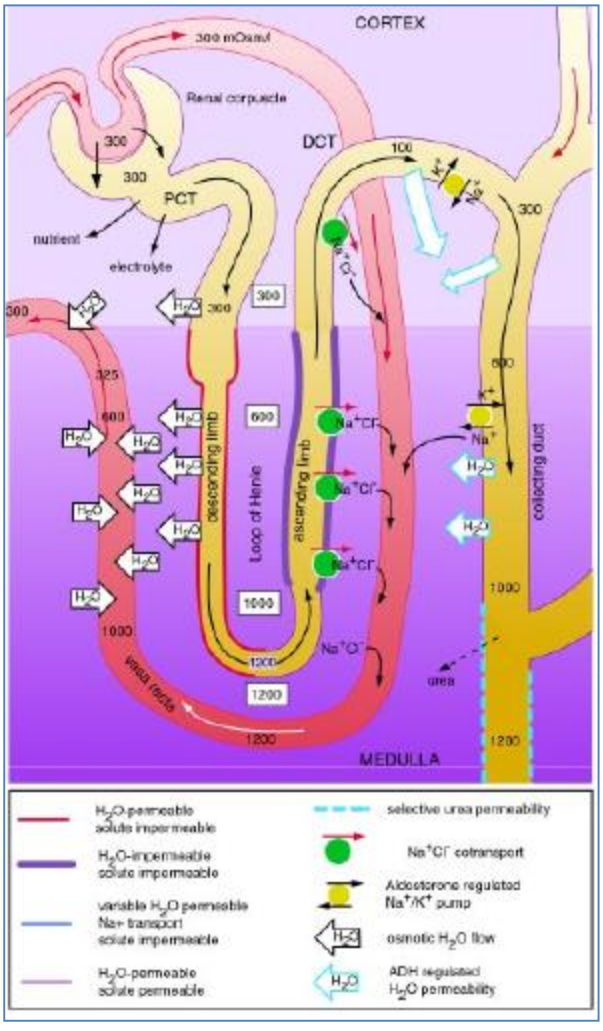
- **Na^+** = High Extracellular Concentration
- **Cl^-** = High Extracellular Concentration
- **K^+** = High Intracellular Concentration (**NB:** too high *Extracellular* K^+ interferes with Cardiac Function = Fatal)

Why Maintain Electrolytes

- **Na^+** = Important for Heart & Nerve Function/Cellular Transport
- **K^+** = Important for Heart Function/Cellular Transport
- **Ca^+** = Important for Muscle, Heart & Nerve Function/Bone Formation
- **Mg^+** = Important for AcetylCholine Release → Important for Neural & Cardiac Function
- **HPO_4^{2-}** = Important for Bone Formation (Bone salts – primarily calcium & phosphates)

Na^+: The Primary Extracellular Electrolyte:

- Primary role in Fluid & Electrolyte Balance (Because Water Follows Na^+ Movement)
- Extracellular [Na^+] is normally stable, Regulated by levels of **Aldosterone.**
- **Aldosterone:**
    - Acts to Increase Na^+ Reabsorption from Distal & Collecting Ducts of the Nephron.
        - Also Indirectly increases Water Reabsorption.
    - Released from Adrenal Glands
    - **Released in response to:**
        - Angiotensin-II, Part of the Renin-Angiotensin System (Due to Renin Release by Kidneys)
    - **Works by ACTIVATING the Na/K-ATPases in the Distal & Collecting Ducts of the Nephrons:**
        - Activates Na^+/K^+-ATPase's in the Distal Tubules & Collecting Ducts.
        - Increases Reabsorption of Na^+ & Cl^- from Distal Tubule→Interstitium
        - – This Movement of Na^+ → ↑Osmolarity of Interstitium → Facilitates H_2O Reabsorption



K^+: The Primary Intracellular Electrolyte:

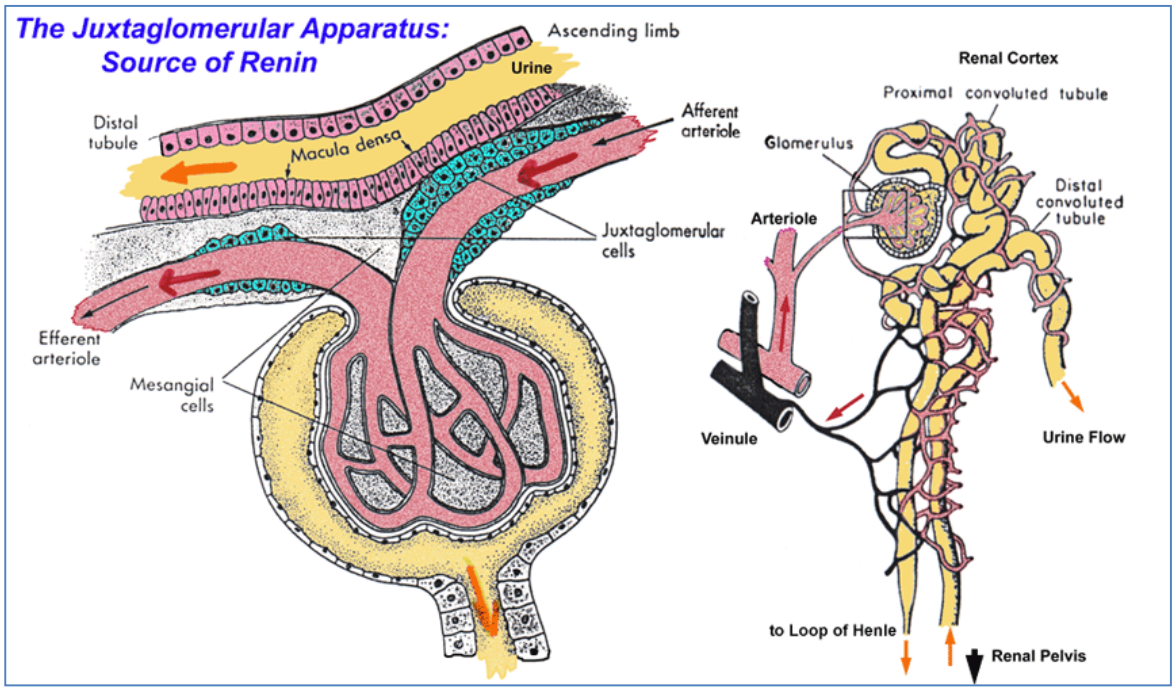
- Primary Roles in Normal Neuromuscular Function, Membrane Potentials & Membrane Transport.
- **Deficient Intracellular K^+:**
  - Cell membrane will be more Negative than normal (Ie. *Hyperpolarised*)
  - Therefore it'll be harder to initialize an action potential as it takes more to reach threshold.
- **Excess Intracellular K^+:**
  - Cell membrane will be more Positive than normal (Ie. *Depolarised*)
  - Therefore it'll be easier to initialize an action potential as it takes less to reach threshold.
- **Affect on the Heart:**
  - The heart is particularly sensitive to K^+ Levels.
  - Both Too High & Too Low K^+ Levels will Disrupt Electrical Conduction of the Heart → Can be Fatal.
- **Regulating K^+ Levels:**
  - Relies solely on K^+ Secretion by the ***"Principal Cells"*** in the Collecting Ducts of the Kidneys.
  - **Principal Cells Detect [K^+] in the Blood:**
    - High Blood [K^+] → K^+ Secretion is Increased
    - High Blood [K^+] → K^+ Secretion is Decreased
  - **Adrenal Glands Detect [K^+] in the Blood:**
    - High Blood [K^+] DIRECTLY Stimulates **Aldosterone** Release from Adrenal Cortex.
  - **Aldosterone** → Activates Na^+/K^+-ATPase's in the Distal Tubules & Collecting Ducts:
    - This Increases Reabsorption of Na^+, Cl^- & H_2O from Distal Tubule→Interstitium
    - But ALSO causes Secretion of K^+ into the Filtrate.

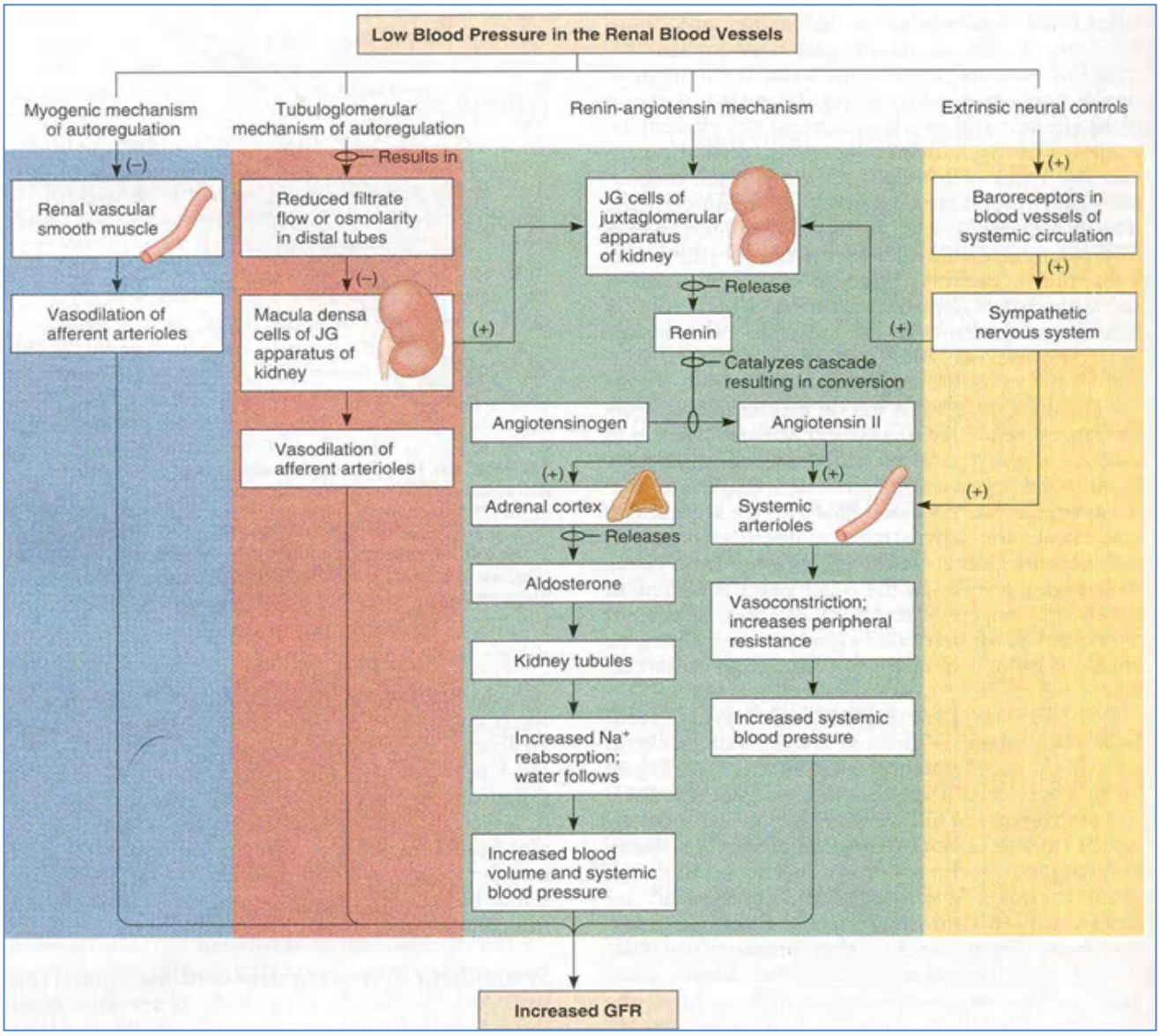
The Renin-Angiotensin System (RAS): - Regulates Extracellular Fluid Volume & Systemic Blood Pressure

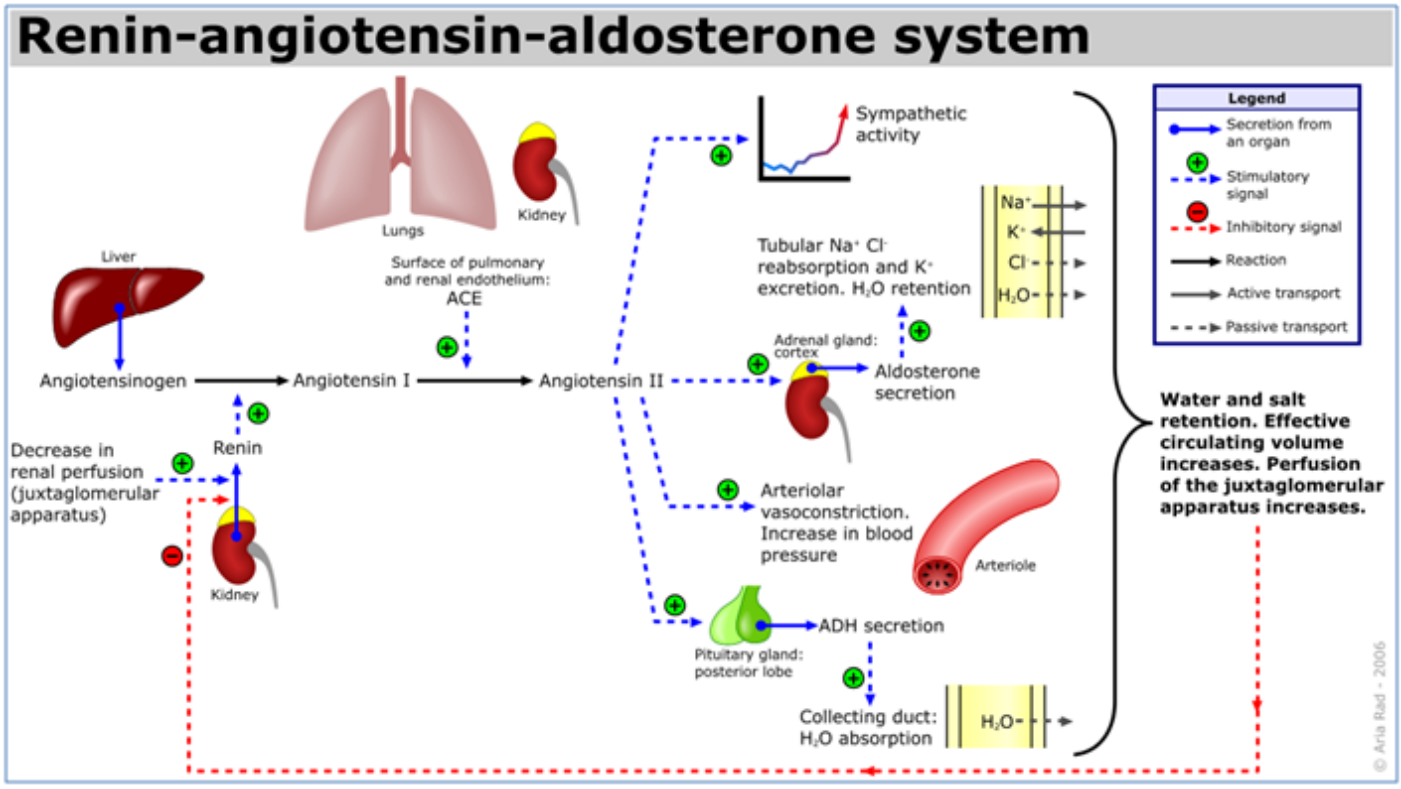
- **The Juxtaglomerular ("beside the glomerulus") Apparatus:**
  - The 'sensor' for the RAS.
  - A region in the Nephron containing 2 Types of Receptor Cells:
    - **1. Juxtaglomerular Cells:**
      - **Mechanoreceptors** – Detect Changes in Blood Pressure in Afferent Arteriole.
        - They are essentially enlarged Smooth-Muscle Cells
        - They contain Secretory Granules of 'Renin'.
      - **Release Renin** in response to:
        - *LOW BLOOD PRESSURE* in the *AFFARENT ARTERIOLE*. (Reduced Stretch – Maybe due to a significant drop in Systemic BP)
        - *DIRECT SYMPATHETIC STIMULATION* of JG-Cells (By Renal Sympathetic Nerves)
        - *ANGIOTENSIN-II* (Direct Stimulation of JG-Cells)
      - **Renin Release Leads To:**
        - Systemic Vasoconstriction (by Angiotensin-II) → Increase in Blood Pressure.

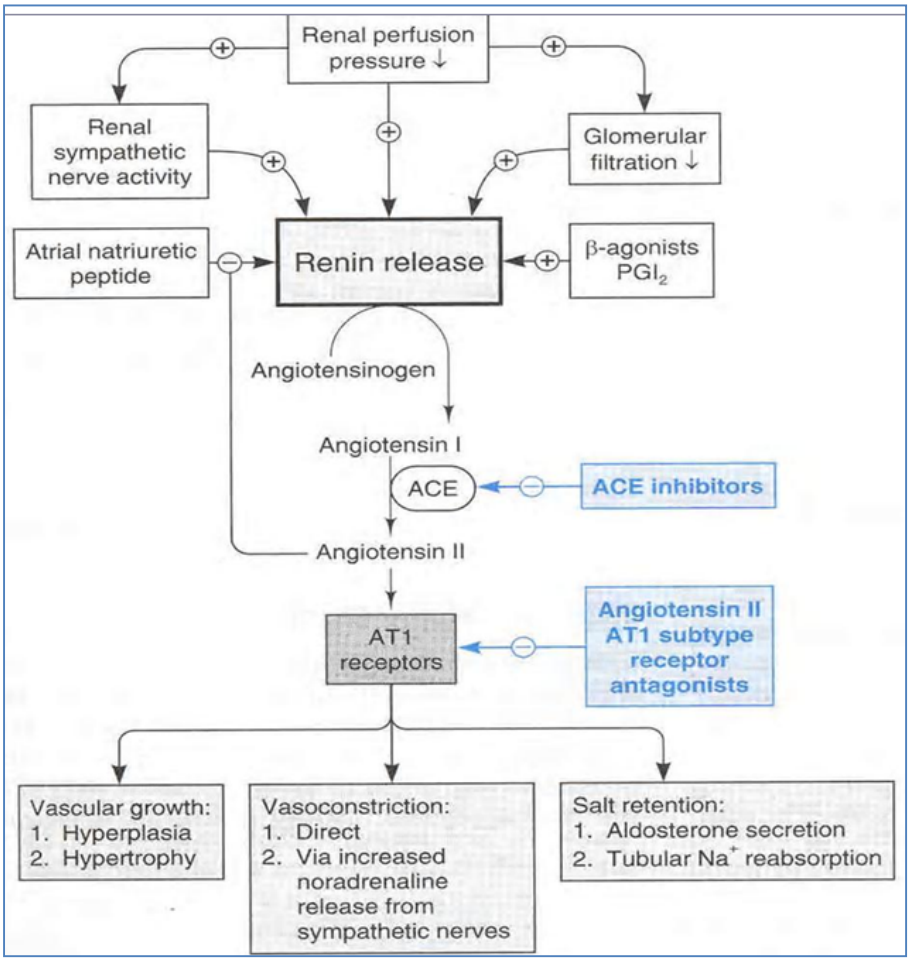
    - **2. Macula Densa:**
      - **Osmoreceptors** – Detect Osmolarity of Distal Tubule Contents.
        - They are a modified epithelium of the Distal Tubule.
        - They are Tall & Densely packed (Compared to the normal Simple Cuboidal)
      - **Stimulate Renin Release** from JG-Cells in response to:
        - *HIGH FILTRATE OSMOLARITY.*
        - *HIGH FILTRATE FLOW RATE* (High flow rate gives the illusion of High Osmolarity as more solutes come in contact with the cells per unit time.)
      - **Renin Release Leads To:**
        - Systemic Vasoconstriction (by Angiotensin-II)
          - Therefore Vasoconstriction of Renal Arteries
          - Therefore Decrease in GFR:
            - Decreases Filtrate Flow Rate
            - Decreases Filtrate Osmolarity (as there is more time for solute reabsorption)

      - **NB: Macula Densa Also Plays a Role in "Tubuloglomerular" Autoregulation of GFR:**
        - High Filtrate Flow/Osmolarity → Promotes Vasoconstriction of Aff. Arteriole
        - Low Filtrate Flow/Osmolarity → Promotes Vasodilation of Aff. Arteriole









FLUID *IMBALANCES*: Volume Vs. Osmolar

Volume:

- **Hypervolaemia:**
  - A Gain of Extracellular Fluid (And an Associated gain in Na^+)
  - **Symptoms:**
    - Hypertension
    - Oedema
  - **May Be Due To:**
    - Excessive Fluid Intake
    - Chronic Renal Failure (↓Urine Output)
    - Endocrine Imbalances (Eg. ADH & Aldosterone)
  - **Treatment:**
    - Diuretics
- **Hypovolaemia:**
  - A Loss of Extracellular Fluid (And an Associated loss of Na^+)
  - **Symptoms:**
    - Hypotension
    - Tachycardia
    - High Resp. Rate
    - Thirst
  - **May Be Due To:**
    - Insufficient Intake of Fluids
    - Haemorrhage
    - Diarrhoea
    - Vomiting
    - Endocrine Imbalances (Eg. ADH & Aldosterone)
  - **Treatment**:
    - Fluid Replacement (Saline IV Fluids or Electrolyte Drink)

Osmolar:

- **Sodium (Na^+):**
  - **Hypernatraemia:**
    - Higher-Than-Normal Blood [Na^+]
    - **May Be Due to Either:**
      - Decreased H_2O Intake/Increased H_2O Loss (Due to Reverse-Dilution Effect)
      - Over-Ingestion of Na^+
      - Renal Insufficiency
    - **Leads to:**
      - Cell-Shrinking (Due to Osmosis)
      - If due to H_2O Loss, then Hypotension → Tachycardia (to ↑Cardiac Output)
      - Excessive Thirst.
    - **Treatment:**
      - Water
  - **Hyponatraemia:**
    - Lower-Than-Normal Blood [Na^+]
    - **May be Due to Either:**
      - Loss of Na^+ from body Fluids...OR
      - Excessive Gain in Extracellular Water (Dilution Effect)
      - (Diuretic Therapy)
      - (Adrenal Insufficiency)
    - **Leads to:**
      - Cell-Swelling (Due to Osmosis) → Oedema
      - Especially Cerebral Oedema → Headache → Eventually Coma
    - **Treatment:**
      - Withdrawal of Diuretic
      - Reduce Fluid Intake

- **Potassium (K^+):**
  - (NB: K^+ is needed to *repolarise* excitable membranes.)
  - **Hyperkalaemia:**
    - Higher-Than-Normal Blood [K^+]
      - Therefore a smaller concentration gradient between Intracellular & Extracellular [K^+]
    - **May Be Due to Either:**
      - Excessive K^+ Intake...OR
      - Renal Failure (Insufficient K^+ Excretion in Urine)
      - Large Crush/Trauma Injuries (Rupturing of Cell membranes → Release of K^+)
    - **Leads to:**
      - Slower/Poor Repolarisation of Excitable Membranes:
        - →Muscle Cramping
        - → ↓Conductivity of the Heart
  - **Hypokalaemia:**
    - Lower-Than-Normal Blood [K^+]
      - Therefore a larger concentration gradient between Intracellular & Extracellular [K^+]
    - **May Be Due to Either:**
      - Insufficient K^+ Intake...OR
      - Excessive Loss of K^+
      - (Use of Diuretics)
    - **Leads To:**
      - Faster/Hyper- Repolarisation of Excitable Membranes:
        - → Decreased Excitability of Muscle/Nerve Cells
        - → Cardiac Irritability → Dysrhythmias

- **Calcium (Ca^+):**
  - (NB: Ca^+ is needed for normal Heart/Cardiac-Nerve Function, as well as Bone Formation)
    - Heart: Important for Depolarisation of Slow-Potentials
    - Heart: Important for 'Plateau' of Fast-Potentials
    - Heart & Skeletal Muscle: Important for Cross-Bridge Cycling during Contraction.
  - **Hypercalaemia:**
    - Higher-Than-Normal Blood [Ca^+]
    - **May be Due to:**
      - Increased Dietary Calcium
      - Decreased Ca^+ Excretion
      - Shift from Bone → Extracellular Fluid.
    - **Leads to:**
      - Shortened AP-Plateau → Cardiac Arrhythmias
      - Muscle Weakness
  - **Hypocalaemia:**
    - Lower-Than-Normal Blood [Ca^+]
    - **May be Due to:**
      - Insufficient Dietary Calcium
      - Increased Ca^+ Excretion
    - **Leads to:**
      - Prolonged Depolarisation of Cardiac Action Potentials
      - Impaired Contraction

- **Phosphates (HPO_4^{2-}):**
  - (NB: HPO_4^{2-} are important for bone formation – Bone Salts = calcium & phosphates)
  - **Hyperphosphataemia:**
    - Higher-Than-Normal Blood [HPO_4^{2-}]
    - **May be Due to:**
      - Hypo-Parathyroidism: Low (PTH) → Phosphate Reabsorption From bone.
      - Renal Failure: Increased Phosphate Retention in the Kidneys
    - **Leads to:**
      - Deposition of Ca^+ Salts in Soft Tissues → Hypocalcaemia
  - **Hypophosphataemia:**
    - Lower-Than-Normal Blood [HPO_4^{2-}]
    - **May be Due to:**
      - Decreased Intake
      - Chronic Alcoholism
      - Long-Term Antacid Use
    - **Leads to:**
      - Decreased ATP (As phosphates are needed for ATP synthesis)
        - →Muscle Weakness
        - →Impaired Cardiac Function
        - →Impaired Neural Function

- **Plasma Proteins:**
  - (NB: Plasma Proteins – Important in regulating blood Volume & Viscosity/Pressure)
  - **Hyperproteinaemia:**
    - Higher-Than-Normal Blood [Protein]
    - Rare. (Not mentioned in lecture)
  - **Hypoproteinaemia:**
    - Lower-Than-Normal Blood [Protein]
    - **May Be Due To:**
      - Liver Failure (As the liver makes the Plasma Proteins)
      - Protein Malnutrition
      - Burns
      - Kidney Failure (Proteinuria – Loss of Protein in Urine)
    - **Leads to:**
      - Reduced Plasma Osmotic Pressure
        - →Widespread Oedema

- **Uric Acid:**
  - (NB: Uric Acid = Metabolic Waste Product of Protein Metabolism. Excreted through Urine)
  - **Hyperuricaemia:**
    - Higher-Than-Normal Blood [Uric Acid]
    - **May Be Due To:**
      - Renal Failure – Plasma Uric Acid isn't being excreted through kidneys.
    - **Leads To:**
      - Gout: Deposition of Uric-Acid Crystals in Joints → Arthritis of Gout.

Urine Analysis:

- **Purpose:**
  - To screen for diseases/pregnancy
  - To monitor treatment
  - To assess patient progress
- **Abnormal Urinary Constituents:**

Substance	Condition	Possible Causes
Glucose	Glycosuria	Non-pathological – excessive intake of sugar Pathological – diabetes mellitus
Proteins	Proteinuria	Non-pathological – excessive physical exertion, pregnancy, high protein diet Pathological – heart failure, severe hypertension, glomerulonephritis

Substance	Condition	Possible Causes
Ketone Bodies	Ketonuria	Excessive formation and accumulation of ketone bodies – starvation and untreated diabetes mellitus
Haemoglobin	Haemoglobin-uria	Transfusion reaction, haemolytic anaemia, severe burns
Bile Pigments	Bilirubinuria	Liver disease (hepatitis, cirrhosis), obstruction of bile ducts from liver to gall bladder

Substance	Condition	Possible Causes
Erythrocytes	Haematuria	Bleeding in urinary tract – trauma, kidney stones, infection, neoplasm
Leukocytes (pus)	Pyuria	Urinary tract infection

Urine Production and Excretion

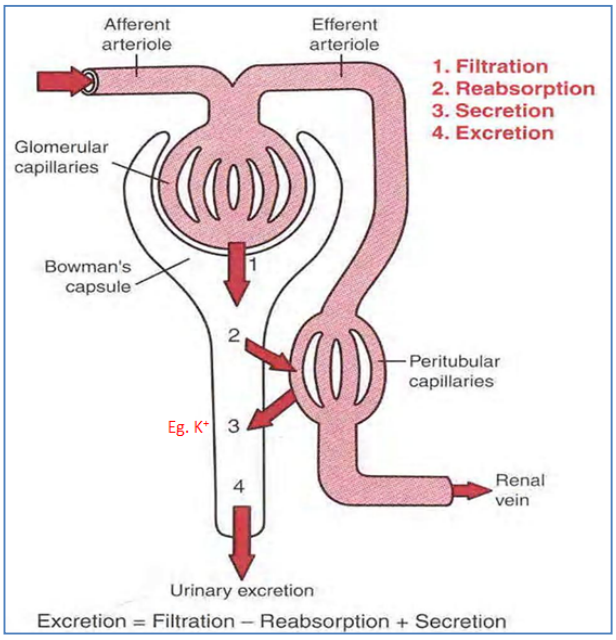
Function of the Kidneys:

- Disposal of Metabolic Wastes & Drugs
  - Relevant to Pharmacology (how long drugs stay in the body & How Long they're effective for)
- Regulate Water Balance
- Regulate Electrolyte Balance
- Regulate Body Fluid Osmolality & Electrolyte Concentrations
- Regulate Acid/Base Balance (in Conjunction with Respiratory System)
- Regulate Arterial Blood Pressure(Long Term)
- Endocrine Function – Excretion of Hormones
- Gluconeogenesis (eg. From Amino Acids)

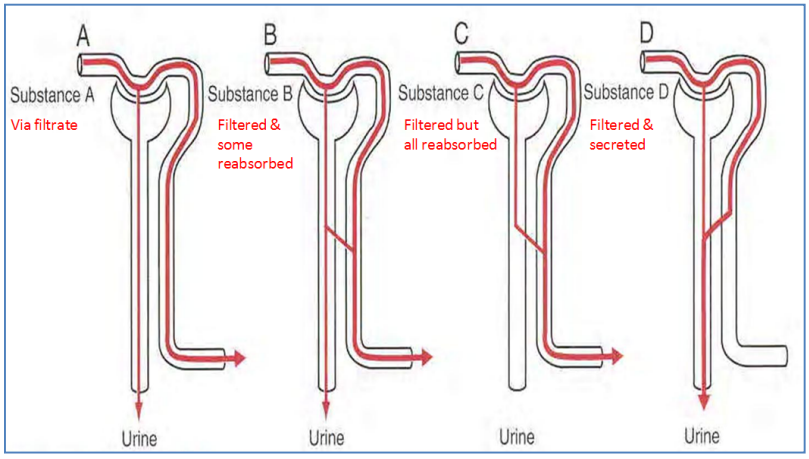
3 Processes of Urine Formation:

- **1. Glomerular Filtration:**
  - Filtration of Blood
- **2. Tubular Reabsorption:**
  - Reabsorption of Certain Filtered Substances (In Renal Tubules) → Back into Blood
- **3. Tubular Secretion:**
  - Active Secretion of Substances From Peritubular Capillaries (Blood) → Into Renal Tubules.

Urine Excretion = Filtrate – Reabsorbed + Secreted



- **NB: Different Substances are Filtered, Reabsorbed & Secreted Differently:**

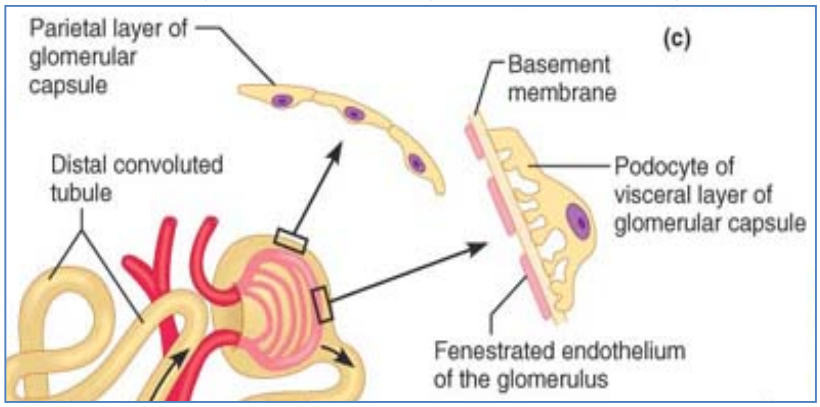


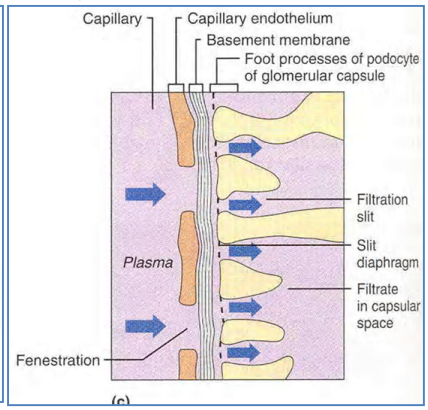
Urine Production

Step 1 – Glomerular Filtration:

- **Filtration of Large Volumes of Blood:**
  - Through Glomerular Capillaries → Glomerular (Bowman's) Space.
  - Filtration is *Passive & Non-Selective* (Fluids & Solutes are forced through via Hydrostatic Pressure)
    - Ie. Forming Filtrate Doesn't Require Energy (ie. Simply a Mechanical Filter)

- **Filtration Through 3 Layers of Capillary (Glomerular) Membrane:**
  - Endothelium
  - Basement Membrane
  - "Podocytes" of Visceral Layer of Glomerular Capsule (NB: "Podocyte" = "Cells with Feet")



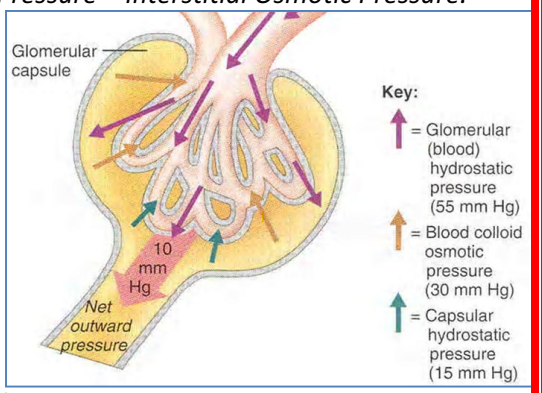


NB: Visceral Membrane of Glomerular Capsule is Relatively *IMPEREABLE TO PROTEINS* – ie. If Proteins/Cells appear in urine →Means Membrane is Damaged

- **Filtrate:**
  - Ie. The Glomerular *FILTRATE* = Similar to Plasma (But *Without* the Proteins)

- **Permeability of Glomerular Membrane:**
  - Filterability of Solutes – Based on Size.
  - Small Chemicals are often bound to Plasma Proteins (Ca^+, FA's, Drugs) – Hence not freely filtered.

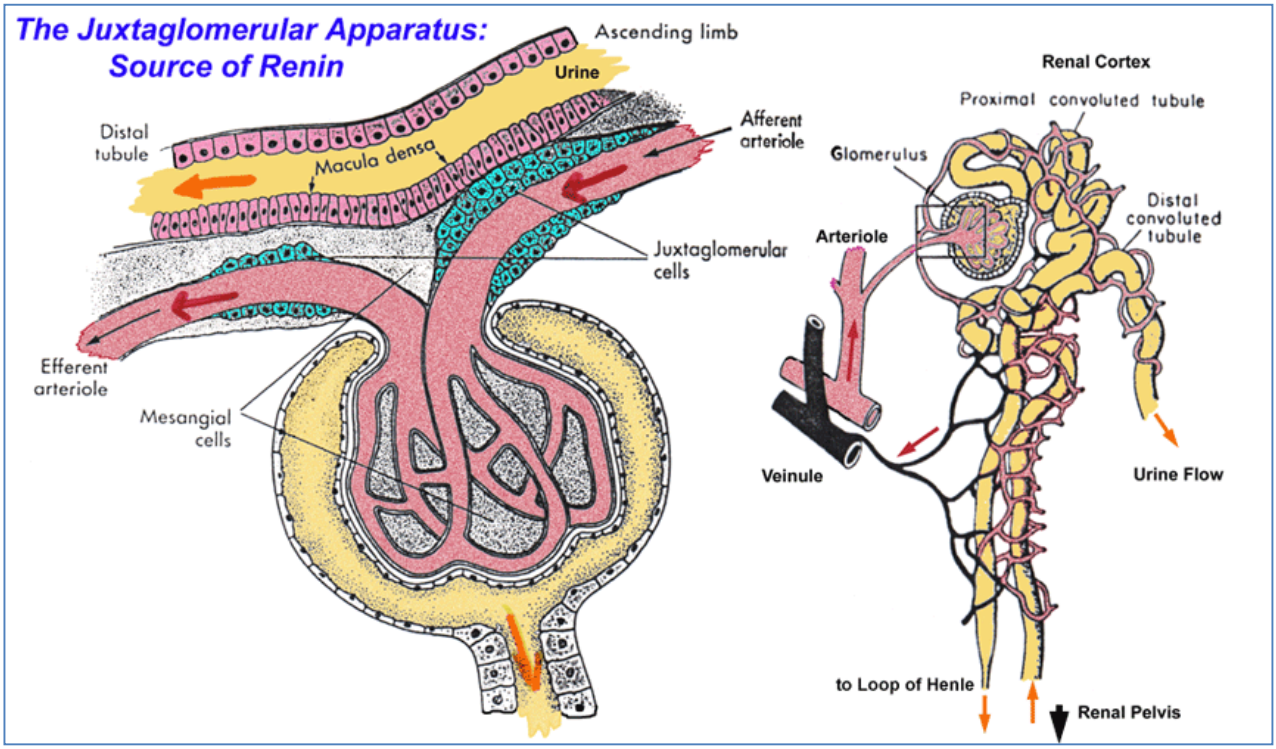
- **Glomerular Filtration Rate:** = Total Filtrate Formed/Per Minute
  - **Determined by Net *Hydrostatic Pressure* and Net *Colloid-Osmotic Pressure*** Across Membrane.
    - **Capillary Hydrostatic Pressure:**
      - The force the blood exerts against the capillary wall.
      - Tends to force fluids through the capillary
      - *Net Hydrostatc Pressure = Capillary Pressure – Interstitial Pressure.*
    - **Colloid Osmotic Pressure:**
      - Opposes hydrostatic pressure
      - Due to non-diffusible molecules (In Plasma) drawing fluid into capillaries.
      - *Net Osmotic Pressure = Capillary Osmotic Pressure – Interstitial Osmotic Pressure.*
  - **Also Determined By:**
    - **Total Surface Area for Filtration**
    - **Membrane Permeability**

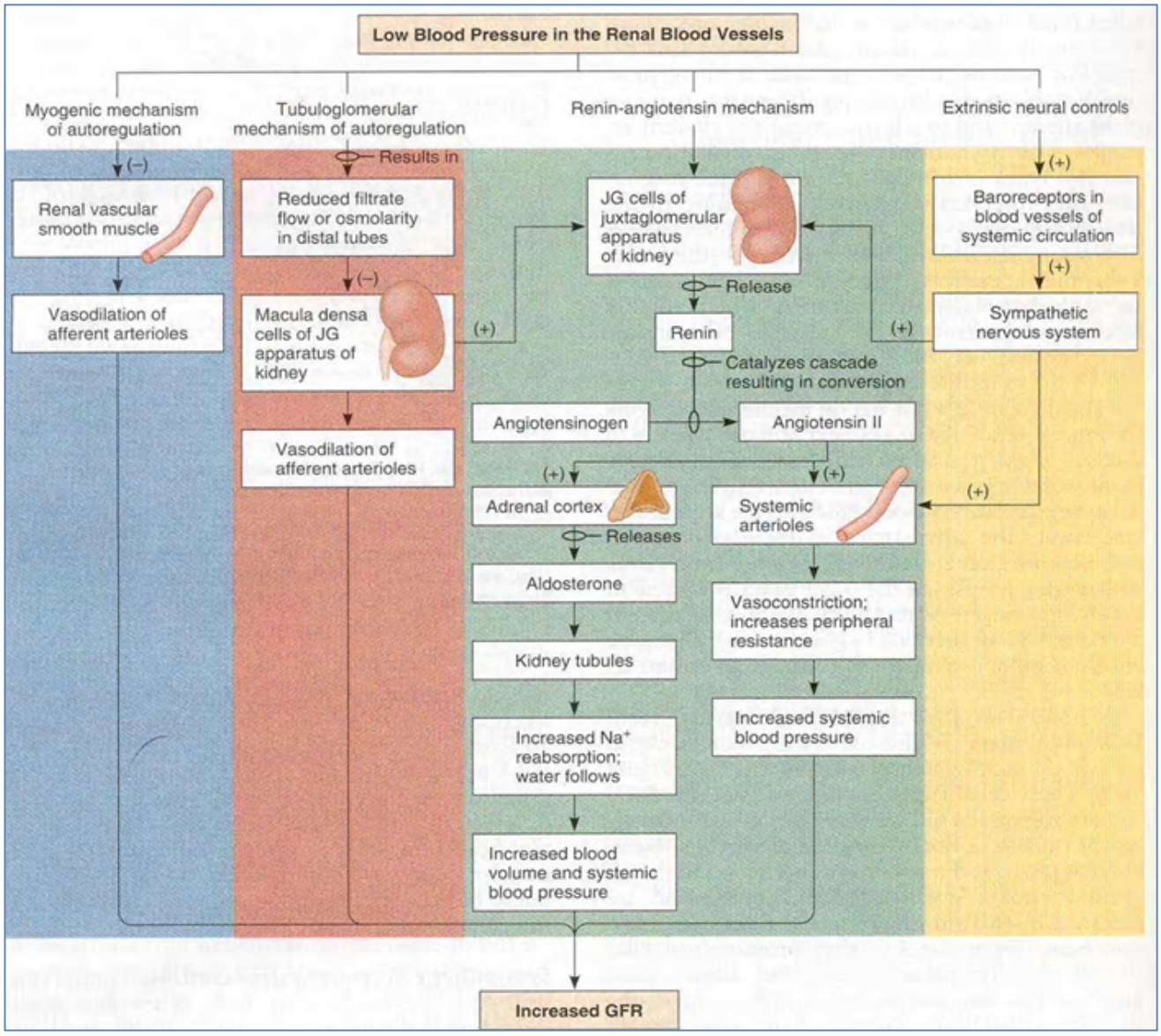


  - Kidneys receive ≈1/4 of Cardiac Output (1L of Blood/min)...
    - Of that ≈125mL of Filtrate is Generated/Min → 180L of Filtrate/Day (From only 3L of Plasma)
    - →Hence, The Blood Is Extremely well Filtered.
    - NB: Most of Filtrate is Reabsorbed into Blood (Via Renal Tubules)

- **Control of GFR:**
  - **Sympathetic NS:** (Fight/Flight)
    - Constriction of Afferent & Efferent Arterioles.
    - →↓Renal Blood Flow
    - →↓GFR
  - **Hormones & Autocrine Secretions:**
    - **Causing Arteriole *CONSTRICTION*:**
      - (ADRENALINE, ENDOTHELIN...others)
        - →↓Renal Blood Flow
        - →↓GFR
    - **Causing Arteriole *DILATION*:**
      - (NITRIC OXIDE, PROSTAGLANDINS, BRADYKININ...others)
        - →↑Renal Blood Flow
        - →↑GFR
  - **Angiotensin II:**
    - Constriction of *EFFERENT ARTERIOLES*
      - →↓Renal Blood Flow
      - BUT – Maintains GFR (By keeping Glomerular Hydrostatic Pressure Up)

- **Control of Renal Blood Flow:**
  - **Autoregulation (Local):** (The first of the body's regulators of Mean Arterial Pressure)
    - Automatic Adjustment of Blood Flow to a Capillary Bed Relative to the Tissue's Requirements
      - Maintains Normal Renal Function (GFR) Despite Changes in Arterial Pressure.
    - **How?...Juxtaglomerular Apparatus is Sensitive to:**
      - **Metabolic Controls: → Vasodilation:**
        - Low Oxygen / Nutrient levels
        - Nitric Oxide
        - Endothelin
      - **Myogenic Control: → Vasoconstriction:**
        - Sheer Stress: Vascular Smooth Muscle Contracts When Stretched





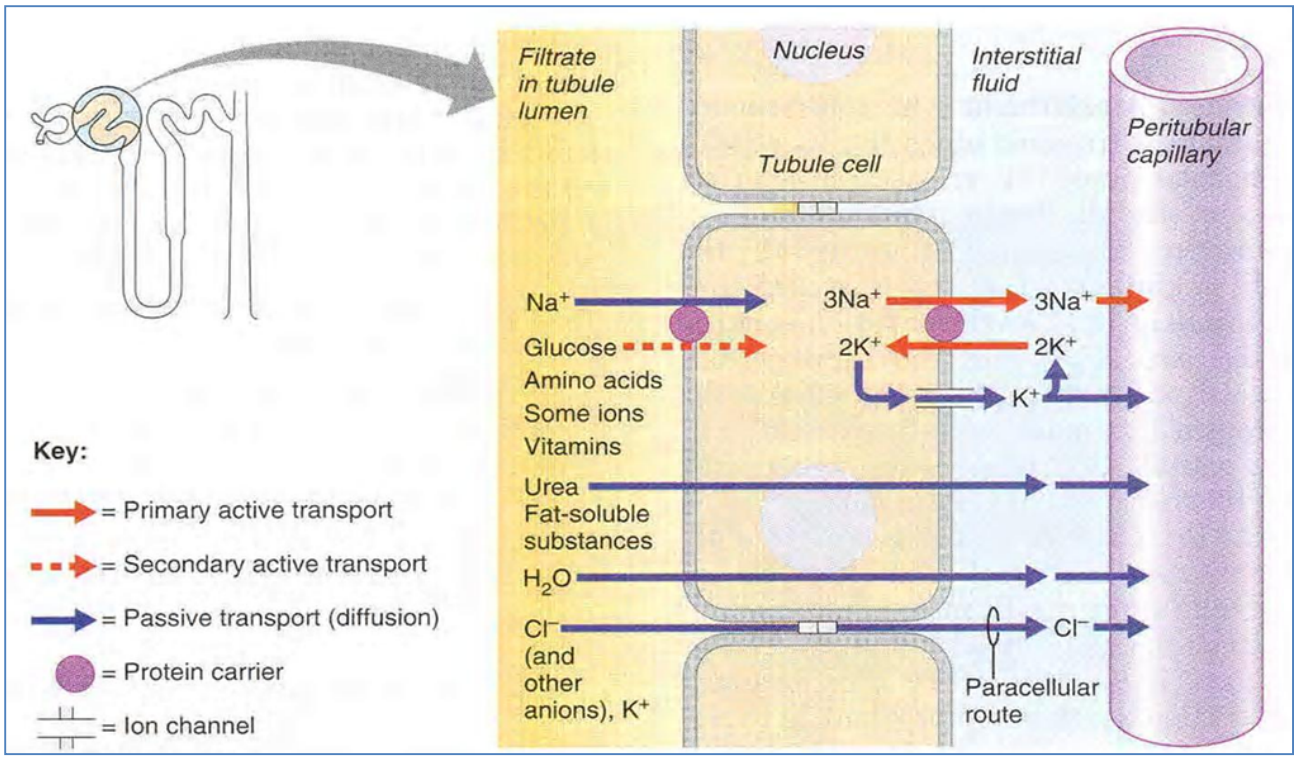
Step 2 – Tubular Reabsorption:

- Normally, 99% of Fltrate is Reabsorbed
- **-Is Highly Selective:**
  - Some Substances (Eg. Glucose) are Almost Completely Reabsorbed.
  - Some Substances (Eg. $NaCl^-$) are Variable.
  - Some Substances (Eg. Urea) are Not Reabsorbed at All.

- **-Is Passive & Active:**
  - **Passive:**
    - Eg. Water – Via Osmosis
  - **Active:**
    - Ie. Moving Solutes Against an Electrochemical Gradient. (Either Primary/Secondary)
    - Eg. Na^+ - (By Na^+/K^+-ATPase)
  - NB: Remember that all Active & Passive Transporters (Excluding Channels) Reach Saturation. (Max.V)
    - Eg. Glucose doesn't normally appear in urine. However, if Filtered Load Exceeds Reabsorption, Urinary Excretion Occurs (ie. In Uncontrolled Diabetes.)

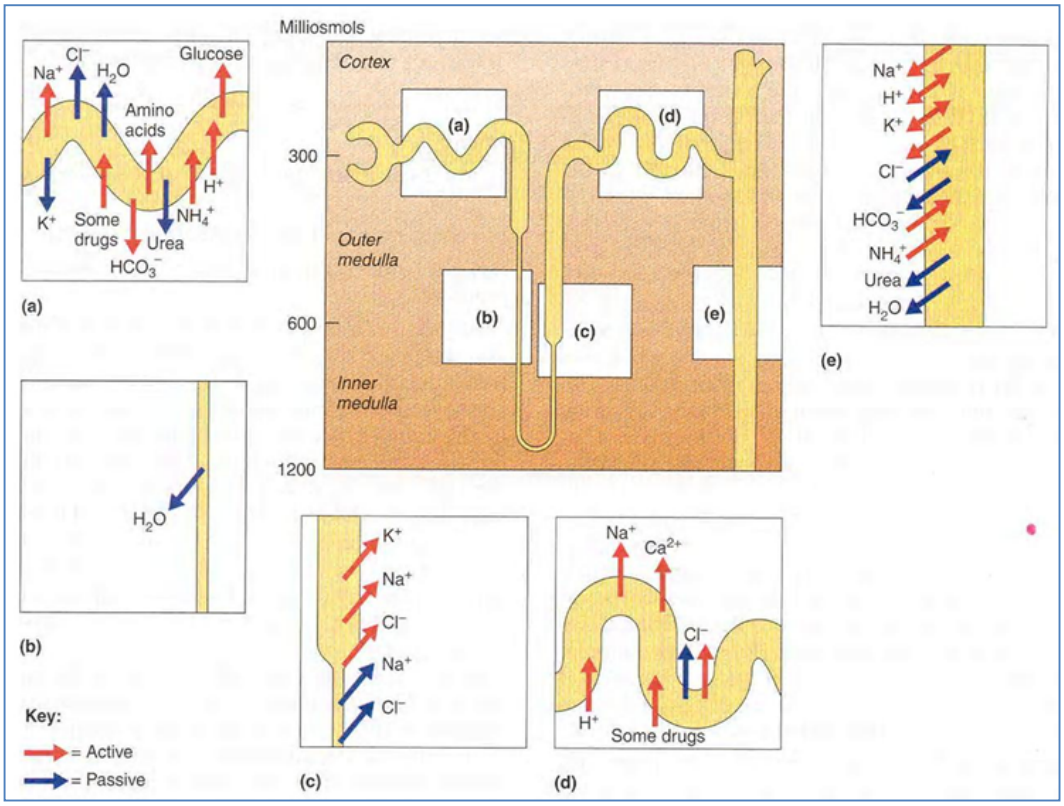
- **Solutes May Be Reabsorbed Via 1 of 2 Routes:**
  - **1.** Transcellular Pathway – Through The Cells
  - **2.** Paracellular Pathway – Between Cells

- **Active Na^+ Reabsorption:**
  - Occurs in Ascending Limb of Loop of Henle.
  - TransCellular Pathway
  - Involves 3 Steps:
    - Na^+ *Passively* Diffuses from Tubule Lumen (Down an Electrochemical Gradient)→ Tubule Cell
    - Na^+ *Actively* Transported across Basolateral Membrane → Interstitium (By Na^+/K^+-ATPase)
    - Na^+ (+Water & Other Solutes) Reabsorbed from Interstitium → Peritubular Capillaries.



Step 3 – Tubular Secretion:

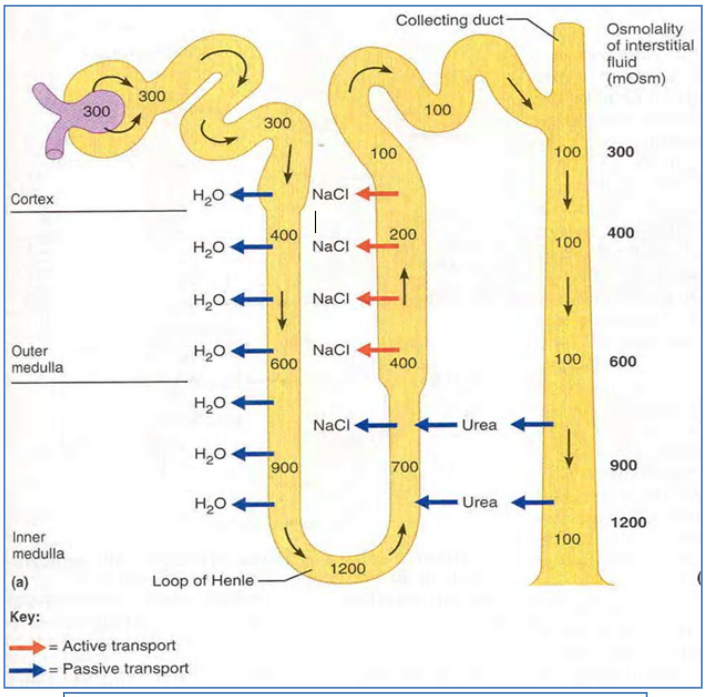
- **Important For:**
  - Disposing of Substances That Weren't Filtered (or Weren't Filtered Enough)
    - Eg. Drugs (eg. Penecillin)
  - Eliminating 'Bad' Substances that have been Passively Reabsorbed
    - Eg. Urea, Uric Acid, etc.
  - Removing Excess K^+ ions.
  - Controlling Blood pH
- **Proximal Tubules:**
  - Site of Secretion of ***Organic Acids/Bases*** (Bile Salts, Oxalate, Uric Acid, etc)
- **Renal Tubules:**
  - Secretion of K^+
  - Secretion of H^+
  - Secretion of Drugs/Toxins (eg. Penecillin)

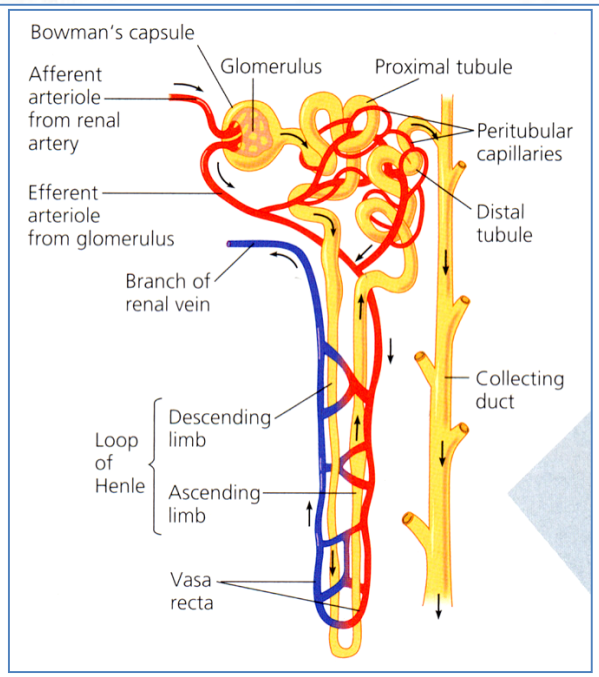


Regulating Urine Volume:

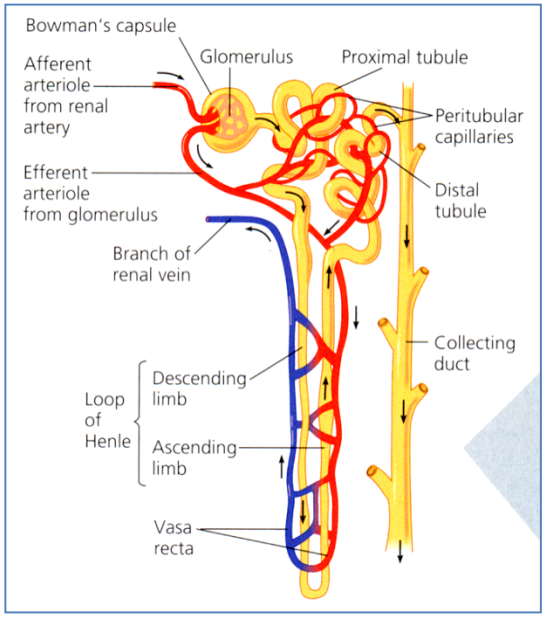
- Kidneys aim to keep Solute-Load (OSMOLALITY) in Blood at around 300mOsm (miliosmols)
- The Kidneys can Regulate the Volume & Nature of Urine Produced...
- **Water Balance:**
  - **Conserve:**
    - By Producing Low Volumes of Concentrated Urine.
  - **Excrete Excess:**
    - By Producing High Volumes of Dilute Urine.

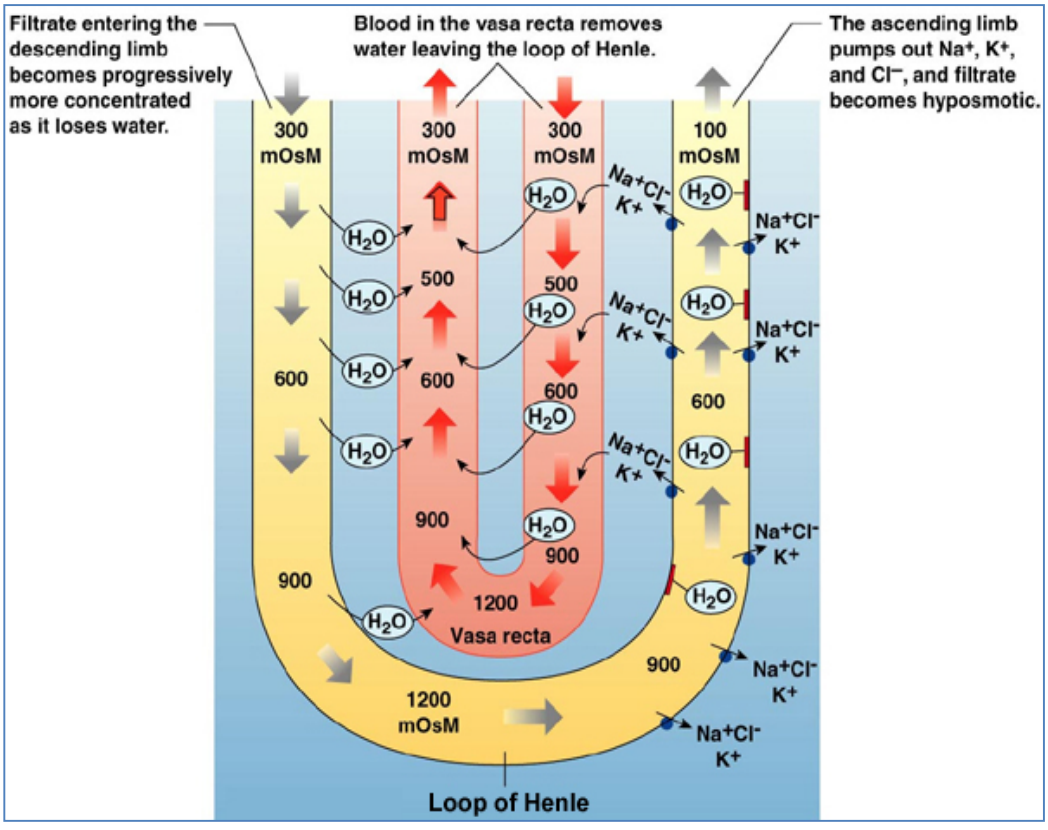
- **The Loop Of Henle:**
  - Actively Creates a High Osmotic Conc. Of Solutes in Interstitial Space of Medulla.
  - **Descending Limb:**
    - Permeable to Water – H_2O Passively Flows into Interstitium (Then →Vasa Recta)
    - Therefore, Desc.Limb Contents Become Progressively More Hyperosmotic (Concentrated)
  - **Ascending Limb:**
    - Active Na^+ Transport From Tubule Lumen→ Tubule Cell →Interstitium (Then→Vasa Recta)
    - Therefore Asc.Limb Contents Become Progressively More Hypo-Osmotic (Diluted)





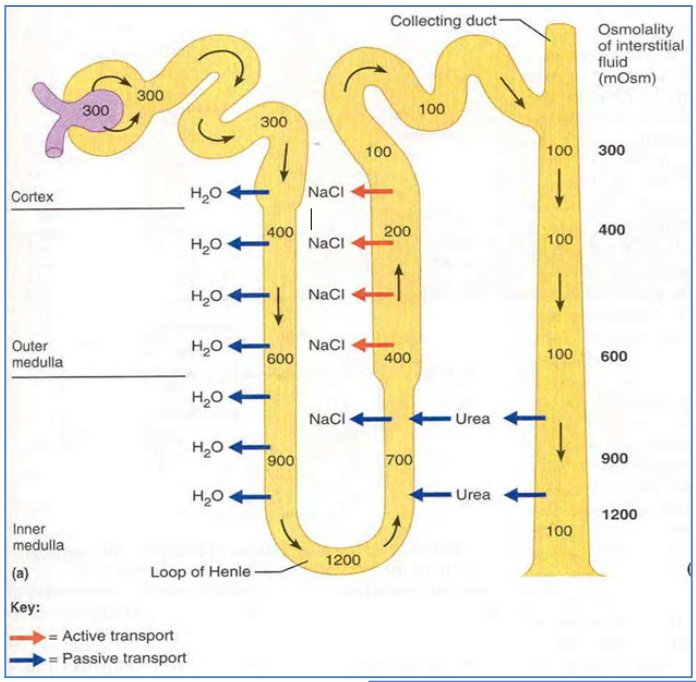
- **The 'Vasa Recta':**
  - Runs ***"Counter-Current"*** to the Loop of Henle.
    - Descending Vasa Recta = Parallel With Ascending Loop of Henle
    - Ascending Vasa Recta = Parallel With Descending Loop of Henle
  - **Descending Vasa Recta:**
    - Absorbs the *Actively-Transported* Na^+ (From Asc.Loop of Henle)
    - Absorbs the *Co-Transported* K^+ & Cl^-
    - *Loses* Some H_2O
      - -Therefore Becomes More Hyper-Osmotic (As you go down)
  - **Ascending Vasa Recta:**
    - Absorbs the H_2O (Lost through Desc.Limb of Loop of Henle)
    - *Loses* Some of the Salts/Ions into the Interstitium. (Na^+, Cl^-, K^+)
      - -Therefore Becomes More Hypo-Osmotic (As you go Up)



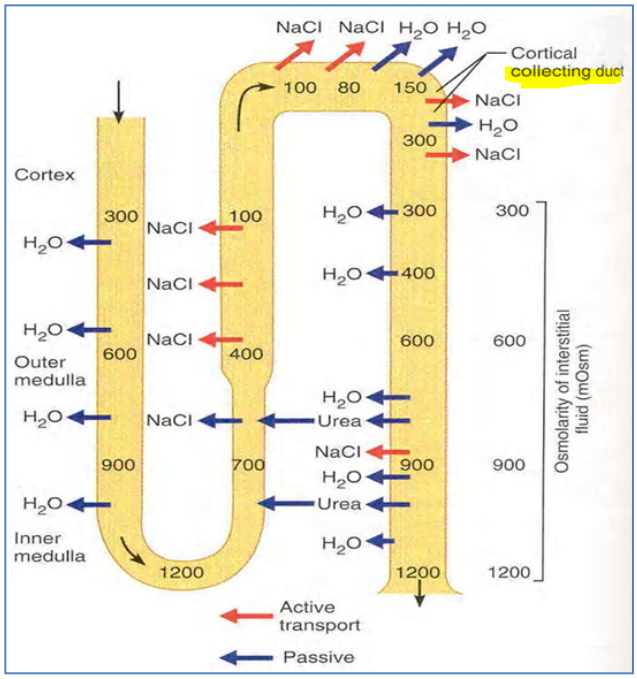


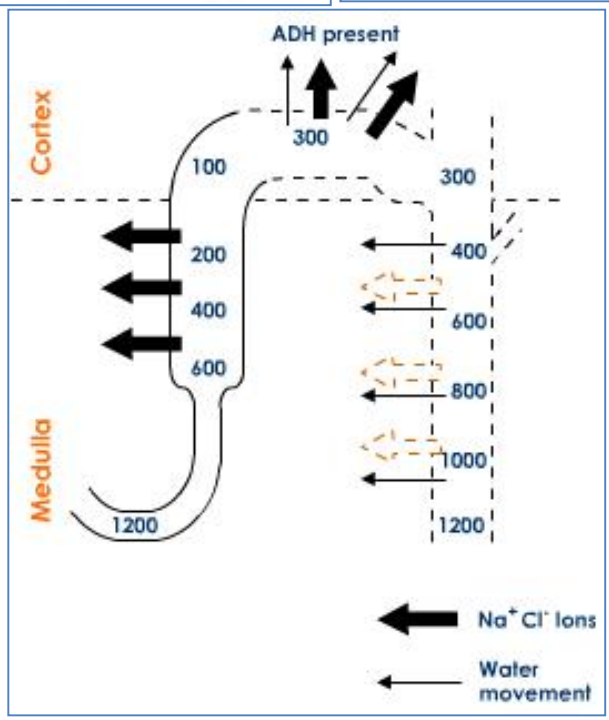
- **Anti-Diuretic Hormone (ADH)** (Aka: "Vasopressin"):
  - Made by Posterior Pituitary (In Response to Angiotensin-II)
  - Primary Regulator of Urine Volume
  - **Affects on Distal & Collecting Ducts:**
    - Distal Tubules & Collecting Ducts are Normally *Impermeable to H_2O.*
    - However, the Presence of ADH → ↑Permeability to H_2O.
      - ↑Permeability to H_2O + High [Solute] in Medulla →H_2O Reabsorption (From Collecting Duct→ Interstitium →Blood)

Absence of ADH

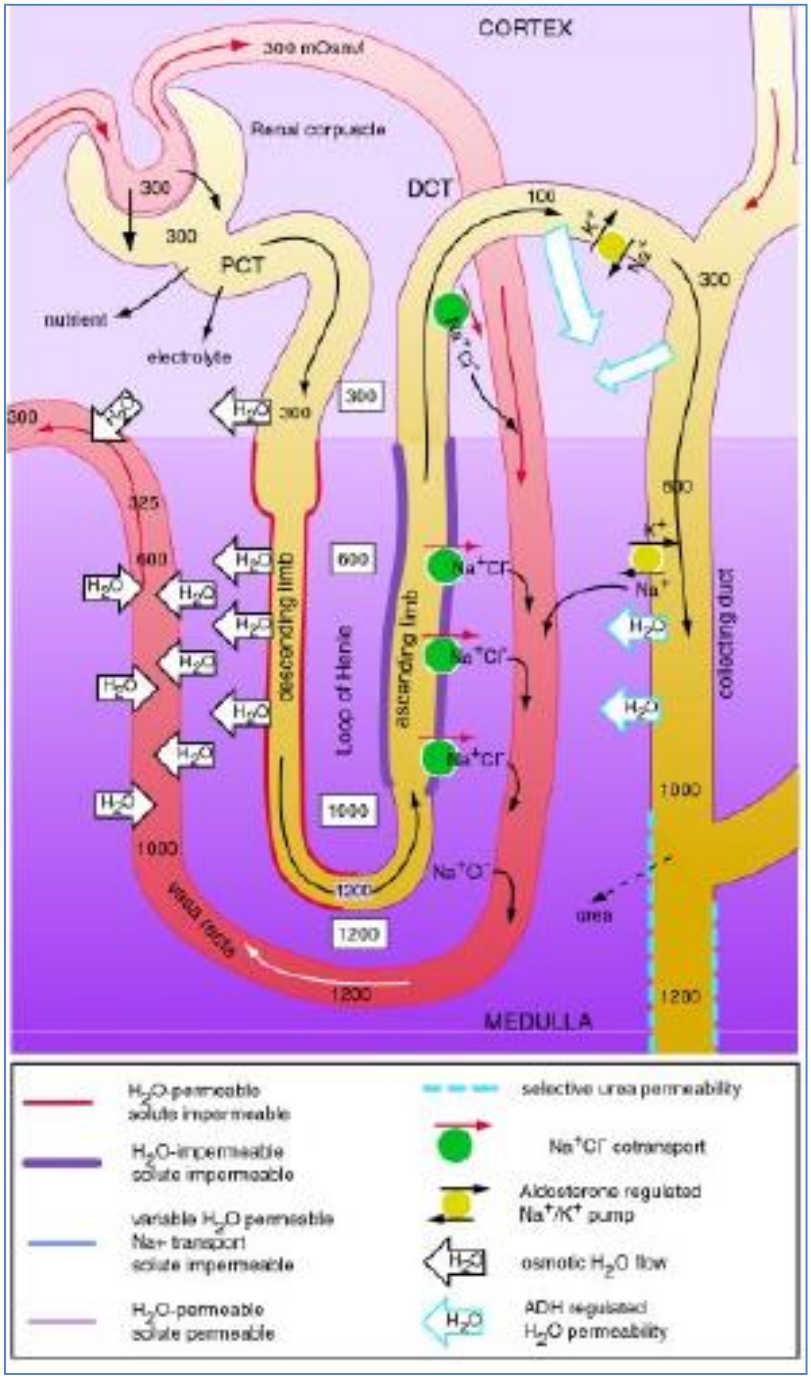


Presence of ADH



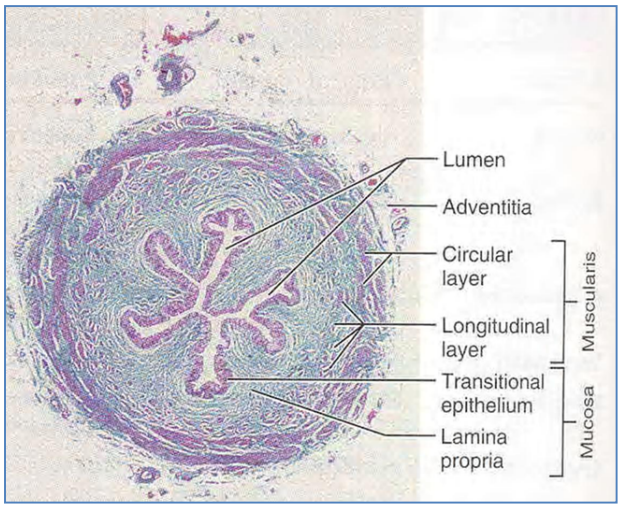


- **Aldosterone:**
  - Released from Adrenal Cortex (In Response to Angiotensin-II)
  - Activates Na^+/K^+-ATPase's in the Distal Tubules & Collecting Ducts.
  - Increases Reabsorption of Na^+ & Cl^- from Distal Tubule→Interstitium
  - – This Movement of Na^+ →↑Osmolarity of Interstitium → Facilitates H_2O Reabsorption



Excretion of Urine From Kidneys:

- Collecting Ducts → Large *Papillary Ducts* → Minor Calyces
- Stretch of Calyces Initiates *Peristaltic Contractions* → Spreads through Renal Pelvis → Ureters → Bladder.
- **The Ureters:**
    - Convey urine from Kidneys to Bladder
    - **3 Layers:**
        - Transitional Epithelium
        - Muscularis (Inner Longitudinal & Outer Circular)
        - External Fibrous Adventitia

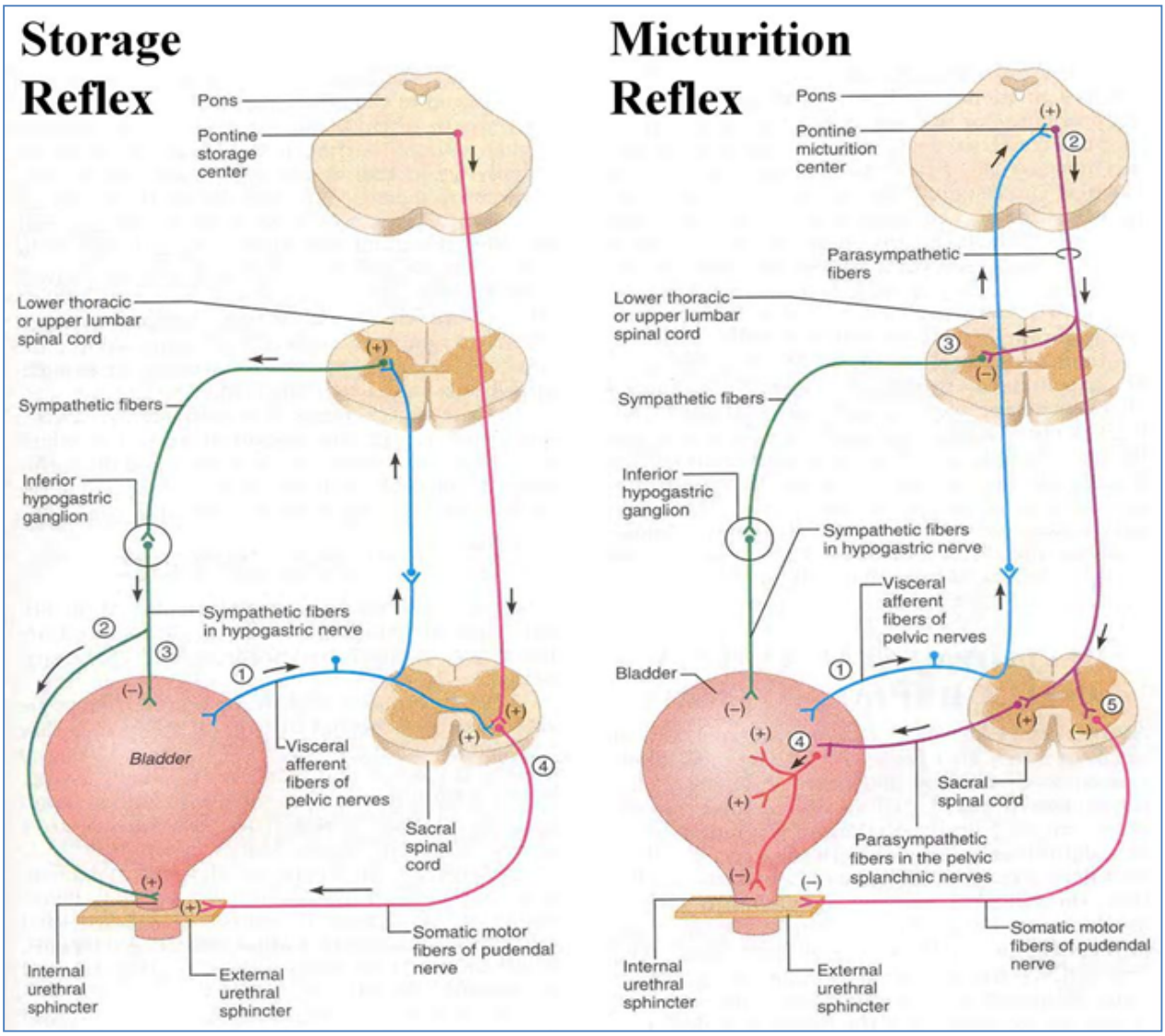


- **The Bladder:**
    - Smooth Muscular Sac
    - Very Distensible
    - Holds ≈ 500mL of urine.
    - **3 Layers:**
        - Transitional Epithelium
        - Thick Smooth Muscle (Detrusor Muscle)
        - Fibrous Adventitia

- **The Urethra:**
    - Thin-Walled Muscular Tube.
    - Drains Urine from Bladder →Outside
    - **Sphincters:**
        - **Internal Urethral Sphincter**
            - @ Bladder-Urethra Junction
            - Prevents leakage between urinations.
        - **External Urethral Sphincter**
            - @ Urethra-Pelvic Diaphragm Junction
            - Voluntary

Micturition:

- Bladder Fills Until Pressure Reaches a Critical Level → Initiates Micturition Reflex
- **Micturition Reflex:**
  - A Spinal-Cord Reflex.
  - Can be Inhibited by Higher Brain Centres.
  - When Person is Ready to Urinate, Brain-Inhibition is removed →:
    - Bladder Smooth-Muscle Contracts.
    - Relaxation of Internal & External Sphincters



CASES & MCQs - Urinary Tract Disease

CPC Case

- **PC:**
  - Mr. M.R. 64y Anglo Australian man, DM2, previous episode of epididymitis, complains " I'm sick of having to get up at night to wee*"
  - *"I've also got a few things happening with the old waterworks, Doc."*
- **HxPc:**
  - Polyuria 2y, getting worse, (day 5-7 & night 3-4 times.
  - sense of incomplete emptying*.
  - No dysuria, no hematuria,.
  - Urgency yes, but cannot empty the bladder, Urinary stream – poor, Urinary incontinence – occasional.
  - Urine frequency (4-5xday; 2xnight); Terminal dribbling. 3y, worsening over months.
- **Sys.Rev:**
  - SOB mild, ? due to cigarettes
- **PMH:**
  - DM2* since 5 years, Atrial Fibrillation*, HPTN* 10y.
  - had epididymitis 3y ago, responded to ciprofloxacin
  - No hx. of STI's.
- **DDx:**
  - Benign prostatic hyperplasia (BPH)
  - Prostatitis, Cancer, stones.
  - Strictures, UTI, STI,
  - Bladder cystitis, instability, polyps, Cancer.
- **Other:**
  - Polyuria – Diabetes, Diuretics,
  - Incontinence – diabetic poly-neuropathy.
  - Spinal injury, Autonomic neuropathy ???

Example Cases of Typical Presentations:

Case presentations:

- 37y male*, mining worker* from Ayr*, severe colicky* flank* pain, vomiting * and sweating* 1hour*. Urine Exam: RBC +*, no casts*, no wbc*, C&S neg, Had similar attack 2 months before*, recovered within minutes. Vitamin supplements*. — **Stone**
- 78y male, dysuria, retention, nocturia, incontinence, dribbling for years gradually getting worse.. — **BPH**
- 84 year old presents with L4 vertebral body compression fracture. (X-Ray osteoblastic lesions), or 81year old male, stony hard prostate on DRE. — **Pr.Ca**
- 46y Male, smoker, flank pain, blood in urine. 3m, intermittent, getting worse. no adiation. Hb 22gm — **RCC**

Symptom	Pathology – Think of
Dysuria	Inflammation urethra, UTI
Poor stream / dribbling.	Bladder neck obstruction. Prostate BPH (rarely stricture/cancer)
Frequency	Prostatitis, UTI, Polyuria
Retention	Prostate-BPH, stone, stricture, tumor
Discharge	UTI, urethritis, gonorrhoea
Ulceration	STI, syphilis
Bone pain	Prostate carcinoma
Raised acid Phosphatase.	Prostate carcinoma
Raised αFP/HCG	Testicular tum teratoma.
Gynaecomastia	Testicular tum.

(RCC = Renal Cell Carcinoma)

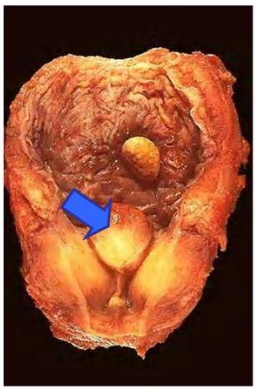
A 59y woman presents with sudden onset of palpitations, flank pain and hematuria. ECG showed short Q-Tc interval, Hypercalcemia & Hypophosphotemia. Image shows her kidney removed at surgery. What is the most likely diagnosis ?

A. Adrenal gland carcinoma.
B. Metastatic medullary carcinoma.
C. Renal cell carcinoma.
D. Endstage kidney disesase.
E. Renal papillary necrosis.

1. List all possible explanations for her Hypercalcemia?
2. Briefly discuss etiology and clinical features of this disease?
3. What other paraneoplastic syndromes are commonly seen in this disorder?

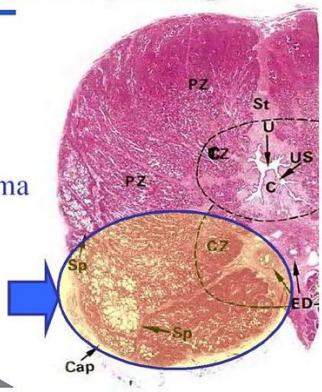
BPH: what feature is shown?

A. Bladder Wall Thickening
B. trabeculation
C. Stone formation
D. Ball valve obstruction
E. Enlarged lateral lobes



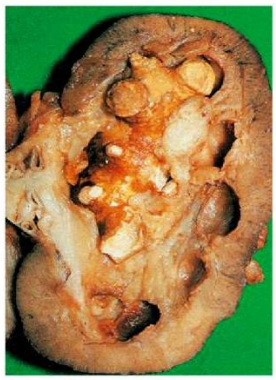
Prostate: Most likely site of ? pathology

A. Benign Hyperplasia.
B. Prostatitis
C. Stone formation
D. Adenocarcinoma
E. Transitional carcinoma



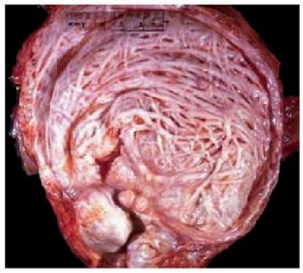
Kidney: What type of stone?

A. Oxalate & calcium
B. Calcium phosphate
C. Pure Uric acid
D. Triple phosphate
E. Cystine



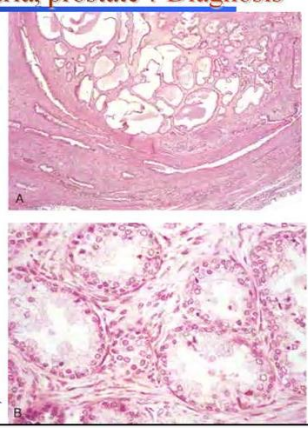
62y male chronic urinary retention. ? Diagnosis

1. Prostatic carcinoma
2. Benign P. Hyperplasia
3. Bladder carcinoma
4. Trabeculations
5. Bladder hypertrophy



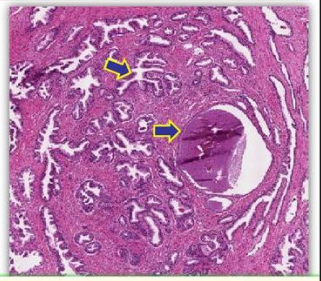
74y M, dysuria, hematuria, prostate ? Diagnosis

A. Prostatitis
B. Benign Prostatic Hyperpl.
C. Low grade carcinoma
D. Transitional carcinoma
E. High grade Carcinoma.



A 68y man investigated for nocturia, is fund on examination to have a slightly enlarged prostate and a PSA level of 7ng/ml (<4ng/ml). Image shows biopsy appearance of his prostate. What is the most likely diagnosis ?

A. Benign prostatic hyperplasia.
B. Mumps prostatitis.
C. Prostatic Cancer grade 4.
D. Metastatic adenocarcinoma.
E. Prostatic cancer.



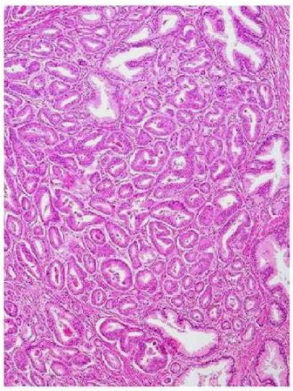
1. Briefly discuss etiology and pathogenesis? (hormone, DHT, hyperplasia)
2. Explain his PSA level? (<4 normal, 4-10 BPH/prostatis,)
3. List complications? (*Obstruction, UTI, cystitis, stones, hydronephrosis/ureter*)
4. What is the prognosis? (*debilitating, not cancer*)

70y backpain, DRE-rock-hard, enlarged prostate. X-rays show multicentric, osteoblastic lesions of the lumbar vertebral bodies. An orchiectomy is performed. What is the rationale for this surgical procedure?

1. Leydig cells release androgenic factors.
2. Prostate carcinomas frequently metastasize to the gonads.
3. Sertoli cells release DHT.
4. The tumor is well known to invade the testes.
5. Tumor cells exhibit androgen-dependent growth.

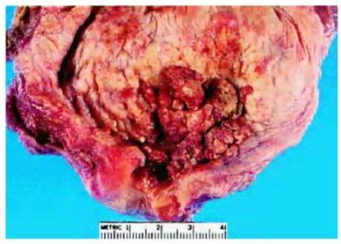
74y male, dysuria, hematuria, prostate ? Diagnosis

A. Prostatitis
B. BPH
C. Adenocarcinoma
D. Transitional carcinoma
E. BPH with carcinoma



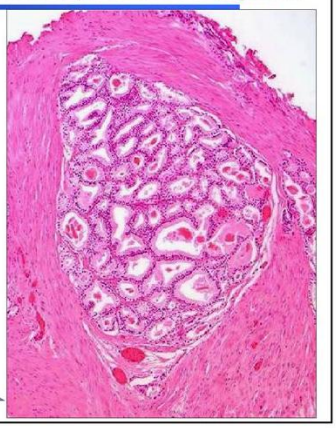
68y male, painless hematuria 4wk. Bladder image. What is the most likely risk factor?

1. Bladder calculi
2. Chronic HPV infection
3. Diabetes mellitus
4. Exposure to Azo dyes
5. Previous Prostatic ca.



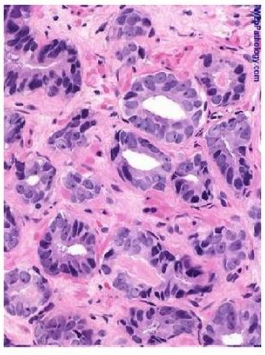
74y male, dysuria, hematuria, prostate ? Diagnosis

A. Prostatitis
B. BPH
C. Adenocarcinoma
D. Transitional carcinoma
E. BPH with carcinoma



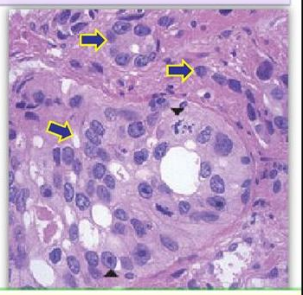
68y male, Image shows prostate biopsy. What is the most likely complication of this lesion?

1. Destructive vertebral lesions.
2. Bladder hypertrophy.
3. Calcium oxalate nephrolithiasis.
4. Gram negative septicaemia.
5. Lead to Prostatic carcinoma



A 79y man with 1.5cm prostatic nodule found on DRE confined to prostate. Has a serum PSA of 13ng/ml (Ref. <4 ng/ml) Image shows biopsy specimen appearnce. What is the most likely diagnosis ?

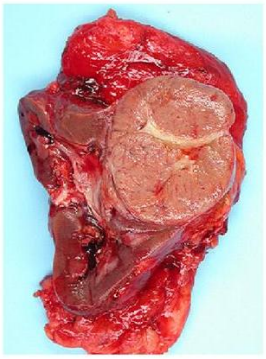
A. Benign prostatic hyperplasia.
B. Mumps prostatitis.
C. Prostatic Cancer grade 4.
D. Metastatic adenocarcinoma.
E. Prostatic cancer.



1. Briefly discuss etiology and pathogenesis?
2. What genetic abnormality common? (*Hypermethylation of GSTP1*)
3. What is the stage of disease? (*Stage-2, confined to prostate*)
4. What is the prognosis? (*good pronosis*)

61y Male, smoker, hematuria, loin pain, polycythemia. Kidney specimen. ? Most likely diagnosis

A. Transitional cell carcinoma.
B. Cortical adenoma
C. Renal cell carcinoma
D. Papillary carcinoma.
E. Wilm's tumor (Nephroblastoma)

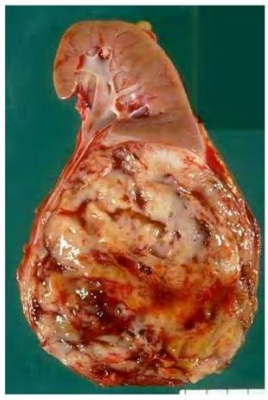


68y man elevated serum PSA (>6 ng/mL). Biopsy of the prostate reveals a poorly differentiated adenocarcinoma. Which of the following best describes the putative precursor of this neoplasm?

1. Basal cell hyperplasia
2. Chronic prostatitis
3. Obstructive uropathy
4. Nodular BPH
5. PIN.

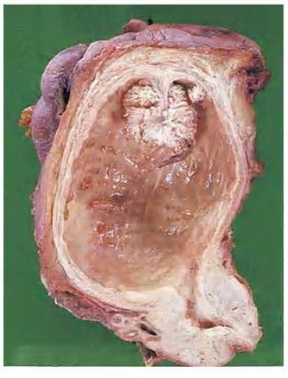
6y Male, Abdominal mass, weight loss Kidney ? diagnosis

A. Transitional cell carcinoma.
B. Cortical adenoma
C. Renal cell carcinoma
D. Metastatic to kidney.
E. Nephroblastoma



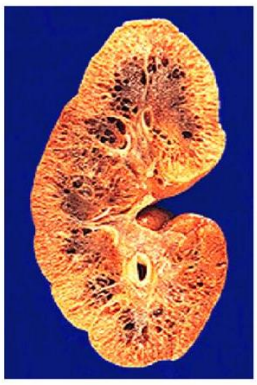
Urinary bladder tumor ? CORRECT STATEMENT

1. Benign papilloma
2. Polyposis of bladder
3. Patient has good prognosis
4. Papillary carcinoma
5. Adenocarcinoma



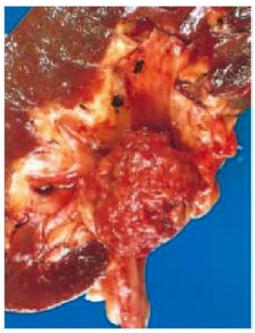
3m female renal & liver failure. Post mortem Kidney specimen ? Most likely diagnosis

A. Cystic Nephroblastoma.
B. Hereditary ARPKD
C. Hereditary ADPKD .
D. Uremic Medullary cystic D.
E. Cystic Renal Dysplasia



61y Male, smoker, hematuria, Kidney ? Diagnosis

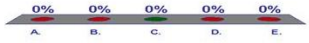
A. Transitional cell carcinoma.
B. Cortical adenoma
C. Renal cell carcinoma
D. Metastatic to kidney.
E. Nephroblastoma



21

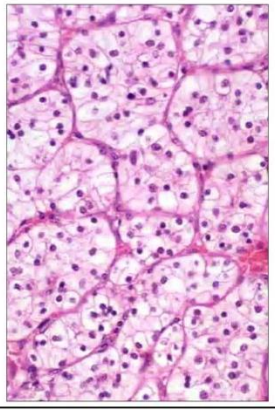
64y man, 4m dysuria and hematuria for 4days. P/H of repeated bouts of acute cystitis. Urine cultures are positive for E. coli. A stone is found in the bladder diverticulum. Most likely predisposing condition ?

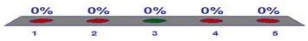
A. Diabetes mellitus
B. Malakoplakia
C. Nodular prostatic hyperplasia
D. Nephrolithiasis
E. Transitional cell carcinoma



56y Male, smoker, hematuria, loin pain. Kidney ? diagnosis

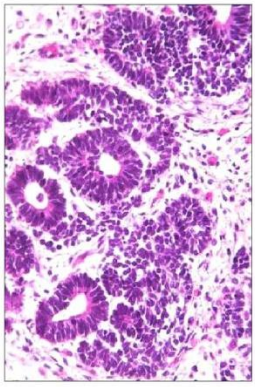
A. Transitional cell carcinoma.
B. Cortical adenoma
C. Clear cell carcinoma
D. Adenocarcinoma.
E. Papillary carcinoma





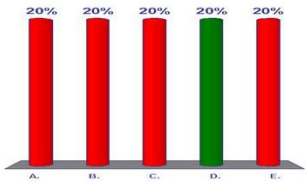
5y Male, Abdominal mass, hematuria, Kidney biopsy ? diagnosis

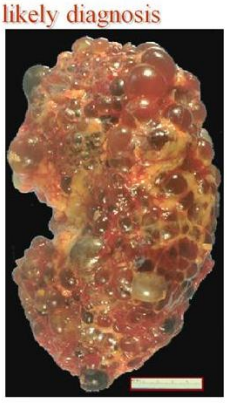
A. Transitional cell carcinoma.
B. Wilm's tumor
C. Clear cell carcinoma
D. Adenocarcinoma.
E. Papillary carcinoma



51y, Hypertension, Chronic renal failure on renal dialysis. Kidney specimen ? Most likely diagnosis

A. Chronic Glom. Nephritis.
B. AR-PKD
C. End stage Kidney dis.
D. AD-PKD - Adult
E. Dialysis induced cysts.

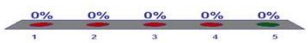




61y flank pain, Hematuria, Most likely diagnosis?

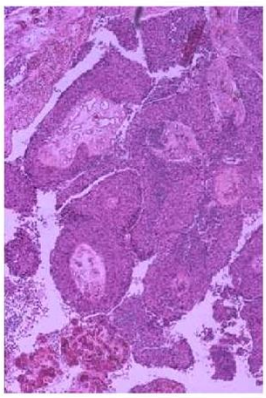
1. Acute glomerulonephritis.
2. Nephroblastoma
3. Renal Cell adenoma
4. Transitional cell carcinoma.
5. Clear cell carcinoma

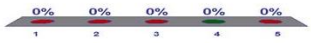
Hct	**57%**
Hb	**19 g/dL**
BUN	12 mg/dL
Creat.	0.7 mg/dL
WBC	7,450/mm^3 normal differential
RBC cytology	**3+, no casts.** No Malignant cells.



62y M, hematuria. 3cm growth in renal pelvis – Biopsy image ? diagnosis

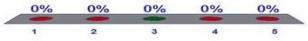
A. Papillary RCC
B. Nephroblastoma
C. Pyelonephritis
D. Transitional Cell Ca
E. Buergers Disesase





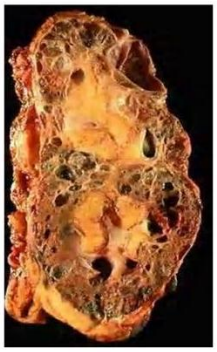
56y asymptomatic hematuria

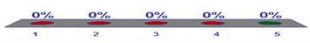
1. ADPKD with hemorrhage.
2. ARPKD
3. Renal cell carcinoma
4. Nephroblastoma
5. Transitional cell carcinoma



62y M, chronic renal failure on dialysis. Shrunken small kidneys. image ? diagnosis

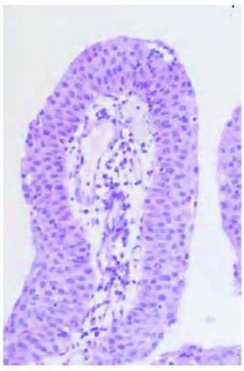
A. ADPKD
B. Endstage kidney disease.
C. Chronic Pyelonephritis
D. Uremic medullary cystic disease.
E. Dialysis associated cysts.

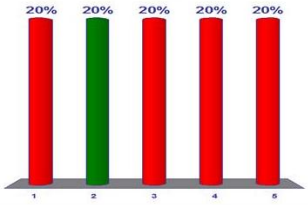




72y female, asymptomatic hematuria. 5 cm papillary tumor in bladder. Image shows biopsy. ?Diagnosis

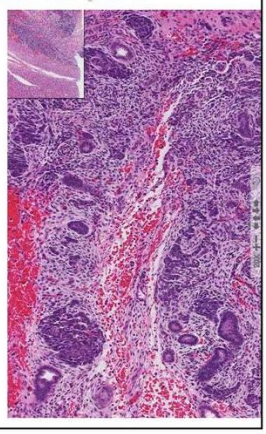
1. Adenocarcinoma
2. Transitional cell carcinoma.
3. Papilloma
4. Tubular adenoma
5. Villous adenoma

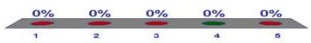




2y M, hematuria, hypertension. 6cm growth in lower pole of left kidney. Biopsy image ? diagnosis

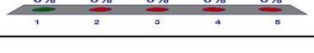
A. Papillary RCC
B. Chronic glomerulonephritis
C. Benign Nephrosclerosis
D. Nephroblastoma
E. Acute glomerulonephritis





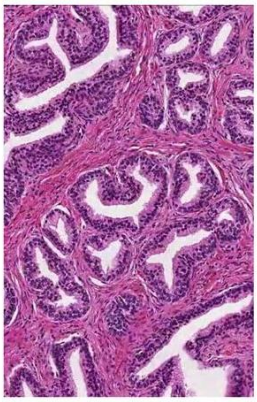
55y man, urinary urgency and frequency. DRE enlarged prostate. PSA of 4.9 (normal = 0–4). Needle biopsy - two cancer-positive needle cores: Gleason grades 4 and 5. Which of the following is the appropriate diagnosis?

1. **Adenocarcinoma**
2. **Nodular BPH**
3. **PIN-3**
4. **Squamous Carcinoma**
5. **Transitional Carcinoma**



78y male, Image shows prostate biopsy. What is the most likely complication?

1. Destructive vertebral lesions.
2. Bladder hypertrophy.
3. Calcium oxalate nephrolithiasis.
4. Gram negative septicemia.
5. Infertility.



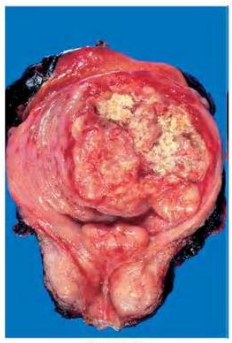
0% 0% 0% 0% 0%
1 2 3 4 5

CPC-4.3– KFP Questions:

- **BPH – etiology, Pathogenesis, morphology & complications.**
- **Testosterone, DHT, Fenosteride.**
- **TURP – brief notes.**
- **Prostatic carcinoma – etiology, Pathogenesis, morphology & spread, metastases.**
- **Staging, Grading & Prognosis.**
- **Urolithiasis : Renal stones**
- **Other obstructive uropathy.**

68y male, Image shows Bladder & prostate. What complication is not shown?

1. Invasive bladder cancer.
2. BPH.
3. Ball valve obstruction.
4. Bladder diverticula.
5. Tumor necrosis & hemorrhage.



© Elsevier 2005

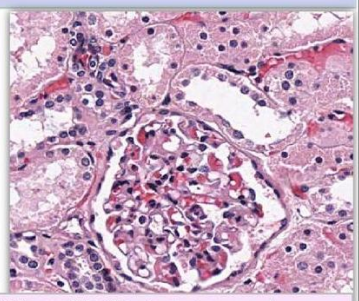
0% 0% 0% 0% 0%
1 2 3 4 5

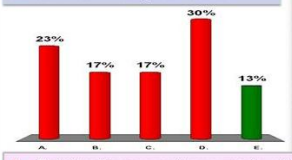
Today is the First Day, of Rest of Your Life...!

Renal Qs

6 year girl presents with facial swelling, polyuria, polydipsia and massive proteinuria following recovery from upper respiratory tract viral infection. Image shows kidney biopsy appearance of her glomerulus. What is the most likely diagnosis?

A. Analgesic nephropathy.
B. Acute renal failure.
C. Membranous GN.
D. Proliferative GN.
E. Minimal change disease.

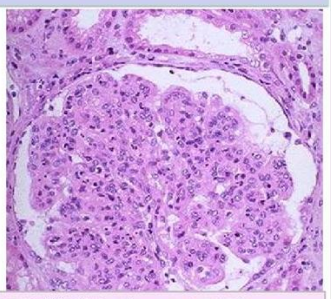


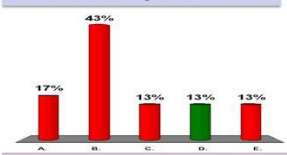


A. Briefly discuss pathogenesis of this condition? (podocyte foot process)
B. List gross and Microscopic feature of this disease? (normal)
C. Other features, Prognosis? (hyperlipidemia, lipiduria, hypoalbuminemia), good.

14 days following an episode of fever, pharyngitis treated with analgesics, a 16y boy presents with severe tiredness, fever. He is passing very little dark brown urine. Urine analysis shows non selective proteinuria, hematuria with many RBC casts. Image shows his renal biopsy appearance. What is the most likely diagnosis?

A. Analgesic nephropathy.
B. Acute streptococcal nephritis.
C. Membranous GN.
D. Diffuse proliferative GN.
E. Minimal change disease.

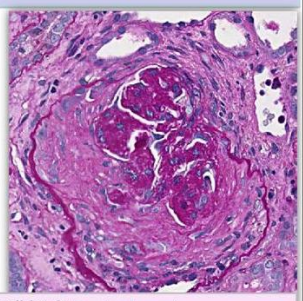




A. Briefly discuss pathogenesis of this condition? (autoimmune, IgG, BM)
B. List gross and Microscopic feature of this disease? (Inflam)
C. List other clinical features, prognosis? Hypertension, recover/CGN

43y man with 3 week history of hemoptysis, hematuria and fever. Past history revealed features of mixed connective tissue disorder treated with steroids in the past year. Labs show rapidly increasing urea & creatinine levels since 1 week. Image from renal biopsy shows appearance of one glomerulus. What is the most likely diagnosis?

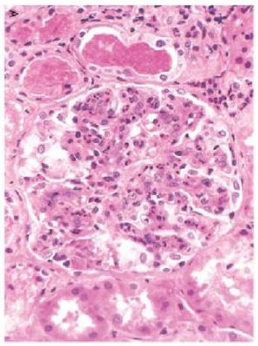
A. Global sclerosis.
B. Crescentic GN.
C. Membranous GN.
D. Diffuse proliferative GN.
E. Chronic GN.



A. Briefly discuss pathogenesis of this condition? (Goodpasteur sy)
B. List gross and Microscopic feature of this disease? (Inflam exudate)
C. List other clinical features, prognosis? Renal failure.

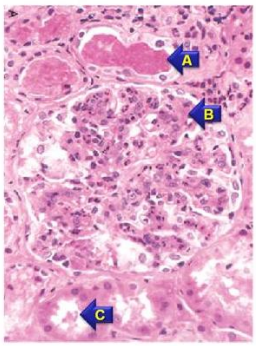
12y Fem, puffy face, Oliguria, smoky urine, hypertension. Recovering from URTI. Kidney biopsy ? Most likely diagnosis

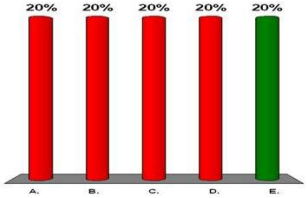
A. Diffuse proliferative GN
B. Membranous GN
C. Minimal change GN
D. Rapidly progressive GN
E. Membranoproliferative GN



12y Fem, puffy face, Oliguria, smoky urine, hypertension. Recovering from URTI. Kidney biopsy ? Feature "A"

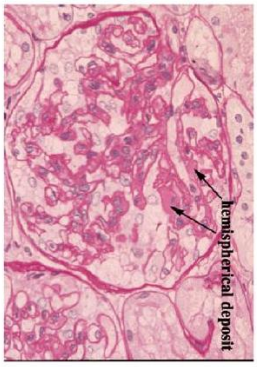
A. Proliferative GN
B. Proliferative GN (Neutrophils)
C. Diffuse glomerulosclerosis
D. WBC cast in tubule.
E. RBC cast in tubule.





21y Male, hematuria, recovering from an URT infection. Had similar attack twice in last two years ? diagnosis

A. Diffuse proliferative GN
B. Membranous GN
C. Nodular Glomerulo sclerosis
D. Minimal change GN
E. Berger's Disease



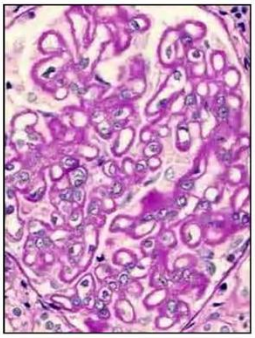
2y girl, Severe albuminuria, facial & pedal edema. Recovering from a viral fever. Glomerulus, ? diagnosis

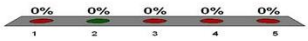
A. Diffuse proliferative GN
B. Membranous GN
C. Minimal change GN
D. Rapidly progressive GN
E. Membranoproliferative GN

A. Briefly discuss pathogenesis of this condition? (podocyte foot process)
B. List gross and Microscopic feature of this disease? (normal)
C. Other features, Prognosis? (hyperlipidemia, lipiduria, hypoalbuminemia), good.

48y Male, proteinuria, lipiduria, pedal edema. On treatment for SLE arthritis. Kidney biopsy PAS stain ? diagnosis

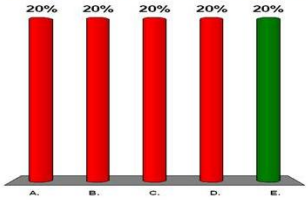
A. Diffuse proliferative GN
B. Membranous GN
C. Minimal change GN
D. Rapidly progressive GN
E. Membranoproliferative GN

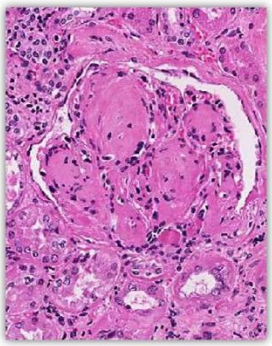




54y Male, past MI, DM2, nocturia, polyuria, recurrent leg ulcers. Kidney biopsy ? diagnosis

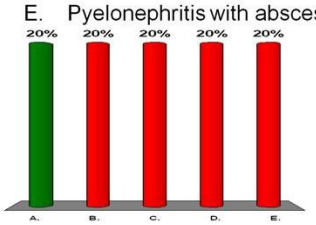
A. Diffuse proliferative GN
B. Membranous GN
C. Minimal change GN
D. Rapidly progressive GN
E. Nodular Glomerulosclerosis

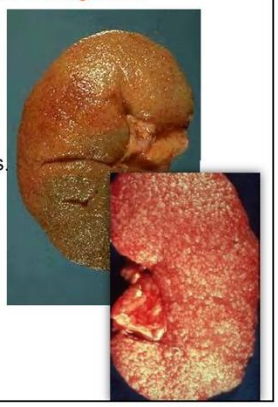




58y Male, Chronic hypertension. Slowly progressive renal failure since 2y. Kidney sp. ? diagnosis

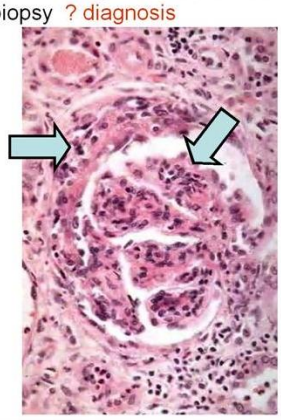
A. Benign nephrosclerosis
B. Papillary necrosis
C. Pyelonephritis with infarction
D. Nodular glomerulosclerosis
E. Pyelonephritis with abscesses





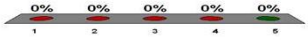
14y Male, severe acute renal failure, history of recent throat infection on treatment. Kidney biopsy ? diagnosis

A. Diffuse proliferative GN
B. Membranous GN
C. Minimal change GN
D. Rapidly progressive GN
E. Membranoproliferative GN



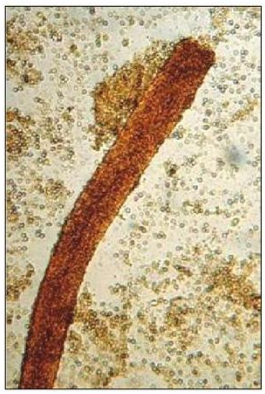
74y Male, Hypertensive, Oliguria & marked fatigue since 2y. Left Kidney gross ? diagnosis

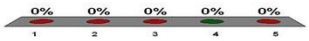
A. Nodular Glomerulo sclerosis.
B. Chronic Pyelonephritis.
C. Polycystic kidney disease.
D. Rapidly progressive GN.
E. Chronic Glomerulonephritis.



46y Male, Hematuria. Urine cytology ? diagnosis

A. Urinary Tract Infection
B. Bladder cancer
C. Renal stones
D. Glomerulonephritis
E. Schistosomiasis

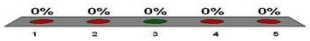




46y Male, 3wk. lethargy. KFT ? diagnosis

A. Nephritic Syndrome
B. Acute renal failure
C. Nephrotic syndrome
D. Chronic Renal failure
E. Renal cell carinoma.

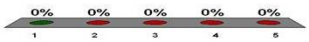
- Selective proteinuria
- Hypoalbuminemia
- Hypercholesterolemia
- Serum creatinine normal



46y Male, 3wk. lethargy. KFT ? diagnosis

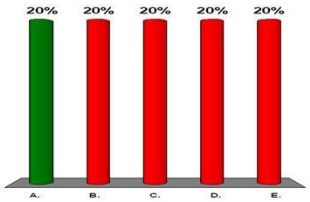
A. Nephritic Syndrome
B. Acute renal failure
C. Nephrotic syndrome
D. Chronic Renal failure
E. Rencal cell cancer.

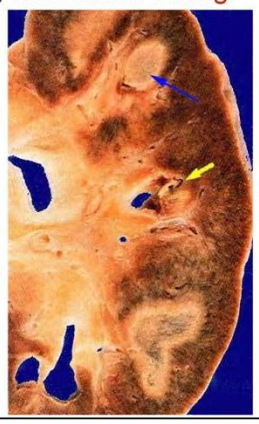
- Oliguria
- Hypertension
- Non Selective proteinuria
- Serum creatinine high
- RBC casts present.



46y Diabetic male. Fever, hematuria ? diag

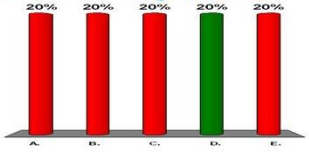
A. Papillary necrosis
B. Pyelonephritis & abscess.
C. Nodular glomerulosclerosis
D. Renal abscesses
E. Chronic Renal failure

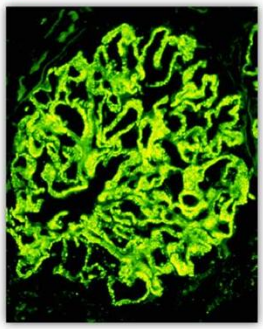




44y man, SOB, swelling of his legs and puffiness around his eyes & Ascitis. Total serum protein is 5.2 g/dL (reference = 5.5–8.0 g/dL), and albumin is 1.9 g/dL (reference = 3.5–5.5 g/dL). Serum cholesterol is elevated at 530 mg/dL. 5 g of protein in a 24-hour urine, with many granular casts but no RBCs or WBC. Image shows renal biopsy stained by direct immunofluorescence for IgG ? Diagnosis

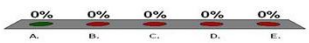
A. Proliferative GN
B. Focal Segmental GS.
C. Proliferative GN
D. Membranous GN
E. Minimal change disease

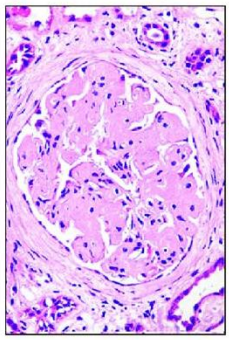




60y man, chronic back pain and fatigue, excessive urination, and increased thirst. X-ray - numerous lytic lesions in the lumbar vertebral bodies. Lab: hypoalbuminemia, 4+ proteinuria & A monoclonal Ig light-chain peak. A bone marrow biopsy 20% atypical plasma cells. Image shows kidney biopsy. ? Diagnosis

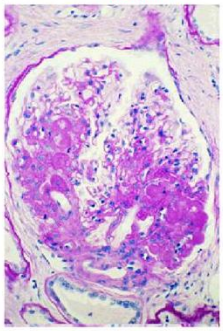
A. Amyloid nephropathy
B. Crescentic glomerulonephritis
C. IgA nephropathy (Berger disease)
D. Membranous glomerulonephritis
E. Nodular glomerulosclerosis.

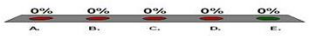




30y man with h/o drug addiction, 6/12 progressive edema & Ascitis, Marked proteinuria (>4 g/24 hours) but no WBC or RBCs in urine. Lab: Hyperlipidemia and hypoalbuminemia. Serum creatinine level is normal. The blood test for ANCA is negative. Recurrent attacks respond to corticosteroids, Upon the third recurrence, becomes steroid resistant. A renal biopsy is shown . ? Diagnosis

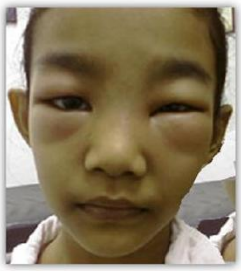
A. Acute glomerulonephritis
B. Amyloidosis
C. Crescentic glomerulonephritis
D. Diffuse proliferative glomerulonephritis
E. Focal segmental glomerulosclerosis

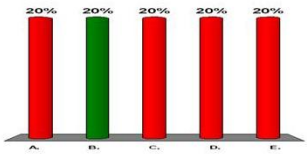




A 6-year-old boy complains of swelling of his face & feet for the past 3 weeks. He is otherwise healthy, with no known previous illness. Vital signs are normal. Physical examination reveals pitting edema of the lower legs and a swollen abdomen. Urinalysis shows 4+ protein but no RBCs or WBCs. ? Most likely Diagnosis.

A. Acute glomerulonephritis
B. Minimal change disease
C. Crescentic glomerulonephritis
D. Diffuse proliferative glomerulonephritis
E. Membranous Glomerulonephritis





9y boy, episode of hematureia 1wk after flulike illness. One month later his urine is red again. Urinealysis pH7, SG 1.015, Proteinuria 1+, 1+ hematuria. No ketones, glucose or urobilinogen. Serum urea & creat. Normal. Renal biopsy shows mesangial proliferation & Antibody complex deposition. Which of the following mechanisms is most likely to produce his symptoms?

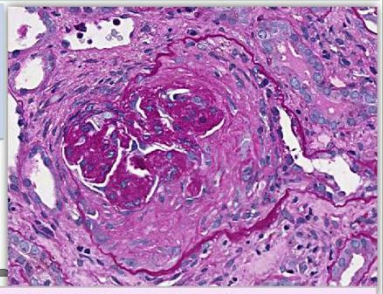
Explanation: Recurrent painless hematuria following a viral illness in a child or young adult is typically associated with IgA nephropathy (Berger's dis). Defective immune regulation causes excessive mucosal IgA synthesis in response to viral or other environmental antigens. IgA complexes are deposited in the mesangium and initiate glomerular injury. Antibodies against type IV collagen are seen in Goodpasture syndrome.

49y male, Ankle & Foot swelling for 2 months. 24h urine yielded 4.1g protein. No H/O DM, SLE or Hypertension. No response to steroid therapy. Renal biopsy showed diffusely thick capillary basement membrane with granular C3 deposition. Two years later he developed chronic renal failure. What is the most likely pathogenesis?

Explanation: This patient has idiopathic MGN & nephrotic syndrome. Diffuse basement membrane thickening caused by the deposition of immune complexes on the basement membrane, which activates complement. Antibodies that react with basement membrane give rise to a linear immunofluorescence pattern. Membranous glomerulopathy has no association with streptococcal infections. There is also no evidence of cytokine- or T-cell-mediated damage in this disease. In 85% of patients is unknown. In the remaining 15%, an associated systemic disease (e.g., SLE) or some known cause of immune complex formation (e.g., drug reaction, viral hepatitis) exists.

39y man with eight week history of cough, fever and skin rash is found to have nasopharyngeal ulcerations, nodular and vaitary lesions on chest x-ray. He develops rapidly progressive renal failure with hematuria and RBC casts in urine. A lung biopsy shows necrotizing vasculitis. Image shows appearance of affected glomerulus. What is the most likely diagnosis?

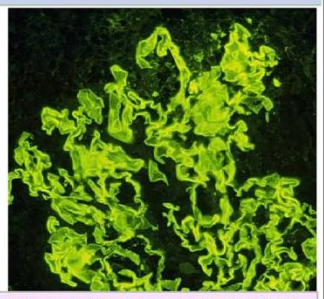
A. Goodpasteur syndrome.
B. Miliary tuberculosis.
C. Wegener's granulomatosis.
D. Endstage renal disease.
E. Berger's disease.



A. Briefly discuss pathogenesis of this condition? (Wegener's)
B. List 3 Microscopic features of this disease? (crescentic GN)
C. List etiology for this renal disorder (RPGN)?.

25y man presents with bout of hematuria, pedal edema and hypertension. On further questioning reveals recent attacks of coughing with blood streaked sputum. Urinalysis shows proteinuria and RBC casts. Image shows renal biopsy with Immunofluorescent stain for anti-IgG antibody. What is the most likely diagnosis?

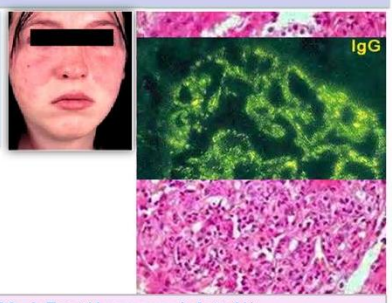
A. Post streptococcal GL.
B. HIV nephropathy.
C. Minimal chande disease.
D. Hep-B Inf. (membranous).
E. Goodpasture Syndrome.



A. Pathogenesis? (*IgG to BM Collagen in lung & Kid → Acute Infl → RPGN*)
B. List gross and Microscopic feature of this disease? (*Inflam, RPGN,Linear*)
C. Clinical features? complications? prognosis? (*Nephritic, CGN, R.Failure)*

31y fem presents with fever , fatigue for 3 months on & off. She has 3kg wt loss. On PE malar rash, pain on deep inspiration, friction rub. Labs showed increased globulins, serum creatinine, decreased serum complements. Renal biopsy reported granular IgG deposits in the basement membrane. What is the most likely diagnosis?

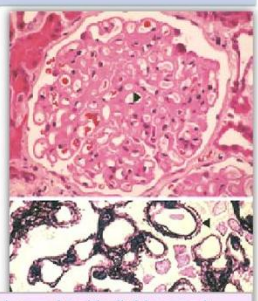
A. SLE (lupus nephritis).
B. Post streptococcal GN.
C. Minimal change disease.
D. Membranous GN.
E. Goodpasture Syndrome.



A. Pathogenesis? (*Genetic DR3 → Env+Hormones → AutoAb*)
B. List gross and Microscopic feature of this disease? (*Inflam, DPGN, Gran.*)
C. Clinical features? complications? prognosis? (*Nephritic, CGN, R.Failure)*

47year man, over the counter use of ibuprofen daily since 7 months following a road traffic accident. Presents with edema & hypertension. Urinalysis shows proteinuria but no hematuria or glucosuria. Kidney biopsy (Image) view of his glomerulus is shown in the image with silver stain (bottom). What is the most likely diagnosis?

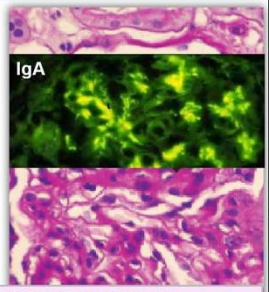
A. SLE (lupus nephritis).
B. Post streptococcal GN.
C. Minimal change disease.
D. Membranous GN.
E. Goodpasture Syndrome.



A. Pathogenesis? (*Drug+Ab complex deposited as subepithelial humps)*
B. List gross and Microscopic feature of this disease? (*Inflam, MGN, Gran.*)
C. What other drugs & Diseases? (*Penicillamine, captopril, Ca, HBV, HCV*)

21year man, a week following mild URI presents with profound weakness, very little dark urine. O/E hypertension, urinalysis showed hematuria with dysmorphic RBC. He recovers within a week, but develops four similar recurrences in the next year. Image shows his renal biopsy specimen. What is the most likely diagnosis?

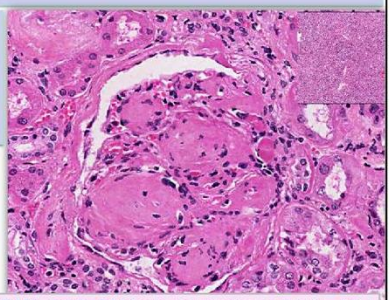
A. Membranous GN.
B. Post streptococcal GN.
C. Berger's disease
D. Minimal change disease.
E. Goodpasture Syndrome.



A. Pathogenesis? (*IgA complex deposited as subepithelial humps)*
B. Microscopic feature of this disease? (*Inflam, Mes-IgA*) Prognosis?
C. Other Disease association? (Pri/Sec, *Henoch Schonlein purpura, Celiac)*

68y man, BMI 41, Peripheral neuropathy, retinopathy and abdominal aortic aneurysm on therapy shows increasing serum creatinine. FBS 12.8 mol, Image shows his renal biopsy. What is the most likely diagnosis?

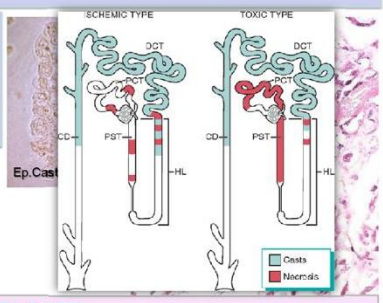
A. Membranous GN.
B. Goodpasture Syndrome.
C. Post streptococcal GN.
D. Berger's disease
E. Nodular glomerulosclerosis



A. Diagnosis? Pathogenesis? (*DM2, AGE, BM leak, nephrotic sy, Renin, AT..)*
B. Microscopic feature of this disease? (*NGS, artereolosclerosis, CGN)*
C. What other complications? (*Atherosclerotic PAD, stroke, MI, etc…)*

19y old boy, Post operative marked oliguria, nausea, malaise following spleenectomy for ruptured spleen following car crash. He was found in shock at the site of crash Immediate lapratomy revealed massive hemoperitoneum. (bladder not distended). Labs anemia, Increased BUN, Creatinine, U:C ratio 10:20. What is the diagnosis?

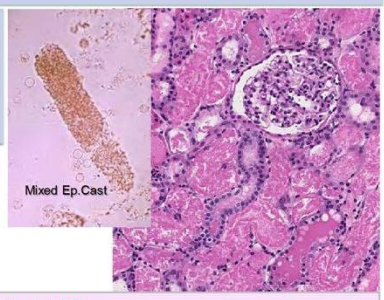
A. Toxic ATN.
B. Papillary necrosis.
C. Rapidly Progressive GN.
D. Berger's disease.
E. Ischemic ATN.



A. Pathogenesis? (*Ischemic ATN → ARF)*
B. Microscopic feature of this disease? (*Necrosis of tubules, more in PCT)*
C. Types of ATN/ARF, list differences? (*Toxic, Ischemic*)

32y woman, chronic headache, relieved by simple over the counter analgesics. Presents with high colored urine with brown pieces of tissue in her urine today. HPE reveals progressively increasing polyuria, anemia, diarrhoea and hypertension since 6 months. Image shows her urine sediment and renal biopsy. What is the likely diagnosis?

A. Toxic ATN.
B. Papillary necrosis.
C. Rapidly Progressive GN.
D. Berger's disease.
E. Ischemic ATN.



A. Pathogenesis? (*Ischemic ATN → ARF)*
B. *Drug induced interstitial nephritis / analgesic nephropathy.*
C. Briefly discuss prognosis? (*ARF, CRF, TCC*)

35y Male, fatigue.

- A previously healthy 35-year-old man complained of recent fatigue and swelling of his **feet and ankles**. He also noted puffy eyes. Physical exam revealed an afebrile man with **lower extremity** edema **extending to the knee,** periorbital **edema**, and a **small amount of ascites**.
- Drug history was negative. ANA, HIV, and hepatitis serologies were negative.
- The patient developed right flank pain the following day. Ultrasound examination revealed renal vein thrombosis. **A renal biopsy** was performed.

Laboratory results:

Urinalysis:	protein - 4+
	glucose - neg
	blood - neg
	bilirubin - neg
Micro:	rare RBCs, no WBCs, **many oval fat bodies**
Creatinine	0.8 mg/dL
BUN	18 mg/dL
Albumin	**1.8 g/dL (3.5-5.1)**
Hematocrit	40%
Liver function tests	normal
Triglycerides	**400 mg/dL (<150) 0.4-2.29 mmol**
Cholesterol	**375 mg/dL (<170) 2-4.39 mmol**
24-hr urine protein	11.2 gm/24 hr

- **Nephrotic / Nephritic?**
- **Where is the pathology?**
- **Why no blood in urine?**

Dx: Membranous Glomerulonephritis

A 27-year-old white man

- who was previously in good health presented to his family physician with increasing fatigue and **red urine**. There was no history of previous illness, and review of systems was negative.
- Physical examination was negative except for **hypertension** (165/110).
- **Urinalysis revealed 2+ protein and 2+ blood; his serum creatinine was 1.8 mg/dL.**

A 27-year-old white man

- A week later deteriorated with intermittent bouts of hematuria and ankle swelling and generalized malaise, nausea and vomiting, and decreasing urine output almost anuric.
- Blood pressure was 170/110.
- An abdominal sonogram showed kidneys of normal size with no evidence of hydronephrosis.
- Laboratory exam revealed:

A 27-year-old white man

Urinalysis:	protein - 2+
	blood - 4+
	glucose - neg
Micro:	> 40 RBCs/HPF (0-2 RBCs/HPF)
	10 WBCs/HPF (0-2 WBCs/HPF)
	5-10 RBC casts/LPF (0 casts/LPF)
Hematocrit	**38%**
Creatinine	**3.9 mg/dL**
BUN	**102 mg/dL**
Liver serology	normal
ANCA, ANA, HIV	negative

Dx: IGA Nephropathy

Renal Pathology & Urine Production Disorders

Overview:

- **Renal Diseases are complex and are the result of abnormalities of one or more of the below:**
  - Glomeruli
  - Tubules
  - Interstitium
  - Blood vessels
- **Some of the above are more vulnerable to specific forms of injury.**
  - Eg. Most Glomerular Diseases are *Immunologically Mediated.*
  - Eg. Most Tubular Diseases are caused by *Toxic/Infectious Agents(Viruses/Bacteria).*
  - Eg. Most Interstitial Diseases are caused by *Toxic/Infectious Agents (Viruses/Bacteria).*
  - NB: Blood Vessel abnormalities are usually the result of one or more of the above.
- NB: Damage to one part always secondarily affects the others → Eventually leading to Chronic Renal Failure

Functional Reserve:

- NB: The Kidneys have a considerable *Functional Reserve:*
  - You only need 1x Kidney to survive – (And even *it* has more function than the body needs)
  - Therefore, with 2 kidneys, large-scale damage must occur for significant functional impairment.
  - However, once the damage is done, it is irreversible and highly debilitating.

*4 Stages of Chronic Renal Failure:

NB: "Renal Failure" = Decreased Glomerular Filtration Rate (GFR)

- **1. Diminished Renal Reserve:**
  - ***GFR = 50% of Normal**
  - Blood Urea Nitrogen (BUN) – Normal
  - Blood Creatinine – Normal
  - – (Ie. Diminished functional reserve, but still enough to maintain bodily/blood homeostasis)
- **2. Renal Insufficiency:**
  - ***GFR = 20-50% of Normal**
  - Blood Urea Nitrogen (BUN) – Elevated
  - Blood Creatinine – Elevated } "**Azotemia**" (High levels of N-containing compounds)
  - Anaemia – (↓[Hb] – Due to ↓Erythropoietin Release by Kidneys)
  - Polyuria – (High Urine Output – due to poor H_2O Retaining Abilities of damaged kidney)
  - Hypertension – (due to fluid overload and production of vasoactive hormones)
- **3. Renal Failure:**
  - ***GFR = <20% of Normal**
  - Blood Urea Nitrogen (BUN) – Highly Elevated
  - Blood Creatinine – Highly Elevated } "**Uraemia**" (More severe form of Azotemia)
  - Uraemia (Elevated Blood Urea) → Toxic to Brain & Nerves.
  - Anaemia – (↓[Hb] – Due to ↓Erythropoietin Release by Kidneys)
  - Polyuria – (High Urine Output – due to poor H_2O Retaining Abilities of damaged kidney)
    - Hypovolaemia
  - Electrolyte Imbalances (K^+, HPO_4, Ca^+)
    - Hyperkalaemia (↑K^+)
    - Hyperphosphataemia (↑HPO_4) – (Phosphate Retained by Failing Kidneys)
    - Hypocalcaemia (↓Ca^+) – (Due to the effects of Hyperphosphataemia & Poor activation of Vit.D in the kidney → $CaPO_4$ Deposition in Tissues & Poor Ca^+ Absorption in GIT – (As Active Vit.D is needed for Ca^+ Absorption))
  - Osteoporosis – (Due to Hypercalcaemia – {resulting from High Phosphate})
  - Haematuria - (Blood in Urine)
- **4. End-Stage Renal Disease:**
  - ***GFR = <5% of Normal**
  - Terminal stage of **Uraemia**

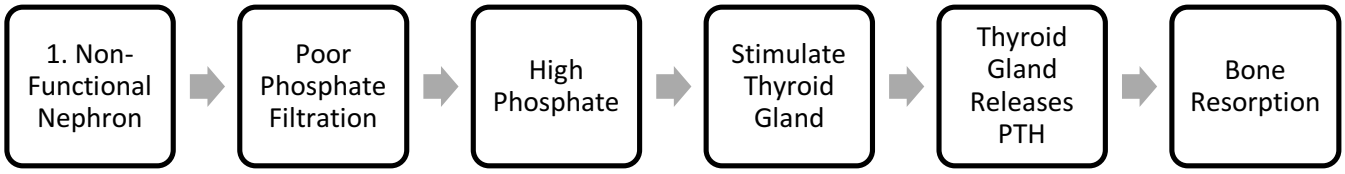
The 2 Greatest Risk Factors For Renal Disease:

- **Hypertension** → Damage to Glomerular Capillaries → Sclerosis & Thickening of Capillary Wall → Tubular Necrosis → Inflammatory Response → Further Renal Disease
- **Diabetes** → ↑[Blood Glucose] → Blood proteins become *sticky* → deposit in small blood vessels → Vessel Inflammation, Damage & Scarring → Tubular Necrosis → Inflammatory Response → Further Renal Disease

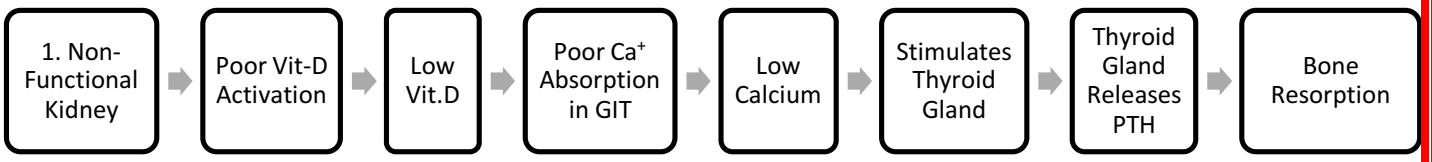
Clinical Complications of Renal Disease

- **Electrolyte Imbalances:**
  - **Hyperphosphataemia (↑Phosphate):**
    - Blood Phosphate (which is usually removed by Kidney) is retained due to poor GFR.
      - →$CaPO_4$ Deposition in Tissues (Tissue Calcification)
      - →Stimulates Thyroid Gland to secrete ParaThyroid-Hormone (PTH) → Bone Resorption.
  - **Hyperkalaemia (↑Potassium):**
    - Blood Potassium (which is usually secreted into lumen) isn't being secreted because Nephrons are non-functional.
      - →Palpitations (Arrhythmias)
      - →Possible Death from Heart Failure
  - **Hypocalcaemia (↓Calcium):**
    - Because The Active Form of Vitamin-D required for Ca^+ Absorption in GIT (Which is usually produced by the kidney) Isn't being produced → Poor Ca^+ Absorption in GIT.
      - →Stimulates Thyroid Gland to secrete ParaThyroid-Hormone (PTH) → Bone Resorption (To Try to Increase Blood-Calcium Levels).
      - → Urinary Calculi
      - →Arrhythmias

- **Renal Bone Disease:**
  - **Damaged Kidney Doesn't Remove Phosphate from Blood & Doesn't Produce Active Vitamin-D:**
    - **→ Hyperphosphataemia:**



    - **→ Poor Ca^+ Absorption in GIT → Hypocalcaemia:**



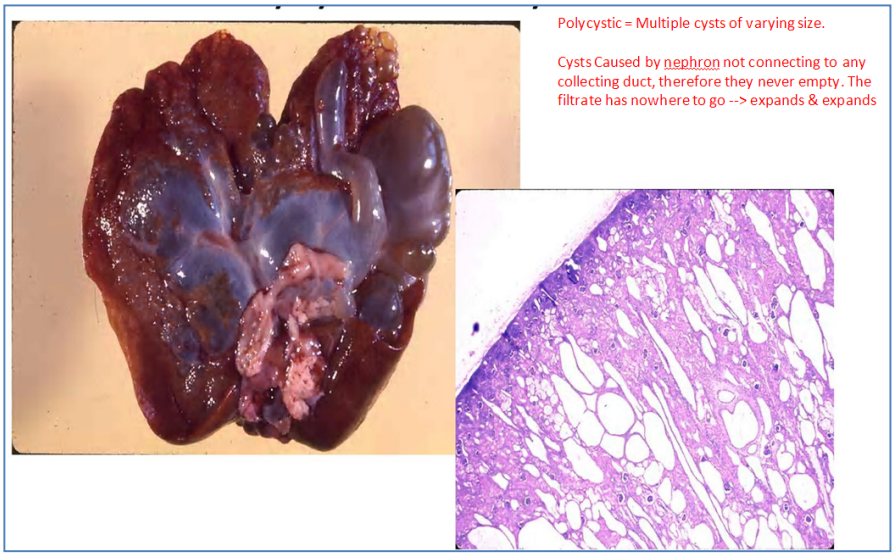
- **Haematologic Complications:**
  - Anaemia (Due to ↓Erythropoietin → ↓RBC Synthesis)

- **Dehydration:**
  - Due to loss of kidney's ability to concentrate urine (Ie. Poor Reabsorbiton of Water)

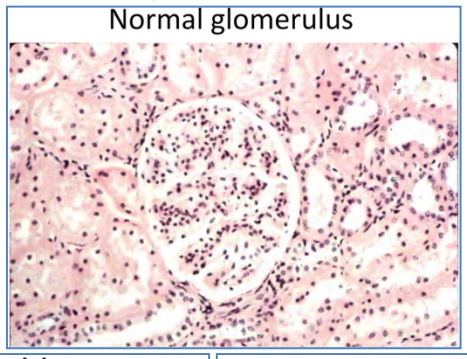
- **Uraemia:**
  - High Blood Urea & Creatinine
    - → Toxic to Brain & Nerves
    - → Irritates the GIT → Vomiting & Nausea
    - → Can cause Uraemia Pericarditis (Deposition of Urea in Pericardium → Inflammation)
    - → Itch (Urea Excretion through skin)

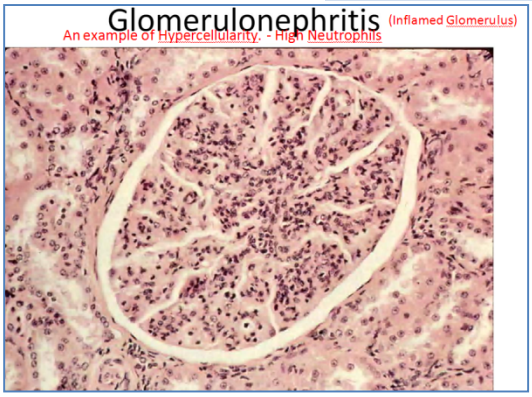
Causes of Renal Disease:

- **Congenital Anomalies:**
  - 10% of people are born with congenital malformations of the renal system – NB: most aren't significant enough to cause disease.
  - **– Eg. Cystic Disease of the Kidney (Polycystic Kidney Disease):**
    - **2 Types (& Modes of Inheritance):**
      - Autosomal Dominant (Adult Variety)
      - Autosomal Recessive (Childhood Variety)
    - **Cysts:**
      - = Bulging, filtrate-filled pouches of kidney.
      - Caused by a Nephron not connecting to any collecting duct – (Ie. Filtrate has nowhere to go → Expands & Expands)
    - **Clinical Features:**
      - Abdominal Discomfort/Pain
      - Haematuria (Blood in Urine – eg. If a cyst ruptures)
      - UTI
      - Renal Insufficiency:
      - - Elevated Serum Creatinine
      - - Anaemia – (↓[Hb] – Due to ↓Erythropoietin Release by Kidneys)
      - - Polyuria – (High Urine Output – due to poor Concentrating Abilities of damaged kidney)
      - - Hypertension

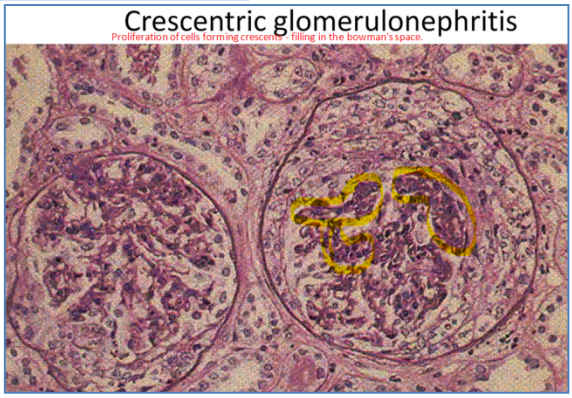


- **Glomerular Diseases:**
  - **– Eg. Glomerulonephritis:**
  - **Causes of Glomerular Diseases:**
    - **Typically Immunologically Mediated...Mechanisms of Injury:**
      - **Antibody-Mediated Injury:**
        - Where *Antibody-Antigen Complexes* form in the Glomerulus → Adheres to Capillary Wall → Causes Inflammation → Infiltration of Leukocytes → Attack the Basement Membrane of Glomeruli → Damage to Glomeruli → Subsequent Damage to Nephron, Vessels & Interstitium.
        - Circulating Infectious/Toxic Agents Deposit in Glomerulus → Causes Inflammation → (Same as above) (Eg. Streptococcal Infections)
      - **Cell-Mediated Injury:**
        - Typically the reaction to an *Antibody-Antigen Complex* (As seen above)
        - Where the Presence of an Antibody-Antigen Complex → Inflammation → Infiltration of Leukocytes → Attack the Basement Membrane of Glomeruli → Damage to Glomeruli → Subsequent Damage to Nephron, Vessels & Interstitium.
      - **Complement-Mediated Injury:**
        - Complement (Cell-killing proteins released in inflammation) → Cause Glomerular Damage.
    - **Also caused by some Systemic Diseases (Hypertension/Diabetes)**
      - (Hypertension Thickens *Basement Membrane* of Glomerulus)
      - (Diabetes Damages *Endothelium* of Glomerular Capillaries)
  - **3 Basic Histological Alterations in Glomerular Disease:**
    - ***1. Hypercellularity:***
      - Proliferation of Endothelial Cells
      - Proliferation of Epithelial Cells
      - Leukocyte Infiltration
      - 'Crescents' of proliferating Epithelial Cells/Leukocytes.
    - ***2. Basement Membrane Thickening:***
      - Thickening of the Membrane between Endothelium of Capillaries & Podocytes of Bowman's Capsule.
    - ***3. Hyalinization & Sclerosis (Scarring):***
      - Accumulation of deposited Protein (Proteinaceous Material)



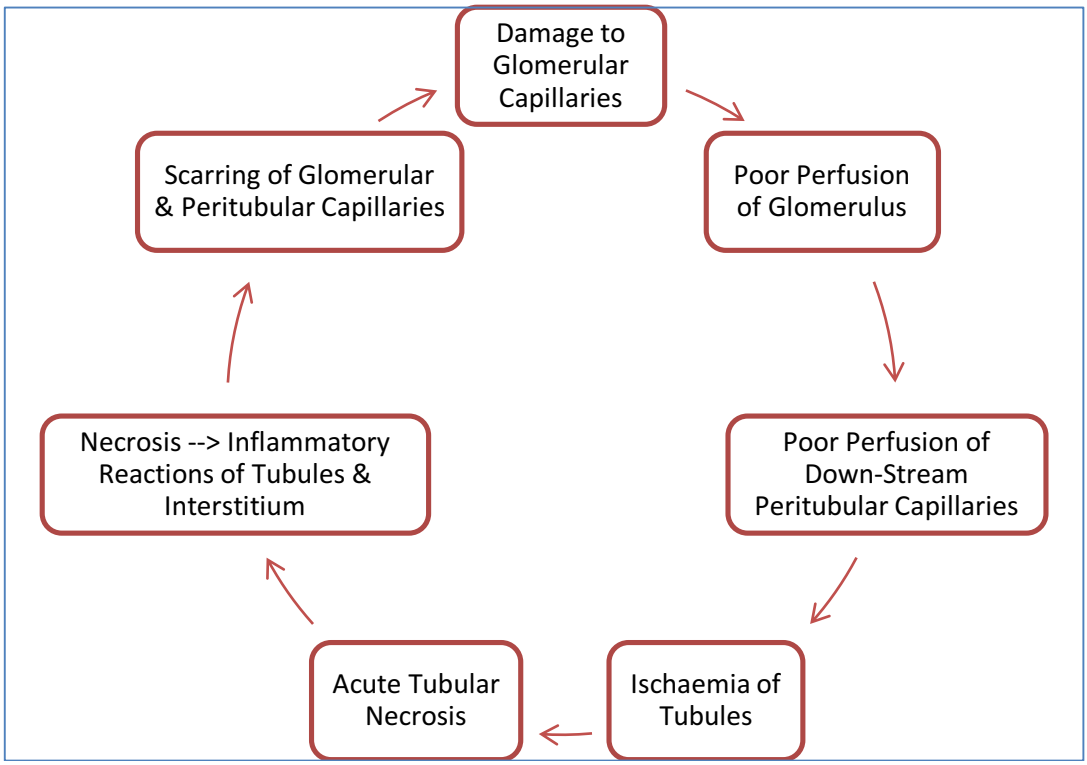


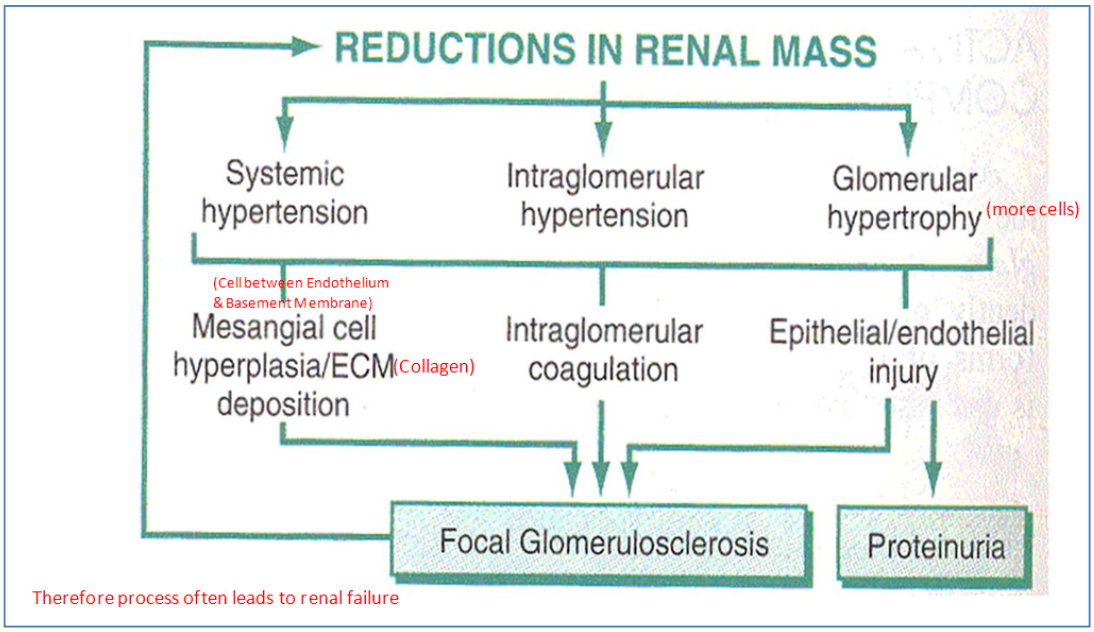
An example of Hypercellularity



Example of 'Crescent' Hypercellularity

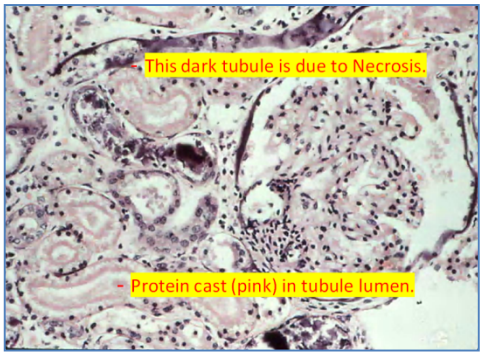
- **Progression of Glomerular Diseases:**
  - NB: once damage causes a GFR reduction to 30-50%, a Viscous Cycle Starts.
    - Focal Segmental Glomerulosclerosis & Tubulointerstitial Inflammation/Fibrosis → Reduction in Functional Renal Mass → Cycle (See Below)

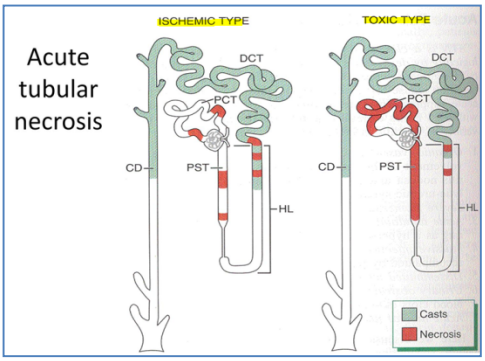




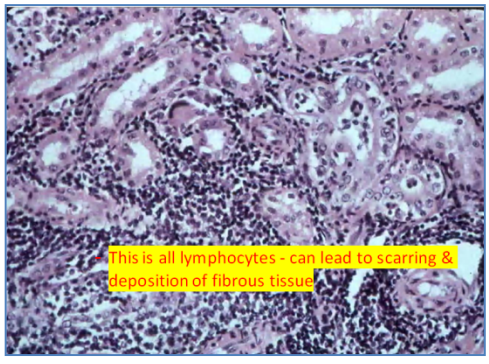
- **Diseases of the Tubules & Interstitium:**
  - **NB: Mostly Caused by Toxic/Infectious Agents → Leading to Either:**
    - **→ Ischaemic Or Toxic Injury to Tubules & Interstitium → Acute Tubular Necrosis**
      - NB: Ischaemia mostly due to Sclerotic (Scarred) Glomeruli – (Ie. Thickening of Artery Walls →↓Lumen Size → ↓Flow → Ischaemia of Distal Tubules)
      - NB: Toxic Injury may be a result of Phosphate/Ammonia Retention or Proteinuria.
    - **→ Inflammatory Reactions in Tubules & Interstitium → TubuloInterstitial Nephritis**
      - NB: Inflammation due to Bacteria/Viruses/Drugs/Toxins/Phosphate Retention/etc. → Leukocytes Infiltration, Fibrous Tissue Deposition & Tubular Degeneration.

  - **Acute Tubular Necrosis:**
    - **Necrosis Caused by Ischaemic Or Toxic Injury to Tubules & Interstitium:**
      - **- Ischaemia** (Poor Blood Flow) in the Peritubular Capillaries → Tubule Cell Death (Necrosis)
      - **- Nephrotoxins** (Chemicals toxic to kidneys) → Tubule Cell Death (Necrosis)
    - **Characterised by:**
      - **Necrosis of Proximal Tubule Cells** – (NB: Proximal Tubules are more prone to Nephrotoxin damage because they're the first to come in contact toxins)
      - **'Casts' of Proteinaceous Material** in Distal-Convoluted Tubule Lumens. (Deposited due to necrosis of proximal Tubule Cells)
      - →Commonly Causes Acute Renal Failure
    - **Characteristics of:**
      - **- Ischaemic Type Tubular Necrosis:**
        - Necrosis is *patchy* throughout PCT & Loop of Henle.
        - 'Casts' throughout the *entire* DCT & Part of Collecting Duct.
      - **- Toxic Type Tubular Necrosis:**
        - Necrosis is *consistent* throughout PCT & Desc.Loop of Henle.
        - 'Casts' throughout the *entire* DCT & Part of Collecting Duct.

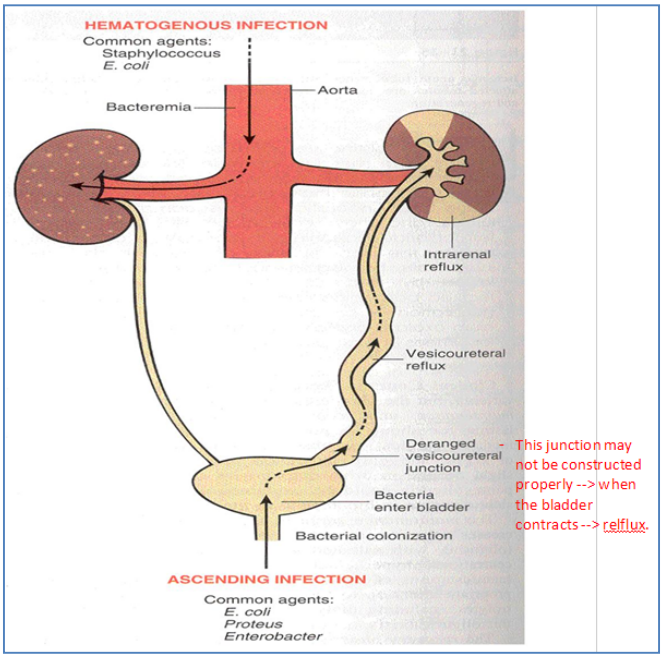




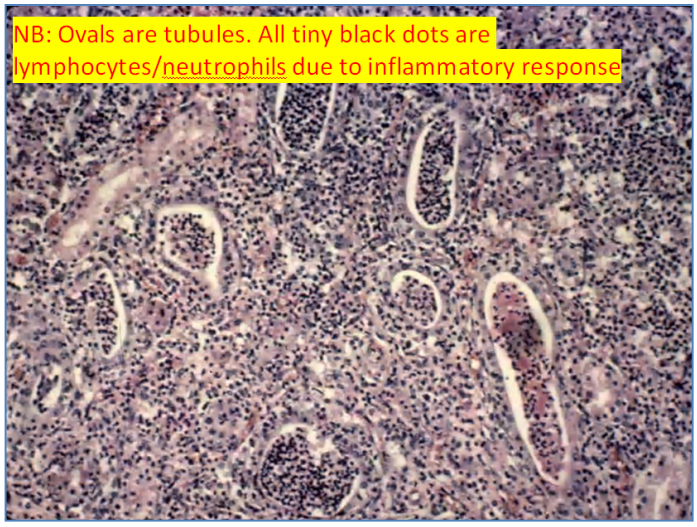
  - **Tubulointerstitial Nephritis:**
    - = Inflammation of Tubules & Interstitium due to Bacteria/Viruses/Drugs/Toxins/Phosphate Retention/etc. → Leukocytes Infiltration, Fibrous Tissue Deposition & Tubular Degeneration.
    - Often Secondary to Acute Tubular Necrosis (Ie. Glomerular/Tubular Necrosis & Protein Casts)
    - NB: Can have *Drug-Induced* Tubulointerstitial Nephritis –Penicillin Reactions/Analgesic Abuse



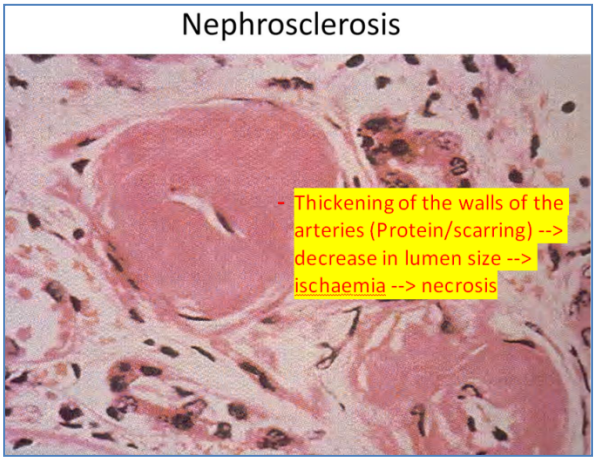
- **Diseases of the Tubules & Interstitium (Continued):**
  - **Eg. Pyelonephritis:**
    - = Inflammation of the Pyelum (Pelvis) of the Kidney (Which spreads to Tubules & Interstitium)
    - **Caused by:**
      - Ascending UTI → Inflammation
      - Or – Bacteria in Blood Depositing in Kidneys → Inflammation
    - **Results in:**
      - Heavy Inflammation of Tubules & Interstitium
      - Infiltration of Lymphocytes



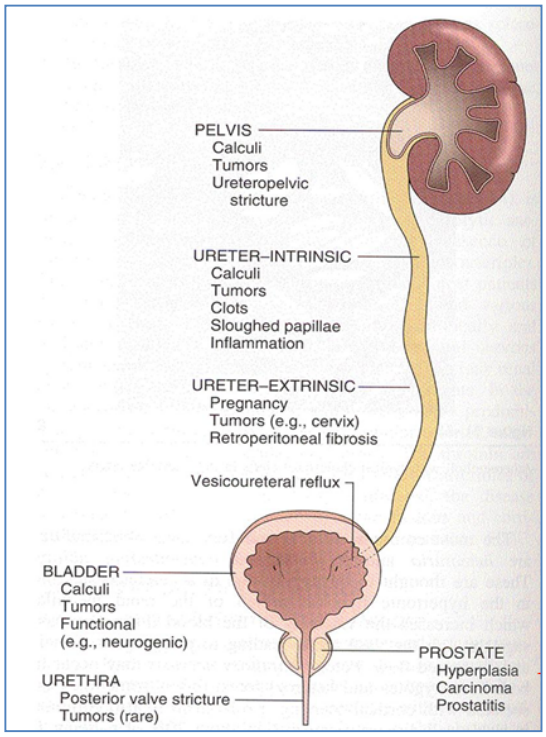
- This junction may not be constructed properly --> when the bladder contracts --> relflux.



- **Disease of The Blood Vessels:**
  - NB: All Kidney Diseases are Either Caused *by* Renal Vascular Damage or *Lead To* Renal Blood Vessels Damage Secondarily.
    - Ie. Kidney Damage → Vessel Damage → ↓Blood Flow → Further Kidney Damage...etc.etc.
  - **– Eg. Nephrosclerosis:**
    - = Scarring of the Nephron (Primarily the Vasculature)
    - Deposition of Protein in Vessel Wall → Thickening of Vessel Wall → Ischaemia → Necrosis.
    - Systemic Diseases (Such as Diabetes & Hypertension) Exacerbate Vessel Damage.
      - **(Diabetes** → ↑[Blood Glucose] → Blood proteins become *sticky* → deposit in small blood vessels → Vessel Inflammation, Damage & Scarring → Nephrosclerosis**)**
      - **(Hypertension** → Damage to Glomerular Capillaries → Sclerosis & Thickening of Capillary Wall → Nephrosclerosis)



- **Obstructive Lesions of the Urinary Tract:**
  - Ie. Where Kidney Stones (Calculi), Tumours, or Clots Typically tend to cause Obstruction.
  - – **Renal Pelvis**
  - **– Ureter (**At the point where it enters the Bony Pelvis**)**
  - **– Prostate**
    - NB: Prostatic Obstruction → Urine Retention in Bladder → Urea, Creatinine & other toxic chemicals are Reabsorbed through bladder wall → Uraemia (↑Blood Urea) → Toxic to Nerves/Brain
  - **– Urethra**



Population Health & Renal Disease

Renal Disease: Significance?:

- Growing health issue
- Economic Costs:
  - Public Health Service
  - Out-of-Pocket (Patients)
- Personal Burden → ↓Quality of Life
- Medical Care → Positive Outcomes

Most Common Renal *Morbidities*:

- **UTI's (Urinary Tract Infections)**:
  - Both Children & Adults
  - Often due to Diabetes → Sugar in Urine → Food For Bacteria
- **Urinary Tract Abnormalities:**
  - Eg. Urinary Reflux – (from Bladder → up the Ureters)
- **Urinary Incontinence:**
  - Childhood Bedwetting
  - Females – Pelvic Floor Weakening (eg. Following pregnancy)
- **Prostatic Hypertrohpy/Cancer:**
  - Hypertrophy happens to all men → older
  - Cancer = common

Most Common Renal *Mortalities*:

- **Prostate Cancer**
- ****End-Stage Renal Disease**

Definitions:

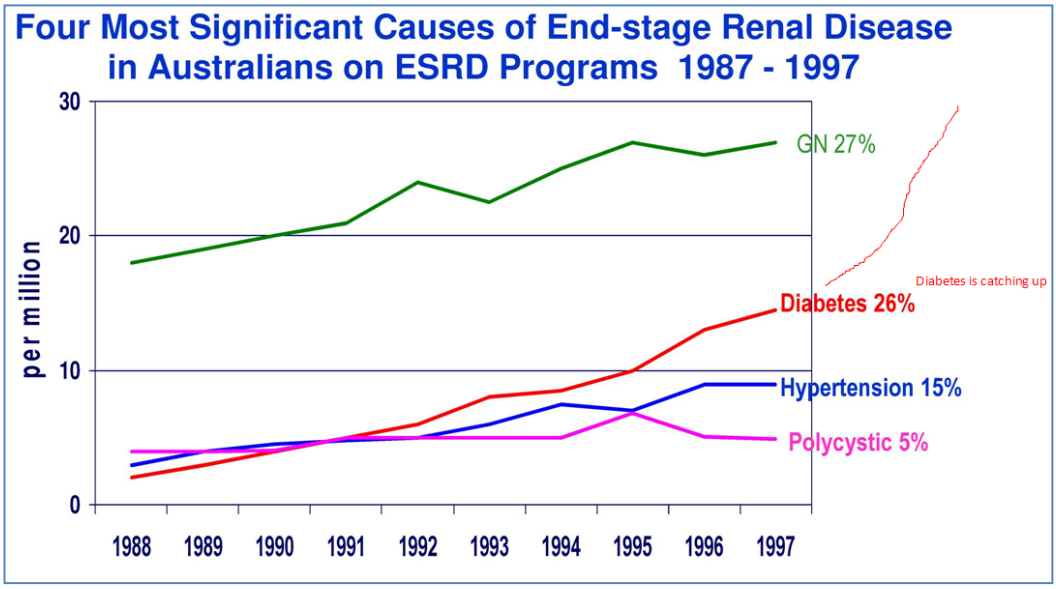
- **Renal Failure:**
  - Sustained, Irreversible reduction in GFR (Glomerular Filtration Rate) to <60mL/min
  - Raised Creatinine (200^{+} micro-mol/L)
  - (On 2 Occasions; 1 Month Apart; With No Acute Illness)
- **End-Stage Renal Disease:**
  - (GFR = <15ml/min)
  - Kidney function *Incompatible With Life* → Require Dialysis/Transplant for Survival

Prevalence of Chronic Renal Failure in AUS:

- **People At Risk:**
  - (Those With Hypertension and/or Diabetes)
  - 3^{+} Million
- **Stage 1-3 - Renal Failure:**
  - (GFR = 30-90ml/min)
  - 2.3 Million People
- **Stage 4 - Renal Failure:**
  - (GFR = 15-30ml/min)
  - 40,000 People
- **Stage 5 – End Stage Renal Disease:**
  - (GFR = <15ml/min)
  - Ie. *Compete* Kidney Failure → Require Dialysis/Transplant for Survival
  - 12,000 People

Epidemiology of End-Stage Renal Disease:

- **Incidence:**
  - Rapid Rise in New Cases over Last Decade
  - Mainly Due to ↑Diabetes.
  - Higher *Rate*-of-*Increase* in Indigenous Population
- **Prevalence:**
  - 1981 ≈ 3200 cases
  - 2003 ≈ 13,500 cases
- **Known Causes:**
  - #1. Glomerulonephritis
  - #2. Diabetes (Slowly Becoming #1)
  - #3. Hypertension
  - #4. Polycystic Kidney



- **ESRD Risk Factors:**
  - Childhood PSGN (Post-Streptococcal Glomerular Nephritis)
    - Auto-immune response to Haemolytic Strep →Inflammatory response manifested by cellular Proliferation & Oedema of the Glomerular tuft.
  - Chronic UTI's
  - Kidney/UT Stones
  - Inter-Uterine Malnutrition:
    - (Risk of ESRD begins in-utero – Foetuses that undergo metabolic Insults [poor nutrition/high Blood Sugar(Diabetic Mother)/etc] Actually grow *Less* Kidney Cells)
  - Low Birth Weight
  - Adult Obesity
  - Diabetes (Poorly Controlled)
  - Hypertension (Poorly Controlled)
  - Smoking
  - Poor Access to Services
  - ***Indigenous:***
    - Tend to get Renal Disease Younger
    - When they get it, it *Advances More Quickly*
    - They have *Less Access* to treatment
    - Die younger as a result.

(Inter-Uterine Malnutrition through Indigenous: Often due to Low Socio-Economic Status)

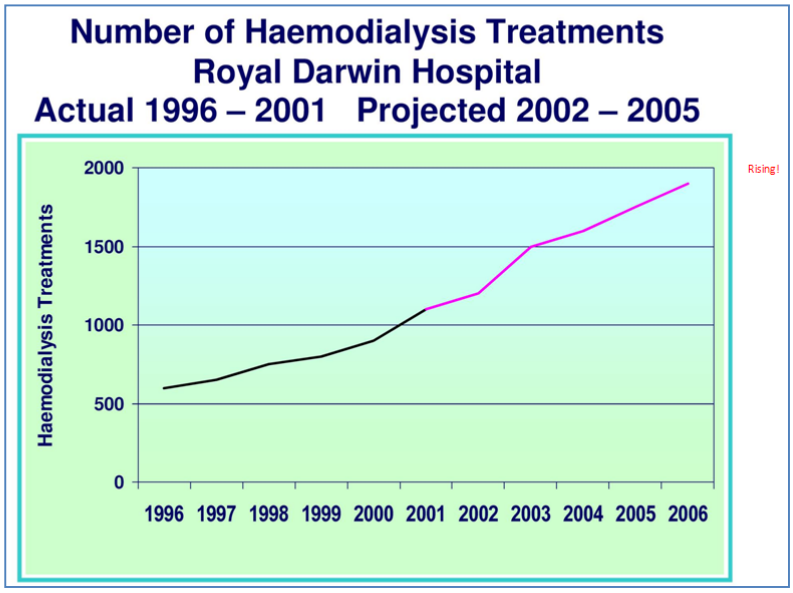
Prevention of Renal Disease:

- **Primary Prevention:**
  - Preventing People Getting the Disease in the First Place.
  - **Improve Early-Life Health:**
    - **NB: Barker Hypothesis:** English Doctor – Found a Correlation between Antenatal Health & Later-Life Health. – This relationship exists for Renal Disease.
    - **Antenatal Care:**
      - Control of Mother's Diabetes
      - Nutritional Supplements for Extra Demands of Foetus
    - **Infant/Childhood Nutrition:**
      - Breast-Feeding - (Best for nutrients & immunity)
      - Avoid Obesity
    - **Exercise**
    - **Growth Monitoring**
  - **Reduce Risk Factors:**
    - Obesity
    - Smoking
    - Fatty Diets
    - Hypercholesterolemia
    - Alcohol

- **Secondary Prevention:**
  - Diagnosing the Disease Early to Optimise Management & Prognosis
  - **Screening For:**
    - Diabetes
    - Hypertension
    - Renal Dysfunction
  - **If Chronic Renal Disease is Present:**
    - Reduce Obesity
    - Exercise
    - Control Fat/Sugar Intake
    - Low GI Foods
    - Medications:
      - Antihypertensives
      - Diabetes Medication
  - **Monitor:**
    - Response to Meds
    - Blood Pressure
    - Blood Sugar Levels
    - Renal Function – Creatinine
  - **Refer:**
    - To Renal Specialists (nephrologists)

ESRD Treatment:

- **Kidney Transplant:**
  - The Best Treatment
    - Most Cost-Effective
    - Most Permanent
- **Dialysis:**
  - **Peritoneal Dialysis:**
    - CAPD – Continual Ambulatory Peritoneal Dialysis
    - Ambulatory Peritoneal Dialysis
  - **Haemodyalisis:**
    - Satellite
    - Hospital
    - Home



Cost of Renal Disease:

- ****Costs of Renal Disease Are PHENOMENAL****
- **Financial:**
  - **Ie. 4.1% of Total Health System Budget in 2001**
  - **Where Does The Money Go?:**
    - Hospital Services
    - GP & Specialist Services
    - Allied Health Costs
    - Prescriptions
- **Personal Burden:**
  - Relocation to Areas With Treatment (If Rural Patient)
  - Loss of Income
  - ↓Quality of Life
  - ↓Social/Family Life (Due to Morbidity/Relocation)

Economics of Renal Disease Treatment:

- **Ie. Getting The *Best Outcomes* for The *Least Money*.**
  - Eg. Peritoneal Dialysis or Heamodialysis?
  - Dialysis or Transplant?
  - Dialysis or Diabetes Prevention?
- **How Do We Compare Outcomes of Different Actions?**
  - **Answer = QALY's (Quality-Adjust Life Years)**
    - **1x QALY** = 1 Full Year of Life @ Full Quality of Life
    - Used to Compare Quality & Length Of Life Gained from Different Interventions & the Costs of Doing So.
  - **Calculating QALY's:**
    - Multiply the Years Gained From an Intervention by the Quality-Of-Life-Percentage.
    - (Where 100% = Full Health)
  - **Eg.**

Evaluating the benefits gained from screening for Proteinuria and how much each QALYS costs.

Screening for Proteinuria	QALYS gained per person	Cost per QALYS USD$
Well people	0.0022	282,818
With hypertension	0.03	18, 621

- ***Cost-Effectiveness* Analysis:**
  - Aim: To find the Cheapest Way to achieve A *Specific Desired Outcome*.

How we use quality of life years to decide the effectiveness of different treatments

Cost of One Quality Adjusted Life Year

	£
Home haemodialysis	17 260
CAPD	19 870
Hospital haemodialysis	21 970
Kidney transplant	4 710

So much more cost-effective.

- ***Cost-Utility Analysis*:**
  - Aim: To Compare Costs of Interventions With *Different Health Outcomes*.

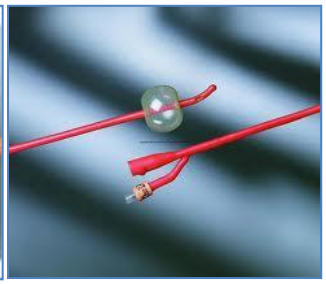
	Cost per QALY (£)
Cholesterol testing and diet therapy	220
Advice to stop smoking from patient's own doctor	270
Hip replacement for arthritis	1 180
Kidney transplant	4 710
Breast cancer screening	5 780
Neurosurgery for malignant brain tumours	107 780

RENAL Pathology:
CATHETERIZATION

Catheterization (Females and Males):

- **Indications:**
  - Urinary retention
  - Urine Sample
  - Post-operative to assess urinary output, perfusion.
  - Prostatic obstruction:
    - BPH [most likely].
    - CA of prostate.
  - Other obstructions:
    - Clots.
    - Stones.
    - Bladder CA.
  - Trauma.
  - Paralysis.
- **Peri-Urethral Structures that might Interfere with Catheterisation:**
  - Labia
  - Foreskin
  - Prostate
  - Urethral Sphincters
- **Different Types of Catheters:**
  - **Foley (Brown Latex):** Cheapest, Commonest
  - **Silastic (Clear Silicone):** can leave in longer than Foley with less chance of complications
  - **Robinson's:** Has no balloon, is used for Short term drainage
  - **Coude:** Angled for easier insertion around prostate



- **Basic Process of Catheterisation:**
  - Initial Steps:
    - Gather Equipment
    - Explain Procedure and get Consent
    - Lay pt into supine position + Spread Legs
    - Prepare Sterile Field + Apply Gloves
    - Cleanse Periurethral Mucosa with Cleansing Solution
  - Check Balloon for Patency
  - Coat the distal 2-5cm with Lubricant
  - Gently Insert Catheter into Urethra until 1-2inches *beyond* the point of Urine Flow.
  - Inflate Balloon with 10cc of Sterile Liquid.
  - Gently Pull Catheter back until Balloon is snug against bladder neck.
  - Connect To Drainage System + Make sure bag is below the level of the bladder.
- **Complications:**
  - Tissue Trauma
  - Infection
  - Bacteruria
  - Renal Inflammation
  - Pyelonephritis
- **Suprapubic Catheters:**
  - If trans-urethral catheterization isn't possible.
  - Involves piercing the bladder (via the peritoneal cavity) with a syringe.

RENAL Pathology:
CONGENITAL KIDNEY ABNORMALITIES

Congenital Anomalies of the Kidney:

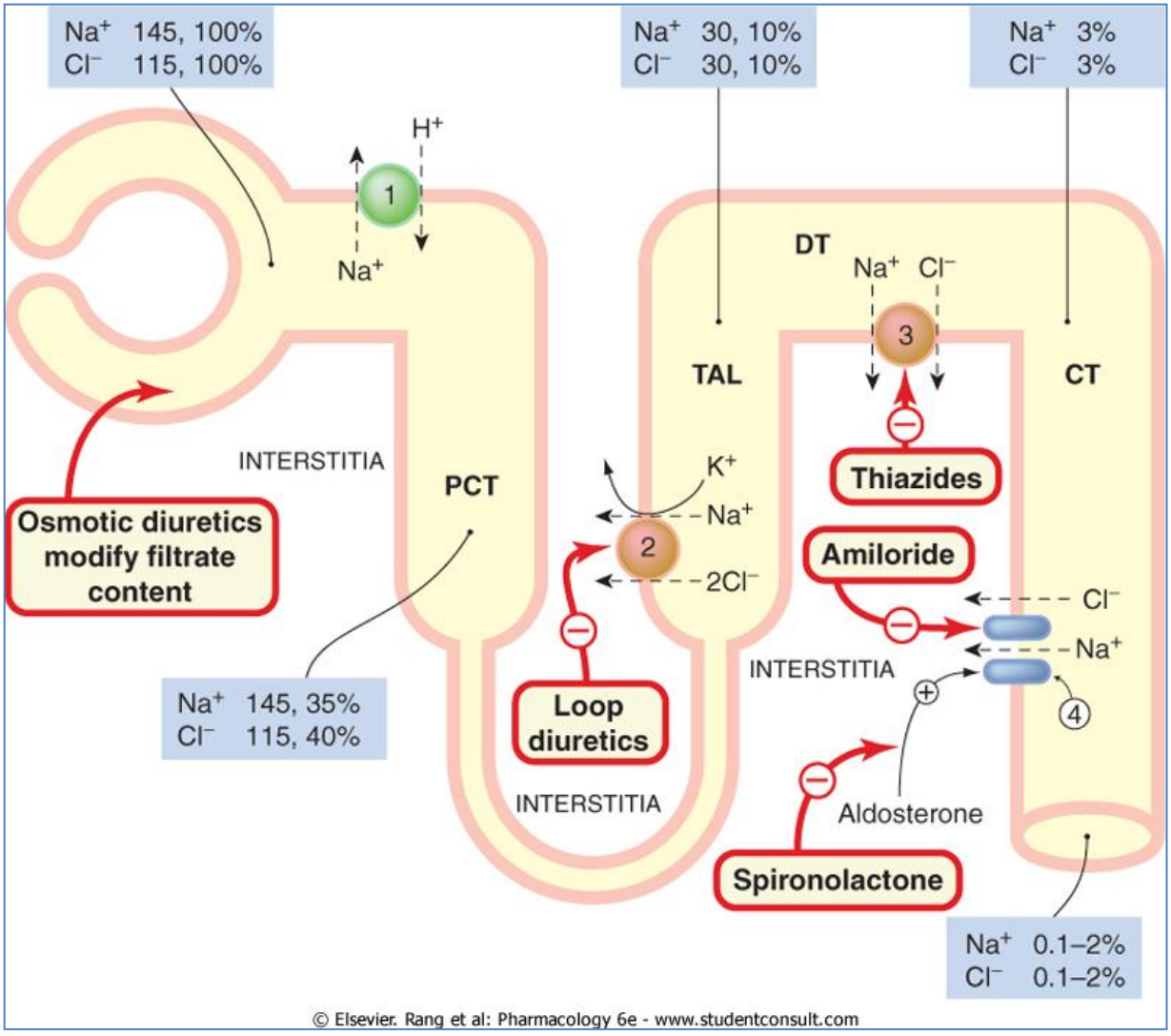
- **Agenesis of the Kidney:**
  - Bilateral is incompatible with life and usually encountered in stillborn infants
  - Often associated with many other congenital disorders (limb defects, hypoplastic lungs) and leads to early death
  - Unilateral is an uncommon anomaly that is compatible with normal life if no other abnormalities exist
  - The opposite kidney is usually enlarged as a result of compensatory hypertrophy
  - Some pts eventually develop progressive glomerular sclerosis in remaining kidney as a result of the adaptive changes in hypertrophied nephron and in time chronic kidney disease ensues
- **Hypoplasia:**
  - Refers to failure of the kidneys to develop to a normal size
  - May occur bilaterally resulting in RF in early childhood but more commonly seen as unilateral
  - True renal hypoplasia is extremely rare
  - Differential between congenital and acquired atrophic kidneys may be impossible but a truly hypoplastic kidney shows no scars and has a reduced number of renal lobes and pyramids, usually 6 or fewer
  - One form of hypoplastic kidney – oligomeganephronia, kidney is small with fewer nephrons that are markedly hypertrophied
- **Ectopic Kidneys:**
  - Lie either just above the pelvic brim or sometimes within the pelvis
  - They are usually normal or slightly small in size but otherwise not remarkable
  - Because of abnormal position, kinking or tortuosity of ureters may cause some obstruction to urinary flow which predisposes to bacterial infections
- **Horseshoe Kidneys:**
  - Fusion of the upper or lower poles of the kidneys produces a horseshoe-shaped structure that is continuous across the midline anterior to the great vessels
  - Is common and found in about 1 in 500-1000 autopsies
  - 90% of such kidneys are fused at lower pole, 10% fused at upper

RENAL Pathology:
DIURETICS

DIURETICS:

- **Drugs that ↓Na^+ Reabsorption in the Kidneys → ↑H_2O Excretion:**
  - **→ Net Loss of Na^+ and therefore Water as well.**

- **NB: The [Na^+] decreases as you travel down the Nephron:**
  - **Therefore, the *Effectiveness* of the Diuretic depends on its *Site of Action*:**
    - **Eg. If Proximal Tubule (Osmotic Diuretics) [65% Na^+]** – Very Effective.
    - **Eg. If Loop of Henle (Loop Diuretics) [25% Na^+]** – Effective.
    - **Eg. If Distal Tubule (Thiazide Diuretics) [5% Na^+]** – Low Effectiveness.
    - **Eg. If Collecting Ducts (K^+ Sparing Diuretics) [2% Na^+] –** Very Low Effectiveness.

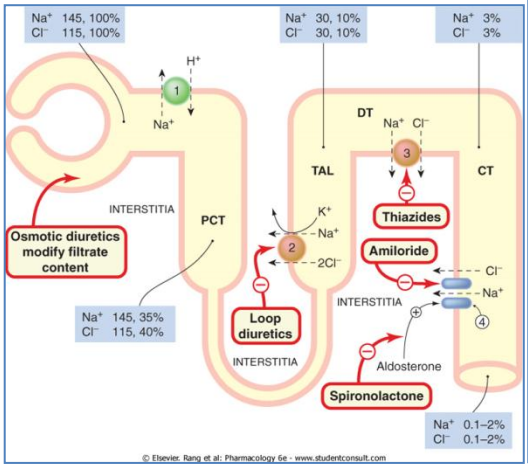


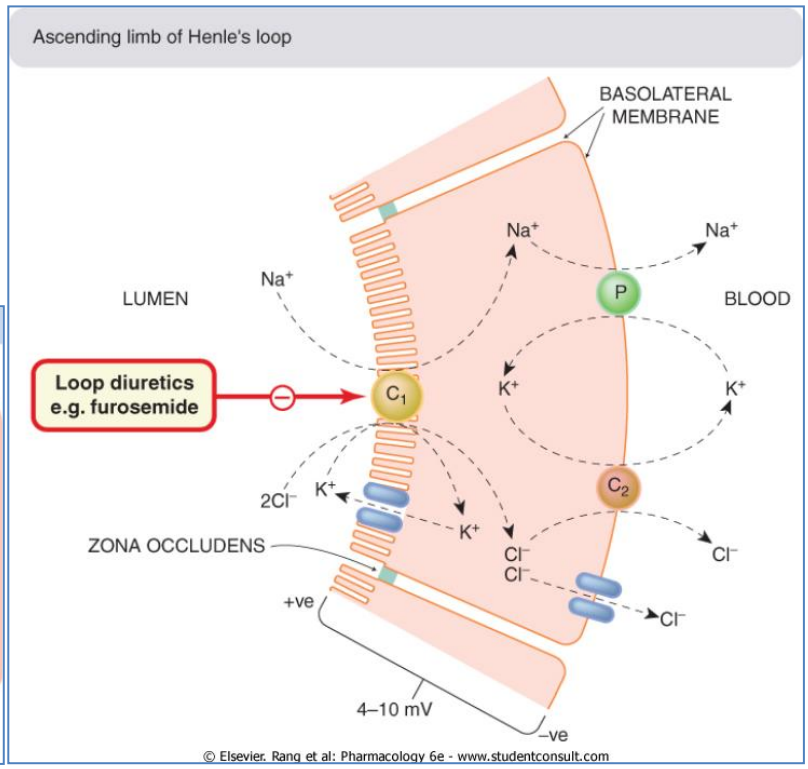
  - **The Catch: It is difficult to *only* manipulate Na^+. (Some are 'K^+-Wasting'; some are 'K^+-Sparing'):**
    - Hence why Combinations – often used to balance K^+ Movement.
    - **However,** *even a 'balanced diet' of Diuretics* can <u>slowly</u> lead to *Hypokalaemia* if not monitored.

- **<u>Why Use Diuretics?:</u>**
  - Treatment of <u>*Mild*</u> Hypertension:
    - NB: Diuretics are better than β-Blockers in *Every Way*. (↓Cost/Side Effects)
  - Treatment of Acute Renal Failure
  - Treatment of Oedema
  - Treatment of Congestive Heart Failure:
    - - to ↓Fluid Volume & ↓BP → ↓Preload → Treat Heart Failure.

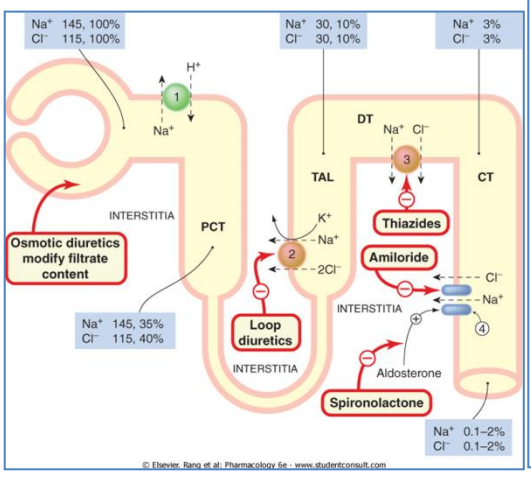
Types of Diuretics:

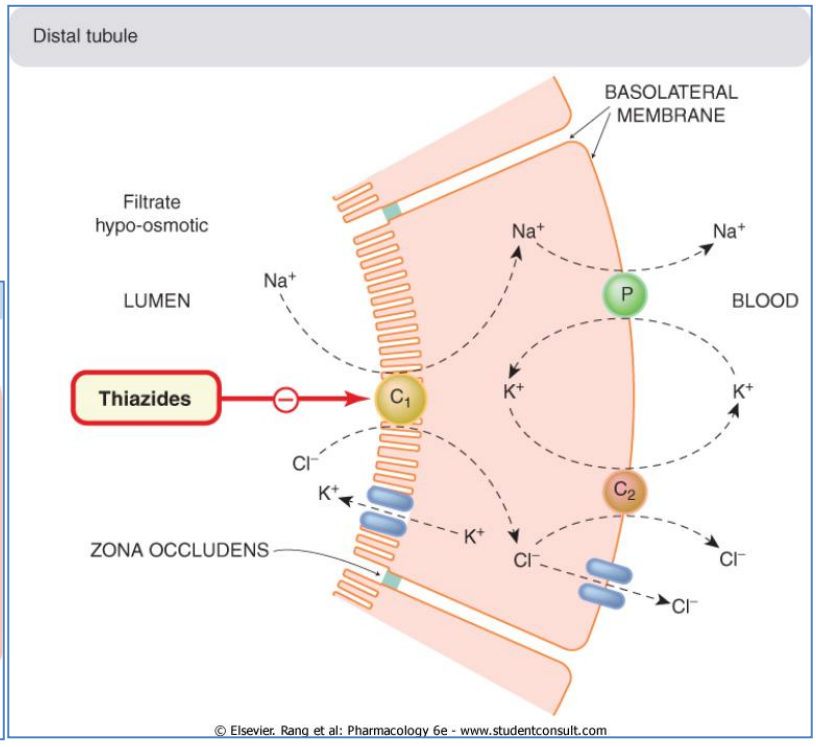
- **Loop Diuretics:** (Most Powerful – *BUT Potassium-Wasting*)
  - **Site of Action:**
    - The Thick Ascending Loop of Henle
  - **Mechanism of Action:**
    - Inhibiting the Na/K/Cl-Transporter in the Thick-Ascending Loop of Henle.
    - → prevents Na^+ Resorption into Interstitium (Therefore Prevents H_2O Resorption)
      - (NB: Also prevents K^+ & Cl^- Reabsorbtion)
    - *→*Prevents* formation of the 'Hyperosmotic Medullary Interstitium' that ordinarily facilitates Water Resorption (under the influence of ADH).
  - **Indications:**
    - Acute Pulmonary Oedema
    - Heart Failure
    - Ascites (due to hepatic cirrhosis)
    - Renal Failure
    - (NB: Thiazides are preferred for Hypertension.)
  - **Side Effects:**
    - Hypovolaemia & Hypotension.
    - Hypokalaemia (Due to inhibition of K^+ Reabsorption):
      - May require Potassium Supplements, Or coupling with **K^+-Sparing Diuretics**.
      - (NB: Can increase Digoxin Toxicity)
    - Metabolic Alkalosis (Due to *reverse dilatation effect* of H_2O loss, but *no* HCO_3 Loss):
      - Aka: "Concentration Alkalosis".
    - Hyperuricaemia → Gout.
    - Reversible Hearing Loss (Same co-transporter is found in the Ear)
  - **Classical Agents:**
    - ***Frusemide**
    - Bumetanide
    - Ethioyic acid



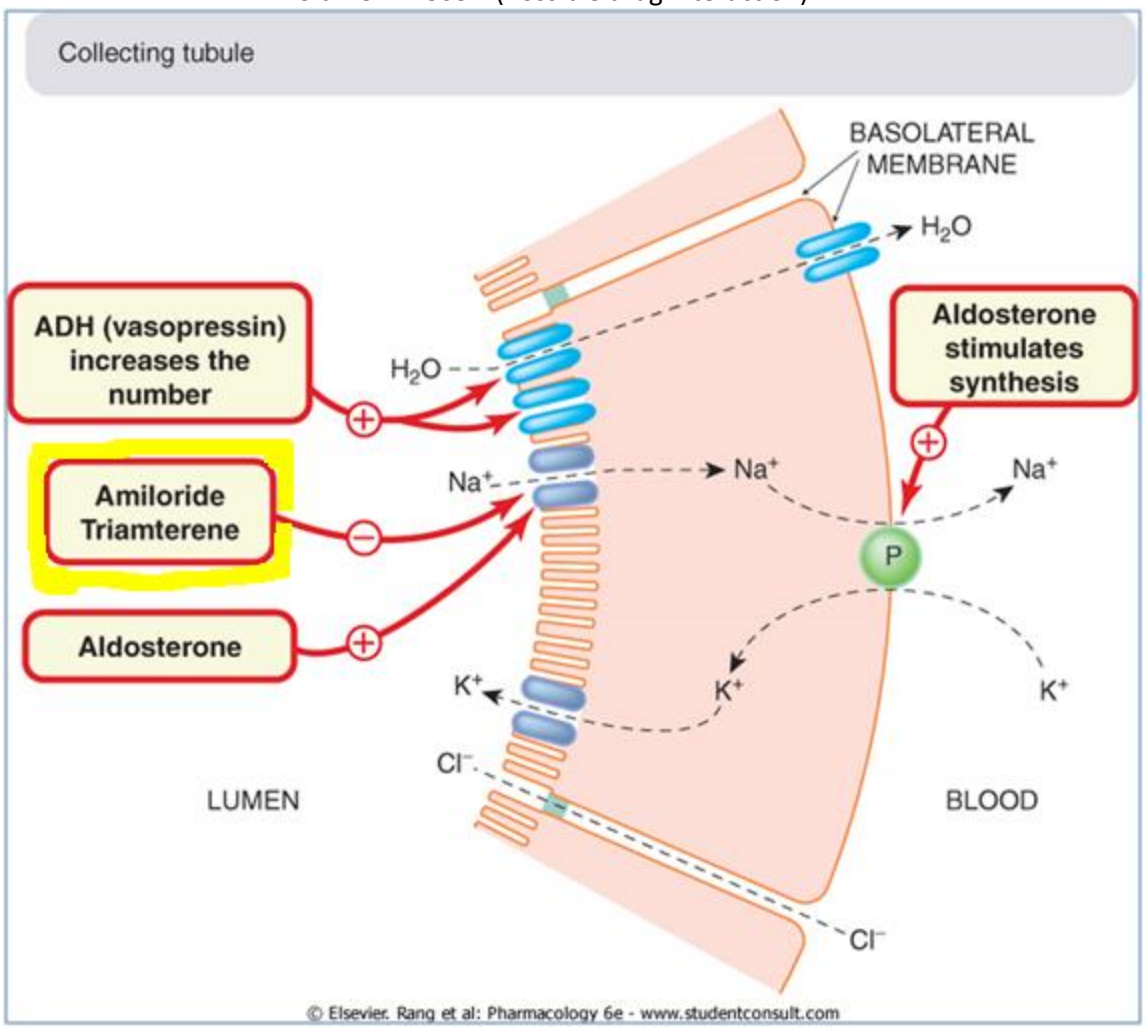


- **Thiazide Diuretics:** (Not as powerful as Loop Diuretics – *And Still Potassium-Wasting*)
  - **Site of Action:**
    - Distal Convoluted Tubules
  - **Mechanism of Action:**
    - Inhibiting the Na/Cl Symporter in the DCT.
    - → prevents Na^+ Resorption into Interstitium (Therefore Prevents H_2O Resorption)
      - (NB: Also prevents Cl^- Reabsorption)
      - (NB: Still K^+ Wasting)
    - Maintains a High Filtrate Osmolarity → Retaining Water in the Tubule.
  - **Indications:**
    - **Uncomplicated Hypertension – (One of the 1st lines of treatment for hypertension)
    - Severe Resistant Oedema
    - Mild Heart Failure
    - Ascites (due to hepatic cirrhosis)
    - Acute Renal Failure
  - **Side Effects:**
    - Hypovolaemia & Hypotension.
    - Hypokalaemia:
      - May require Potassium Supplements, Or coupling with **K^+-Sparing Diuretics**.
      - (NB: Can increase Digoxin Toxicity)
    - Hyponatraemia:
      - Can be Fatal.
    - Hypomagnesaemia
    - Hypocalciuria (Hypercalcaemia):
      - (NB: May be beneficial in elderly patients for Bone Metabolism)
    - Metabolic Alkalosis (Due to *reverse dilatation effect* of H_2O loss, but *no* HCO_3 Loss):
      - Aka: "Concentration Alkalosis".
    - Hyperuricaemia → Gout
    - Hyperglycaemia:
      - Can unmask latent Diabetes Mellitis.
    - Reversible Erectile Dysfunction
  - **Classical Agents:**
    - ***Chlorothiazide**
    - Chlortalidone

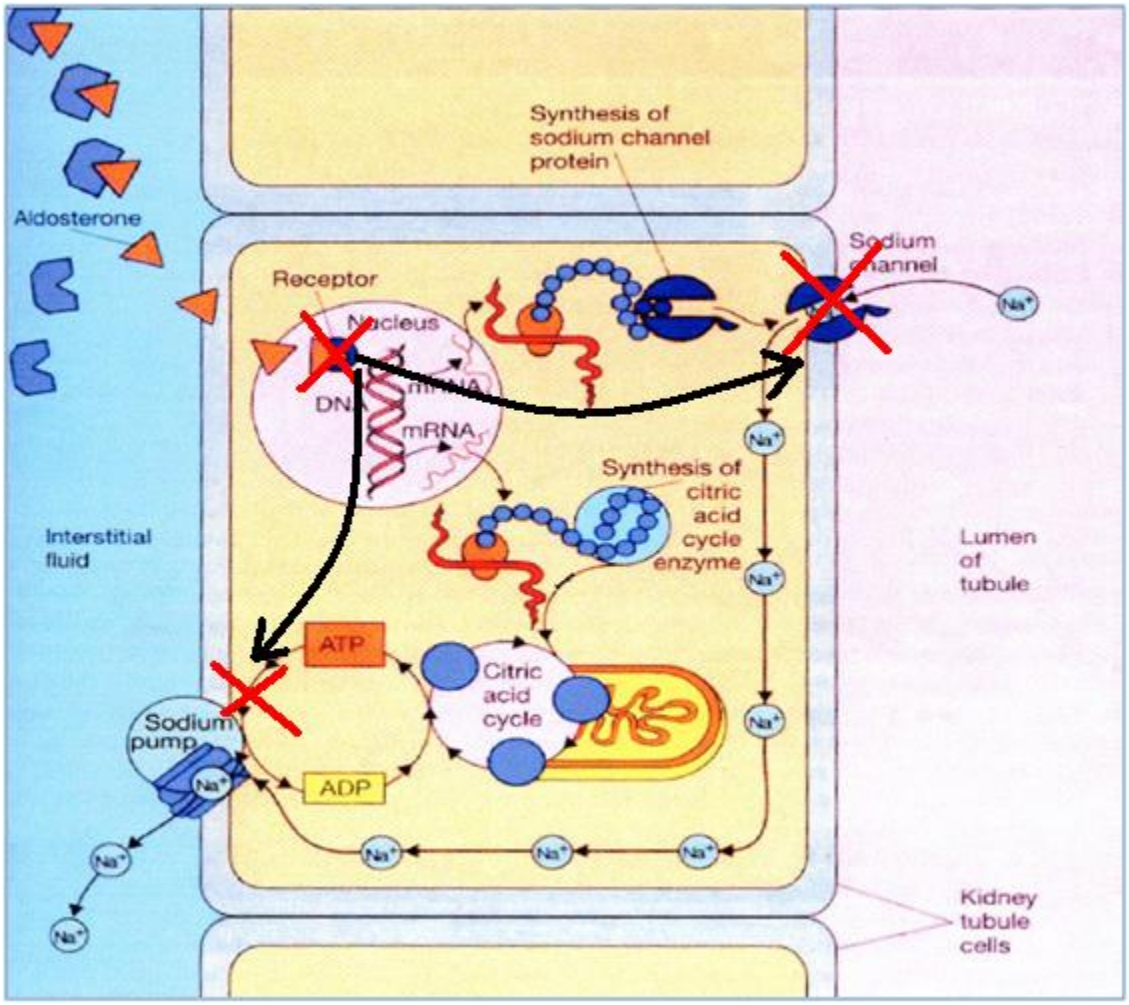




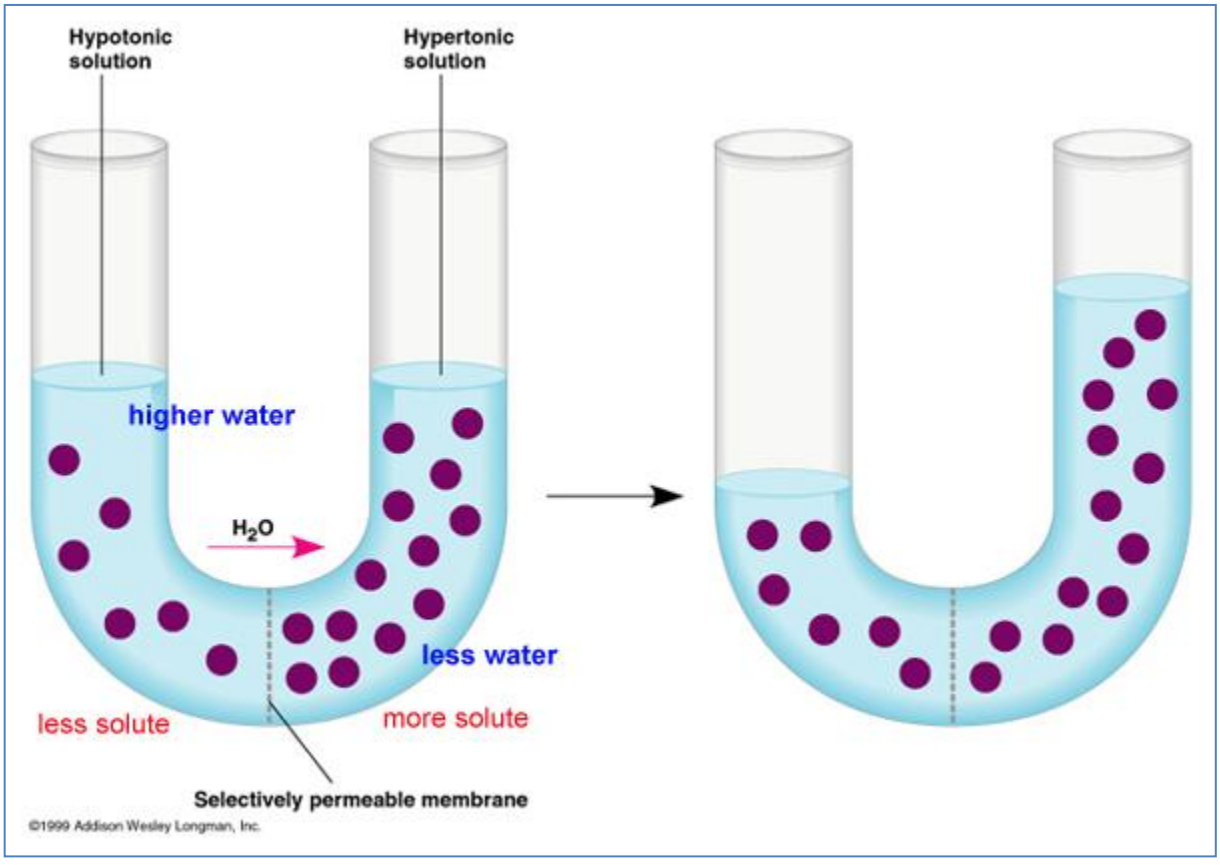
- **K+ Sparing Diuretics:**
  - **Site of Action:**
    - Collecting Ducts
  - **Indications – (Common for both):**
    - Used in Pts where K^+ Loss is Hazardous – (Eg. Pts on Digoxin or Amiodarone)
    - Heart Failure
    - Hyperaldosteronism
    - Resistant Essential Hypertension (Eg. Low-Renin Hypertension)
    - Ascites (Due to Hepatic Cirrhosis)
  - **1. Epithelial Na^+ Channel Inhibitors:**
    - **Mechanism of Action:**
      - **Directly Inhibits the *Aldosterone-Activated* Na^+ Channels in walls of Collecting Ducts:**
        - → Inhibits H_2O Resorption.
      - **K^+ Sparing Effect** comes from a *Loss* of Na^+-Concentration Gradient which normally powers a *Secondary-Active Na/K-Symporter* on Basal Membrane.
    - **Classical Agents:**
      - *Amiloride
      - Triamterene
    - **Side Effects:**
      - Hyperkalaemia – (Potentially Fatal)
        - Hence: Avoid in Pts with Renal Failure/ACE-Inhibitors/K^+ Supplements.
      - Avoid NSAID Use – (Possible drug interaction)



- **2. Aldosterone Antagonists:**
  - **Background on Aldosterone Function:**
    - Aldosterone is a Steroid Hormone → Causes Expression of Proteins:
      - Na^+ Channel Proteins – (Responsible for Na^+ Resorbtion).
      - TCA-cycle Enzymes → ↑ATP – (ATP is responsible for Na Pump).
    - Therefore, Aldosterone is Responsible for Na^+ Resorbtion in Collecting Duct.
  - **Mechanism of Action of *Aldosterone Antagonists*:**
    - **Prevents Aldosterone from binding to its Nuclear Receptor → Prevents Expression of the Above Proteins.**
      - → ↓Na^+ Channel Proteins → ↓Na^+ Resorption → Inhibits H_2O Resorbtion.
      - → ↓TCA Enzymes → ↓ATP → ↓Na^+ Pump Function → ↓Na^+ Resorbtion.
    - **Ultimately → ↓ H_2O Resorbtion**.
    - **NB:** ONLY works when Renin-Angiotensin System is Active.
      - Ie. Efficacy depends on Endogenous Aldosterone Level.
    - **K^+ Sparing Effect** comes from a *Loss* of Na^+-Concentration Gradient which normally powers a *Secondary-Active Na/K-Symporter* on Basal Membrane.
  - **Classical Agents:**
    - *Spirinolactone
  - **Side Effects:**
    - Hyperkalaemia – (Potentially Fatal)
      - Hence: Avoid in Pts with Renal Failure/ACE-Inhibitors/K^+ Supplements.
    - GI Upset
    - Gynaecomastia
    - Menstrual Disorders
    - Testicular Atrophy



- **Osmotic Diuretic Drugs:**
  - **Site of Action:**
    - Filtered in the Glomerulus.
    - Affects Any Nephron that is Freely Permeable to Water.
    - **- Mainly The Loop of Henle
  - **Mechanism of Action:**
    - Inert Substances (Eg. Sugars) that are filtered by the Kidneys, but not reabsorbed.
      - →Increases Filtrate Osmolarity to:
        - →Inhibit Passive Water Reabsorption.
        - →Facilitate Passive Water Excretion.
    - Ie. An example of *Physiological Antagonism*.
  - **Indications:**
    - Acute Renal Failure – Prevent kidneys from drying out.
    - Cerebral Oedema & Intraocular Pressure:
      - Simply by increasing Plasma Osmolarity.
      - Relieves such pressures via osmosis.
    - Rapid Reversal of Oedema
  - **Classical Agent:**
    - *Mannitol
    - Isosorbide
    - Glycerin
  - **Side Effects:**
    - Transient Hypervolaemia (Ie. ↑Extracellular Fluid – due to ↑Plasma Osmolarity)
      - Can →Dilution Hyponatraemia
      - Can →Heart Failure
      - Can →Pulmonary Oedema
    - Headache, Nausea & Vomiting.



RENAL Pathology:
ELECTROLYTE IMBALANCES

Osmolar Imbalances:

- **Sodium (Na^+):**
  - **Hypernatraemia:**
    - Higher-Than-Normal Blood [Na^+]
    - **May Be Due to:**
      - Decreased H_2O Intake/Increased H_2O Loss (Due to Reverse-Dilution Effect)
      - Over-Ingestion of Na^+
      - Renal Insufficiency
    - **Leads to:**
      - Cell-Shrinking (Due to Osmosis)
      - If due to H_2O Loss, then Hypotension → Tachycardia (to ↑Cardiac Output)
      - Excessive Thirst.
    - **Treatment:**
      - ***Water***
  - **Hyponatraemia:**
    - Lower-Than-Normal Blood [Na^+]
    - **May be Due to:**
      - Loss of Na^+ from body Fluids...OR
      - Excessive Gain in Extracellular Water (Dilution Effect)
      - (Diuretic Therapy)
      - (Adrenal Insufficiency)
    - **Leads to:**
      - Cell-Swelling (Due to Osmosis) → Oedema
      - Especially Cerebral Oedema → Headache → Eventually Coma
    - **Treatment:**
      - Withdrawal of Diuretic
      - ***Normal Saline***

- **Calcium (Ca^+):**
  - (NB: Ca^+ is needed for normal Heart/Cardiac-Nerve Function, as well as Bone Formation)
  - **Hypercalaemia:**
    - Higher-Than-Normal Blood [Ca^+]
    - **May be Due to:**
      - Increased Dietary Calcium
      - Decreased Ca^+ Excretion
      - Shift from Bone → Extracellular Fluid.
    - **Leads to:**
      - Shortened AP-Plateau → Cardiac Arrhythmias
      - Muscle Weakness
    - **Treatment:**
      - ***IV Saline*** + ***Frusemide*** to depress renal Ca^+ Resorbtion.
  - **Hypocalaemia:**
    - Lower-Than-Normal Blood [Ca^+]
    - **May be Due to:**
      - Insufficient Dietary Calcium
      - Increased Ca^+ Excretion
    - **Leads to:**
      - Prolonged Depolarisation of Cardiac Action Potentials
      - Impaired Contraction
    - **Treatment:**
      - ***IV Calcium Replacement***.

- **Potassium (K^+):**
  - (NB: K^+ is needed to *repolarise* excitable membranes.)
  - **Hyperkalaemia:**
    - Higher-Than-Normal Blood [K^+]
    - **May Be Due to:**
      - Excessive K^+ Intake...OR
      - Renal Failure (Insufficient K^+ Excretion in Urine)
      - Large Crush/Trauma Injuries (Rupturing of Cell membranes → Release of K^+)
    - **Leads to:**
      - Slower/Poor Repolarisation of Excitable Membranes:
        - →Muscle Cramping
        - → ↓Conductivity of the Heart
    - **Treatment:**
      - **1.** ***Calcium Infusion*** – (to ↓Cardiac Excitability).
      - **2.** ***IV Insulin*** **+** ***Dextrose*** → Shifts K^+ into the cells.
      - **3. Potassium Binders –** ***Resonium*** – (to ↓K^+ Level)
      - **Bicarbonate Therapy** – (If Metabolic Acidosis)
      - **Dialysis –** (If severe Renal Failure)
  - **Hypokalaemia:**
    - Lower-Than-Normal Blood [K^+]
    - **May Be Due to:**
      - Insufficient K^+ Intake...OR
      - Excessive Loss of K^+ (Eg. Loop Diuretics)
    - **Leads To:**
      - Faster/Hyper- Repolarisation of Excitable Membranes:
        - → Decreased Excitability of Muscle/Nerve Cells
        - → Cardiac Irritability → Dysrhythmias
    - **Treatment:**
      - **Treat the Cause** (Eg. Diet/Diarrhoea/Medication)
      - **+** ***IV-Potassium*** **("Banana Bag").**

- **Phosphates (HPO_4^{2-}):**
  - (NB: HPO_4^{2-} are important for bone formation – Bone Salts = calcium & phosphates)
  - **Hyperphosphataemia:**
    - Higher-Than-Normal Blood [HPO_4^{2-}]
    - **May be Due to:**
      - Hypo-Parathyroidism: Low (PTH) → Phosphate Reabsorption From bone.
      - Renal Failure: Increased Phosphate Retention in the Kidneys
    - **Leads to:**
      - Deposition of Ca^+ Salts in Soft Tissues → Hypocalcaemia
    - **Treatment:**
      - ***Phosphate Binders*** (→↓Dietary Absorption of Phosphates)
  - **Hypophosphataemia:**
    - Lower-Than-Normal Blood [HPO_4^{2-}]
    - **May be Due to:**
      - Decreased Intake
      - Chronic Alcoholism
      - Long-Term Antacid Use
    - **Leads to:**
      - Decreased ATP (As phosphates are needed for ATP synthesis)
        - →Muscle Weakness
        - →Impaired Cardiac Function
        - →Impaired Neural Function
    - **Treatment:**
      - ***IV Phosphate Replacement***

- **Plasma Proteins:**
  - (NB: Plasma Proteins – Important in regulating blood Volume & Viscosity/Pressure)
  - **Hyperproteinaemia:**
    - Higher-Than-Normal Blood [Protein]
    - Rare. (Not mentioned in lecture)
  - **Hypoproteinaemia:**
    - Lower-Than-Normal Blood [Protein]
    - **May Be Due To:**
      - Liver Failure (As the liver makes the Plasma Proteins)
      - Protein Malnutrition
      - Burns
      - Kidney Failure (Proteinuria – Loss of Protein in Urine)
    - **Leads to:**
      - Reduced Plasma Osmotic Pressure→Widespread Oedema
    - **Management:**
      - ***IV Albumin / Hartmann's Solution***

- **Uric Acid:**
  - (NB: Uric Acid = Metabolic Waste Product of Protein Metabolism. Excreted through Urine)
  - **Hyperuricaemia:**
    - Higher-Than-Normal Blood [Uric Acid]
    - **May Be Due To:**
      - Renal Failure – Plasma Uric Acid isn't being excreted through kidneys.
    - **Leads To:**
      - Gout: Deposition of Uric-Acid Crystals in Joints → Arthritis of Gout.
    - **Management:**
      - ***Allopurinol***

RENAL Pathology:
FLUID IMBALANCES

Volume Imbalances:

- **Hypervolaemia:**
  - A Gain of Extracellular Fluid (And an Associated gain in Na^+)
  - **Symptoms:**
    - Hypertension
    - Oedema
  - **May Be Due To:**
    - Excessive Fluid Intake
    - Chronic Renal Failure (↓Urine Output)
    - Endocrine Imbalances (Eg. ADH & Aldosterone)
  - **Treatment:**
    - Diuretics
- **Hypovolaemia:**
  - A Loss of Extracellular Fluid (And an Associated loss of Na^+)
  - **Symptoms:**
    - Hypotension
    - Tachycardia
    - High Resp. Rate
    - Thirst
  - **May Be Due To:**
    - Insufficient Intake of Fluids
    - Haemorrhage
    - Diarrhoea
    - Vomiting
    - Endocrine Imbalances (Eg. ADH & Aldosterone)
  - **Treatment**:
    - Fluid Replacement (Saline IV Fluids or Electrolyte Drink)

RENAL Pathology:
INTRA-RENAL FAILURES

Congenital Anomalies:

- **– Eg. *Polycystic Kidney Disease* – See Separate Notes:**

Glomerular Diseases:

- **– Eg. Glomerulonephritis → (*Nephrotic / Nephritic Syndromes*):**
  - **Typically Immune-Mediated Damage:**
    - **Immune Complex (Ag:Ab) Deposition:**
      - *Ab-Ag Complexes* Deposit in Glomerulus → **Inflammation & Damage**
    - **Anti Glomerular-Basement Membrane (Anti GBM):**
      - Infectious/Toxic Agents Deposit in Glomerulus → **Inflammation & Damage**
  - **→→If…**
    - **…*Incomplete* Glomerular-Membrane Damage → Nephrotic Syndrome:**
      - → Selective Albuminuria, Proteinuria, (But NO Haematuria)
    - **…*Complete* Glomerular-Membrane Damage → Nephritic Syndrome:**
      - → Oliguria (due to ↓↓Filtration), Haematuria & Hypertension
- **-Eg. *Diabetic Nephropathy* → (*Nephrotic Syndrome*)**
  - **Deposition of AGE proteins in the Basement Membrane → Direct Glomerular Damage**
    - **…*Incomplete* Glomerular-Membrane Damage → Nephrotic Syndrome:**
      - → Selective Albuminuria, Proteinuria, (But NO Haematuria)

Tubulo-Interstitial Diseases:

- **- Eg. *Acute Tubular Necrosis*:**
  - **Ischaemic / Toxic Injury to Tubules**
- **- Eg. *Pyelonephritis*:**
  - **Ascended/Seeded Bacterial Infection of Kidney/s**
- **- Eg. *Interstitial Nephritis*:**
  - **Chronic Analgesic Use**

Vascular Disorders:

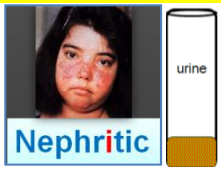
- **- Eg. *Nephrosclerosis* (Diabetes/HTN)**
- **- Eg. *SLE-Lupus Nephritis***

Glomerular Diseases – Different Types (Nephritic/Nephrotic):

- **NEPHROTIC SYNDROMES – (Incomplete Glomerular-Membrane Damage):**
  - **Clinical Features:**
    - **Normal GFR**
    - **+++Polyuria**
    - **++++ Proteinuria (>3000mg/day :. Nephrotic)**
      - **→ Granular (Protein) Casts.**
      - **→ Oedema (Especially Periorbital)**
      - **→ Hypercoaguability –** (Loss of Antithrombin-III in Urine)
      - **→ Immunocompromise –** (Loss of Ig in Urine)
      - **→ Hyperlipidaemia –** (Attempted Hepatic Compensation for ↓Plasma Osmolarity)
    - **↑Serum Creatinine –** Mildly Elevated
    - **(NB: Dehydrated due to Polyuria; But Oedematous due to Proteinuria)**

  - **Eg. MCD – Minimal Change Disease ("*Foot Process Disease*"/"*Nil Disease*"):**
    - **MCD = *THE Childhood cause of Nephrotic Syndrome* (1-8yrs)**
    - **Aetiology:**
      - Post-Infective (URTI)
    - **Clinical Features:**
      - **Eg.** 2yo Boy with sudden onset Polyuria, Oedema & Proteinuria following URTI.
      - **Children** – 1-8yrs
      - **Prognosis -** Spontaneous Remission in <70% of Pts; Some may progress to FSGS.
  - **Eg. MGN – Membranous Glomerulonephrosis:**
    - **MGN = *>50% of Adult Nephrotic Syndrome***
    - **Aetiology:**
      - Autoimmune – Ag:Ab Complex Deposition
    - **Clinical Features:**
      - **Eg.** 35y female, Tired for years*, Worsened since two months. She has noted* swelling of her legs *and* **puffiness around eyelids (Periorbital Oedema – A classic sign of nephrotic syndrome)**.
      - **Adults -** 40-60yrs
      - **Nephrotic Syndrome** – Polyuria, +++ Proteinuria, Oedema.
      - **Prognosis –** Good, but Occasionally progresses to ESRD.
  - **Eg. FSGS – Focal Segmental Glomerulosclerosis:**
    - **FSGS = *<35% of Adult Nephrotic Syndrome*.**
    - ***NB: Very Similar to Minimal Change Disease, but in Adults.***
    - **Aetiology – (**As with MCD**):**
      - Often History of Recent URTI.
    - **Clinical Features:**
      - **Eg.** 49y, Nephrotic Syndrome non-responsive.
      - **Nephrotic Syndrome** – +++Selective Proteinuria, Oedema, Polyuria.
      - **Prognosis – Poor:** 30% Remission, 50% CKD & 20% RPGN.

- **NEPHRITIC SYNDROMES – (Complete Glomerular-Membrane Damage):**
  - **Clinical Features of Nephritic Syndrome:**
    - **↓GFR:**
    - **Oliguria**
      - **→Renal Hypertension** (Hypoperfusion of JG Cells due to ↓GFR)
      - **→Fluid Overload Oedema –** (↓Plasma Osmolality & Na + H_2O Retention)
    - **Microalbuminuria**
    - **++++ Haematuria**
      - **→*RBC (Cellular)* Casts**.
      - **→ Anaemia**
    - **↑ Creatinine**
    - **(NB: Fluid Overloaded due to Oliguria; And Oedematous due to Fluid Overload)**

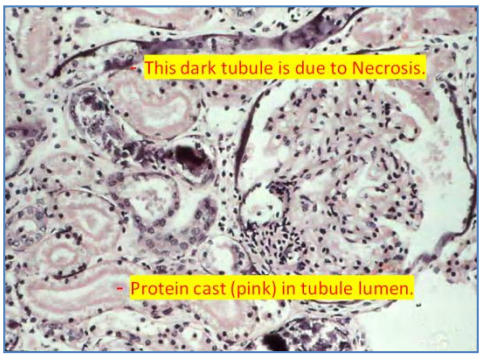


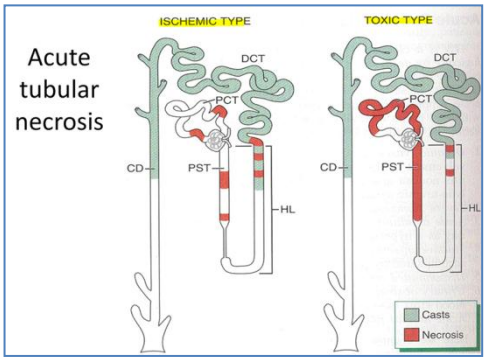
  - **PSGN – Post-Strep Glomerulonephritis:**
    - **PSGN = *THE Childhood cause of Nephritic Syndrome (3-15yrs)***
    - **Eg.** 8 year old girl with fever, oliguria, smoke coloured urine & hypertension following upper respiratory tract infection.
    - **Aetiology:**
      - Post-Infective *(GAβ-Streptococcal Pharyngitis)* Ag:Ab Complex Deposition
    - **Clinical Features:**
      - **Nephritic Syndrome –** Oliguria, Painless Haematuria, Non-Selective Proteinuria, Oedema, Hypertension
      - **Prognosis–** Good Prognosis in Children (But progressive in Adults)
  - **IgA Nephropathy ("Berger's Disease"):**
    - **IgA-Nephropathy = *THE Adult (15-30yrs) Cause of Nephritic Syndrome***
    - **Eg.** 18y male ***Recurrent, Episodic Painless +++Hematuria***, 3-6 days, usually following URTI.
    - **Aetiology:**
      - Autoimmune - Ag:IgA Complex Deposition in Glomerulus
    - **Clinical Features:**
      - **Nephritic Syndrome –** Oliguria, Painless Haematuria, Non-Selective Proteinuria, Oedema, Hypertension
      - **High Serum IgA**
      - **Prognosis:**
        - 30% → Slowly Progressive
        - 10% → Renal Failure
  - **RPGN – Rapidly Progressive Glomerulonephritis:**
    - **RPGN = *NOT a Separate Disease; ANY Glomerulonephritis can → RPGN***
    - **Aetiology:**
      - Progression of any Glomerulonephritis (Autoimmune)
    - **Pathogenesis:**
      - Rapidly Progressing Glomerulonephritis → Renal Failure within Weeks.
    - **Clinical Features:**
      - **Nephritic Syndrome –** Oliguria, Painless Haematuria, Non-Selective Proteinuria, Oedema, Hypertension
      - **Prognosis – Poor:** Quickly progresses to ESRF.

- **DIABETIC KIDNEY PATHOLOGY:**
  - **Diabetic Glomerulosclerosis**
    - **Aetiology:**
      - Deposition of AGE proteins in the Basement Membrane → Nephrotic Syndrome
    - **50% of Diabetics have Nephrotic Syndrome**
    - **Management:**
      - Initial Rx with ***Ace Inhibitors***
    - **Prognosis:** 30% of Diabetics will → ESRF.
  - **Renal Papillary Necrosis:**
    - **Aetiology:**
      - An ischaemic complication of diabetic glomerular damage → Tubular Ischaemia.
    - **Presentation:**
      - → Fever, Chills, Flank/Abdo Pain, & **Haematuria**
    - **(NB: Also in –** Analgesic Abuse, Obstructive Uropathy, Pyelonephritis, Alcoholism**)**

Diseases of the Tubules:

- **NB: Mostly Caused by Toxic/Infectious Agents → Leading to Either:**
  - **→ Ischaemic Or Toxic Injury to Tubules & Interstitium → Acute Tubular Necrosis**
  - **→ Inflammatory Reactions in Tubules & Interstitium → TubuloInterstitial Nephritis**
- **ACUTE TUBULAR NECROSIS**
  - **Aetiology:**
    - Ischaemic/Toxic/Infective Injury to Tubules & Interstitium
  - **Pathophysiology:**
    - **- Ischaemia** (Poor Blood Flow) in the Peritubular Capillaries → Tubule Cell Death (Necrosis)
    - **- Nephrotoxins** (Eg. Drugs, Toxins, Mercury) → Tubule Cell Death (Necrosis)
  - **Diagnosis:**
    - Muddy-Brown 'Casts' of Cellular Debris in DCT & Collecting Ducts.
  - **Management:**
    - Avoid/Treat Precipitating Factor
    - Supportive Mx





Diseases of the Interstitium:

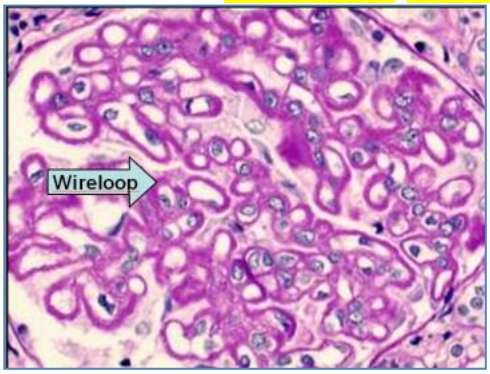
- **PYELONEPHRITIS:**
  - = Inflammation of the Pyelum (Pelvis) of the Kidney (Which spreads to Tubules & Interstitium)
  - **Aetiology:**
    - ***E.coli = Most Common***
  - **Pathogenesis:**
    - Ascending UTI OR Septicaemia
  - **Clinical Features:**
    - Fever, Nausea/Vomiting
    - Pyuria +/- Haematuria
    - Dysuria, Frequency, Urgency
    - Flank→Groin Pain
    - **Renal Angle Tenderness** (Murphey's Kidney Punch Positive)
  - **Complications:**
    - Sepsis
    - Acute Renal Failure
  - **Treatment:**
    - **Antibiotics – *Trimethoprim-Sulfamethoxazole***

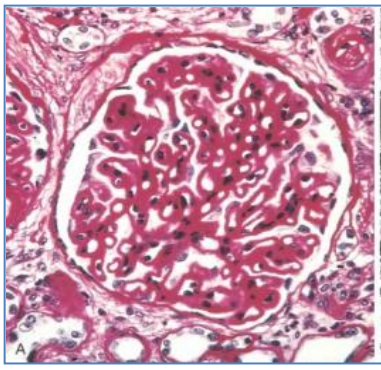
- **INTERSTITIAL NEPHRITIS (Analgesic Nephropathy):**
  - **Aetiology:**
    - Chronic Analgesic Use/Drug Side Effect
  - **Clinical Features:**
    - **Asymptomatic until Onset of Renal Failure.**
      - → ↓Urine Output, Fluid Retention & Oedema
      - → Hypertension
      - → Haematuria
      - → Fever
      - **→ *Rash**
  - **Management:** – Avoid Precipitants (Medications), Give Steroids, & Limit Protein Intake.

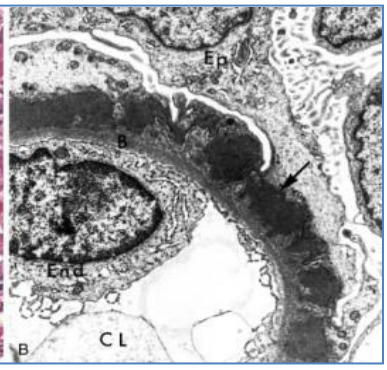
Vascular Disorders:

- **NEPHROSCLEROSIS (Diabetes/Hypertension):**
  - **Aetiology:**
    - Diabetes &/Or Hypertension
  - **Pathogenesis:**
    - **(Diabetes** → ↑[Blood Glucose] → Blood proteins become *sticky* → deposit in small blood vessels → Vessel Inflammation, Damage & Scarring → Nephrosclerosis**)**
    - **(Hypertension** → Damage to Glomerular Capillaries → Sclerosis & Thickening of Capillary Wall → Nephrosclerosis)
  - **Clinical Features:**
    - Mild Kidney Failure (Variably ↓GFR)
    - Mild Proteinuria

- **SLE – Lupus Nephritis:**
  - **Aetiology:**
    - Complication of SLE (Autoimmune)
  - **Pathogenesis:**
    - Immune Complex Deposition in Glomerulus → Inflammation → Glom.BM Damage – (incomplete) → Nephrotic Syndrome
  - **Clinical Features:**
    - Fluid Retention, Hypertension, Oedema
    - **Nephrotic Syndrome** – +++ Selective Proteinuria, Oedema, Polyuria.
  - **Diagnosis:**
    - ANA Titer, ACCP Lupus Test
  - **Treatment:**
    - ***Corticosteroids***
    - ***NSAIDS***
    - ***Methotrexate*/*Sulfasalazine*/*Cyclophosphamide***)







RENAL Pathology:
DRUGS - URINE pH DRUGS

DRUGS ALTERING THE pH URINE:

Clinical Significance:

- The pH of the Urine affects the Excretion Rates of different Drugs. (Depending if drug is acidic or basic)
- **Urine Alkalinisation:**
  - **Excretion:**
    - Increases the Excretion of Weak-Acid Drugs. (Eg. Salicylates/Aspirin & Barbiturates)
      - Ie. Bicarbonate is sometimes used to treat Overdoses of the above.
    - Decreases the Excretion of Weak-Base Drugs.
  - **Precipitation:**
    - Can prevent Weak-Acid Drugs from Precipitating in the Urine (↓kidney stones).
    - Also decreases Precipitation of Uric Acid Crystals in the Urine (↓kidney stones).
- **Urine Acidification – (Rarely Ever Used):**
  - **Excretion:**
    - Increases the Excretion of Weak-Base Drugs.
    - Decreases the Excretion of Weak-Acid Drugs. (Eg. Salicylates & Barbiturates)
  - **Precipitation:**
    - Can prevent Weak-Base Drugs from Precipitating in the Urine (↓kidney stones).

Urinary Alkalizers:

- **Carbonic Anhydrase Inhibitors:**
  - **Mechanism of Action:**
    - Blocks Bicarbonate Reabsorbtion → Alkaline Urine (but Metabolic Acidosis)
- **Oral Citrate:**
  - **Mechanism of Action:**
    - Metabolised via TCA-Cycle → Produces Bicarbonate as a by-product.

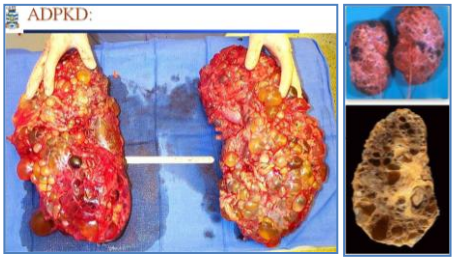
Urinary Acidifiers – (Rarely Ever Used):

- **Ammonium Choride:**
  - Only Used Clinically for an oral Acid-Loading test to Diagnose *Renal Tubular Acidosis*.

RENAL Pathology:
POLYCYSTIC KIDNEY DISEASE

Adult: *AUTOSOMAL DOMAINANT POLYCYSTIC KIDNEY DISEASE (ADPKD):*

- **Aetiology:**
  - Genetic – Autosomal Dominant
  - (:. Fairly Common - 1:1000)
- **Pathogenesis:**
  - Many tubules don't empty into Calyces → Obstruction → Cysts
- **Morphology:**
  - Bilateral, large cystic kidney
  - Some areas of Haemorrhage
  - Some normal kidney tissue between cysts



- **Clinical Features:**
  - **Onset** @ 30-40yrs
  - **Symptoms:**
    - Flank pain (Stretching of the Renal Capsule → Pain)
    - Intermittent Gross Haematuria (Cyst Rupture)
    - Hypertension & Oedema (Fluid Retention)
- **Complications:**
  - → **UTI**
  - → **Renal Failure**/End Stage Disease At ~50yrs
  - **Associated Features:**
    - **Liver Cysts (30%)**
    - **Cerebral Berry Aneurysms (20%)**
- **Treatment:**
  - ***Dialysis***
  - ***Kidney Transplant***

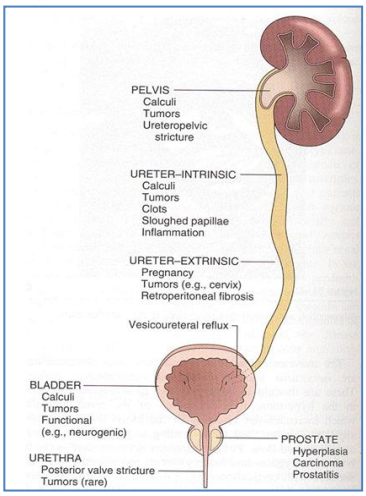
Infantile: *Autosomal Recessive Polycystic Kidney Disease (ARPKD):*

- **Aetiology:**
  - Genetic – Autosomal Recessive (:.Very Rare – 1:30000)
- **Pathogenesis:**
  - 100% of Tubules are Affected :. Worse prognosis
- **Morphology:**
  - Regularly arranged, Spongy Kidney
- **Clinical Features:**
  - **Symptoms/Signs:**
    - Enlarged, Palpable Kidneys soon after birth (Bilateral Abdo Masses)
    - Poor Urinary Concentrating Ability
    - Metabolic Acidosis
    - Hypertension
    - Progression to ESRD by 15yrs
- **Poor Life Expectancy:**
  - 50% of Neonates Die
  - Most Surviving Babies develop End-Stage Kidneys by 15yrs
- **Treatment:**
  - ***Dialysis***
  - ***Kidney Transplant***

RENAL Pathology:
POST-RENAL FAILURES

POST-RENAL FAILURE:

- **Aetiology:**
  - ***Anything that Obstructs Urine Outflow from the Kidneys...Eg:***
    - Papillary Necrosis
    - Ureteric Obstruction
    - Urethral Obstruction
    - Calculi (Nephrolithiasis)
    - Neurogenic Bladder Disease
    - Prostatic Hypertrophy/Ca.
- **Pathophysiology:**
  - **Urine Outflow Obstruction → Backup of Urine into the Kidney → "Hydronephrosis"**
    - → ↑Pressure within the Kidney
      - → Destruction of Delicate Filtration System
      - → Compression of Tubule Vasculature → Renal Ischaemia
        - → Progressive Atrophy of the Kidney
  - **Kidney Stones (Calculi), Tumours, or Clots Typically tend to cause Obstruction.**
    - **– Renal Pelvis**
    - **– Ureter (**At the point where it enters the Bony Pelvis**)**
    - **- Urethra**
  - **– Prostate Hypertrophy/Cancer**
  - **– Urethra – (Stricture/Cancer)**



- **Clinical Features:**
  - Kidney Stone → Severe Flank pain
  - Nausea/Vomiting
  - Urethral/Bladder-outlet Obstructions → Severe Suprapubic (Bladder) Pain
- **Dx:**
  - Bladder Ultrasound reveals ↑Post-Void Residual Volume.
  - Oliguria, but NO dehydration.
- **Complications:**
  - Commonly UTI (due to ↓Urethral Flushing) → Fever, Pyuria & Haematuria.
  - Complete Obstruction → Kidney Failure → ↑Creatinine, ↑Urea, & Electrolyte Imbalance.
- **Management:**
  - Relieve Obstruction
  - Fluid Restriction
  - Treat any UTIs

RENAL Pathology:
PRE-RENAL FAILURES

PRE-RENAL FAILURE:

- **Aetiology:**
  - ***Anything that ↓ Bloodflow to the Kidneys...Eg:***
    - Hypovolaemia (Diarrhoea/Haemorrhage/Vomiting/Burns)
    - Shock (Hypotension)
    - Heart Failure (CCF/Ascites)
    - Renal Artery/Vein Thrombosis/Stenosis
    - Etc.etc....
- **Pathophysiology:**
  - Renal Hypoperfusion → ↓GFR → Kidney Failure
    →Renal Ischaemia → Infarction of Tubules → ↓Kidney Function
- **Clinical Features:**
  - ↓GFR
    - → Oliguria/Anuria
    - → Uraemia/Azotaemia → Fatigue, Malaise, Headache
    - → ↑Creatinine
  - Thirst & Dehydration – if due to Fluid Depletion.
- **Complications:**
  - Complete Renal Failure
  - Other Multi-Organ Failure (if Shock)

RENAL Pathology:
RENAL & PERINEPHRIC ABSCESSES

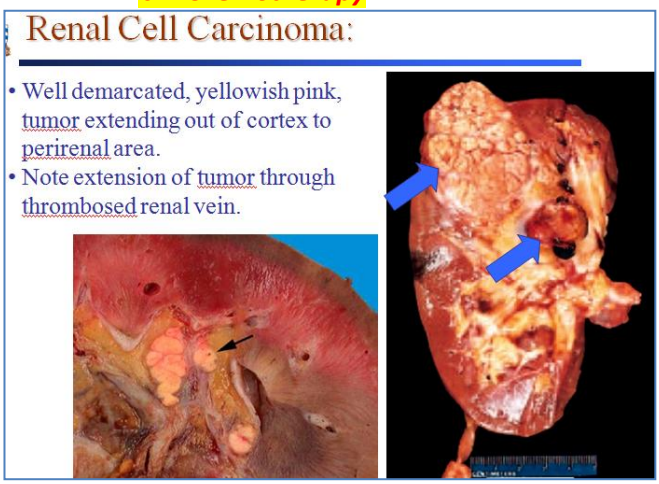
Renal and Perinephric Abscess

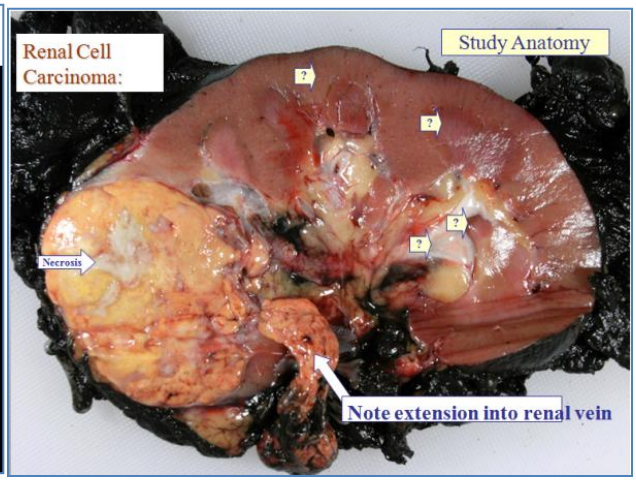
- **Aetiology:**
  - **Complication of pyelonephritis**. Commonly ***E. Coli***.
- **Presentation:**
  - Similar to severe pyelonephritis:
  - fever, flank pain, abdominal pain, dysuria and/or frequency. A palpable mass may or may not be present
  - In perinephric abscess there may be an inflammatory reaction in the overlying skin.
- **Treatment:**
  - **FNA – (*Drain abscess*).**
  - **Antibiotics – (*Trimethoprim-Sulphamethoxazole*)**
  - ***Treat underlying cause*** **(if stones etc)**

RENAL Pathology:
RENAL CELL CARCINOMA

(Adults) RENAL CELL CARCINOMA: *"Clear-Cell Carcinoma"*:

- **Aetiology:**
  - **Genetic** - VHL Gene Mutation
  - **Risk Factors** – Smoking, Obesity, Analgesic Abuse, M3:F1, >50yrs
- **Pathogenesis:**
  - Carcinogenesis of Cells of the *PROXIMAL Convoluted Tubules*.
- **Morphology:**
  - Enlarged Kidney
  - Yellowish-Orange Tumour (lots of fat)
  - Looks Well Demarcated/Encapsulated
  - Areas of Haemorrhage and Necrosis
  - **+*Invasion into the Renal Vein**
- **Clinical Features:**
  - The Most common Renal Malignancy.
  - ***TRIAD* of Symptoms:**
    - **1. Painless Haematuria** – Most Common Symptom
    - **2. Flank pain**
    - **3. Mass**
- **Diagnosis:**
  - **Abdo CT – (Diagnosis & Staging)**
- **Complications:**
  - **Metastasis** – Hematogenous Spread into Renal Vein + Local Abdominal Spread
  - **Paraneoplastic Syndromes:**
    - **↑PTH → Hypercalcaemia** (Can → Calcium Stones)
    - **↑EPO → Polycythaemia**
  - **Death** – 40% 5yr survival
- **Treatment:**
  - ***Nephrectomy***
  - ***Chemotherapy***





RENAL Pathology:
RENAL FAILURE – GENERAL INFO

(NB: The 2 Greatest Risk Factors For Renal Disease):

- **Hypertension**
- **Diabetes**

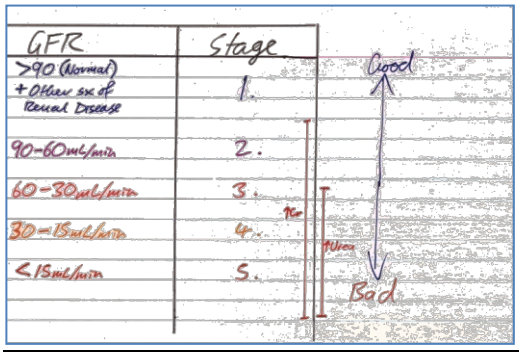
Terminologies - Pathogenesis of Renal Symptoms / Signs:	
Proteinuria	GBM Damage – Selective (albumin)-nephrotic, non selective nephritic syndrome.
Oliguria <500ml or anuria <50ml	Dehydration, GN-Nephritic Sy, renal failure, obstruction.
Polyuria >3L	Excessive fluid, Osmotic (DM), GN-Nephrotic Sy, Tubule dysfunction (D.Insipidus)
Dysuria - pain	Inflammation, Obstruction, stone, tumor, stricture.
Renal colic	Calculus, blood clot or tumour in ureter
Haematuria	Infection, stones, tumor, Glomerulonephritis (red cell casts)
Casts:	Tubule/Glom injury - Coagulation of proteins in renal tubules.
• Hyaline/Gr. casts	Protein loss from glomeruli or necrotic cells
• RBC, WBC, Ep.	Protein with cell loss from glomeruli/tubules.
• Waxy casts	Degenerated cast following prolonged retention (chronic RF)
Hypertension	Renal ischaemia, decreased GFR → Renin* aldosterone*
Oedema periorbital*	Hypoalbuminaemia due to albumin loss in urine (glomerulonephritis) Aldosterone.

Pathogenesis of Renal Symptoms / Signs:	
Uremia - disease	**(Fatigue, Nausea, vomiting, encephalopathy) Renal failure**
Azotemia – lab.	***uremia* is clinical manifestations of severe *azotemia***
Fatigue/Malaise	Renal failure – Azotemia / Uremia.
Headache	Fluid retention, acidosis, uremia.
Flank pain	Ureteric Colic – stones.
SOB, pallor	Anemia – decreased erythropoietin
Nausea / Vom.	Renal Osteodystrophy – renal failure.
Pruritis	Uremic neuropathy.
Pigmentation	Endocrine abnormality in uremia
Smoky urine	Microscopic hematuria (glomerular, RBC casts – Nephritic sy)
Hematuria	UTI, Glomerulonephritis, tumor or Glomerulonephritis.
Painless Hematu.	DM, IgA Nephropathy, TB, Cancer.

Acute Renal Failures:

Acute Renal Failure – General Information:

- **Aetiology:**
  - ***= "Rapid loss of kidney function"***
  - **1. *Pre-Renal* Renal Failure -** *Before the Blood Reaches the Kidney* (Ie. ↓Glomerular Perfusion)
    - Eg. Hypovolaemia (Eg. Blood Loss)
    - Eg. Decreased cardiac output (Eg. Heart Failure)
    - Eg. Renal artery obstruction (Eg. Embolism)
  - **2. *Intra-Renal* Renal Failure -** The ***kidney itself is damaged***
    - Eg. *Acute glomerular nephritis*
    - Eg. *Tubular diseases* e.g. acute tubular necrosis
    - Eg. *Interstitial diseases* e.g. auto immune disorders such as SLE
    - Eg. *Vascular diseases* e.g. polyarteritis nodosa
  - **3. *Post-Renal* Renal Failure -** Due to ***outflow obstruction*** from the kidneys
    - Eg. Cancer – Bladder / Prostate / Ureteric / Cervical
    - Eg. Blood clot
    - Eg. Calculi (Kidney stones – Bilateral)
    - Eg. Accidental surgical ligation
- **Clinical Features:**
  - **Uraemia** – (Fatigue, Malaise, Anorexia, Headache, Nausea, Vomiting)
  - **Hyperkalaemia** → Brady-Arrhythmias
  - **Fluid Retention** → Oedema (Peripheral & Pulmonary)
    - →...& RARELY, Hypertension & Cardiac Tamponade.
  - **Haematuria** – Painless (Cancer) or Painful (Stones/LUTS)
  - **Flank pain** (in specific conditions – Particularly Inflammatory or Ischaemic)
- ***4 Stages of Chronic Renal Failure:**

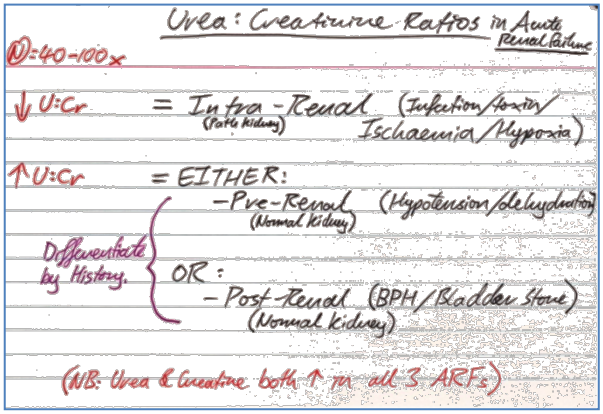


Clinical Complications of Renal Disease

- **General Effects/Problems Encountered in Renal Failure:**
  - (Recall the functions of the kidney and then infer what happens when they are eliminated!)
    - Acid Base Balance (Renal Failure → ***Met. Acidosis***)
    - Electrolyte Balance (Renal Failure → ***Na^+ & K^+ Retention***)
    - Fluid Balance (Renal Failure → ***Fluid Overload***)
    - ↓Erythropoiesis (Renal Failure → ***Anaemia***)
    - Renin Angiotensin System ***Renal Hypertension***
    - Calcium Metabolism (Renal Failure → ***Osteoporosis*** & ***2^oHyper-Parathyroidism***)
    - ***Uraemia***
    - ↓Urine Output
    - ↓Toxin Excretion (Renal Failure → Accumulation of ***Urea & Creatinine***)

Investigations:

- **Blood Urea:Creatinine Ratio – Distinguishing Between Intra/Pre/Post-Renal Failure:**

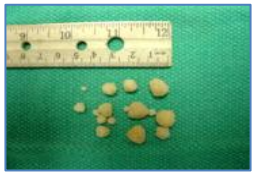


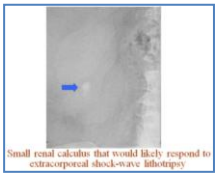
- **Urine Protein:Creatinine Ratio – Is there Proteinuria?**
  - **Interpretation:**
    - **Daily Creatinine Excretion is Constant :. ↑P:CR = ↑Protein in Urine = Proteinuria**
    - 30-300mg = **Microalbuminuria**
    - >300mg = **Macroalbuminuria/"Proteinuria":**
    - >3000mg = **Nephrotic Syndrome**

RENAL Pathology:
RENAL STONES

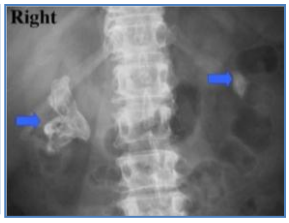
NEPHROLITHIASIS & UROLITHIASIS:

- **Aetiology:**
  - **1. Hypercalcaemia (Eg. ↑Intake, or Hyper-PTH)→ Calcium Stones 80%**
  - **2. Chronic UTI → Triple Phosphate/Struvite/"Staghorn" Stones 15%**
  - **3. Uraemia → Urate Stones (+ Gout)**
- **Pathogenesis:**
  - **1. Hypercalcaemia →** Calcium in Urine Precipitates out of Solution → **Calcium Stones 80%**
  - **2. Chronic UTI →** Gram-Neg Rods (Proteus, Pseudomonas & Klebsiella – NOT E.Coli) → **Triple Phosphate/Struvite/"Staghorn" Stones 15%**
  - **(May → Urinary Obstruction → Hydronephrosis → Stretching of Renal Capsule → Pain)**
- **Morphology:**
  - **Calcium Stones 80%:**
    - Small, hard Stones (1-3mm)
    - Stones have sharp edges
    - Radio-Opaque

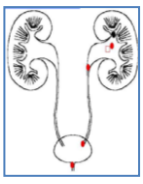
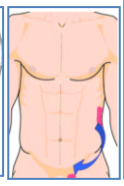
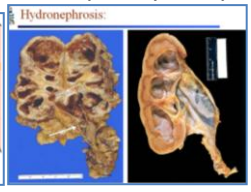


  - **Triple Phosphate/Struvite/"Staghorn" Stones 15%:**
    - Large Stones (Moulds to Renal Pelvis/Calyces) – Hence "Staghorn".
    - Chronic Irritation of Epithelium surrounding Stone → Squamous Metaplasia

- **Clinical Features:**
  - Usually Unilateral
  - **Painful Hematuria** – Macro/Micro
  - ***"Writhing in pain, pacing about, and unable to lie still"***
  - **Hydronephrosis →** Stretching of Renal Capsule → Flank Pain & Tenderness.
  - **Stone in Ureteropelvic Junction →** Deep flank pain. No radiation. Distension of the Renal Capsule.
  - **Stone in Ureter →** Intense, Colicky Pain (Loin → Inguinal Region → Testes/Vulva) + N/V.
  - **Stone in Ureterovesical Junction →** Dysuria, Frequency, + Tip of penis pain

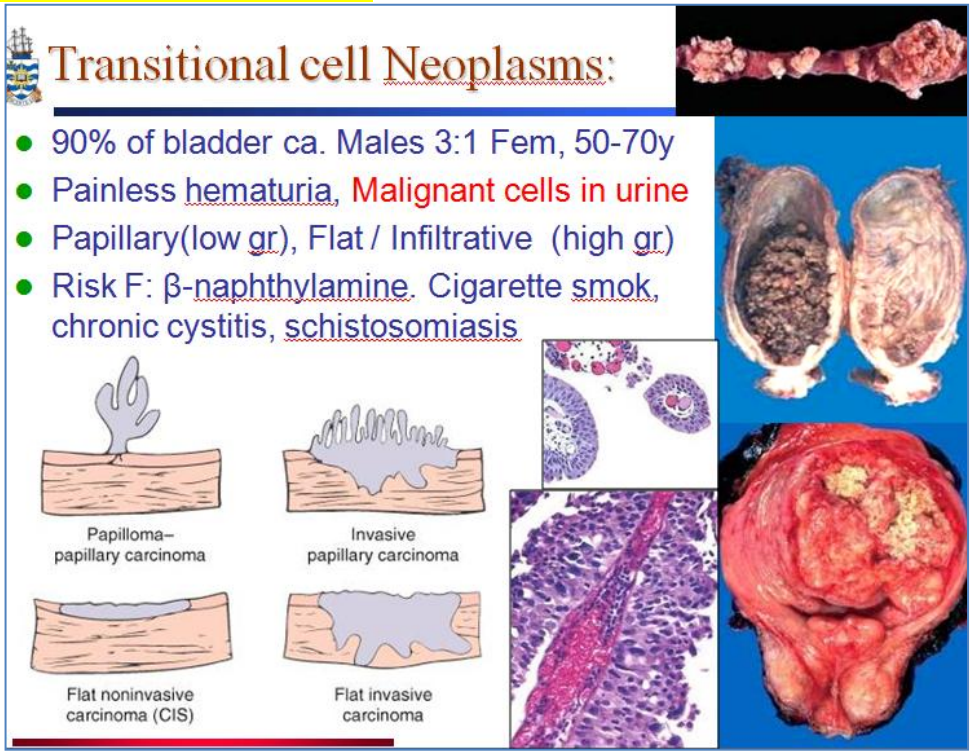




- **Complications:**
  - Hydronephrosis
  - Post-Renal Failure
  - Infection – (UTI/Pyelonephritis/Perinephric Abscess)
- **Investigations:**
  - **Abdo USS –** (Confirm Stone)
  - **Abdo XR –** (Confirm Calcium Vs Radio-Lucent Stone)
  - **UECs –** (?↑Calcium or ↑Urea)
- **Management:**
  - **Conservative – (**Daily ***Na-Bicarbonate Tablets*** to Alkalyse Urine → Dissolve Urate Stones**)**
  - **(ESWL)** ***Extracorporal Shock-Wave Lithotripsy*** – (For Calcium Stones)
  - ***Surgical*** **– (**For All Stones *Not* Amenable to the above**)**

RENAL Pathology:
URINARY TRACT (TRANSITIONAL CELL) CARCINOMAS

(Urinary Tract Tumours) TRANSITIONAL CELL CARCINOMAS:

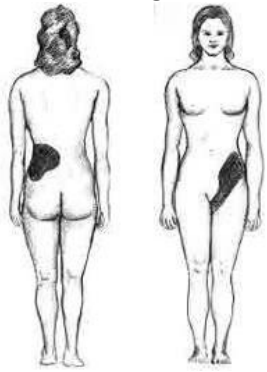
- **Aetiology:**
  - Risk Factors – Smoking, Chronic Cystitis, Male, Old Age
- **Pathogenesis:**
  - Carcinogenesis of the Transitional-Cell Epithelium lining the Urinary Tract
- **Morphology:**
  - **Commonest in bladder** → Can extend all the way from the bladder to the kidney
  - **Papillary projections into hilum or ureters** → May cause Bladder Obstruction → Hydronephrosis
- **Clinical Features:**
  - **Painless Haematuria**
  - **Bladder Obstruction → Hydronephrosis**
- **Diagnosis:**
  - **Urine MCS** - Malignant cells in the urine
- **Management:**
  - **Surgery + Chemo/Radiotherapy**



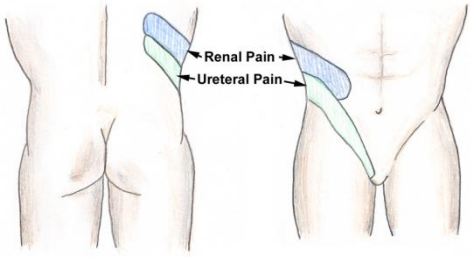
RENAL Pathology:
UROGENIC PAIN

Urogenic Pain:

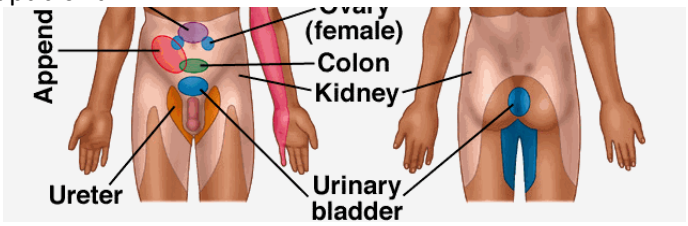
- **Nature of Pain may Vary:**
  - **Colicky Pain (Comes & Goes):**
    - Commonly caused by kidney stones
    - Pain comes in Waves due to Ureteric Peristalsis
  - **Constant Pain:**
    - Caused by a constant pathological process (Eg. Pyelonephritis, Ascending UTI, etc)
- **Location of Pain Varies Depending on Organ Affected:**
  - **Kidney Pain:**
    - Unilateral Flank/Back pain Radiating to Groin.



  - **Ureteral Pain:**
    - Flank-Groin Colicky-Type (Comes & Goes) Pain



  - **Bladder Pain:**
    - Suprapubic Pain

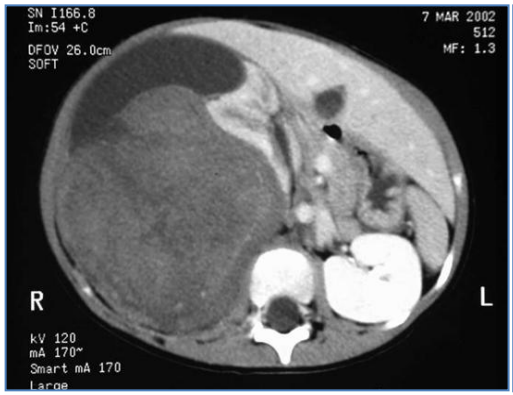


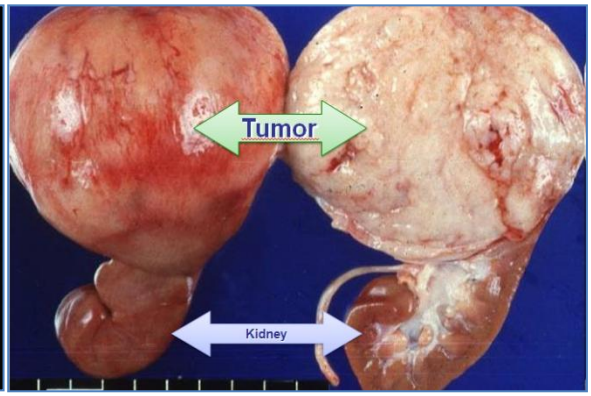
  - **Urethra Pain:**
    - Localised to the Urethra.

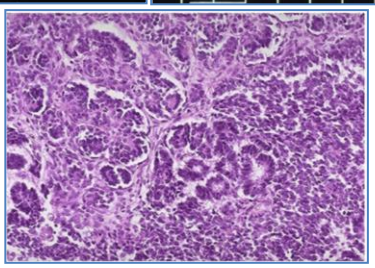
RENAL Pathology:
WILM'S TUMOUR ("NEPHROBLASTOMA") (PAEDS)

WILM'S TUMOUR / "NEPHROBLASTOMA":

- **Aetiology:**
  - Sporadic - Unilateral (80%)
  - Familial - Bilateral (20%)
- **Pathogenesis:**
  - A *Blast*oma – Ie. Carcinogenesis of embryonic Renal *Blast*-Cells.
- **Morphology:**
  - Huge, Pale, Gray-White Tumour Replacing Kidney Tissue
  - Well Encapsulated
  - Some focal Haemorrhage & Necrosis
- **Clinical Features:**
  - **Childhood tumor (2-5y)**
  - **Symptoms:**
    - May have Hematuria
    - Palpable Abdo Mass
    - Abdo Pain
    - Anorexia, Nausea/Vomiting
- **Diagnosis:**
  - **Abdo USS – (Diagnosis)**
  - **Abdo CT – (Staging)**
- **Complications:**
  - **Metastasis** → Lung, Liver, Bone, Brain.
- **Treatment:**
  - ***Nephrectomy + Chemo/Radio-Therapy***
- **Prognosis:**
  - **80% 5yr Survival Rate.**







Continue Reading For Bonus Supplementary Study Materials…

NP Nephrology

Eric Coomes and **Tamara Gimon,** chapter editors
Hart Stadnick and **Kevin Yau,** associate editors
Alex Cressman, EBM editor
Dr. Ramesh Prasad and **Dr. Gemini Tanna,** staff editors

Basic Anatomy Review

Anatomy of the Kidney

- see Urology, U2

Renal Structure and Function

The Nephron

- basic structural and functional unit of the kidney, approximately 1 million per kidney
- 2 main components: glomerulus and attached renal tubule
- direction of blood flow: afferent arteriole → glomerular capillaries → efferent arteriole → vasa recta (the capillaries surrounding the tubules) → renal venules

Table 1. Major Functions of the Kidneys

Function	Mechanism	Affected Elements
1. Waste Excretion	Glomerular filtration	Excretion of nitrogenous products of protein metabolism (urea, Cr)
	Tubular secretion	Excretion of organic acids (urate) and organic bases (Cr)
	Tubular catabolism	Breakdown and excretion of drugs (antibiotics, diuretics) and peptide hormones (most pituitary hormones, insulin, glucagon)
2. Electrolyte Balance and Osmoregulation	Tubular NaCl and water reabsorption	Controls volume status and osmolar balance
	Tubular K^+ secretion	Controls potassium concentration
	Tubular H^+ secretion	Acid-base balance
	HCO_3^- synthesis and reabsorption	Acid-base balance
	Tubular Ca^{2+}, Mg^{2+}, PO_4^{3-} transport	Alters Ca^{2+}, Mg^{2+}, PO_4^{3-} homeostasis
	Synthesize osmolytes	Increase osmolality of own cytoplasm to match intersitium
3. Hormonal Synthesis	Erythropoietin production (cortex)	Red blood cell production
	Vitamin D activation: 25(OH)VitD converted to $1,25(OH)_2$VitD	Calcium homeostasis
	Renin production (juxtaglomerular apparatus)	Alters vascular resistance and aldosterone secretion
4. Blood Pressure Regulation	Na^+ excretion	Alters ECF volume
	Renin production	Alters vascular resistance
5. Glucose Homeostasis	Gluconeogenesis (from lactate, pyruvate, and amino acids)	Glucose supply maintained in prolonged starvation

The Glomerulus

- site where blood constituents are filtered through to the kidney tubules for excretion or reabsorption
- filtration occurs across the glomerular filtration barrier (endothelium, GBM, podocytes) into Bowman's space
- particles are selectively filtered by size (<60 kDa) and charge (negative charge repelled)
- consists of following cell types
  1. Mesangial cells
     - structural cells that support the vascular tree; they are also contractile and produce vasoactive substances to help control blood flow
  2. Capillary endothelial cells
     - one of the cells of the glomerular filtration barrier; help form the plasma filtration apparatus due to their sinusoidal nature and glycocalyx; contribute to the production of the GBM
  3. Visceral epithelium (podocytes)
     - one of the cells of the glomerular filtration barrier; help form the plasma filtration apparatus due to their interdigitated foot process that form slit diaphragms; contribute to the production of the GBM
  4. Parietal epithelium
     - lines the interior of Bowman's capsule and contains a podocyte progenitor population
  5. Juxtaglomerular cells
     - smooth muscle cells in lining of afferent arteriole; produce, store and secrete renin

Acronyms

ACEI	angiotensin converting enzyme inhibitor
ACR	albumin to creatinine ratio
ADH	antidiuretic hormone
AG	anion gap
AIN	acute interstitial nephritis
AKI	acute kidney injury
ANA	antinuclear antibody
ARB	angiotensin receptor blocker
ASA	acetylsalicylic acid
ASOT	anti-streptolysin-O titer
ATN	acute tubular necrosis
AVM	arteriovenous malformation
c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
C&S	culture and sensitivity
CHF	congestive heart failure
CKD	chronic kidney disease
Cr	creatinine
CrCl	creatinine clearance
D5W	5% dextrose in water
DCT	distal convoluted tubule
DDAVP	1-desamino-8-d-arginine vasopressin
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DKA	diabetic ketoacidosis
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
FF	filtration fraction
FSGS	focal segmental glomerulosclerosis
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GN	glomerulonephritis
HCTZ	hydrochlorothiazide
HPF	high power field
HSP	Henoch-Schönlein purpura
HTN	hypertension
HUS	hemolytic uremic syndrome
IVP	intravenous pyelogram
LOC	level of consciousness
MDRD	modification of diet in renal disease
NS	normal saline
p-ANCA	perinuclear anti-neutrophil cytoplasmic antibody
PCKD	polycystic kidney disease
PTH	parathyroid hormone
R&M	routine and microscopy
RAAS	renin-angiotensin-aldosterone system
RBF	renal blood flow
RPF	renal plasma flow
RCC	renal cell carcinoma
RPGN	rapidly progressive glomerulonephritis
RRT	renal replacement therapy
RTA	renal tubular acidosis
SIADH	syndrome of inappropriate antidiuretic hormone
SLE	systemic lupus erythematosis
TBW	total body water
TIN	tubulointerstitial nephritis
TTP	thrombotic thrombocytopenic purpura
UAG	urine anion gap
UTI	urinary tract infection

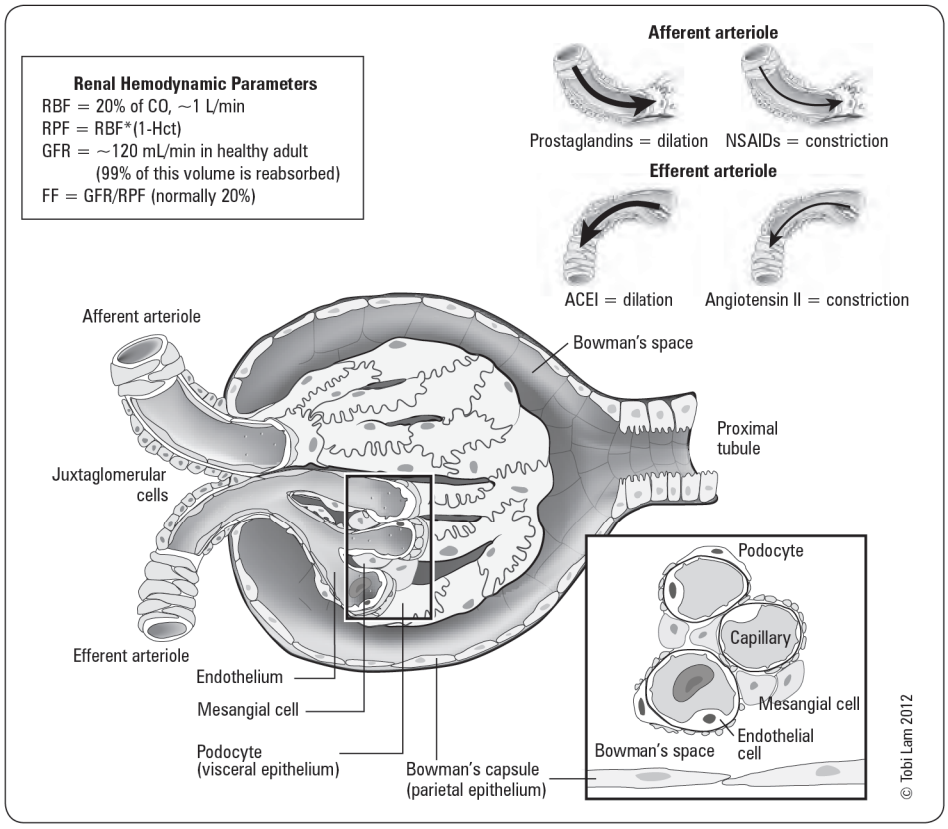


Figure 1. The glomerulus

The Renal Tubules

- reabsorption and secretion occur between the renal tubules and vasa recta forming urine for excretion
- each segment of the tubule selectively transports various solutes and water and is targeted by specific diuretics

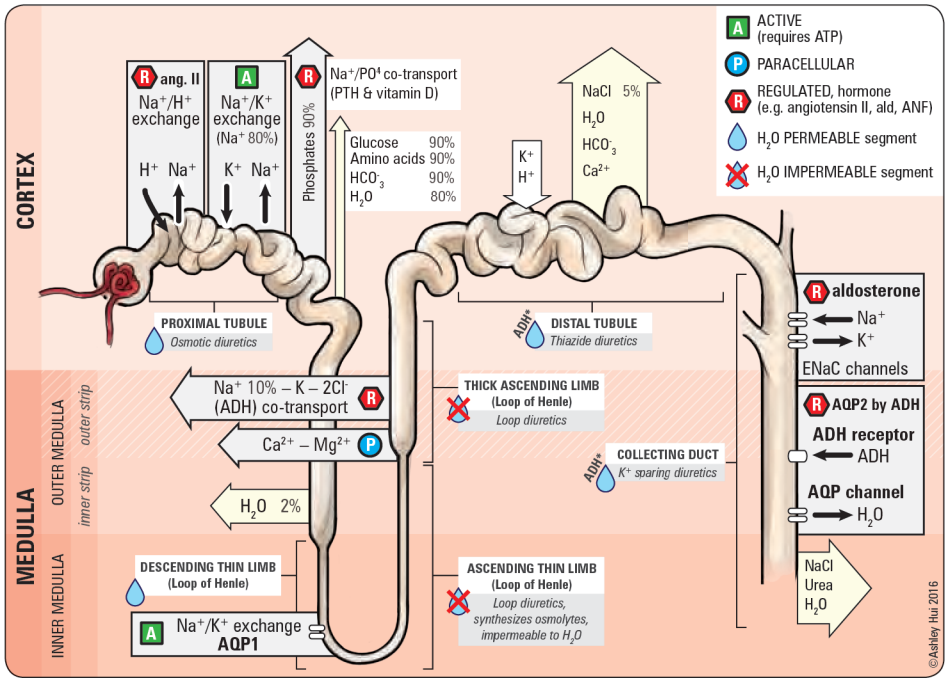


Figure 2. Tubular segments of the nephron

Avoid NSAIDs in patients with diarrhea, heart failure or renal failure

Renal Hemodynamics

- GFR
  - the rate of fluid transfer between glomerular capillaries and Bowman's space
  - 180 L/d, of which 99% is reabsorbed, giving a daily urine output of 1.0-1.5 L
  - normal urine output is 0.5-2.0 ml/kg/h in adults
  - GFR is highest in early adulthood, and decreases thereafter
- renal autoregulation maintains constant GFR over mean arterial pressures of 70-180 mmHg
- 2 mechanisms of autoregulation
  - myogenic mechanism: release of vasoactive factors in response to changes in perfusion pressure (e.g. ↑ perfusion pressure → afferent arteriolar constriction → ↓ GFR)
  - tubuloglomerular feedback: changes in Na^+ delivery to macula densa lead to changes in afferent arteriolar tone (e.g. increased delivery causes afferent constriction)
- FF
  - percentage of RPF filtered across the glomeruli
  - expressed as a ratio: FF = GFR/RPF; normal = 0.2 or 20%
  - angiotensin II constricts renal efferent arterioles which increases FF, thereby maintaining GFR
- renin is released from juxtaglomerular apparatus in response to decreased RPF

Glomerular Filtration Rate

$GFR = K_f(\Delta P - \Delta\Pi)$

K_f = ultrafiltration coefficient

ΔP = hydrostatic pressure difference between glomerular capillaries and Bowman's space

$\Delta\Pi$ = osmotic pressure difference between glomerular capillaries and Bowman's space

$\Delta P - \Delta\Pi$ = net outward pressure

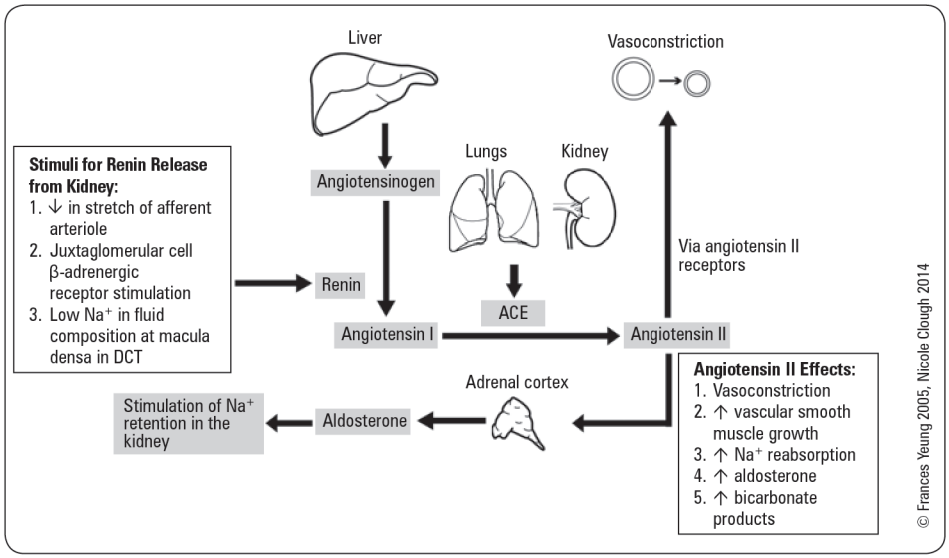


Figure 3. Renin-angiotensin-aldosterone system

Assessment of Renal Function

Measurement of Renal Function

- GFR = rate of filtration of plasma by the glomeruli
- most renal functions decline in parallel with a decrease in GFR
- inulin clearance is the gold standard for measuring GFR, but very rarely used clinically
- clinically, GFR is estimated using serum creatinine concentration, [Cr]
- Cr is a metabolite of creatine (intermediate in muscle energy metabolism)
- Cr is freely filtered at the glomerulus with no tubular reabsorption
- tubular secretion varies based on level of renal function (10% to >50%)
- increased muscle mass increases rate of production of Cr
- Cr filtered ≈ Cr excreted (at steady state)

$Cr_{filtered} = Cr_{excreted}$

$[Cr]_{plasma} \times GFR = [Cr]_{urine} \times$ urine flow rate (mL/min)

$$GFR = \frac{[Cr]_{urine} \times \text{urine flow rate}}{[Cr]_{plasma}}$$

At steady state $[Cr]_{serum} \propto 1/CrCl$

Ways to Estimate GFR Using Serum Creatinine Concentration

1. **Measure CrCl**
- calculation provides reasonable estimate of GFR
- measure plasma [Cr], 24 h urine volume, and urine [Cr]
  - GFR/d = (urine [Cr] x urine volume/d)/(plasma [Cr])
  - must use same units for urine [Cr] and plasma [Cr]

2. **Estimate CrCl using Cockcroft-Gault formula**
  - serum Cr used along with age, gender, and weight (kg) to estimate GFR
  - normal range is >90 mL/min (>1.5 mL/s)

Cockcroft-Gault Formula

$$CrCl\ (mL/min) = \frac{(\text{weight in kg})\ (140 - \text{age}) \times 1.23}{(\text{serum creatinine}\ (\mu mol/L)}$$

Multiply above by 0.85 for females

3. **Estimate GFR using MDRD formula**
   - most common way in which GFR is estimated (MDRD 7 equation)
   - complex formula incorporating age, gender, serum Cr, and African descent, but does not include weight
   - GFR is reported as mL/min/1.73 m^2 body surface area
4. **Estimate GFR using CKD-EPI equation**
   - the best current equation
   - calculated using serum Cr, age, sex, and race

MDRD Equation
GFR (mL/min/1.73 m^2) = 186 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)

Limitations of Using Serum Cr Measurements

1. must be in steady state
   - constant GFR and rate of production of Cr from muscles
   - sudden injury may reduce GFR substantially, but it takes time for Cr to accumulate and then re-establish steady state
   - clinical correlation: in AKI, the rise in Cr is often delayed
2. GFR must fall substantially before plasma [Cr] rises above normal laboratory range
   - with progressive renal failure, remaining nephrons compensate with hyperfiltration
   - GFR is relatively preserved despite significant structural damage
3. plasma [Cr] is influenced by the rate of Cr production
   - lower production with smaller muscle mass (e.g. female, elderly, low weight)
     - for example, consider plasma [Cr] of 100 µmol/L in both of these patients
       - 20 yr old man who weighs 100 kg, GFR = 144 mL/min
       - 80 yr old woman who weighs 50 kg, GFR = 30.6 mL/min
   - clinical correlation: GFR decreases with age but would not be reflected as a rise in serum Cr due to the age-associated decline in muscle mass
4. tubular secretion of Cr increases as GFR decreases
   - serum Cr and CrCl overestimate low GFR
   - certain drugs (cimetidine, trimethoprim) interfere with Cr secretion
5. errors in Cr measurement
   - very high bilirubin level causes [Cr] to be falsely low
   - acetoacetate (a ketone body) and certain drugs (cefoxitin) create falsely high [Cr]

Cystatin C
Cystatin C is a protease which is completely filtered by the glomerulus and is not affected by muscle mass; it is not currently used in clinical practice, but may be a more accurate way to measure renal function in the future, particularly in DM

Measurement of Urea Concentration

- urea is the major end-product of protein metabolism
- plasma urea concentration reflects renal function but should not be used alone as it is modified by a variety of other factors
- urea production reflects dietary intake of protein and catabolic rate; increased protein intake or catabolism (sepsis, trauma, GI bleed) causes urea level to rise
- ECF volume depletion causes a rise in urea independent of GFR or plasma [Cr]
- in addition to filtration, a significant amount of urea is reabsorbed along the tubule
- reabsorption is increased in hypernatremic states such as ECF volume depletion
- typical ratio of urea to [Cr] in serum is 1:12 in SI units (using mmol/L for urea and µmol/L for Cr)

Clinical Settings in which Urea Level is Affected Independent of Renal Function

Disproportionate Increase in Urea
- Volume depletion (prerenal azotemia)
- GI hemorrhage
- High protein diet
- Sepsis
- Catabolic state with tissue breakdown
- Corticosteroid or cytotoxic agents

Disproportionate Decrease in Urea
- Low protein diet
- Liver disease

Urinalysis

- use dipstick in freshly voided urine specimen to assess the following:

1. Specific Gravity

- ratio of the mass of equal volumes of urine/H_2O
- range is 1.001 to 1.030
- values <1.010 reflect dilute urine, values >1.020 reflect concentrated urine
- value usually 1.010 in ESRD (isosthenuria: same specific gravity as plasma)

Estimating Urine Osmolality
Last 2 digits of the specific gravity x 30 = urine osmolality approximately (e.g. specific gravity of 1.020 = 600 mOsm)

2. pH

- urine pH is normally between 4.5-7.0; if persistently alkaline, consider
  - RTA
  - UTI with urease-producing bacteria (e.g. *Proteus*)

3. Glucose

- freely filtered at glomerulus and reabsorbed in proximal tubule
- causes of glucosuria include
  1. hyperglycemia >9-11 mmol/L leads to filtration that exceeds tubular resorption capacity
  2. increased GFR (e.g. pregnancy)
  3. proximal tubule dysfunction (e.g. Fanconi's syndrome)

24 h Urine Collection
- Discard first morning specimen
- Collect all subsequent urine for the next 24 h
- Refrigerate between voids
- Collect second morning specimen

Clarity: Cloudiness may indicate infection
Colour: usually pale yellow or amber, but may be colourless (diabetes insipidus, excess water intake), bright yellow (due to riboflavin ingestion or vitamin tablets), or dark yellow (concentrated urine in intravascular volume depletion)

4. Protein

- dipstick only detects albumin; other proteins (e.g. Bence-Jones, Ig, Tamm-Horsfall) may be missed
- microalbuminuria (defined as ≥2.0 mg/mmol Cr in males and ≥2.8 mg/mmol Cr in females) is not detected by standard dipstick (see *Diabetes*, NP28)
- sulfosalicylic acid detects all protein in urine by precipitation
- gold standard: 24 h timed urine collection for total protein

5. Leukocyte Esterase
- enzyme found in WBC and detected by dipstick
- presence of WBCs indicates infection (e.g. UTI) or inflammation (e.g. AIN)

6. Nitrites
- nitrates in urine are converted by some bacteria to nitrites
- high specificity, low sensitivity for UTI

7. Ketones
- positive in alcoholic/diabetic ketoacidosis, prolonged starvation, fasting

8. Hemoglobin
- positive in hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis), and true hematuria (RBCs seen on microscopy)

Nitrite Negative Bacteria
- *Enterococci*
- *Staphylococci*

Nitrite Positive Bacteria
- *Enterobacteriacae (e.g. E. coli)*

Urine Microscopy

- centrifuge urine specimen for 3-5 min, discard supernatant, resuspend sediment and plate on slide
- shaking tube vigorously may disrupt casts

Table 2. Comparison of Urinary Sediment Findings

	Active Sediment = Suggestive of Parenchymal Kidney Disease	Bland Sediment = Less Likely Parenchymal Kidney Disease
Any one or more of the following seen on microscopy	Red cell casts White cell casts Muddy-brown granular or epithelial cell casts >2 red cells per HPF >4 white cells per HPF	Only hyaline casts Small quantities of crystals Small amount of bacteria <2 red cells per HPF <4 white cells per HPF

1. CELLS

Erythrocytes
- normal range = up to 2-3 RBCs per HPF
- hematuria = greater than 2-3 RBCs per HPF
- dysmorphic RBCs and/or RBC casts suggest glomerular bleeding (e.g. proliferative GN)
- isomorphic RBCs, no casts suggest extraglomerular bleeding (e.g. bladder Ca)

Leukocytes
- normal range = up to 3 WBCs per HPF
- pyuria = greater than 3 WBCs per HPF
- indicates inflammation or infection
- if persistent sterile pyuria present (i.e. negative culture), consider: chronic urethritis, prostatitis, interstitial nephritis, calculi, papillary necrosis, renal TB, viral infections

Positive dipstick for leukocyte esterase and nitrites is 94% specific for diagnosing a UTI

Eosinophils
- detected using Wright's or Hansel's stain (not affected by urine pH)
- consider AIN, atheroembolic disease

Oval Fat Bodies
- renal tubular cells filled with lipid droplets
- seen in heavy proteinuria (e.g. nephrotic syndrome)

2. CASTS
- cylindrical structures formed by intratubular precipitation of Tamm-Horsfall mucoprotein; cells may be trapped within the matrix of protein

Table 3. Interpretation of Casts

Casts	Interpretation
Hyaline casts	Physiologic (concentrated urine, fever, exercise)
RBC casts	Glomerular bleeding (GN, vasculitis)
WBC casts	Infection (pyelonephritis) Inflammation (interstitial nephritis)
Pigmented granular casts (heme granular casts, muddy brown)	ATN Acute GN
Fatty casts	Heavy proteinuria (>3.5 g/d)

3. CRYSTALS

- uric acid: consider acid urine, hyperuricosuria
- calcium phosphate: alkaline urine
- calcium oxalate: consider hyperoxaluria, ethylene glycol poisoning
- sulfur: sulfa-containing antibiotics

Urine Biochemistry

- commonly measure: Na^+, K^+, Cl^-, osmolality, and pH
- no "normal" values; electrolyte excretion depends on intake and current physiological state
- results must be interpreted in the context of a patient's current state, for example:
  1. ECF volume depletion: expect low urine [Na^+] (kidneys should be retaining Na^+)
     - urine [Na^+] >40 mmol/L suggests a renal problem or the action of a diuretic
       - i.e. high urine [Na+] (>40 mmol/L) in the setting of AKI: suggests renal disease
       - i.e. high urine [Na+] (>40 mmol/L) in the setting of hyponatremia: generally from causes such as diuretics, tubular disease (e.g. Bartter's syndrome), SIADH
     - urine [Na^+] <20 mmol/L suggests a prerenal problem
  2. daily urinary potassium excretion rate should be decreased (<20 mmol/d) in hypokalemia
     - if higher than 20 mmol/d, suggests renal contribution to hypokalemia
- osmolality is useful to estimate the kidney's concentrating ability
- FE_{Na} refers to the fractional excretion of Na^+
  - FE_{Na} = urine [Na^+] x plasma [Cr] / (plasma [Na^+] x urine [Cr])
  - FE_{Na} <1% suggests the pathology is prerenal
- urine pH is useful to grossly assess renal acidification
  - low pH (<5.5) in the presence of low serum pH is an appropriate renal response
  - a high pH in this setting might indicate a renal acidification defect (e.g. RTA)

Fractional Excretion of Sodium

$$FE_{Na} = \frac{[Na^+]_{urine} \times [Cr]_{plasma}}{[Na^+]_{plasma} \times [Cr]_{urine}} \times 100$$

Many formulas used in nephrology are derived from the division of two fractions, each of which compare a urine and plasma concentration (e.g. $U_1/P_1 \div U_2/P_2$); in the case of FE_{Na}, it is $U_{Na}/P_{Na} \div U_{Cr}/P_{Cr}$, which then gives the above equation)

Electrolyte Disorders

Sodium Homeostasis

- hyponatremia and hypernatremia are disorders of water balance
  - hyponatremia usually suggests too much water in the ECF relative to Na^+ content
  - hypernatremia usually suggests too little water in the ECF relative to Na^+ content
- solutes (such as Na^+, K^+, glucose) that cannot freely traverse the plasma membrane contribute to effective osmolality and induce transcellular shifts of water
  - water moves out of cells in response to increased ECF osmolality
  - water moves into cells in response to decreased ECF osmolality
- ECF volume is determined by Na^+ content rather than concentration
  - Na^+ deficiency leads to ECF volume contraction
  - Na^+ excess leads to ECF volume expansion
- clinical signs and symptoms of hyponatremia and hypernatremia are secondary to cells (especially in the brain) shrinking (hypernatremia) or swelling (hyponatremia)

Table 4. Clinical Assessment of ECF Volume (Total Body Na^+)

Fluid Compartment	Hypovolemic	Hypervolemic
Intravascular		
JVP	Decreased	Increased
Blood pressure	Orthostatic drop	Normal to increased
Auscultation of heart	Tachycardia	S3
Auscultation of lungs	Normal	Inspiratory crackles
Interstitial		
Skin turgor	Decreased	Normal/increased
Edema (dependent)	Absent	Present
Other		
Urine output	Decreased*	Variable
Body weight	Decreased	Increased
Hematocrit, serum protein	Increased	Decreased

*If there is a renal abnormality (e.g. osmotic diuresis), the urine output may be increased despite the presence of hypovolemia

Hyponatremia

- hyponatremia: serum [Na^+] <135 mmol/L
- can be associated with hypo-osmolality (most common), iso-osmolality, or hyperosmolality
- consider if it is "appropriate" vs. "inappropriate" ADH secretion
- if appropriate ADH secretion, is it real vs. effective volume loss?

If the urine osmolality is unknown, assume the urine is hypo-osmolar/dilute

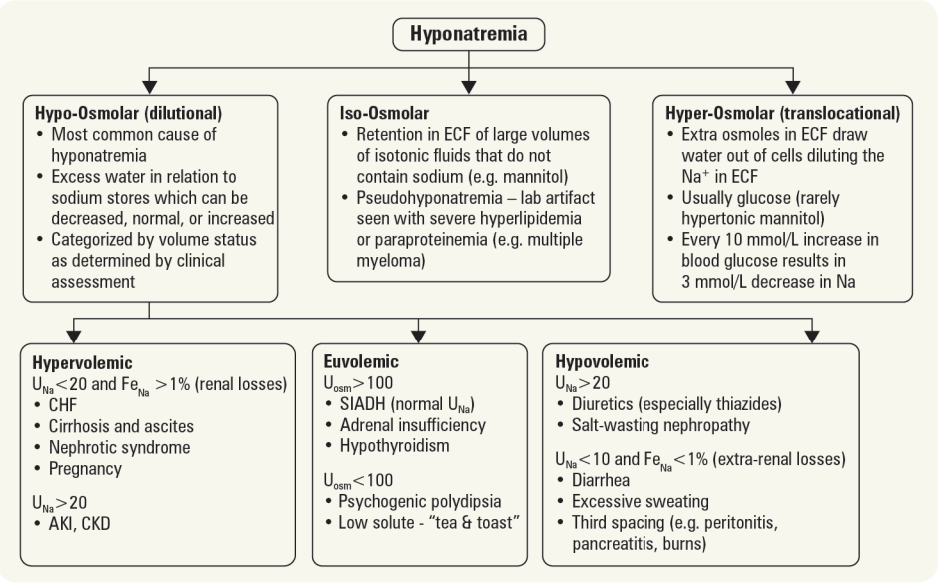


Figure 4. Approach to hyponatremia

Signs and Symptoms

- depend on degree of hyponatremia and more importantly, velocity of progression from onset
- hyponatremia = swollen cells
- acute hyponatremia (<24-48 h) more likely to be symptomatic
- chronic hyponatremia (>24-48 h) less likely to be symptomatic due to adaptation
  - adaptation: normalization of brain volume through loss of cellular electrolytes (within hours) and organic osmolytes (within days)
  - adaptation is responsible for the risks associated with overly rapid correction
- neurologic symptoms predominate (secondary to cerebral edema): headache, nausea, malaise, lethargy, weakness, muscle cramps, anorexia, somnolence, disorientation, personality changes, depressed reflexes, decreased LOC

Complications

- seizures, coma, respiratory arrest, permanent brain damage, brainstem herniation, death
- risk of brain cell shrinkage with rapid correction of hyponatremia
  - can develop osmotic demyelination of pontine and extrapontine neurons; may be irreversible (e.g. central pontine myelinolysis: cranial nerve palsies, quadriplegia, decreased LOC)

Symptoms of Central Pontine Myelinolysis
- Cranial nerve palsies
- Quadriplegia
- Decreased LOC

Risk Factors for Osmotic Demyelination

- rise in serum [Na^+] with correction >8 mmol/L/d if chronic hyponatremia
- associated hypokalemia and/or malnutrition (e.g. low muscle mass)
- if patient with hyponatremia and hypovolemia is given large volume of isotonic fluid (ADH is stimulated by hypovolemia; when hypovolemia is corrected, the ADH level falls suddenly causing sudden brisk water diuresis, and therefore rapid rise in serum Na^+ level)
- patient with psychogenic polydipsia, deprived of water

Investigations

- ECF volume status assessment (see Table 4)
- serum electrolytes, glucose, Cr
- serum osmolality, urine osmolality
- urine Na^+ (urine Na^+ <10-20 mmol/L suggests volume depletion as the cause of hyponatremia)
- assess for causes of SIADH (see Table 5)
- TSH, free T4, and cortisol levels
- consider CXR and possibly CT chest if suspect pulmonary cause of SIADH (e.g. small cell lung cancer)
- consider CT head if suspect CNS cause of SIADH

Treatment of Hyponatremia

- general measures for all patients
  1) treat underlying cause (e.g. restore ECF volume if volume depleted, remove offending drug, treat pain, nausea, etc.)
  2) restrict free water intake
  3) promote free water loss
  4) carefully monitor serum Na^+, urine volume, and urine tonicity
  5) ensure frequently that correction is not occurring too rapidly
     - monitor urine output frequently: high output of dilute urine is the first sign of dangerously rapid correction of hyponatremia

A. Known Acute (known to have developed over <24-48 h)

- commonly occurs in hospital (dilute IV fluid, post-operative increased ADH)
- less risk from rapid correction since adaptation has not fully occurred
- if symptomatic
  - correct rapidly with 3% NaCl 1-2 cc/kg/h up to serum $[Na^+]$ = 125-130 mmol/L
  - may need furosemide to address volume overload
- if asymptomatic, treatment depends on severity
  - if marked fall in plasma $[Na^+]$, treat as symptomatic

B. Chronic or Unknown

1. if severe symptoms (seizures or decreased LOC)
   - must partially correct acutely
   - aim for increase of Na^+ by 1-2 mmol/L/h for 4-6 h
   - limit total rise to 8 mmol/L in 24 h
   - IV 3% NaCl at 1-2 cc/kg/h
   - may need furosemide
2. if asymptomatic
   - water restrict to <1 L/d fluid intake
   - consider IV 0.9% NS + furosemide (reduces urine osmolality, augments excretion of H_2O)
   - consider NaCl tablet or Oxocubes® as a source of Na^+
3. refractory
   - furosemide and oral salt tablets
   - oral urea (osmotic aquaresis)
   - V2 receptor antagonists (e.g. tolvaptan)
4. always pay attention to patient's ECF volume status – if already volume-expanded, unlikely to give NaCl; if already volume-depleted, almost never appropriate to give furosemide

C. Options for Treatment of Overly-Rapid Correction

- give water (IV D5W)
- give ADH to stop water diuresis (DDAVP 1-2 μg IV)

Impact of IV Solution on Serum $[Na^+]$

- formula to estimate the change in serum $[Na^+]$ caused by retention of 1 L of any infusate [TBW = (for men) 0.6 x wt(kg); (for women) 0.5 x wt(kg)]

$$\text{change in serum } [Na^+] = \frac{\text{infusate } [Na^+] - \text{serum } [Na^+]}{\text{TBW} + 1\text{ L}}$$

- formula assumes there are no losses of water or electrolytes

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

1. urine that is inappropriately concentrated for the serum osmolality
2. high urine sodium (>20-40 mmol/L)
3. high FE_{Na}

Beware of Rapid Correction of Hyponatremia

- Inadvertent rapid correction of hyponatremia can easily occur (e.g. patient with hyponatremia due to SIADH from nausea)
  - Anti-emetic given for relief of hyponatremia-induced nausea
  - ADH quickly turned off in the absence of nausea, the kidneys rapidly excrete the excess free water, and the serum $[Na^+]$ rises rapidly
  - Patient at risk of osmotic demyelination
- High output dilute urine (>100 cc/h, <100 mOsm/L) in the setting of hyponatremia is usually the first sign of dangerously rapid correction of serum sodium

Correction of Na^+ in hyponatremia should not exceed 8 mmol/L/24 h unless definitely known to be <24-48 h duration; frequent monitoring of serum Na^+ and urine output is essential

Concentration of $[Na^+]$ in Common Infusates

- $[Na^+]$ in 0.45% NaCl = 77 mmol/L
- $[Na^+]$ in 0.9% NaCl = 154 mmol/L
- $[Na^+]$ in 3% NaCl = 513 mmol/L
- $[Na^+]$ in 5% NaCl = 855 mmol/L
- $[Na^+]$ in Ringer's lactate = 130 mmol/L
- $[Na^+]$ in D5W = 0

Table 5. Disorders Associated with SIADH

Cancer	Pulmonary	CNS	Drugs	Miscellaneous
Small cell cancer Bronchogenic carcinoma Pancreatic adenocarcinoma Hodgkin's lymphoma Thymoma Leukemia	Pneumonia Lung abscess TB Acute respiratory failure Asthma COPD Positive pressure ventilation	Mass lesion Encephalitis Subarachnoid hemorrhage Stroke Head trauma Acute psychosis Acute intermittent porphyria	**Antidepressants** TCAs SSRIs **Antineoplastics** Vincristine Cyclophosphamide **Anti-epileptics** Carbamazepine Barbiturates Chlorpropamide ACEI **Other** DDAVP Oxytocin Nicotine	Post-operative state Pain Severe nausea HIV

Hypernatremia

- hypernatremia: serum [Na^+] >145 mmol/L
- too little water relative to total body Na^+; always a hyperosmolar state
- usually due to NET water loss, rarely due to hypertonic Na^+ gain
- less common than hyponatremia because patients are protected against hypernatremia by thirst and release of ADH

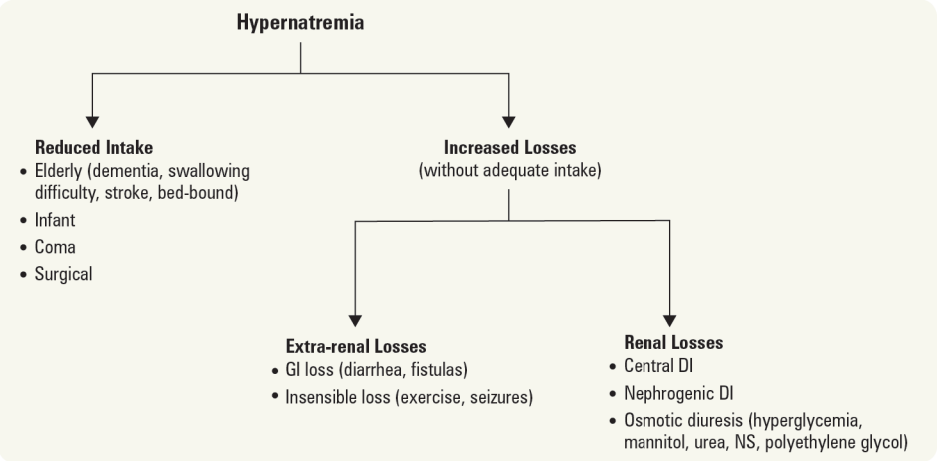


Figure 5. Approach to hypernatremia

Signs and Symptoms

- with acute hypernatremia no time for adaptation, therefore more likely to be symptomatic
- adaptive response: cells import and generate new osmotically active particles to normalize size
- due to brain cell shrinkage: altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, seizures, coma, death
- ± polyuria, thirst, signs of hypovolemia

Complications

- increased risk of vascular rupture resulting in intracranial hemorrhage
- rapid correction may lead to cerebral edema due to ongoing brain hyperosmolality

Treatment of Hypernatremia

- general measures for all patients
  - give free water (oral or IV)
  - treat underlying cause
  - monitor serum Na^+ frequently to ensure correction is not occurring too rapidly
- if evidence of hemodynamic instability, must first correct volume depletion with NS bolus
- loss of water is often accompanied by loss of Na^+, but a proportionately larger water loss
- use formula to calculate free water H_2O deficit and replace
- encourage patient to drink pure water, as oral route is preferred for fluid administration
- if unable to replace PO or NG, correct H_2O deficit with hypotonic IV solution (IV D5W, 0.45% NS [half normal saline], or 3.3% dextrose with 0.3% NaCl ["2/3 and 1/3"])
- use formula (see *Hyponatremia*, NP8) to estimate expected change in serum Na^+ with 1 L infusate
- aim to lower [Na^+] by no more than 12 mmol/L in 24 h (0.5 mmol/L/h)
- must also provide maintenance fluids and replace ongoing losses
- general rule: give 2 cc/kg/h of free water to correct serum [Na^+] by about 0.5 mmol/L/h or 12 mmol/L/d

H_2O Deficit and TBW Equations

- TBW = 0.6 x wt (kg) men
  TBW = 0.5 x wt (kg) women
- H_2O deficit = TBW x ([Na^+]plasma – 140) / 140

Correction of serum [Na^+] in hypernatremia should not exceed 12 mmol/L/24 h

1 L D5W approximately equals 1 L of free water

1 L 0.45% NS approximately equals 500 mL of free water

DIABETES INSIPIDUS

- collecting tubule is impermeable to water due to absence of ADH or impaired response to ADH
- defect in central release of ADH (central DI) or renal response to ADH (nephrogenic DI)

Etiology

- central DI: neurosurgery, granulomatous diseases, trauma, vascular events, and malignancy
- nephrogenic DI: lithium (most common), hypokalemia, hypercalcemia, and congenital

Diagnosis

- urine osmolality inappropriately low in patient with hypernatremia (U_{osm} <300 mOsm/kg)
- serum vasopressin concentration may be absent or low (central), or elevated (nephrogenic)
- dehydration test: H_2O deprivation until loss of 3% of body weight or until urine osmolality rises above plasma osmolality; if urine osmolality remains <300 (fails to concentrate urine), most likely DI
- administer DDAVP (exogenous ADH) (10 μg intranasally or 2 μg SC or IV)
  - central DI: diagnosed if there is rise in urine osmolality, fall in urine volume
    - treat with DDAVP
  - nephrogenic DI: exogenous ADH fails to concentrate urine as kidneys do not respond
    - treat with water (IV D5W or PO water), thiazides may help as well (reduced ECF volume stimulates proximal tubular reabsorption of sodium and water, leading to less delivery of glomerular filtrate to ADH sensitive parts of renal tubule, and therefore lower urine volume results)

Potassium Homeostasis

- approximately 98% of total body K^+ stores are intracellular
- normal serum K^+ ranges from 3.5-5.0 mEq/L
- in response to K^+ load, rapid removal from ECF is necessary to prevent life-threatening hyperkalemia
- insulin, catecholamines, and acid-base status influence K^+ movement into cells
  - aldosterone has a minor effect
- potassium excretion is regulated at the distal nephron
  - K^+ excretion = urine flow rate x urine $[K^+]$

Factors which Increase Renal K^+ Loss

- hyperkalemia
- increased distal tubular urine flow rate and Na^+ delivery (thiazides and loop diuretics)
- increased aldosterone activates epithelial sodium channels in cortical collecting duct, causing Na^+ reabsorption and K^+ excretion
- metabolic alkalosis (increases K^+ secretion)
- hypomagnesemia
- increased non-reabsorbable anions in tubule lumen: HCO_3^-, penicillin, salicylate (increased tubular flow rate increases K^+ secretion)

Hypokalemia

- serum $[K^+]$ <3.5 mEq/L

Signs and Symptoms

- usually asymptomatic, particularly when mild (3.0-3.5 mmol/L)
- N/V, fatigue, generalized weakness, myalgia, muscle cramps, and constipation
- if severe: arrhythmias, muscle necrosis, and rarely paralysis with eventual respiratory impairment
- arrhythmias occur at variable levels of K^+; more likely if digoxin use, hypomagnesemia, or CAD
- ECG changes are more predictive of clinical picture than serum $[K^+]$
  - U waves most important (low amplitude wave following a T wave)
  - flattened or inverted T waves
  - depressed ST segment
  - prolongation of Q-T interval
  - with severe hypokalemia: P-R prolongation, wide QRS, arrhythmias; increases risk of digitalis toxicity

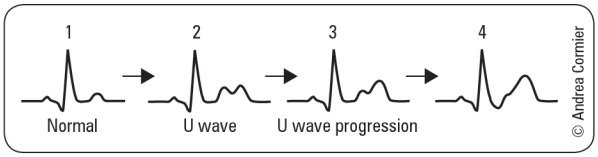


Figure 6. ECG changes in hypokalemia

Approach to Hypokalemia

1. emergency measures: obtain ECG; if potentially life threatening, begin treatment immediately
2. rule out transcellular shifts of K^+ as cause of hypokalemia
3. assess contribution of dietary K^+ intake
4. spot urine K:Cr (should be less than 1 in setting of hypokalemia)
   - if <1 consider GI loss
   - if >1 consider a renal loss
5. consider 24 h K^+ excretion
6. if renal K^+ loss, check BP and acid-base status
7. may also assess plasma renin and aldosterone levels, serum $[Mg^{2+}]$

- Hypokalemia often accompanied by metabolic alkalosis
- Potassium leaves cells, replaced by H^+
- Kidney tubular cells see high H^+, think acidosis and increase ammonium synthesis and excretion
- Increase in bicarbonate generation

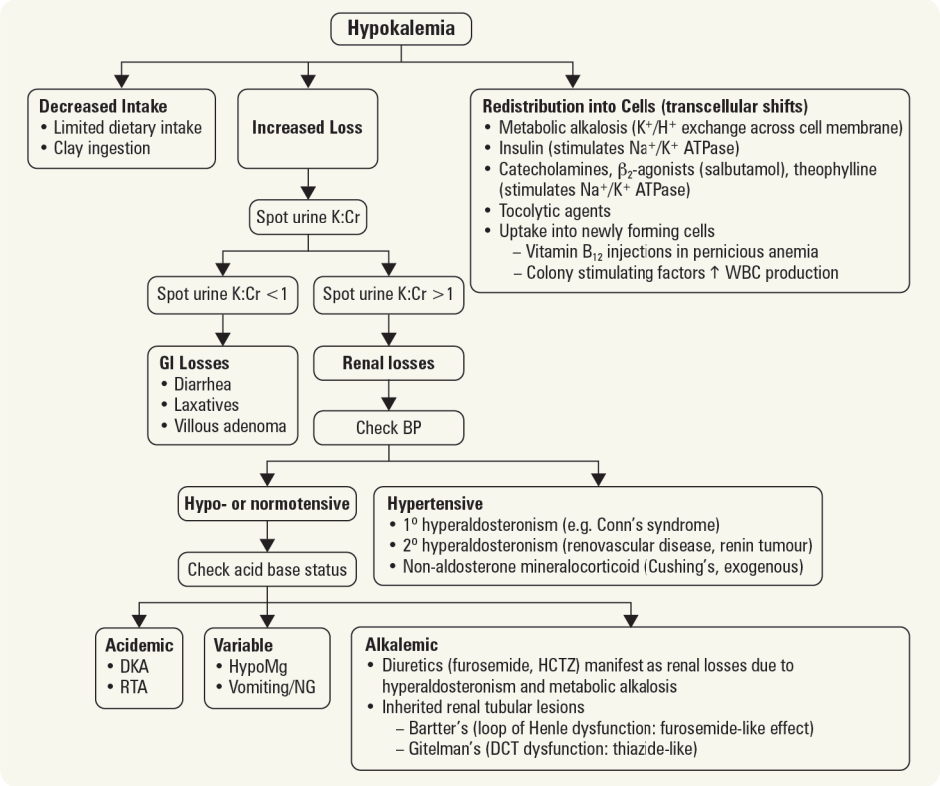


Figure 7. Approach to hypokalemia

Treatment

- treat underlying cause
- if true K^+ deficit, potassium repletion (decrease in serum $[K^+]$ of 1 mEq is roughly 100-200 mEq of total body loss)
  - oral sources – food, tablets (K-Dur™), KCl liquid solutions (preferable route if the patient tolerates PO medications)
  - IV – usually KCl in saline solutions, avoid dextrose solutions (may exacerbate hypokalemia via insulin release)
  - max 40 mmol/L via peripheral vein, 60 mmol/L via central vein, max infusion 20 mmol/h
- K^+-sparing diuretics (triamterene, spironolactone, amiloride) can prevent renal K^+ loss
- restore Mg^{2+} if necessary
- if urine output and renal function are impaired, correct with extreme caution
- risk of hyperkalemia with potassium replacement especially high in elderly, diabetics, and patients with decreased renal function
- beware of excessive potassium repletion, especially if transcellular shift caused hypokalemia

Hyperkalemia

- serum $[K^+]$ >5.0 mEq/L

Signs and Symptoms

- usually asymptomatic but may develop nausea, palpitations, muscle weakness, muscle stiffness, paresthesias, areflexia, ascending paralysis, and hypoventilation
- impaired renal ammoniagenesis and metabolic acidosis

- ECG changes and cardiotoxicity (do not correlate well with serum [K^+])
  - peaked and narrow T waves
  - decreased amplitude and eventual loss of P waves
  - prolonged PR interval
  - widening of QRS and eventual merging with T wave (sine-wave pattern)
  - AV block
  - ventricular fibrillation, asystole

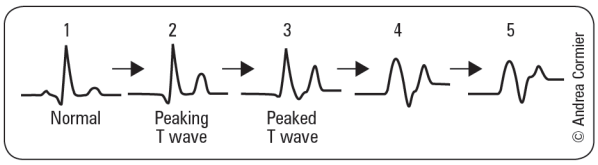


Figure 8. ECG changes in hyperkalemia

Table 6. Causes of Hyperkalemia

Factitious	Increased Intake	Transcellular Shift	Decreased Excretion
Sample hemolysis* Sample taken from vein where IV KCl is running Prolonged use of tourniquet Leukocytosis (extreme) Thrombocytosis (extreme)	Diet KCl tabs IV KCl Salt substitute	Intravascular hemolysis Rhabdomyolysis Tumour lysis syndrome Insulin deficiency Acidemia Drugs • β-blockers • Digitalis overdose (blocks Na^+/K^+ ATPase) • Succinylcholine	Decreased GFR • Renal failure • Low effective circulating volume • NSAIDs in renal insufficiency Normal GFR but hypoaldosteronism

*Most common

Table 7. Causes of Hyperkalemia with Normal GFR

Decreased Aldosterone Stimulus (low renin, low aldosterone)	Decreased Aldosterone Production (normal renin, low aldosterone)	Aldosterone Resistance (decreased tubular response)
Associated with diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV	• Adrenal insufficiency of any cause (e.g. Addison's disease, AIDS, metastatic cancer) • ACEI • Angiotensin II receptor blockers • Heparin • Congenital adrenal hyperplasia with 21-hydroxylase deficiency	K^+-sparing drugs • Spironolactone • Amiloride • Triamterene Renal tubulointerstitial disease

Approach to Hyperkalemia

1. emergency measures: obtain ECG, if life threatening begin treatment immediately
2. rule out factitious hyperkalemia; repeat blood test
3. hold exogenous K^+ (PO and IV) and any K^+ retaining medications
4. assess potential causes of transcellular shift
5. estimate GFR (calculate CrCl using Cockcroft-Gault)

Treatment

- acute therapy is warranted if ECG changes are present or if patient is symptomatic
- tailor therapy to severity of increase in [K^+] and ECG changes
  - [K^+] <6.5 and normal ECG
    - treat underlying cause, stop K^+ intake, increase the loss of K^+ via urine and/or GI tract
  - [K^+] between 6.5 and 7.0, no ECG changes: add insulin to above regimen
  - [K^+] >7.0 and/or ECG changes: first priority is to protect the heart, add calcium gluconate to above

1. Protect the Heart

- calcium gluconate 1-2 amps (10 mL of 10% solution) IV
- antagonizes cardiac toxicity of hyperkalemia, protects cardiac conduction system, no effect on serum [K^+]
- onset within minutes, lasts 30-60 min (may require repeat doses during treatment course of hyperkalemia)

In patients with DM and increased [K^+] and hyperglycemia, often just giving insulin to restore euglycemia is sufficient to correct the hyperkalemia

Treatment of Hyperkalemia

C BIG K DROP
C – Calcium gluconate
BIG – β-agonist, Bicarbonate, Insulin, Glucose
K – Kayexalate®
DROP – Diuretics, Dialysis

2. Shift K^+ into Cells

- regular insulin (Insulin R) 10-20 units IV, with 1-2 amp D50W (give D50W before insulin)
  - onset of action 15-30 min, lasts 1-2 h
  - monitor capillary blood glucose q1h because of risk of hypoglycemia
  - can repeat every 4-6 h
  - caution giving D50W before insulin if hyperkalemia is severe as it can cause a serious arrhythmia
- $NaHCO_3$ 1-3 ampules (given as 3 ampules of 7.5% or 8.4% $NaHCO_3$ in 1L D5W)
  - onset of action 15-30 min, transient effect, drives K^+ into cells in exchange for H^+
  - more effective if patient has metabolic acidosis
- β_2-agonist (Ventolin®) in nebulized form (dose = 2 cc or 10 mg inhaled) or 0.5 mg IV
  - onset of action 30-90 min, stimulates Na^+/K^+ ATPase
  - caution if patient has heart disease as may result in tachycardia

3. Enhance K^+ Removal from Body

- via urine (preferred approach)
  - furosemide (≥40 mg IV), may need IV NS to avoid hypovolemia
  - fludrocortisone (synthetic mineralocorticoid) if suspect aldosterone deficiency
- via gastrointestinal tract
  - cation-exchange resins: calcium resonium or sodium polystyrene sulfonate (Kayexalate®)
    - increasingly falling out of favour due to risk of colonic necrosis; works by binding Na^+ in exchange for K^+, and controversial how much K^+ is actually removed
    - lactulose PO to avoid constipation (must ensure that patient has a bowel movement after resin is administered - main benefit may be the diarrhea caused by lactulose)
  - Kayexalate® enemas with tap water
- dialysis (renal failure, life threatening hyperkalemia unresponsive to therapy)

Acid-Base Disorders

- acid-base homeostasis influences protein function and can critically affect tissue and organ function with consequences to cardiovascular, respiratory, metabolic, and CNS function
- see Respirology, R6 for more information on respiratory acidosis/alkalosis
- normal concentration of HCO_3^- = 24 mEq/L (range: 22-30 mEq/L)
- normal pCO_2 = 40 mmHg (range: 36-44 mmHg)
- each acid base disorder has an appropriate compensation
  - inadequate compensation or overcompensation can indicate the presence of a second acid-base disorder (e.g. in metabolic acidosis, inadequate compensation means there is also respiratory acidosis; overcompensation means there is also respiratory alkalosis)

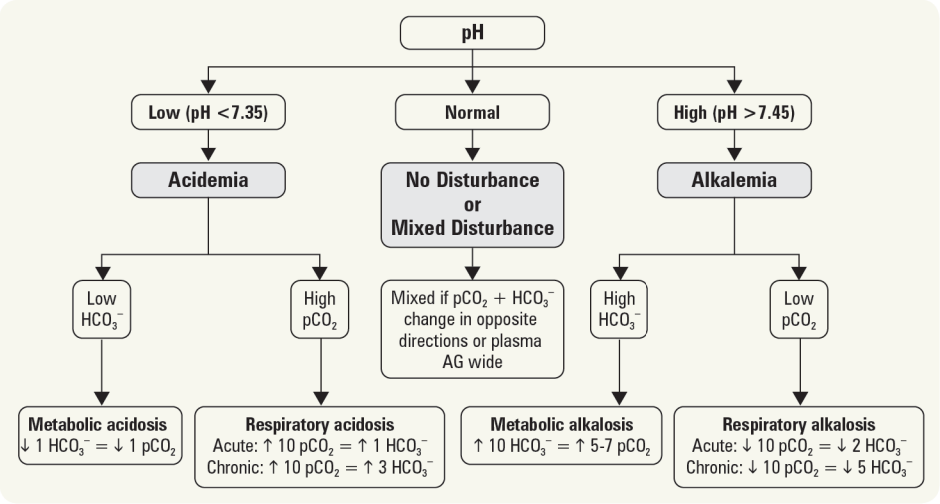


Figure 9. Approach to acid-base disorders

Approach

1. Identify the primary disturbance (see Figure 9)
- respiratory acidosis, metabolic acidosis, respiratory alkalosis, metabolic alkalosis

2. Evaluate compensation. If compensation is not appropriate, a second acid-base disorder is likely present
- compensation occurs in the same direction as the primary disturbance

3. Calculate Plasma AG
- AG = $[Na^+]$ – ($[HCO_3^-]$ + $[Cl^-]$)
- baseline = 12, range 10-14 mEq/L
- AG can be altered by plasma albumin level: for each 10 g/L fall in albumin, lower baseline AG by 3 mEq/L (e.g. if plasma [albumin]= 20 g/L, expect AG = 6 mEq/L)

4. If AG elevated, compare increase in AG with decrease in HCO_3^-
- if increase in AG < decrease in HCO_3^-, there is a coexisting non-AG metabolic acidosis
- if increase in AG > decrease HCO_3^-, there is a coexisting metabolic alkalosis

5. Calculate Osmolar Gap
- osmolar gap = measured osmolality – calculated osmolality
  - calculated osmolality = (2 x $[Na^+]$) + [urea] + [glucose] (all units are in mmol/L)
  - normal osmolar gap <10
  - if AG >10, consider: methanol poisoning, ethylene glycol poisoning, or another cause of acidosis plus ethanol ingestion

Causes of Increased Osmolar Gap
- Methanol
- Ethylene glycol
- Ethanol
- Polyethelene glycol
- Mannitol
- Sorbitol

Useful Equations
- AG = $[Na^+]$ - $[Cl^-]$ - $[HCO_3^-]$ (normal range = 10-14 mEq/L)
- Osmolar Gap = measured serum osmolality – calculated osmolality (normal <10 mEq/L) – "Two Salts and a Sticky BUN"
- Calculated Osmolality = 2$[Na^+]$ + [Urea] + [Glucose] (+1.25[Ethanol])

Metabolic Acidosis

Etiology and Pathophysiology

1. Increased AG Metabolic Acidosis (4 types)

1. Lactic acidosis (2 types)
   - L-lactic acid
     - Type A: due to tissue hypoperfusion (any cause of shock), ischemic bowel, profound hypoxemia
     - Type B: non-hypoxic – multiple causes; the most common is failure to metabolize normally produced lactic acid in the liver due to severe liver disease; other causes include: excessive alcohol intake, thiamine deficiency, metformin accumulation (metformin interferes with electron transport chain), certain anti-retrovirals, large tumours, mitochondrial myopathies
   - D-lactic acid: rare syndrome characterized by episodes of encephalopathy and metabolic acidosis
     - occurs in the setting of carbohydrate malabsorption (e.g. short bowel syndrome), colonic bacteria metabolize carbohydrate load into D-lactic acid, diminished colonic motility and impaired D-lactate metabolism
2. Ketoacidosis
   - diabetic
   - starvation
   - alcoholic (decreased carbohydrate intake and vomiting)
3. Toxins
   - methanol (toxic to brain and retina, can cause blindness and brain death): metabolized to formic acid
   - ethylene glycol (toxic to brain and kidneys): metabolized to oxalic acid (envelope shaped crystals in urine) and multiple other acids
   - salicylate (e.g. ASA) overdose: causes acidosis due to salicylic acid, and also accumulation of lactic acid (salicylate at toxic levels impairs electron transport chain) and ketoacid (salicylate activates fat breakdown)
4. Advanced renal failure (e.g. serum Cr increased at least 5x above baseline – a very low GFR causes anion retention, and renal disease leads to impaired bicarbonate production)

2. Normal AG Metabolic Acidosis (Hyperchloremic Acidosis)
- diarrhea (HCO_3^- loss from GI tract)
- RTA
  - type I RTA (distal): inability to secrete H^+ in collecting duct, leading to impaired excretion of ammonium into urine
  - type II RTA (proximal): impaired HCO_3^- reabsorption
  - type III RTA: combination of Types I and II and is extremely rare
  - type IV RTA: defective ammoniagenesis due to decreased aldosterone, hyporesponsiveness to aldosterone, or hyperkalemia

Causes of Increased AG Metabolic Acidosis

MUDPILES CAT
Methanol
Uremia
Diabetic ketoacidosis
Paraldehyde
Isopropyl alcohol/**I**ron/**I**buprofen/ **I**ndomethacin
Lactic acidosis
Ethylene glycol
Salicylates
Cyanide and **C**arbon monoxide
Alcoholic ketoacidosis
Toluene

or

KARMEL
Ketoacidosis
ASA
Renal failure
Methanol
Ethylene glycol
Lactic acidosis

Causes of Non-AG Metabolic Acidosis

HARDUP
Hyperalimentation
Acetazolamide
RTA*
Diarrhea*
Ureteroenteric fistula
Pancreaticoduodenal fistula

*Most common

- to help distinguish renal causes from non-renal causes, use Urine AG = $(Na^+ + K^+) - Cl^-$
- calculation establishes the presence or absence of unmeasured positive ions (e.g. NH_4^+) in urine
  - if UAG <0, suggests adequate NH_4^+ excretion in urine (likely nonrenal cause: diarrhea)
  - if UAG >0, suggests problem is lack of NH_4^+ in urine (e.g. distal RTA)

Treatment of Metabolic Acidosis

1. treat underlying cause
   - fluid resuscitation insulin for DKA
   - restore tissue perfusion for Type A lactic acidosis
   - ethanol/fomepizole +/- dialysis for methanol or ethylene glycol poisoning
   - alkaline diuresis ± dialysis if ASA overdose
2. correct coexisting disorders of K^+ (see *Hyperkalemia*, NP13)
3. consider treatment with exogenous alkali (e.g. $NaHCO_3$) if
   - severe reduction in $[HCO_3^-]$ e.g. <8 mmol/L, especially with very low pH (<7)
   - no metabolizable anion (e.g. salicylate, formate, oxalate, or sulphate); note that lactate and ketoacid anions can be metabolized to HCO_3^-

- note: risks of sodium bicarbonate therapy
  - hypokalemia: causes K^+ to shift into cells (correct K^+ deficit first)
  - ECF volume overload: Na^+ load given with $NaHCO_3$, can exacerbate pulmonary edema
  - overshoot alkalosis: abrupt, poorly tolerated transition from overly aggressive alkali loading, partial conversion of accumulated organic anions to HCO_3^-, and persisting hyperventilation

3 Clinical Scenarios that Produce a Mixed Disorder with Near Normal pH
(e.g. increased AG metabolic acidosis + respiratory alkalosis)
- Cirrhosis
- ASA overdose
- Sepsis

Metabolic Alkalosis

Pathophysiology

- requires initiating event and maintenance factors
- precipitating factors
  - GI (vomiting, NG tube) or renal loss of H^+
  - exogenous alkali (oral or parenteral administration), milk alkali syndrome
  - diuretics (contraction alkalosis): decreased excretion of HCO_3^-, decreased ECF volume, therefore increased $[HCO_3^-]$
  - post-hypercapnia: renal compensation for respiratory acidosis is HCO_3^- retention, rapid correction of respiratory disorder results in transient excess of HCO_3^-
- maintenance factors
  - volume depletion: increased proximal reabsorption of $NaHCO_3^-$ and increased aldosterone
  - hyperaldosteronism (1° or 2°): distal Na^+ reabsorption in exchange for K^+ and H^+ excretion leads to HCO_3^- generation; aldosterone also promotes hypokalemia
  - hypokalemia: transcellular K^+/H^+ exchange, stimulus for ammoniagenesis and HCO_3^- generation

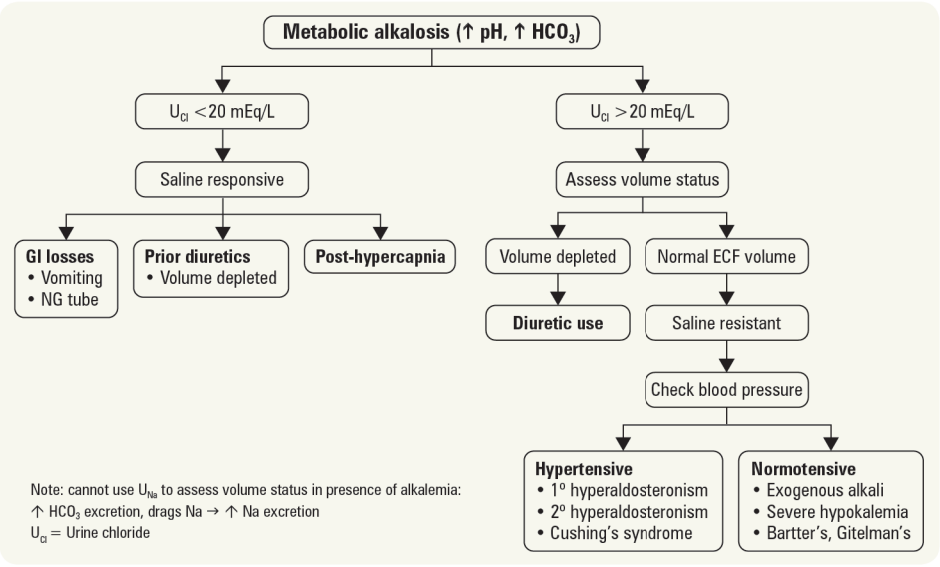


Figure 10. Approach to metabolic alkalosis

Evaluate Compensation (identify co-existing respiratory acid-base disorders)

- hypoventilation (an upper limit to compensation exists – breathing cannot be stopped)

Treatment

- treat underlying cause
- correct underlying disease, replenish K^+ and Mg^{2+} deficits, and possibly K^+-sparing diuretic

- saline sensitive metabolic alkalosis (most common)
  - volume repletion ± carbonic anhydrase inhibitor (e.g. acetazolamide) to facilitate loss of HCO_3^- in urine
- saline resistant metabolic alkalosis
  - remove source of aldosterone or glucocorticoid ± spironolactone

Acute Kidney Injury

Definition
- abrupt decline in renal function leading to increased nitrogenous waste products normally excreted by the kidney
- formerly known as acute renal failure

Clinical Presentation
- azotemia (increased BUN, Cr)
- abnormal urine volume: formally <0.5 ml/kg/h for >6 h but can manifest as anuria, oliguria, or polyuria

The 2 most common causes of acute kidney injury in hospitalized patients are prerenal azotemia and ATN; remember that prerenal failure can lead to ATN

Approach to AKI

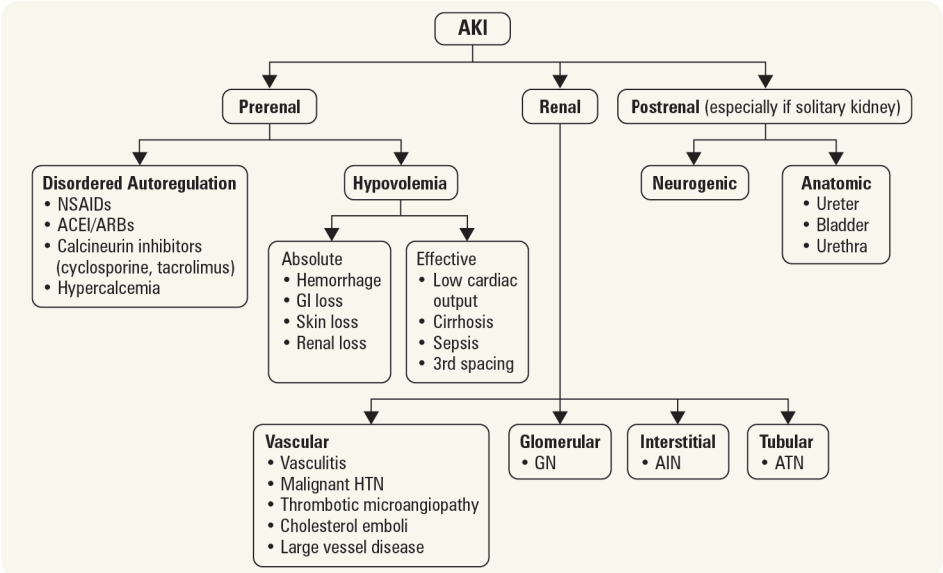


Figure 11. Approach to AKI

Clues to Prerenal Etiology
- Clinical: Decreased BP, increased HR, and orthostatic HR and BP changes
- Increased [urea] >> Increased [Cr]
- Urine [Na^+] <10-20 mmol/L
- Urine osmolality >500 mOsm/kg
- Fractional excretion of Na^+ <1%

Clues to Renal Etiology
- Appropriate clinical context
- Urinalysis positive for casts:
  - Pigmented granular – ATN
  - WBC – AIN
  - RBC – GN

Clues to Postrenal Etiology
- Known solitary kidney
- Older man
- Recent retroperitoneal surgery
- Anuria
- Palpable bladder
- Ultrasound shows hydronephrosis

Investigations
- blood work: CBC, electrolytes, Cr, urea (think prerenal if increase in urea is relatively greater than increase in Cr), Ca^{2+}, PO_4^{3-}
- urine volume, C&S, R&M: sediment, casts, crystals
- urinary indices: electrolytes, osmolality
- Foley catheterization (rule out bladder outlet obstruction)
- fluid challenge (e.g. fluid bolus to rule out most prerenal causes)
- imaging: abdomen U/S (assess kidney size, hydronephrosis, postrenal obstruction)
- indications for renal biopsy
  - diagnosis is not certain
  - prerenal azotemia or ATN is unlikely
  - oliguria persists >4 wk

Differentiating Prerenal from ATN

	Prerenal	ATN
Urinalysis	Normal	RBC, pigmented granular casts
Urine [Na^+]	<20	>40 mEq/L
Urine[Na^+]/[Cr]	<20	>40
Urine osmolality	>500	<350 mOsm/kgH_2O
FeNa	<1%	>1%

Treatment
1. preliminary measures
   - prerenal
     - correct prerenal factors: optimize volume status and cardiac performance using fluids that will stay in the plasma subcompartment (NS, albumin, blood/plasma), hold ACEI/ARB (gently rehydrate when needed, e.g. CHF)
   - renal
     - address reversible renal causes: discontinue nephrotoxic drugs, treat infection, and optimize electrolytes

Drugs Implicated in Prerenal Azotemia
- Diuretics
- NSAIDs
- ACEI/ARBs

Renal transplant is not a therapy for AKI

- postrenal
  - consider obstruction: structural (stones, strictures) vs. functional (neuropathy)
  - treat with Foley catheter, indwelling bladder catheter, nephrostomy, stenting

2. treat complications
   - fluid overload
     - NaCl restriction
     - high dose loop diuretics
   - hyperkalemia (see *Approach to Hyperkalemia*, NP12)
   - adjust dosages of medications cleared by kidney (e.g. amiodarone, digoxin, cyclosporin, tacrolimus, some antibiotics, and chemotherapeutic agents)
   - dialysis
3. definitive therapy depends on etiology

Indications for Dialysis (refractory to medical therapy)

AE IOU
Acidosis
Electrolyte imbalance (K^+)
Intoxication
Overload (fluid)
Uremic encephalopathy, pericarditis, urea >35-50 mM

Prognosis
- high morbidity and mortality in patients with sustained AKI and multi-organ failure

Parenchymal Kidney Diseases

Glomerular Diseases

HISTOLOGICAL TERMS OF GLOMERULAR CHANGES

Extent of Changes
- histological term describing the number of glomeruli affected in a given condition:
  - diffuse: majority of glomeruli abnormal
  - focal: some glomeruli affected
- histological term describing the extent to which individual glomeruli are affected in a given condition
  - global: entire glomerulus abnormal
  - segmental: only part of the glomerulus abnormal

Types of Changes
- proliferation: hyperplasia of one of the glomerular cell types (mesangial, endothelial, parietal epithelial), with or without inflammatory cell infiltration
- membranous changes: capillary wall thickening due to immune deposits or alterations in basement membrane
- crescent formation: parietal epithelial cell proliferation and mononuclear cell infiltration form crescent-shape in Bowman's space

CLINICAL PRESENTATION OF GLOMERULAR DISEASE

Important Points to Remember
- glomerular diseases have diverse clinical presentations including hematuria, proteinuria, HTN, edema, and decreased GFR
  - each glomerulopathy presents as one of four major glomerular syndromes (these are NOT diagnoses)
    1. asymptomatic urinary abnormalities
       - proteinuria
       - hematuria
    2. nephritic syndrome
       - acute GN
       - rapidly progressive GN
    3. nephrotic syndrome
    4. ESRD
- glomerulopathies can be caused by a primary disease or can occur secondary to a systemic disease
- some glomerulopathies can present as more than one syndrome at different times

The Nephritic-Nephrotic Spectrum
- glomerular pathology can present with a clinical picture anywhere on a spectrum with pure nephritic and pure nephrotic syndromes at the extremes

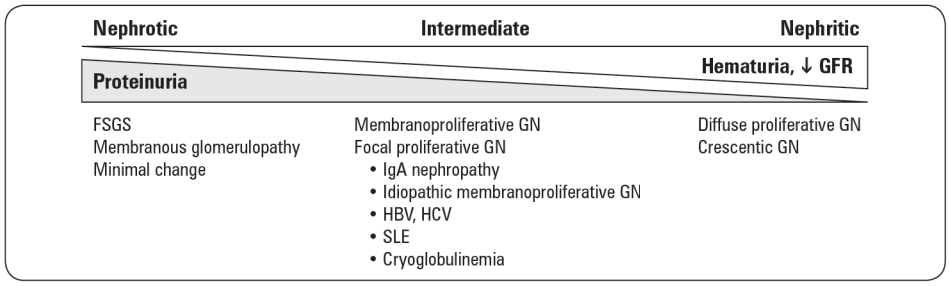


Figure 12. Spectrum of glomerular pathology

PROTEINURIA

- hallmark of nephrotic syndromes
- 24 h urine protein: gold standard to assess degree of proteinuria
- urine ACR: used to screen for diabetic nephropathy
  - microalbuminuria
    - defined as ACR ≥2.8 mg/mmol (female) or ≥2.0 mg/mmol (male)
    - marker of vascular endothelial function
    - an important prognostic marker for kidney disease in DM and HTN (see *Diabetes*, NP28)
  - microalbuminuria is the earliest sign of diabetic nephropathy
- composition of normal total urine protein
  - upper limit of normal daily excretion of total protein is 150 mg/d
  - upper limit of normal daily excretion of albumin is 30 mg/d
  - the other normally excreted proteins are either filtered low molecular weight proteins (such as immunoglobulin light chains or β-2 microglobulin) or proteins secreted by the tubular epithelial cells (e.g. Tamm-Horsfall mucoprotein)

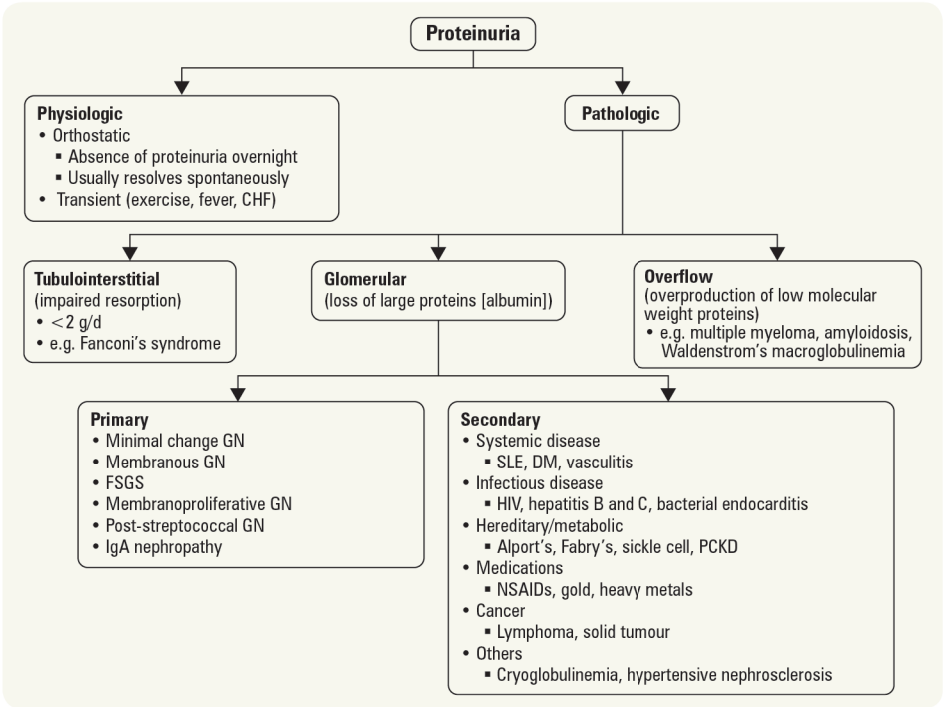


Figure 13. Classification of proteinuria

Table 8. Daily Excretion of Protein

Daily Excretion	Meaning
<150 mg total protein (and <30 mg albumin)	Normal
30-300 mg albumin	Microalbuminuria
>3500 mg total protein/1.73m^2 BSA	Nephrotic range proteinuria
Variable amount of proteinuria	Can be seen with glomerular disease
Up to 2000 mg per d	Possible tubular disease because of failure to reabsorb filtered proteins

Pathologic Proteinuria

Tubulointerstitial
- Normally low molecular weight proteins (<60 kDa) pass through glomerular filtration barrier and are reabsorbed in proximal tubule
- Proximal tubule dysfunction causes impaired reabsorption and increased excretion of low molecular weight proteins
- Albumin (>60 kDa) is not affected; thus, edema is partly secondary to salt and water retention

Glomerular
- Normally, the filtration barrier is selectively permeable to **size** (<60 kDa) and **charge** (repels negative particles); thus, albumin is filtered to a very limited extent through a normal glomerulus
- Damage to any component of the glomerular filtration barrier results in loss of albumin and other high molecular weight proteins; thus, edema is secondary to hypoalbuminemia (low oncotic pressure), but also due to enhanced renal tubular reabsorption of filtered sodium and water (possibly due to filtered proteins stimulating the action of cortical collecting duct epithelial sodium channel)

Overflow
- Increased production of low molecular weight proteins which exceeds the reabsorptive capacity of the proximal tubule
- Plasma cell dyscrasias: produce light chain Ig (multiple myeloma, Waldenstrom's macroglobulinemia, monoclonal gammopathy of undetermined significance)

Investigations
- urine R&M, C&S, urea, Cr
- further workup (if degree of proteinuria >0.5 g/d, casts, and/or hematuria)
  - CBC, glucose, electrolytes, 24 h urine protein, and Cr
  - urine and serum immunoelectrophoresis, abdominal/pelvic U/S
  - serology: ANA, RF, p-ANCA (MPO), c-ANCA (PR3), Hep B, Hep C, HIV, ASOT
- indications for nephrology referral
  - generally, if there is "heavy" proteinuria (ACR >30 mg/mmol), should refer to nephrologist
  - definitely if there is nephrotic syndrome: marked proteinuria >3.5 g/1.73m^2/d with hypoalbuminemia (<35 g/L)

HEMATURIA
- hallmark of nephritic syndromes
- presence of blood or RBCs in urine
  - gross hematuria: pink, red, or tea-coloured urine
    - in gross hematuria, the urine should be centrifuged
      - if the sediment is red, true hematuria
      - if the supernatant is red, test for heme with a dipstick
        - if supernatant positive for heme: myoglobinuria or hemoglobinuria
        - if negative for heme: pseudohematuria; consider medications (e.g. rifampin), food dyes (e.g. beets), or metabolites (e.g. porphyria)
  - microscopic hematuria: blood in the urine that is invisible to the naked eye, >2-3 RBCs/HPF on microscopy

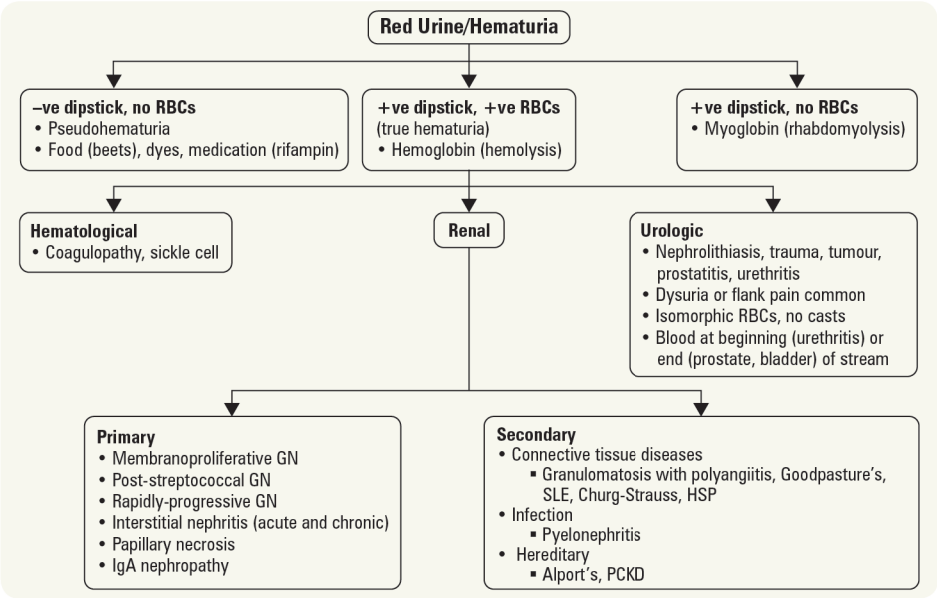


Figure 14. Approach to red urine

Investigations for Hematuria
- Hx and P/E: family history of nephrolithiasis, hearing loss (Alport's), cerebral aneurysm (PCKD), diet, recent URTI, irritative and obstructive urinary symptoms (UTI)
- urine R&M, C&S, urea, Cr
- renal U/S
- 24 h urine stone workup if there is a history of stone formation or if there is a stone noted on imaging: calcium, oxalate, citrate, magnesium, uric acid, cysteine
- further workup (if casts and/or proteinuria): CBC, electrolytes, 24 h urine protein and Cr, serology (ANA, RF, C3, C4, p-ANCA, c-ANCA, ASOT)
- consider urology consult and possible cystoscopy if not clearly a nephrologic source for hematuria or if >50 yr of age

Glomerular Syndromes

1. ASYMPTOMATIC URINARY ABNORMALITIES

Clinical/Lab Features
- proteinuria (usually <2 g/d) and/or microscopic or macroscopic hematuria
  - isolated proteinuria
    - can be postural
    - occasionally can signal beginning of more serious GN (e.g. FSGS, IgA nephropathy, amyloid, diabetic nephropathy)

- hematuria with or without proteinuria
  - IgA nephropathy (Berger's disease): most common type of primary glomerular disease worldwide, usually presents after viral URTI
  - hereditary nephritis (Alport's disease): X-linked nephritis often associated with sensorineural hearing loss; proteinuria <2 g/d
  - thin basement membrane disease: usually autosomal dominant, without proteinuria; benign
  - benign recurrent hematuria: hematuria associated with febrile illness, exercise, or immunization; a diagnosis of exclusion after other possibilities are ruled out

2. NEPHRITIC SYNDROME

ACUTE NEPHRITIC SYNDROME

- a subset of nephritic syndrome in which the clinical course proceeds over days

IgA nephropathy is the most common type of primary glomular disease worldwide

Etiology

- etiology can be divided into low and normal complement levels
- frequently immune-mediated, with Ig and C3 deposits found in GBM
- outcome dependent on etiology

Clinical/Lab Features

- proteinuria (but <3.5 g/1.73 m^2/d), abrupt onset hematuria (microscopic or macroscopic), azotemia (increased Cr and urea), RBC casts and/or dysmorphic RBCs in urine, oliguria, HTN (due to salt and water retention), peripheral edema/puffy eyes, smoky urine

Features of Nephritic Syndrome

PHAROH
Proteinuria
Hematuria
Azotemia
RBC casts
Oliguria
HTN

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS/CRESCENTIC GLOMERULONEPHRITIS

- a subset of nephritic syndrome in which the clinical course proceeds over weeks to months
- clinical diagnosis, not histopathological
- any cause of GN can present as RPGN (except minimal change disease)
- additional etiologies seen only as RPGN: Goodpasture's syndrome and granulomatosis with polyangiitis (previously called Wegener's granulomatosis)

Clinical/Lab Features

- fibrous crescents typically present on renal histopathology
- RBC casts and/or dysmorphic RBCs in urine
- classified by immunofluorescence staining
- Type I: Anti-GBM mediated (15% of cases)
- Type II: Immune Complex Mediated (24% of cases)
- Type III: Non-Immune Mediated (60% of cases)
- Type IV: Double Antibody Positive
- treatment: underlying cause for postinfectious; corticosteroids + cyclophosphamide or other cytotoxic agent + plasmaphoresis in select cases
- prognosis: 50% recovery with early treatment, depends on underlying cause

3. NEPHROTIC SYNDROME

Clinical/Lab Features

- heavy proteinuria (>3.5 g/1.73m^2/d)
- hypoalbuminemia
- edema
- hyperlipidemia (elevated LDL cholesterol), lipiduria (fatty casts and oval fat bodies on microscopy)
- hypercoagulable state (due to antithrombin III, Protein C, and Protein S urinary losses)
- patient may report frothy urine
- glomerular pathology on renal biopsy
  - minimal change disease (or minimal lesion disease or nil disease) – e.g. glomeruli appear normal on light microscopy
  - membranous glomerulopathy
  - focal segmental glomerulosclerosis (FSGS)
  - membranoproliferative GN
  - nodular glomerulosclerosis
- each can be idiopathic or secondary to a systemic disease or drug (sirolimus can cause proteinuria without obvious glomerular pathology)

Presentation of Nephrotic Syndrome

HELP
Hypoalbuminemia
Edema
Lipid abnormalities
Proteinuria

Table 9. Nephrotic Syndrome

	Minimal Change	Membranous Glomerulopathy	Focal Segmental Glomerulosclerosis	Membranoproliferative Glomerulonephritis	Nodular Glomerulosclerosis
Secondary Causes	Hodgkin's lymphoma	HBV, SLE, solid tumours (lung, breast, GI)	Reflux nephropathy, HIV, HBV, obesity	HCV, malaria, SLE, leukemia, lymphoma, shunt nephritis	DM, amyloidosis
Drug Causes	NSAIDs	Gold, penicillamine	Heroin		
Therapy	Steroids	Reduce BP, ACEI, steroids	Steroids, ACEI/ARB for proteinuria	Aspirin®, ACEI, dipyridamole (Persantine®) – controversial	Treat underlying cause

4. END STAGE RENAL DISEASE

- see *End Stage Renal Disease*, NP35

INVESTIGATIONS FOR GLOMERULAR DISEASE

- blood work
  - first presentation: electrolytes, Cr, urea, albumin, fasting lipids
  - determining etiology: CBC, ESR, serum immunoelectrophoresis, anti-GBM, C3, C4, ANA, p-ANCA, c-ANCA, cryoglobulins, HBV and HCV serology, ASOT (anti-streptolysin titres), VDRL, HIV
- urinalysis: RBCs, WBCs, casts, protein
- 24 h urine for protein and CrCl
- radiology
  - CXR (infiltrates, CHF, pleural effusion)
  - renal U/S
- renal biopsy (percutaneous or open) if heavy proteinuria or renal insufficiency and cause is not obviously diabetic nephropathy
- urine immunoelectrophoresis
  - for Bence-Jones protein if proteinuria present

SECONDARY CAUSES OF GLOMERULAR DISEASE

Amyloidosis

- nodular deposits of amyloid in mesangium, usually related to amyloid light chain (AL)
- presents as nephrotic range proteinuria with progressive renal insufficiency
- can be primary or secondary
- secondary causes: multiple myeloma, TB, rheumatoid arthritis, malignancy

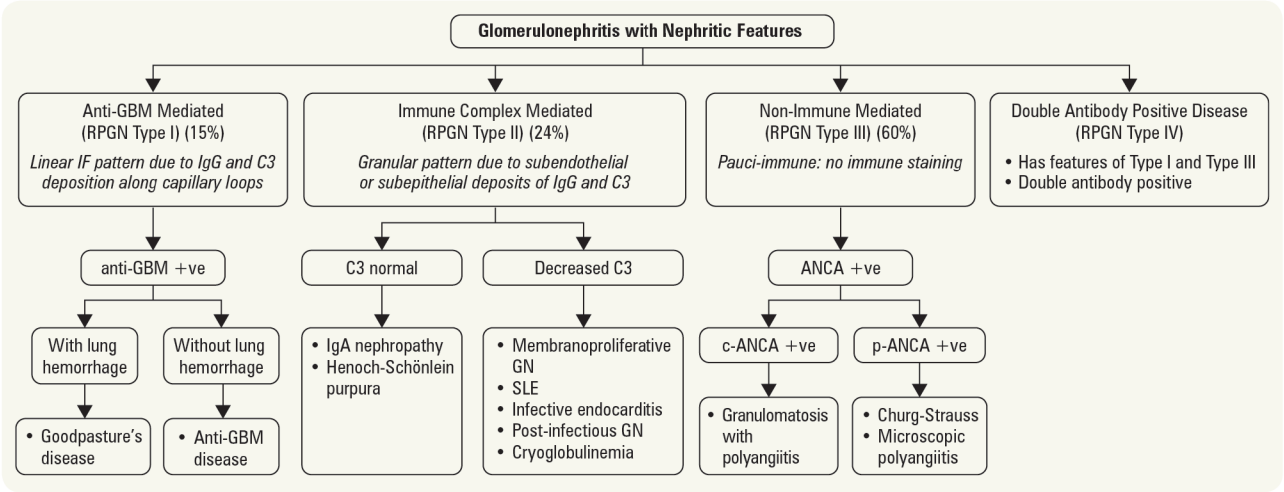


Figure 15. Approach to nephritic syndrome

Systemic Lupus Erythematosus

- lupus nephritis can present as any of the glomerular syndromes
- nephrotic syndrome with an active sediment is most common presentation
- GN caused by immune complex deposition in capillary loops and mesangium with resulting renal injury
- serum complement levels are usually low during periods of active renal disease
- children and males with SLE are more likely to develop nephritis

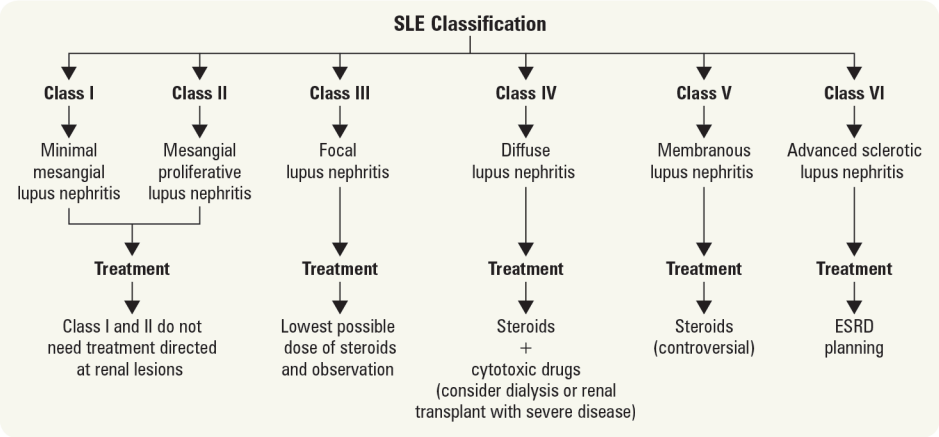


Figure 16. International Society of Nephrology/Renal Pathology Society classification of lupus nephritis 2003

EULAR Recommendations for the Management of Systemic Lupus Erythematosus (SLE)
Ann Rheum Dis 2008;67:195-205
Lupus Nephritis Recommendations
Monitoring: Renal biopsy, urine sediment analysis, proteinuria, and kidney function may have independent predictive ability for clinical outcome in therapy of lupus nephritis but need to be interpreted in conjunction. Changes in immunological tests (anti-dsDNA, serum C3) have limited ability to predict response to treatment and may be used only as supplemental information.
Treatment: In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens, which are associated with considerable adverse effects. In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared with pulse cyclophosphamide and a more favourable toxicity profile. Failure to respond by 6 mo should evoke discussions for intensification of therapy. Flares following remission are not uncommon and require diligent follow-up.
End-stage renal disease: Dialysis and transplantation in SLE have long-term patient and graft-survival rates comparable with those observed in non-diabetic non-SLE patients, with transplantation being the method of choice.

Henoch-Schönlein Purpura
- seen more commonly in children
- purpura on buttocks and legs, abdominal pain, arthralgia, and fever
- glomeruli show varying degrees of mesangial hypercellularity
- IgA and C3 staining of mesangium
- usually benign, self-limiting course, 10% progress to CKD

Goodpasture's Disease
- antibodies against type IV collagen present in lungs and GBM
- more common in 3rd and 6th decades of life, males slightly more affected than females
- present with RPGN type I and hemoptysis/dyspnea
- pulmonary hemorrhage more common in smokers and males
- treat with plasma exchange, cyclophosphamide, prednisone

ANCA-Associated Vasculitis (e.g. Granulomatosis with Polyangiitis and Microscopic Polyangiitis)
- PR3-ANCA (c-ANCA) most commonly associated with the clinical picture of granulomatosis with polyangiitis
- MPO-ANCA (p-ANCA) most commonly associated with the clinical picture of microscopic polyangiitis
- renal involvement very common
- focal segmental necrotizing RPGN with no immune staining
- may be indolent or fulminant in progression
- vasculitis and granulomas rarely seen on renal biopsy
- treatment typically involves cyclophosphamide and prednisone

Cryoglobulinemia
- cryoglobulins: monoclonal IgM and polyclonal IgG which precipitate at reduced temperatures
- presents as purpura, fever, Raynaud's phenomenon, and arthralgias
- at least 50% of patients have hepatitis C
- renal disease seen in 40% of patients (isolated proteinuria/hematuria progressing to nephritic syndrome)
- most patients have decreased serum complement (C4 initially)
- treat hepatitis C, plasmapheresis
- overall prognosis: 75% renal recovery

Shunt Nephritis
- immune-complex mediated nephritis associated with chronically infected ventriculoatrial shunts inserted for treatment of hydrocephalus
- presents as acute nephritic syndrome with decreased serum complement
- nephrotic range proteinuria in 25% of patients

HIV-Associated Renal Disease
1. direct nephrotoxic effect of HIV infection, anti-retroviral drugs (e.g. tenofovir, indinavir), and other drugs used to treat HIV-associated infections
2. HIV-associated nephropathy
   - histology: focal and segmental glomerular collapse with mesangial sclerosis; "collapsing FSGS"
   - tubular cystic dilation and tubulo-reticular inclusions
   - clinical features: predominant in African American men, heavy proteinuria, progressive renal insufficiency
   - prognosis: kidney failure within 1 yr without treatment
   - therapy: short-term, high dose steroids, ACEI, HAART

Infective Endocarditis
- manifests as mild form of acute nephritic syndrome with decreased serum complement
- *S. aureus* is most common infecting agent
- treatment with appropriate antibiotics usually resolves GN

Hepatitis B
- can result in membranous nephropathy, polyarteritis nodosa, membranoproliferative GN

Hepatitis C
- can result in membranous nephropathy, cryoglobulinemia, and membranoproliferative GN

Syphilis
- can result in membranous GN

Tubulointerstitial Disease

TUBULOINTERSTITIAL NEPHRITIS

Definition
- cellular infiltrates affecting primarily the renal interstitium and tubular cells
- functional tubule defects are disproportionately greater than the decrease in GFR
- classified as acute or chronic

Signs and Symptoms
- manifestation of disease depends on site of tubule affected
  1. proximal tubule (e.g. multiple myeloma, heavy metals)
     - Fanconi syndrome: decreased reabsorption in proximal tubule causing glycosuria, aminoaciduria, phosphaturia, hyperuricosuria
     - proximal RTA (decreased bicarbonate absorption): Type II RTA
  2. distal tubule (e.g. amyloidosis, obstruction)
     - distal RTA (Type I RTA), usually hypokalemic
     - Na^+-wasting nephropathy
     - ± hyperkalemia leading to type IV RTA (where reduced renal bicarbonate production is caused by hyperkalemia)
  3. collecting duct (e.g. sickle cell anemia, analgesics, PCKD)
     - urinary concentrating defect leading to mild nephrogenic DI
     - polyuria

1. ACUTE TUBULOINTERSTITIAL NEPHRITIS

Definition
- rapid (days to weeks) decline in renal function
- 10-20% of all AKI

Etiology
- hypersensitivity
  1. antibiotics: β-lactams, sulfonamides, rifampin, quinolones, cephalosporins
  2. other: NSAIDs, allopurinol, furosemide, thiazides, triamterene, PPIs, acyclovir, phenytoin, cimetidine
- infections
  - bacterial pyelonephritis, *Streptococcus*, brucellosis, *Legionella*, CMV, EBV, toxoplasmosis, leptospirosis
- immune
  - SLE, acute allograft rejection, Sjögren's syndrome, sarcoidosis, mixed essential cryoglobulinemia
- idiopathic

Pathophysiology
- acute inflammatory cell infiltrates into renal interstitium

Signs and Symptoms
- AKI
- if hypersensitivity reaction: may see fever, skin rash, arthralgia, serum sickness-like syndrome (particularly rifampin)
- if pyelonephritis: flank pain and costovertebral angle (CVA) tenderness
- other signs and symptoms based on underlying etiology
- HTN and edema are uncommon

Investigations
- urine
  - mild, non-nephrotic range proteinuria and microscopic hematuria
  - sterile pyuria, WBC casts
  - eosinophils if AIN
- blood work
  - increased Cr and urea
  - eosinophilia if drug reaction
  - normal AG metabolic acidosis (RTA)
  - hypophosphatemia, hyperkalemia, hyponatremia
- gallium scan often shows intense signal due to inflammatory infiltrate
- renal biopsy definitive

Treatment
- treat underlying cause (e.g. stop offending medications, antibiotics if pyelonephritis)
- corticosteroids (may be indicated in allergic or immune disease)

Prognosis
- recovery within 2 wk if underlying insult can be eliminated
- the longer the patient is in renal failure, the less likely they will have a full renal recovery

2. CHRONIC TUBULOINTERSTITIAL NEPHRITIS

Definition
- characterized by slowly progressive renal failure, moderate proteinuria, and signs of abnormal tubule function

Etiology
- persistence or progression of acute TIN
- urinary tract obstruction: most important cause of chronic TIN (tumours, stones, bladder outlet obstruction, vesicoureteral reflux)
- chronic pyelonephritis due to vesicoureteral reflux or UTI with obstruction
- nephrotoxins
  - exogenous
    - analgesics: NSAIDs (common), acetaminophen
    - cisplatin, lithium, cyclosporine, tacrolimus
    - heavy metals (lead, cadmium, copper, lithium, mercury, arsenic)
    - Chinese herbs (aristolochic acid)
  - endogenous
    - hypercalcemia, hypokalemia, oxalate, uric acid
- vascular disease: ischemic nephrosclerosis, atheroembolic disease
- malignancies: multiple myeloma, lymphoma
- granulomatous: TB, sarcoidosis, granulomatosis with polyangiitis
- immune: SLE, Sjögren's, cryoglobulinemia, Goodpasture's, amyloidosis, renal graft rejection, vasculitis
- hereditary: cystic diseases of the kidney, sickle cell disease
- others: radiation, Balkan (endemic) nephropathy

Pathophysiology
- fibrosis of interstitium with atrophy of tubules, mononuclear cell inflammation

Signs and Symptoms
- tubular dysfunction (e.g. acidosis, electrolyte disturbances)
- progressive renal failure with azotemia and uremia
- dependent on underlying etiology

Treatment
- stop offending agent or treat underlying disease
- supportive measures: correct metabolic disorders (Ca^{2+}, PO_4^{3-}) and anemia

Findings which Suggest Chronic Tubulointerstitial Nephritis
- normal AG metabolic acidosis
- hyperkalemia (out of proportion to degree of renal insufficiency)
- polyuria, nocturia
- partial or complete Fanconi's syndrome
- urine: mild proteinuria, few RBCs and WBCs, no RBC casts
- U/S: shrunken kidneys with irregular contours

3. ACUTE TUBULAR NECROSIS

Definition
- abrupt and sustained decline in GFR within minutes to days after ischemic/nephrotoxic insult
- GFR reduced (this serves the purpose of avoiding life-threatening urinary loss of fluid and electrolytes from non-functioning tubules)

Etiology

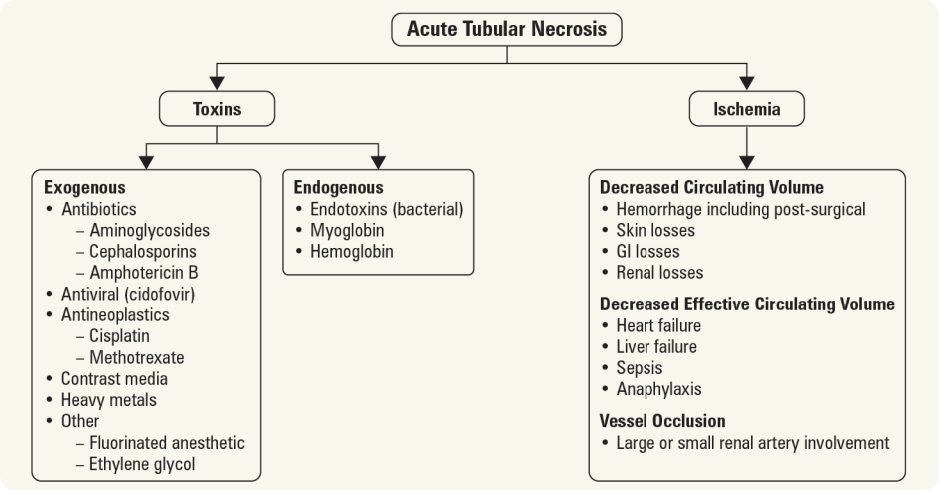


Figure 17. Etiology of ATN

Clinical Presentation
- typically presents as an abrupt rise in urea and Cr after a hypotensive episode, sepsis, rhabdomyolysis, or administration of nephrotoxic drug
- urine: high FE_{Na^+}, pigmented-granular casts

Complications
- hyperkalemia: can occur rapidly and cause serious arrhythmias
- metabolic acidosis, decreased Ca^{2+}, increased PO_4^{3-}, hypoalbuminemia

Investigations
- blood work: CBC, electrolytes, Cr, urea, Ca^{2+}, PO_4^{3-}, blood gases
- urine: R&M, electrolytes, osmolality, microscopic urinalysis searching for pigmented granular casts
- ECG
- abdominal U/S
- rule out other causes of prerenal/postrenal azotemia and intrinsic AKI (GN, AIN, vasculitis)

Treatment
- largely supportive once underlying problem is corrected
- loop diuretics may help manage volume overload and reduce tubular metabolic requirements to allow for recovery (controversial)
- consider early dialysis in severe/rapidly progressing cases to prevent uremic syndrome

Prevention
- correct fluid balance before surgical procedures
- for patients with chronic renal disease requiring radiographic contrast:
  - give N-acetylcysteine 600-1200 mg PO bid day before and day of procedure, give intravenous isotonic fluid (either NaCl or $NaHCO_3$)
  - isotonic $NaHCO_3$ at 3 mL/kg over 1 h before procedure and 1 mL/kg/h for 6 h post-procedure if not contraindicated
  - avoid giving diuretics, ACEI, cyclosporine on morning of procedure if possible
- use renal-adjusted doses of nephrotoxic drugs in patients with renal insufficiency

Meta-Analysis: Effectiveness of Drugs for Preventing Contrast-Induced Nephropathy
Ann Intern Med 2008;148:284-294
Purpose: To determine the effectiveness of N-acetylcysteine, theophylline, fenoldopam, dopamine, iloprost, statin, furosemide, or mannitol on preventing nephropathy.
Study Selection: RCTs that used these agents in patients receiving iodinated contrast.
Results: In the 41 RCTs included N-acetylcysteine (RR=0.62 [0.44-0.88]) and theophylline (RR=0.49 [0.23-1.06]) reduced the risk of nephropathy more than saline alone. Furosemide increased the risk (RR=3.27 [1.48-7.26]). Other agents did not affect risk of nephropathy.
Conclusion: N-acetylcysteine is more renoprotective than hydration alone.

Vascular Diseases of the Kidney

LARGE VESSEL DISEASE

Table 10. Summary of Vascular Diseases

Large Vessel Disease	Small Vessel Disease
Acute renal artery occlusion (infarct) Renal artery stenosis (ischemia) Renal vein thrombosis	Hypertensive nephrosclerosis Atheroembolic renal disease Thrombotic microangiopathy Scleroderma Calcineurin inhibitor nephropathy

1. RENAL INFARCTION (ACUTE RENAL ARTERY OCCLUSION)

- important, potentially reversible cause of renal failure

Etiology

- abdominal trauma, surgery, embolism, vasculitis, extra-renal compression, hypercoagulable state, aortic dissection
- kidney transplant recipients more vulnerable

Signs and Symptoms (depend on presence of collateral circulation)

- fever, N/V, flank pain
- leukocytosis, elevated AST, ALP
- marked elevated LDH (LDH >4x upper limit of normal with minimal elevations in AST/ALT strongly suggestive)
- acute onset HTN (activation of RAAS) or sudden worsening of long-standing HTN
- renal dysfunction, e.g. elevated Cr (if bilateral, or solitary functioning kidney)

Investigations

- renal arteriography (more reliable but risk of atheroembolic renal disease)
- contrast-enhanced CT or MR angiography, duplex Doppler studies (operator dependent)

Treatment

- prompt localization of occlusion and restoration of blood flow
- anticoagulation, thrombolysis, percutaneous angioplasty or clot extraction, surgical thrombectomy
- medical therapy in the long-term to reduce risk (e.g. antihypertensives)

2. ISCHEMIC RENAL DISEASE (RENAL ARTERY STENOSIS)

- chronic renal impairment secondary to hemodynamically significant renal artery stenosis or microvascular disease
- significant cause of ESRD: 15% in patients >50 yr (higher prevalence if significant vascular disease)
- usually associated with large vessel disease elsewhere
- causes of renal artery stenosis
  - atherosclerotic plaques (90%): proximal 1/3 renal artery, usually males >55 yr, smokers
  - fibromuscular dysplasia (10%): distal 2/3 renal artery or segmental branches, usually young females (typical onset <30 yr)
- when there is decreased RBF, GFR is dependent on angiotensin II-induced efferent arteriolar constriction which raises the FF (GFR/RBF)
- most common cause of secondary HTN ("renovascular HTN"), 1-2% of all hypertensive patients
  - etiology
    - decreased renal perfusion of one or both kidneys leads to increased renin release and subsequent angiotensin production
    - increased angiotensin raises blood pressure in two ways
      1. causes generalized arteriolar constriction
      2. release of aldosterone increases Na^+ and water retention
  - elevated blood pressure can in turn lead to further damage of kidneys and worsening HTN

Risk Factors

- >50 yr
- smoking
- other atherosclerotic disease (dyslipidemia, DM, diffuse atherosclerosis)

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation (ELITE-Symphony Trial)
NEJM 2007;257:2562-2575
Study: Multicentre, RCT with 12 mo follow-up.
Patients: 1,645 patients scheduled to receive a single organ kidney transplant.
Intervention: Mycophenolate mofetil, corticosteroids, and either: 1) standard dose cyclosporine; 2) low dose cyclosporine with daclizumab induction; 3) low dose tacrolimus with daclizumab induction; 4) low dose sirolimus with daclizumab induction.
Primary Outcome: Estimated Cockcroft-Gault GFR 12 mo after transplantation.
Results: The tacrolimus arm showed significantly higher eGFR at 12 mo compared to all other arms (65.4 mL/min vs. 57.1, 59.4, 56.7 for arms 1, 2, 4 respectively, $p \leq 0.001$). The tacrolimus arm also showed decreased rates of acute rejection at 6 mo and 12 mo vs. all arms ($p < 0.001$), improved allograft survival against standard dose cyclosporine and sirolimus, and decreased treatment failure against all other arms. There was no difference in overall patient survival between groups. Sirolimus had the highest incidence of lymphoceles, delayed wound healing, and serious adverse events; tacrolimus had significantly higher rates of new-onset DM; and cyclosporine regimes had the lowest incidence of diarrhea but highest opportunistic infection rates.
Conclusion: Immunosuppression regiments using low dose tacrolimus and daclizumab induction decrease nephrotoxicity while maintaining therapeutic immunosuppression in renal transplant patients.

Stenting and Medical Therapy for Atherosclerotic Renal Artery Stenosis
NEJM 2014;370:13-22
Study: Multicentre, unblinded RCT, median follow-up of 43 mo.
Patients: 947 patients with atherosclerotic renal-artery stenosis who also have significant systolic HTN or CKD.
Intervention: Percutaneous revascularization (stenting) with medical therapy (statins, ARB, calcium channel blockers, HCTZ and BP control) versus medical therapy alone.
Outcomes: Occurrence of adverse CV or renal event (composite of death from CV or renal cause, MI, stroke, hospitalization for CHF, progressive renal insufficiency, or need for renal replacement therapy) and all-cause mortality.
Results: No significant difference in primary composite end point between participants who received stenting or those on medical therapy alone. No significant differences between the treatment groups in the rates of the individual components of the primary end point or in all-cause mortality.
Conclusion: Renal artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal artery stenosis and HTN or CKD.

Signs and Symptoms
- severe/refractory HTN and/or hypertensive crises, with negative family history of HTN
- asymmetric renal size
- epigastric or flank bruits
- spontaneous hypokalemia (renin activation in under-perfused kidney)
- increasing Cr with ACEI/ARB
- flash pulmonary edema with normal LV function

Investigations
- must establish presence of renal artery stenosis and prove it is responsible for renal dysfunction
- duplex Doppler U/S (kidney size, blood flow): good screening test (operator dependent)
- digital subtraction angiography (risk of contrast nephropathy)
- CT or MR angiography (effective noninvasive tests to establish presence of stenosis, for MR avoid gadolinium contrast if eGFR <30 mL/min because of risk of systemic dermal fibrosis)
- ACEI renography (e.g. captopril renal scan)
- renal arteriography (gold standard)

Treatment
- surgical: percutaneous angioplasty ± stent, surgical revascularization, occasionally surgical bypass
- medical: BP lowering medications (ACEI is drug of choice if unilateral renal artery disease but contraindicated if bilateral renal artery disease)
- little or no benefit if therapy is late (e.g. kidney is already shrunken), however, therapy can be considered to save the opposite kidney if normal

3. RENAL VEIN THROMBOSIS

Etiology
- hypercoagulable states (e.g. nephrotic syndrome, especially membranous), ECF volume depletion, extrinsic compression of renal vein, significant trauma, malignancy (e.g. RCC), sickle cell disease
- clinical presentation determined by rapidity of occlusion and formation of collateral circulation

Signs and Symptoms
- acute: N/V, flank pain, hematuria, elevated plasma LDH, ± rise in Cr, sudden rise in proteinuria
- chronic: PE (typical first presenting symptom), increasing proteinuria and/or tubule dysfunction

Investigations
- renal venography (gold standard), CT or MR angiography, duplex Doppler U/S

Treatment
- thrombolytic therapy ± percutaneous thrombectomy for acute renal vein thrombosis
- anticoagulation with heparin then warfarin (1 yr or indefinitely, depending on risk factors)

SMALL VESSEL DISEASE

1. HYPERTENSIVE NEPHROSCLEROSIS
- see *Hypertension*, NP31

2. ATHEROEMBOLIC RENAL DISEASE
- progressive renal insufficiency due to embolic obstruction of small- and medium-sized renal vessels by atheromatous emboli
- spontaneous or after renal artery manipulation (surgery, angiography, percutaneous angioplasty)
- anticoagulants and thrombolytics interfere with ulcerated plaque healing and can worsen disease
- investigations
  - eosinophilia, eosinophiluria, and hypocomplementemia
  - renal biopsy: needle-shaped cholesterol clefts (due to tissue-processing artifacts) with surrounding tissue reaction in small-/medium-sized vessels
- treatment
  - no effective treatment; avoid angiographic and surgical procedures in patients with diffuse atherosclerosis, medical therapy for concomitant cardiovascular disease
- prognosis: poor overall, at least one third will develop ESRD

3. THROMBOTIC MICROANGIOPATHY

- see Hematology, H30
- etiologies include the spectrum of TTP-HUS, DIC, severe preeclampsia
- renal involvement more common in HUS than TTP
- renal involvement characterized by fibrin thrombi in glomerular capillary loops ± arterioles
- treatment
  - depends on cause
  - supportive therapy
  - TTP-HUS: plasma exchange, corticosteroids (splenectomy and rituximab if refractory)
- avoid platelet transfusions and ASA

4. CALCINEURIN INHIBITOR NEPHROPATHY

- cyclosporine and tacrolimus
- causes both acute reversible and chronic, largely irreversible nephrotoxicity
- major cause of kidney failure in other solid organ transplants (e.g. heart)
- acute: due to afferent and efferent glomerular capillary constriction leading to decreased GFR (tubular vacuolization)
  - prerenal azotemia
  - treatment: calcium channel blockers or prostaglandin analogs, reduce dose of cyclosporine or switch to another immunosuppressive drug
- chronic: result of obliterative arteriolopathy causing interstitial nephritis and CKD (striped fibrosis), less frequent now due to lower doses of calcineurin inhibitors

Analgesic Nephropathies

1. Vasomotor AKI

- clinically: develop prerenal azotemia within a few days of starting NSAID
- normally prostaglandins vasodilate afferent renal arteriole to maintain blood flow
- NSAIDs act by blocking cyclooxygenase enzyme, thereby preventing prostaglandin synthesis and causing renal ischemia
- more common in elderly, underlying renal disease, hypovolemia (diuretics, CHF, cirrhosis, nephrotic syndrome)
- treatment: discontinue NSAID, dialysis rarely needed

2. Acute Interstitial Nephritis

- fenoprofen (60%), ibuprofen, naproxen
- may be associated with minimal change glomerulopathy and nephrotic range proteinuria
- resolves eventually with discontinuation of NSAID, may require interval dialysis
- short-term high dose steroids (1 mg/kg/d of prednisone) may hasten recovery

3. Chronic Interstitial Nephritis

- due to excessive consumption of antipyretics (phenacetin or acetaminophen) in combination with NSAIDs
- seen in patients who also have emotional stress, psychiatric symptoms, and GI disturbance
- papillary necrosis
  - gross hematuria, flank pain, declining renal function
  - calyceal filling defect seen with IVP – "ring sign"
- increased risk of transitional cell carcinoma of renal pelvis
- good prognosis if discontinue analgesics

4. Acute Tubular Necrosis

- can be caused by acetaminophen
  - incidence of renal dysfunction is related to the severity of acetaminophen ingestion
- vascular endothelial damage can also occur
- both direct toxicity and ischemia contribute to the tubular damage
- renal function spontaneously returns to baseline within 1-4 wk
- dialysis may be required during the acute episode of ingestion

5. Other Effects of NSAIDs

- sodium retention (2° to reduced GFR)
- hyperkalemia, HTN (2° to hyporeninemic hypoaldosteronism)
- excess water retention (2° to loss of antagonistic effect of prostaglandins on ADH)

Systemic Disease with Renal Manifestation

Diabetes

- diabetic nephropathy: presence of microalbuminuria or overt nephropathy (e.g. macroalbuminuria) in patients with DM who lack indicators of other renal diseases
- most common cause of end-stage renal failure in North America
- 35-50% of patients with type 1 DM will develop nephropathy, unknown percentage of type 2
- at diagnosis up to 30% of patients with type 2 DM have albuminuria (75% microalbuminuria, 25% overt nephropathy)
- microalbuminuria is a risk factor for progression to overt nephropathy and cardiovascular disease
- once macroalbuminuria is established, renal function declines, 50% of patients reach ESRD within 7-10 yr
- associated with HTN and diabetic retinopathy (especially type 1 DM) and/or neuropathy (especially type 2 DM)
- indication of possible non-diabetic cause of renal disease in patients with DM
  - rising Cr with little/no proteinuria
  - lack of retinopathy or neuropathy (microvascular complications)
  - persistent hematuria (microscopic or macroscopic)
  - signs or symptoms of systemic disease
  - inappropriate time course; rapidly rising Cr, renal disease in a patient with short duration of DM
  - family history of non-diabetic renal disease (e.g. PCKD, Alport's)

DM is one of the causes of ESRD that does not result in small kidneys at presentation of ESRD; the others are amyloidosis, HIV nephropathy, PCKD, and multiple myeloma

Abnormal Urine ACR Values from 2008 Canadian DM Association CPG
>2.0 mg/mmol in males
>2.8 mg/mmol in females

ACEI can cause hyperkalemia; therefore, be sure to watch serum K^+, especially if patient has DM and renal insufficiency

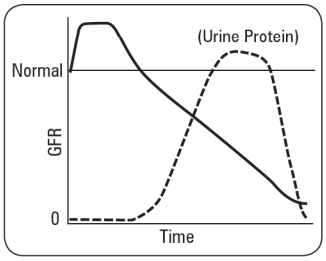


Figure 18. GFR and urine protein over time in DM

DIABETIC RENAL COMPLICATIONS

1. Progressive Glomerulosclerosis

- classic diabetic glomerular lesion: Kimmelstiel-Wilson nodular glomerulosclerosis (15-20%)
- more common lesion is diffuse glomerulosclerosis with a uniform increase in mesangial matrix

Table 11. Stages of Diabetic Progressive Glomerulosclerosis

Stage 1	Stage 2	Stage 3	Stage 4
• ↑ GFR (120-150%) – compensatory hyperfiltration • ± slightly increased mesangial matrix	• Detectable microalbuminuria (0-300 mg/24 h) • Albumin-Cr ratio (ACR) 2.0–20 mg/mmol in men (18-180 mg/d), • ACR 2.8-28 mg/mmol in women (25-250 mg/d) • ↑ mesangial matrix	• Macroalbuminuria (>300 mg/24 h) • ACR in men >20 mg/mmol, (>180 mg/d) • ACR in women >28 mg/mmol (>250 mg/d) • Proteinuria (positive urine dipstick) • Normal GFR • ↑↑↑ mesangial matrix	• ↑ proteinuria (>500 mg/24 h) • ↓ GFR • <20% glomerular filtration surface area present • Sclerosed glomeruli

2. Accelerated Atherosclerosis

- common finding
- decreased GFR
- may increase angiotensin II production resulting in increased BP
- increased risk of ATN secondary to contrast media

3. Autonomic Neuropathy

- affects bladder leading to functional obstruction and urinary retention
- residual urine promotes infection
- obstructive nephropathy

4. Papillary Necrosis

- type 1 DM susceptible to ischemic necrosis of medullary papillae
- sloughed papillae may obstruct ureter
- can present as renal colic or with obstructive features ± hydronephrosis

Protein Restriction for Diabetic Renal Disease
Cochrane DB Syst Rev 2007;4:CD002181
Purpose: To review the effects of dietary protein restriction on the progression of diabetic nephropathy.
Study Selection: RCTs and before and after studies of the effects of restricted protein diet on renal function in subjects with DM. 12 studies were reviewed.
Results: The risk of end-stage renal disease or death was lower in patients on low-protein diet. In patients with type 1 DM no effect on GFR was noted in the low-protein diet group.

Renoprotective Effect of Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 DM
NEJM 2001;345:851-860
Study: Multicentre, RCT, mean follow-up of 2.6 yr.
Patients: 806 patients (mean age 70 yr) with type 2 DM, HTN, and nephropathy (24 h proteinuria >900 mg, serum Cr 88-265 μmol/L [male], serum Cr 106-265 μmol/L [female]).
Intervention: BP control with irbesartan vs. amlodipine vs. placebo, with use of adjuncts (not including ACEIs, ARBs, or CCI) as needed.
Outcomes: Primary composite endpoint included doubling of serum Cr, ESRD, or death. Secondary composite endpoint included morbidity and mortality from CVD causes.
Results: BP control was similar in all three arms. Irbesartan had a relative risk reduction of 20% vs. placebo and 23% vs. amlodipine for the primary end point. The irbesartan group had a 33% risk reduction vs. placebo and 37% reduction vs. amlodipine for risk of doubling serum Cr. Serum Cr increased more slowly in the irbesartan group versus placebo or amlodipine. No difference in absolute mortality or secondary end point.
Conclusion: Irbesartan conferred significant renoprotective benefits in patients with type 2 DM and nephropathy, independent of blood pressure lowering effects.

2013 Canadian Diabetes Association Clinical Practice Guidelines on Chronic Kidney Disease in Diabetes

- screen for microalbuminuria with a random urine test for albumin to Cr ratio (ACR) and eGFR with a serum Cr (e.g. using MDRD equation)
  - type 1 DM: annually in post-pubertal individuals after 5 yr of diagnosis
  - type 2 DM: at diagnosis, then annually
  - If eGFR >60 mL/min or ACR <2.0 mg/mmol: there is no CKD, re-screen in 1 yr
  - If urine ACR >20.0 mg/mmol: diagnose CKD
  - If ACR <20.0 mg/mmol but >2.0 mg/mmol: order serum Cr for eGFR in 3 mo and 2 repeats of random urine ACRs over the next 3 mo; at 3 mo: if eGFR ≤60 ml/min or if >2/3 ACRs are >2.0 mg/mmol, diagnose CKD
  - if CKD diagnosed, ordered urine R+M and dipstick, if negative then diagnose CKD in DM
  - with CKD in DM: urine ACR and serum Cr (for eGFR) every 6 mo
  - delay screening if transient cause of albuminuria or low eGFR
- evaluate for other causes of proteinuria, rule out non-diabetic renal disease
- avoid unnecessary potential nephrotoxins (NSAIDs, aminoglycosides, dye studies)

Priorities in the Management of Patients with DM

1. vascular protection for all patients with DM
   - ACEI, antiplatelet therapy (as indicated)
   - BP control, glycemic control, lifestyle modification, lipid control
2. optimization of BP in patients who are hypertensive
   - treat according to HTN guidelines
3. renal protection for DM patients with nephropathy (even in absence of HTN)
   - type 1 DM: ACEI
   - type 2 DM: CrCl >60 mL/min: ACEI or ARB – CrCl <60 mL/min: ARB
   - 2nd line agents: nondihydropyridine calcium channel blockers (diltiazem, verapamil)
   - combination of ACEI and ARB not recommended for proteinuria
- check serum Cr and K^+ levels within 1 wk of initiating ACEI or ARB and at time of acute illness
- serum Cr can safely be allowed to rise up to 30% with initiation of ACEI or ARB, usually stabilizes after 2-4 wk, monitor for significant worsening of renal function or hyperkalemia
- if >30% rise in serum Cr or hyperkalemia, discontinue medication and consider 2nd line agent
- consider holding ACEI, ARB, and/or diuretic with acute illness and in women before becoming pregnant
- consider referral to nephrologist if ACR >60 mg/mmol, eGFR <30 mL/min, progressive kidney function loss, unable to achieve BP targets, or unable to stay on ACEI or ARB

Renal Outcomes with Telmisartan, Ramipril, or Both in People at High Vascular Risk (ONTARGET Study)
Lancet 2008;372:547-553
Study: Prospective, multicentre, double-blind, RCT.
Participants: 25,620 patients with median follow-up of 56 mo.
Intervention: Patients received either ramipril (10 mg/d; n=8,576), telmisartan (80 mg/d; n=8,542), or a combination of both drugs (n=8,502).
Primary Outcome: Composite of dialysis, doubling of creatinine level, and death.
Results: The number of outcome events was similar for telmisartan (n=1,147) and ramipril (1,150; HR 1.00, 95% CI 0.92-1.09), but was increased with combination therapy (1,233; HR 1.09, 1.01-1.18, p=0.037). The need for dialysis or doubling of serum creatinine, was similar with telmisartan (189) and ramipril (174; HR 1.09, 0.89-1.34) and more frequent with combination therapy (212; HR 1.24, 1.01-1.51, p=0.038). Estimated GFR declined least with ramipril compared with telmisartan or combination therapy (p<0.001). The increase in urinary albumin excretion was less with telmisartan (p=0.004) and combination therapy (p=0.001) than with ramipril.
Conclusion: Renal outcomes were similar in both telmisartan and ramipril monotherapy. Combination therapy reduced proteinuria to a greater extent than monotherapy, but was associated with poorer renal outcomes.

Scleroderma

- see Rheumatology, RH13
- 50% of scleroderma patients have renal involvement (mild proteinuria, high Cr, HTN)
- renal involvement usually occurs early in the course of illness
- histology: media thickened, "onion skin" hypertrophy of small renal arteries, fibrinoid necrosis of afferent arterioles and glomeruli
- 10-15% of scleroderma patients have a "scleroderma renal crisis" (occurs in first few years of disease): malignant HTN, ARF, microangiopathy, volume overload, visual changes, HTN encephalopathy
- treatment: BP control with ACEI slows progression of renal disease

Long-Term Outcomes of Scleroderma Renal Crisis
Ann Intern Med 2000;133:600-603
Study: Prospective observational cohort study with follow up of 5-10 yr.
Patients: 145 patients with scleroderma renal crisis who received ACEI and 662 patients with scleroderma who did not have renal crisis.
Primary Outcome: The need for dialysis and early death among patients with renal crisis.
Results: 61% of patients with renal crisis had good outcomes (55 had no dialysis and 34 received temporary dialysis); only 4 of these patients progressed to chronic renal failure and permanent dialysis. Greater than 50% of the patients who initially required dialysis discontinued it 3-18 mo later. Permanent dialysis or early death occurred in 39% of the patients.
Conclusion: Renal crisis can be managed when HTN is aggressively controlled with ACEI.

Multiple Myeloma

- see Hematology, H49
- malignant proliferation of plasma cells in the bone marrow with the production of immunoglobulins
- patients may present with severe bone disease and renal failure
- light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine (monoclonal light chains)
- kidney damage can occur by several mechanisms
  - hypercalcemia
  - light chain cast nephropathy or "myeloma kidney"
  - hyperuricemia
  - infection
  - secondary amyloidosis
  - monoclonal Ig deposition disease
  - diffuse tubular obstruction
- light chain cast nephropathy
  - large tubular casts in urine sediment (light chains + Tamm-Horsfall protein)
  - proteinuria and renal insufficiency, can progress rapidly to kidney failure

Features of Multiple Myeloma

CARLI
Calcium (elevated)
Anemia
Renal Failure
Lytic Bone Lesions
Infections

- monoclonal Ig deposition disease
  - deposits of monoclonal Ig in kidney, liver, heart, and other organs
  - mostly light chains (85-90%)
  - causes nodular glomerulosclerosis (similar to diabetic nephropathy)
- lab features: increased BUN, increased Cr, urine protein immunoelectrophoresis positive for Bence-Jones protein (not detected on urine dipstick)
- poor candidates for kidney transplantation

Malignancy

- cancer can have many different renal manifestations
- kidney transplantation cannot be performed unless malignancy is cured
  - solid tumours: mild proteinuria or membranous GN
  - lymphoma: minimal change GN (Hodgkin's) or membranous GN (non-Hodgkin's)
  - renal cell carcinoma
  - tumour lysis syndrome: hyperuricemia, diffuse tubular obstruction
  - chemotherapy (especially cisplatin): ATN or chronic TIN
  - pelvic tumours/mets: postrenal failure secondary to obstruction
  - 2° amyloidosis
  - radiotherapy (radiation nephritis)

Chronic Kidney Disease

Definition

- progressive and irreversible loss of kidney function
- abnormal markers (Cr, urea)
  - GFR <60 mL/min for >3 mo; or
  - kidney pathology seen on biopsy; or
  - decreased renal size on U/S (kidneys <9 cm)

Clinical Features

- volume overload and HTN
- electrolyte and acid-base balance disorders (e.g. metabolic acidosis)
- uremia

Table 12. Stages of CKD (KDIGO, 2013)

			Persistent Albuminuria Categories		
		GFR (mL/min/1.73m^2)	A1 <30 mg/g <3 mg/mmol	A2 30-300 mg/g 3-30 mg/mmol	A3 >300 mg/g >30 mg/mmol
GFR Categories (mL/min/1.73m^2)	G1	≥90	1 if CKD	1	2
	G2	60-89	1 if CKD	1	2
	G3a	45-59	1	2	3
	G3b	30-44	2	3	3
	G4	15-29	3	3	4+
	G5	<15 (kidney failure)	4+	4+	4+

The numbers in the boxes are a reflection of the risk of progression and are a guide to the frequency of monitoring/year
"D" is added to G5 for patients requiring dialysis
Classification is based on cause, GFR, and amount of albuminuria
Rate of progression and risk of complications are determined by the cause of CKD

Incidence of Etiologies of CKD

DM	42.9%
HTN	26.4%
Glomerulonephritis	9.9%
Other/Unknown	7.7%
Interstitial nephritis/ Pyelonephritis	4.0%
Cystic/Hereditary/Congenital	3.1%
Secondary GN/Vasculitis	2.4%

Management of Complications of CKD

NEPHRON

N – Low-**n**itrogen diet
E – **E**lectrolytes: monitor K^+
P – **p**H: metabolic acidosis
H – **H**TN
R – **R**BCs: manage anemia with erythropoietin
O – **O**steodystrophy: give calcium between meals (to increase Ca^{2+}) and calcium with meals (to bind and decrease PO_4^{3-})
N – **N**ephrotoxins: avoid nephrotoxic drugs (ASA, gentamicin) and adjust doses of renally excreted medications

Renin Angiotensin System Blockade and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Proteinuria: A Meta-Analysis
Am Heart J 2008;155:791-805
Purpose: To evaluate the role of RAS blockade in improving cardiovascular CV outcomes in patients with CKD.
Study Selection: RCT that analyzed CV outcomes in patients with CKD/proteinuria treated with RAS blockade (ACEI/ARB). RAS blockade-based therapy was compared with placebo and control therapy (β-blocker, calcium-channel blockers, and other antihypertensive-based therapy) in the study.
Results: Twenty-five trials (n=45,758) were included. Compared to placebo, RAS blockade reduced the risk of heart failure in patients with diabetic nephropathy. In patients with non-diabetic CKD, RAS blockade decreased CV outcome compared to control therapy.
Conclusions: RAS blockade reduced CV outcomes in diabetic nephropathy as well as non-diabetic CKD.

Management of Chronic Kidney Disease

- diet
  - preventing HTN and volume overload
    - Na+ and water restriction
  - preventing electrolyte imbalances
    - K+ restriction (40 mmol/d)
    - PO_4^{3-} restriction (1 g/d)
    - avoid extra-dietary Mg^{2+} (e.g. antacids)
  - preventing uremia and potentially delaying decline in GFR
    - protein restriction with adequate caloric intake in order to limit endogenous protein catabolism

- medical
  - adjust dosages of renally excreted medications
  - HTN: ACEI (target 130/80 or less), loop diuretics when GFR <25 mL/min
  - dyslipidemia: statins
  - calcium and phosphate disorders
    - calcium supplements (e.g. TUMS®) treats hypocalcemia when given between meals and binds phosphate when given with meals
    - consider calcitriol (1,25-dihydroxy-vitamin D) if hypocalcemic
    - sevelamer (phosphate binder) if both hypercalcemic and hyperphosphatemic
    - vitamin D analogues are being introduced in the near future
    - cinacalcet for hyperparathyroidism (sensitizes parathyroid to Ca^{2+}, decreasing PTH)
  - metabolic acidosis: sodium bicarbonate
  - anemia: erythropoietin injections (hematocrit <30%); target hematocrit 33-36%
  - clotting abnormalities: DDAVP if patient has clinical bleeding or invasive procedures (acts to reverse platelet dysfunction)
- dialysis (hemodialysis, peritoneal dialysis)
- renal transplantation

Prevention of Progression

- as above
- control of HTN, DM, cardiovascular risk factors (e.g. smoking cessation)
- avoid nephrotoxins
- address reversible causes of AKI

Effects of Lowering LDL Cholesterol with Simvastatin and Ezetimibe in Patients with Chronic Kidney Disease
Lancet 2011;377:2181-2192
Purpose: To assess the efficacy and safety of the combination of simvastatin and ezetimibe in patients with moderate to severe CKD.
Study: Randomized, double-blind trial with 9,270 patients with CKD with no known history of myocardial infarction or coronary vascularization. Patients were randomized to simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo.
Primary Outcome: First major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure).
Results: The simvastatin plus ezetimibe group was associated with an average LDL cholesterol difference of 0.85 mmol/L during a median follow-up of 4.9 yr. There was a 17% proportional reduction in major atherosclerotic events in the simvastatin plus ezetimibe group compared to placebo.
Conclusions: Reducing LDL cholesterol with a treatment regimen of simvastatin plus ezetimibe safely reduced the incidence of major atherosclerotic events in patients with moderate to severe CKD.

Hypertension

- see Family Medicine, FM35
- HTN occurs in about 20% of population
- etiology classified as primary ("essential"; makes up 90% of cases) or secondary
- primary HTN can cause kidney disease (hypertensive nephrosclerosis), which may in turn exacerbate the HTN
- secondary HTN can be caused by renal parenchymal or renal vascular disease

Hypertensive Nephrosclerosis

Table 13. Chronic vs. Malignant Nephrosclerosis

	Chronic Nephrosclerosis	Malignant Nephrosclerosis
Histology	Slow vascular sclerosis with ischemic changes affecting intralobular and afferent arterioles	Fibrinoid necrosis of arterioles, disruption of vascular endothelium
Clinical Picture	Black race, underlying CKD, chronic hypertensive disease	Acute elevation in BP (dBP >120 mmHg) HTN encephalopathy
Urinalysis	Mild proteinuria, normal urine sediment	Proteinuria and hematuria (RBC casts)
Therapy	Blood pressure control, (target <140/90) with frequent follow-up	Lower dBP to 100-110 mmHg within 6-24 h More aggressive treatment can cause ischemic event Identify and treat underlying cause of HTN
Prognosis	Can progress to renal failure despite patient adherence	Lower survival if renal insufficiency develops

Renovascular Hypertension

- see *Vascular Diseases of the Kidney*, NP27

Renal Parenchymal Hypertension

- HTN secondary to GN, AIN, diabetic nephropathy, or any other chronic renal disease
- mechanism of HTN not fully understood but may include
  - excess RAAS activation due to inflammation and fibrosis in multiple small intra-renal vessels
  - production of unknown vasopressors, lack of production of unknown vasodilators, or lack of clearance of endogenous vasopressor
  - ineffective sodium excretion with fluid overload

Investigations
- as well as investigations for renovascular HTN, additional tests may include
  - 24 h urinary estimations of CrCl and protein excretion
  - imaging (U/S, CT)
  - serology for collagen-vascular disease
  - renal biopsy

Treatment
- most chronic renal disease is irreversible, but treatment of HTN can slow the progression of renal insufficiency
- control ECF volume: Na^+ restriction (2g/d intake), diuretic, dialysis with end-stage disease
- ACEI or ARB may provide added benefit (monitor K^+ and Cr) if there is significant proteinuria (>300 mg/d)

Cystic Diseases of the Kidney

- characterized by epithelium-lined cavities filled with fluid or semisolid debris within the kidneys
- includes: simple cysts (present in 50% of population >50), medullary cystic kidney, medullary sponge kidney, polycystic kidney disease (autosomal dominant and recessive), and acquired cystic kidney disease (in chronic hemodialysis patients)

Adult Polycystic Kidney Disease

- autosomal dominant; at least 2 genes: *PKD1* (chr 16p) and *PKD2* (chr 4q)
- *PKD1* (1:400), *PKD2* (1:1,000) accounts for about 10% of cases of renal failure
- patients generally heterozygous for mutant polycystin gene but accumulate a series of second 'somatic hits' precipitating the condition
- *PKD1* encodes a protein that is responsible for cell-cell and cell-matrix interaction and sensing fluid flow by associating with cilia
- *PKD2* encodes a protein that is a Ca^{2+} permeable nonselective cation channel that associates with cilia and is thought to control intracellular Ca^{2+} in response to flow
- defect leads to abnormal proliferation and apoptosis of tubular epithelial cells leading to cyst growth
- most common extrarenal manifestations: multiple asymptomatic hepatic cysts (33%), mitral valve prolapse (25%), cerebral aneurysm (10%), diverticulosis
- polycystic liver disease rarely causes liver failure
- less common extrarenal manifestations: cysts in pancreas, spleen, thyroid, ovary, seminal vesicles, and aorta

Hypercalcemia complicates many cancers and can cause multiple kinds of renal disorders (renal vasoconstriction with reduced GFR, salt-wasting with volume depletion, risk of calcium kidney stones)

External Manifestations of PCKD
- Hepatic cysts
- Mitral valve prolapse
- Cerebral aneurysms
- Diverticulosis

Signs and Symptoms
- often asymptomatic; discovered incidentally on imaging or by screening those with FHx
- acute abdominal flank pain/dull lumbar back pain
- hematuria (microscopic frequently initial sign, gross)
- nocturia (urinary concentrating defect)
- rarely extra-renal presentation (e.g. ruptured berry aneurysm, diverticulitis)
- HTN (increased renin due to focal compression of intrarenal arteries by cysts) (60-75%)
- ± palpable kidneys

Common Complications
- urinary tract and cyst infections, HTN, chronic renal failure, nephrolithiasis (5-15%), flank and chronic back pain

Clinical Course
- polycystic changes are always bilateral and can present at any age
- clinical manifestations rare before age 20-25
- kidneys are normal at birth but may enlarge to 10x normal size
- variable progression to renal functional impairment (ESRD in up to 50% by age 60)

Investigations
- radiographic diagnosis: best accomplished by renal U/S (enlarged kidneys, multiple cysts throughout renal parenchyma, increased cortical thickness, splaying of renal calyces)
- CT abdo with contrast (for equivocal cases, occasionally reveals more cystic involvement)
- gene linkage analysis for *PKD1* for asymptomatic carriers
- Cr, BUN, urine R&M (to assess for hematuria)

Treatment
- goal: to preserve renal function by prevention and treatment of complications
- educate patient and family about disease, its manifestations, and inheritance pattern
- genetic counselling: transmission rate 50% from affected parent
- prevention and early treatment of urinary tract and cyst infections (avoid instrumentation of GU tract)
- TMP/SMX, ciprofloxacin: able to penetrate cyst walls, achieve therapeutic levels
- adequate hydration to prevent stone formation
- avoid contact sports due to greater risk of injury to enlarged kidneys
- screen for cerebral aneurysms if family history of aneurysmal hemorrhages
- monitor blood pressure and treat HTN with ACEI
- dialysis or transplant for ESRD (disease does not recur in transplanted kidney)
- may require nephrectomy to create room for renal transplant

Medullary Sponge Kidney
- common, autosomal dominant, usually diagnosed in 4^{th}-5^{th} decades
- multiple cystic dilatations in the collecting ducts of the medulla
- renal stones, hematuria, and recurrent UTIs are common features
- an estimated 10% of patients who present with renal stones have medullary sponge kidney
- nephrocalcinosis on abdominal x-ray in 50% patients, often detect asymptomatic patients incidentally
- diagnosis: contrast filled medullary cysts on IVP leading to characteristic radial pattern ("bouquet of flowers"), "Swiss cheese" appearance on histological cross-section
- treat UTIs and stone formation as indicated
- does not result in renal failure

Autosomal Recessive Polycystic Kidney Disease
- 1:20,000 incidence
- prenatal diagnosis by enlarged kidneys
- perinatal death from respiratory failure
- patients who survive perinatal period develop CHF, HTN, CKD
- treated with kidney and/or liver transplant

End Stage Renal Disease
- ESRD represents a decline in kidney function requiring renal replacement therapy which can occur over days to weeks (AKI), over months to years (CKD), or as a combination of the two

Presentation of End Stage Renal Disease

1. Volume Overload
- due to increase in total body Na^+ content
- signs: weight gain, HTN, pulmonary or peripheral edema

2. Electrolyte Abnormalities
- high
  - K^+ (decreased renal excretion, increased tissue breakdown)
  - PO_4^{3-} (decreased renal excretion, increased tissue breakdown)
  - Ca^{2+} (rare; happens during recovery phase after rhabdomyolysis-induced AKI or in settings where hypercalcemia contributes to renal failure, such as in multiple myeloma or sarcoidosis)
  - uric acid
- low
  - Na^+ (failure to excrete excessive water intake)
  - Ca^{2+} (decreased Vitamin D activation, hyperphosphatemia, hypoalbuminemia)
  - HCO_3^- (especially with sepsis or severe heart failure)

3. Uremic Syndrome
- manifestations result from retention of urea and other metabolites as well as hormone deficiencies

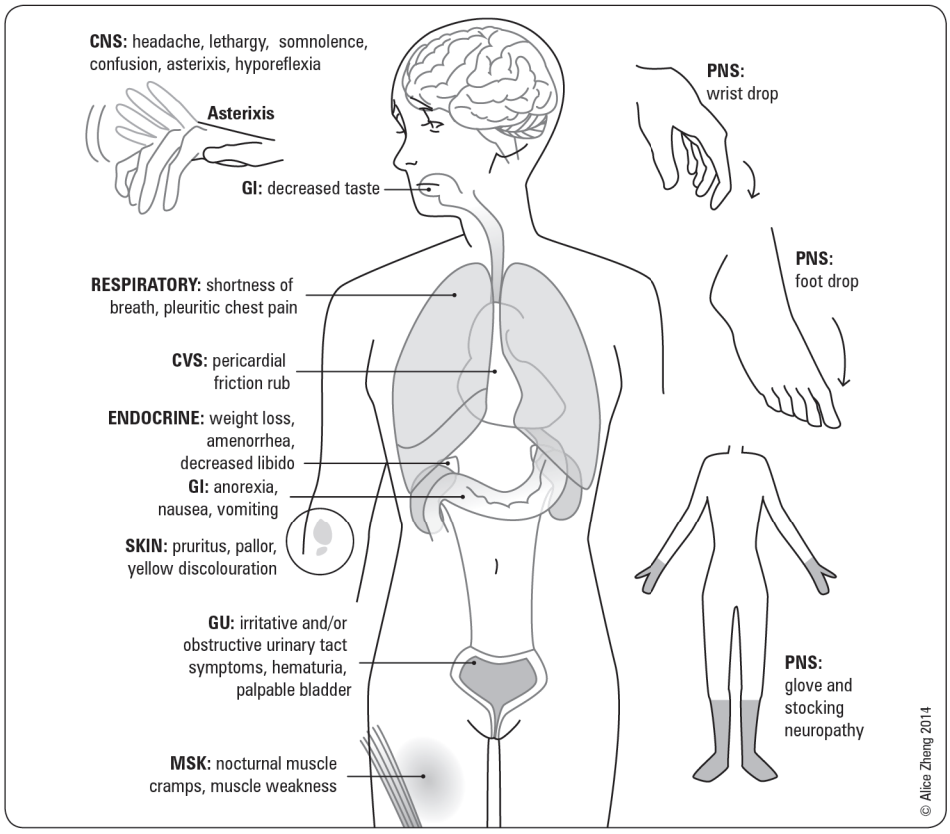


Figure 19. Signs and symptoms of end stage renal disease

Complications

- CNS: decreased LOC, stupor, seizure
- CVS: cardiomyopathy, CHF, arrhythmia, pericarditis, atherosclerosis
- GI: peptic ulcer disease, gastroduodenitis, AVM
- hematologic: anemia, bleeding tendency (platelet dysfunction), infections
- endocrine
  - decreased testosterone, estrogen, progesterone
  - increased FSH, LH
- metabolic
  - renal osteodystrophy: secondary increased PTH due to decreased Ca^{2+}, high PO_4^{3-}, and low active vitamin D
    - osteitis fibrosa cystica
  - hypertriglyceridemia, accelerated atherogenesis
  - decreased insulin requirements, increased insulin resistance
- dermatologic: pruritus, ecchymosis, hematoma, calciphylaxis (vascular Ca^{2+} deposition)

Renal Replacement Therapy

Dialysis

Indications for Dialysis in Chronic Kidney Disease

Table 14. Indications for Dialysis

Absolute Indications	Relative Indications
• Volume overload* • Hyperkalemia* • Severe metabolic acidosis* • Neurologic signs or symptoms of uremia (encephalopathy, neuropathy, seizures) • Uremic pericarditis • Refractory accelerated HTN • Clinically significant bleeding diathesis • Persistent severe N/V • Plasma Cr >1060 μmol/L or Urea >36 mmol/L (clinical picture also important)	• Anorexia • Decreased cognitive functioning • Profound fatigue and weakness • Severe anemia unresponsive to erythropoietin • Persistent severe pruritus • Restless leg syndrome

*Unresponsive to medications

- **hemodialysis:** blood is filtered across a semipermeable membrane removing accumulated toxic waste products, solutes, excess fluid (ultrafiltration), and restoring buffering agents to the bloodstream
  - available as intermittent (e.g. 3x/wk), continuous (CVVHD) or sustained low efficiency (SLED)
  - can be delivered at home or in-centre, nocturnal
  - vascular access can be achieved through a central line, an artificial graft, or an AV fistula
- patients with CKD should be referred for surgery to attempt construction of a primary AV fistula when their eGFR is <20 mL/min, the serum Cr level quoted as >350 μmol/L, or within 1 yr of an anticipated need
- **peritoneal dialysis:** peritoneum acts as a semipermeable membrane similar to hemodialysis filter
  - advantages: independence, fewer stringent dietary restrictions, better rehabilitation rates
  - available as continuous ambulatory (CAPD; four exchanges per day) or cyclic (CCPD; machine carries out exchanges overnight)
- refer patients with chronic renal disease to a nephrologist early on to facilitate treatment and plan in advance for renal replacement therapy (RRT)

Table 15. Peritoneal Dialysis vs. Hemodialysis

	Peritoneal Dialysis	Hemodialysis
Rate	Slow	Fast
Location	Home	Hospital (usually)
Ultrafiltration	Osmotic pressure via dextrose dialysate	Hydrostatic pressure
Solute Removal	Concentration gradient and convection	Concentration gradient and convection
Membrane	Peritoneum	Semi-permeable artificial membrane
Method	Indwelling catheter in peritoneal cavity	Line from vessel to artificial kidney
Complications	Infection at catheter site Bacterial peritonitis Metabolic effects of glucose Difficult to achieve adequate clearance in patients with large body mass	Vascular access (clots, collapse) Bacteremia Bleeding due to heparin Hemodynamic stress of extracorporeal circuit Disequilibrium syndrome (headache, cerebral edema, hypotension, nausea, muscle cramps related to solute/water flux over short time)
Preferred When	Young, high functioning, residual renal function Success depends on presence of residual renal function	Bed-bound, comorbidities, no renal function Residual renal function not as important

How to Write Dialysis Orders (MUST BE INDIVIDUALIZED)

- Filter Type (e.g. F80)
- Length (e.g. 4 h 3x/wk or 2 h daily)
- Q Blood Flow (max 500 cc/min)
- Ultrafiltration (e.g. 2 L or to target dry weight)
- Na^+ 140 (can be adjusted by starting at 155 and "ramping" down to minimize cramping)
- K^+ (based on serum K^+)

Serum K^+	Dialysate
4-6	1.5
3.5-4	2.5
<3.5	3.5

- Ca^{2+} 1.25
- HCO_3^- 40
- Heparin (none, tight [500 U/h] or full [1000 U/h])
- IV fluid to support BP (e.g. NS)

When to Initiate Dialysis

CrCl <20 mL/min
- Educate patient regarding dialysis; if not a candidate for peritoneal dialysis, make arrangements for AV fistula

CrCl <15 mL/min
- Weigh risk and benefits for initiating dialysis

CrCl <10 mL/min
- Dialysis should be initiated

NOTE
- Cockcroft-Gault equation (or MDRD equation) should be used to measure kidney function
- Monitor for uremic complications
- Significant benefits in quality of life can occur if dialysis started before CrCl <15 mL/min
- It is unclear whether patients who start dialysis early have increased survival
- A preemptive transplant can be considered if patient is stable, in order to avoid dialysis

Source: National Kidney Foundation Kidney Disease Outcomes Quality Initiative

Commonly Used Immunosuppressive Drugs

Calcineurin inhibitors
- Cyclosporine
- Tacrolimus

Antiproliferative medications
- Mycophenolate mofetil
- Azathioprine

Other agents
- Sirolimus
- Prednisone

Anti-lymphocyte antibodies
- Thymoglobulin
- Basiliximab

Renal Transplantation

- provides maximum replacement of GFR
- preferred modality of RRT in CKD, not AKI
  - best way to reverse uremic signs and symptoms
  - only therapy shown to improve survival in CKD patients with ESRD
- native kidneys usually left *in situ*
- 2 types: deceased donor, living donor (related or unrelated)
- kidney transplanted into iliac fossa, transplant renal artery anastomosed to external iliac artery of recipient
- 1 yr renal allograft survival rates ≥90%

Complications

- acute rejection: graft site tenderness, rise in Cr, oliguria, ± fever, although symptoms are uncommon
- leading causes of late allograft loss: interstitial fibrosis/tubular atrophy (IFTA) and death with functioning graft
- #1 cause of mortality in transplanted patients is cardiovascular disease
- immunosuppressant drug therapy: side effects include infections, malignancy (skin, Kaposi's sarcoma, post-transplant lymphoproliferative disorder)
- *de novo* GN (usually membranous)
- new-onset DM (often due to prednisone use)
- cyclosporine or tacrolimus nephropathy (see *Small Vessel Disease*, NP18)
- chronic allograft nephropathy
  - early allograft damage caused by episodes of acute rejection and acute peritransplant injuries
  - immunologic and nonimmunologic factors (HTN, hyperlipidemia, age of donor, quality of graft, new onset DM)
  - transplant glomerulopathy from antibody injury causes nephrotic proteinuria
- CMV (cytomegalovirus) infection and other opportunistic infections usually occur between 1 and 6 mo post-transplant
- BK virus (polyoma virus) nephropathy can result from over-immunosuppression and lead to graft loss

Common Medications

Table 16. Common Medications in Nephrology

Classification	Examples	Site of Action	Mechanism of Action (Secondary Effect)	Indication	Dosing	Adverse Effects
Loop Diuretics	furosemide (Lasix®) bumetanide (Bumex®/Buinex®) ethacrynate (Edecrin®) torsemide (Demadex®)	Thick ascending limb of Loop of Henle	↓ $Na^+/K^+/2Cl^-$ transport ± renal and peripheral vasodilatory effects (K^+ loss; ↑ H^+ secretion; ↑ Ca^{2+} excretion)	Management of edema secondary to CHF, nephrotic syndrome, cirrhotic ascites; ↑free water clearance (e.g. in SIADH-induced hyponatremia), ↓ BP (less effective due to short action)	furosemide: edema: 20-80 mg IV/IM/PO q6-8h (max 600 mg/d) until desired response HTN: 20-80 mg/d PO OD/bid dosing	Allergy in sulfa-sensitive individuals Electrolyte abnormalities; hypokalemia, hyponatremia, hypocalcemia, hypercalciuria (with stone formation) Volume depletion with metabolic alkalosis Precipitates gouty attacks
Thiazide Diuretics	hydrochlorothiazide (HCTZ) chlorothiazide (Diuril®) indapamide (Lozol®, Lozide®) metolazone (Zaroxolyn®) chlorthalidone (Hygroton®)	Distal convoluted tubule	Inhibit Na^+/Cl^- transporter (K^+ loss; ↑ H^+ secretion; ↓ Ca^{2+} excretion)	1st line for essential HTN Treatment of edema Idiopathic hypercalciuria and stones Diabetes insipidus (nephrogenic)	HCTZ: edema: 25-100 mg PO OD HTN: 12.5-25 mg PO OD (max 50 mg/d) nephrolithiasis/hypercalciuria: 25-100 mg OD	Hypokalemia Increased serum urate levels Precipitates gouty attacks, hypercalcemia Elevated lipids Glucose intolerance
Potassium-Sparing Diuretics	spironolactone (Aldactone®) triamterene (Dyrenium®) amiloride (Midamor®)	Cortical collecting duct (↓ Na^+ reabsorption)	Aldosterone antagonist (spironolactone) Block Na^+ channels (triamterene and amiloride)	Reduces K^+ loss caused by other diuretics Edema/hypervolemia Severe CHF, ascites (spironolactone), cystic fibrosis (amiloride↓ viscosity of secretions)	spironolactone: 25-200 mg/d OD/bid dosing HTN: 50-200 mg/d OD/bid dosing Hyperaldosteronism: 100-400 mg/d OD/bid dosing amiloride: edema/HTN: 5-10 mg PO OD	Hyperkalemia (caution with ACEI) Triamterene can be nephrotoxic (rare) Nephrolithiasis Gynecomastia (estrogenic effect of spironolactone)
Combination Agents	Dyazide® (triamterene + HCTZ) Aldactazide® (spironolactone + HCTZ) Moduretic® (amiloride + HCTZ) Vaseretic® (enalapril + HCTZ) Zestoretic® (lisinopril + HCTZ)		Combination of ACEI and thiazide have a synergistic effect	Combine K^+-sparing drug with thiazide to reduce hypokalemia		
Osmotic Diuretics	mannitol (Osmitrol®) glycerol urea	Renal tubules (proximal and collecting duct)	Non-reabsorbable solutes increase osmotic pressure of glomerular filtrate – inhibits reabsorption of water and ↑urinary excretion of toxic materials	To↓ intracranial or intraoccular pressure Mobilization of excess fluid in renal failure or edematous states	mannitol: ↓ ICP: 0.25-2 g/kg IV over 30-60 min	Transient volume expansion Electrolyte abnormalities (↓/↑ Na^+, ↓/↑ K^+)
ACEI	ramipril (Altace®) enalapril (Vasotec®) lisinopril (Prinivil®) trandolapril (Mavik®) captopril (Capoten®)	Lungs Tissues diffusely	Inhibits angiotension converting enzyme, preventing formation of angiotensin II Prevents angiotensin II vasoconstricting vascular smooth muscle → net vasodilation →↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↑ Na^+ and H_2O excretion →↓ BP Reduces fibrosis and atherogenesis	HTN Cardioprotective effects (see Cardiology and Cardiac Surgery, C31,C38) Renoprotective effects	ramipril: HTN: 2.5-20 mg PO OD/bid dosing renoprotective use; 10 mg PO OD trandolapril: HTN; 1-4 mg PO OD	Cough Asthma Hyperkalemia Angioedema Agranulocytosis (captopril) AKI Teratogenic
ARB	losartan (Cozaar®) candesartan (Atacand®) irbesartan (Avapro®) valsartan (Diovan®) telmisartan (Micardis®) eprosartan (Teveten®) olmesartan (Olmetec®)	Vascular smooth muscle, adrenal cortex, proximal tubules	Competitive inhibitor at the angiotensin II receptor: prevents angiotensin II vasoconstricting action on vascular smooth muscle →↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↑ Na^+ and H_2O excretion	HTN Cardioprotective effects (see Cardiology and Cardiac Surgery, C31,C38) Renoprotective effects	HTN: losartan 25-100 mg PO OD candesartan 8-32 mg PO OD irbesartan 150-300 mg PO OD valsartan 80-320 mg PO OD telmisartan 20-80 mg PO OD eprosartan 400-800 mg PO OD olmesartan 20-40 mg PO OD	Hyperkalemia Caution – reduce dose in hepatic impairment AKI Teratogenic
Renin Antagonists	aliskiren (Rasilez®)	Direct renin antagonist	Inhibits renin production and activity Cardioprotective and renoprotective abilities being evaluated	HTN	aliskiren 150-300 mg PO OD	Hyperkalemia

Landmark Nephrology Trials

Trial	Reference	Results
4D	*NEJM* 2005; 353:238-48	Patients with type 2 DM receiving maintenance hemodialysis were randomized to 20 mg of atorvastatin per day or matching placebo; no difference in composite index of death from cardiac causes, nonfatal myocardial infarction, and stroke
AASK	*JAMA* 2001; 285:2719-28	Ramipril, compared with amlodipine, slows progression of hypertensive renal disease and proteinuria and may benefit patients without proteinuria as well
ACCOMPLISH	*NEJM* 2008; 359:2417-20	Combination treatment with an ACEI and a CCB (benazepril-amlodipine) was more successful than a combination of ACEI and a thiazide diuretic (benzapril-HCTZ) in reducing cardiovascular events in patients with HTN who were at risk for such events
ACEI and Diabetic	*NEJM* 1993; 329:1456-62	Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood pressure control alone
ALERT	*Lancet* 2003; 361:2024-31	The use of fluvastatin in renal transplant recipients did not significantly decrease the risk of the occurrence of a major adverse cardiac event (defined as cardiac death, non-fatal MI, or coronary intervention procedure) compared with placebo; however, there was a significant reduction in cardiac deaths or non-fatal MI
ALTITUDE	Early Termination (Unpublished Results; protocol – *NDT* 2009; 24:1663-71)	Combining Aliskiren with ACEI or ARB in high-risk patients with type 2 DM leads to increased incidence of nonfatal stroke, hyperkalemia, and hypotension
ASTRAL	*NEJM* 2009; 361:1953-62	Renal artery revascularization compared to medical therapy does not improve renal function, BP, renal or cardiovascular events, or mortality, and carries significant operative risks
AURORA	*NEJM* 2009; 360:1395-407	Patients receiving maintenance hemodialysis randomized to rosuvastatin 10 mg daily or placebo; rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
BENEDICT	*NEJM* 2004; 351:1941-51	Treatment with ACEI trandolapril alone or trandolapril combined with verapamil decreased the incidence of microalbuminuria in patients with type 2 DM and HTN with normoalbuminuria
CHOIR	*NEJM* 2006; 355:2085-98	Patients with CKD were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 135 g/L or 113 g/L; the higher target group had an increased risk of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy), or stroke
CORAL	*NEJM* 2014; 370:13-22	Renal-artery stenting did not confer a significant benefit with respect to the prevention of renal or cardiac events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease
CREATE	*NEJM* 2006; 355:2071-84	Patients with CKD (15-35 mL/min) and mild to moderate anemia (110-125 g/L) were randomized to normal (130-150 g/L) or sub-normal (105-115 g/L) hemoglobin levels; early and complete correction of hemoglobin did not reduce the risk of cardiovascular events
DETAIL	*NEJM* 2004; 351:1952-61	The ARB telmisartan and the ACEI enalapril are equally effective in slowing renal function deterioration in type 2 DM with mild to moderate HTN and early nephropathy
ELITE-SYMPHONY	*NEJM* 2007; 357:2562-75	Daclizumab induction, MMF, steroids, and low-dose tacrolimus effectively maintain stable renal function following renal transplantation, without the negative effects on renal function commonly reported for standard CNI regimens
FHN	*NEJM* 2010;363:2287-300	Patients were randomized to dialysis 6x/wk (frequent) or 3x/wk (conventional); frequent hemodialysis was associated with improvement in composite outcomes of death, or change in left ventricular mass and death, or change in a physical-health composite score; frequent hemodialysis caused more frequent interventions related to vascular access
HEMO	*NEJM* 2002; 347:2010-19	Use of high dose dialysis or high flux membranes versus standard dose or low flux in thrice-weekly dialysis does not improve survival or outcomes; possible benefit in cardiac-related outcomes with high flux membranes
IDEAL	*NEJM* 2010; 363:609-19	Patients with progressive CKD and GFR between 10 and 15 mL/min randomized to initiate dialysis at GFR of 10-14 mL/min (early) or 5-7 mL/min (late); early initiation of dialysis in patients with stage G5 CKD was not associated with an improvement in survival or clinical outcomes
IDNT	*NEJM* 2001; 345:851-60	Treatment with irbesartan reduced the risk of developing end-stage renal disease and worsening renal function in patients with type 2 DM and diabetic nephropathy
IRMA	*NEJM* 2001; 345:870-8	Irbesartan is renoprotective independently of its blood pressure lowering effect in patients with type 2 DM and microalbuminuria
MDRD	*Ann Intern Med* 1995; 123:754-62	Patients with proteinuria of more than 1 g/d should have a target BP <125/75 mmHg; patients with proteinuria of 0.25 to 1.0 g/d should have a target BP <130/80 mmHg
ONTARGET	*Lancet* 2008; 372:547-53	Telmisartan and ramipril monotherapy reduced proteinuria and rise in Cr in patients with high vascular risk; combination of the two agents led to increased acute renal failure episodes, syncope, and hypotension
REIN	*Lancet* 1999; 354:359-64	In non-diabetic nephropathy, ACEI were renoprotective in patients with non-nephrotic range proteinuria
REIN2	*Lancet* 2005; 365:939-46	In non-diabetic nephropathy already on ACEI, no further benefit from intensified BP control (sBP/dBP<130/80 mmHg) by adding a CCB versus conventional BP control (dBP<90 mmHg) on ACEI alone
RENAAL	*NEJM* 2001; 345:861-9	Losartan conferred significant renal benefits in patients with type 2 DM and nephropathy and was generally well-tolerated
RENAL	*NEJM* 2009; 361:1627-38	High intensity continuous renal-replacement therapy in AKI does not improve survival or outcomes compared to low intensity treatment, and is associated with higher rates of hypophosphatemia

Trial	Reference	Results
Rituximab in Children with Steroid-Dependent Nephrotic Syndrome	*JASN* 2015; 26 DOI: ASN.2014080799	Rituximab is non-inferior to steroids in maintaining remission in juvenile steroid dependent nephrotic syndrome
ROAD	*JASN* 2007; 18:1889-98	Uptitration of either ACEI benazepril or ARB losartan to optimal anti-proteinuria doses conferred benefit on renal outcome in patients without DM who had proteinuria and renal insufficiency
ROADMAP	*NEJM* 2011; 364:907-17	The use of the ARB olmesartan was more effective than placebo in delaying the onset of microalbuminuria in patients with type 2 DM, normoalbuminuria, and good blood pressure control; however, a higher rate of fatal cardiovascular events was found amongst patients with preexisting coronary heart disease in the olmesartan group
SHARP	*Lancet* 2011; 377:2181-92	Randomized placebo-controlled trial in patients with CKD and no history of MI or coronary revascularization took simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo; simvastatin 20 mg plus ezetimibe 10 mg daily resulted in reduction of LDL cholesterol with associated reduction of major atherosclerotic events in patients with CKD
TREAT	*NEJM* 2009; 361:2019-32	Patients with type 2 DM, CKD, and anemia were randomized to darbepoetin targeting a hemoglobin of 13 g/dL or placebo; darbepoetin did not reduce the risk of death, a cardiovascular event, or a renal event, and was associated with an increased risk of stroke
Tolvaptan in ADPKD	*NEJM* 2012; 367: 2407-18	Tolvaptan (vs. placebo) slowed the increase in total kidney volume and decline in kidney function over a 3-year period in patients with ADPKD but was associated with a higher discontinuation rate, due to adverse events

References

Adler SG, Salant DJ. An outline of essential topics in glomerular pathophysiology, diagnosis and treatment for nephrology trainees. Am J Kidney Dis 2003;42:395-418.

Androgue HJ, Madias NM. Management of life threatening acid-base disorders part I. NEJM 1999;338:26-33.

Androgue HJ, Madias NM. Management of life threatening acid-base disorders part II. NEJM 1999;338:107-111.

Androgue HJ, Madias NE. Hyponatremia. NEJM 2000;342:1581-1589.

Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. Lancet 2011;377:2181-2192.

Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. NEJM 2004;351:1952-1961.

Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal cardiovascular outcomes in patients with type 2 diabetes and nephropathy. NEJM 2001;345:861-869.

Churchill DN, Blacke PG, Jindal KK, et al. Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. J Am Soc Nephrol 1999;10(Suppl 13):S238-291.

Cooper CJ, Murphy DP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. NEJM 2014;370:13-22.

Donadio JV, Grande JP. Medical progress: IgA nephropathy. NEJM 2002;347:738-748.

Gabow PA. Autosomal dominant polycystic kidney disease. NEJM 1993;329:332-342.

Greenberg AR. Primer on kidney diseases, 3rd ed. San Diego: Academic Press, 2001.

Hakim R, Lazarus M. Initiation of dialysis. J Am Soc Nephrol 1995;6:1319-1328.

Halperin ML, Goldstein MB, Kersey R, et al. Fluid, electrolyte, and acid-base physiology: a problem-based approach, 3rd ed. New York: Harcourt Brace, 1998.

Halperin ML, Kamel K. Potassium. Lancet 1998;352:135-140.

Hudson BG, Tryggvason K, Sundaramoorthy M, et al. Mechanisms of disease: Alport's syndrome, goodpasture's syndrome, and type IV collagen. NEJM 2003;348:2543-2556.

Johnson CA, Levey AS, Coresh J, et al. Clinical practice guidelines for chronic kidney disease in adults: Part II. Glomerular filtration rate, proteinuria, and other markers. Am Fam Phys 2004;70:1091-1097.

Johnson RJ, Feehally J (editors). Comprehensive clinical nephrology. New Nork: Mosby, 1999.

K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification: 2000 executive update. Available from: http://www. kidney.org/professionals/dogi/kdogi/toc.htm.

Keane WF, Garabed E. Proteinuria, albuminuria, risk assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. Amer J Kid Dis 1999;33:1004-1010.

Lewis EJ, Hunsicker LG, Bain RP, et al. The effects of angiotensin-converting enzyme inhibition on diabetic nephropathy. NEJM 1993;329:1456-1462.

McFarlane P, Tobe S, Houlden R, et al. Nephropathy: Canadian Diabetes Association clinical practice guidelines expert committee. 2003. Available from: http://www.diabetes.ca/cpg2003/downloads/nephropathy.pdf.S66-S71.

Myers A. Medicine, 4th ed. Baltimore: Lipincott Williams & Wilkins, 2001.

ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. NEJM 2008;358:1547-1559.

Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. NEJM 2002;346:305-310.

Schreiber M. Seminars for year 3 University of Toronto Medicine clinical clerks on medicine: hyponatremia and hypernatremia. October 29, 2002.

Smith K. Renal disease: a conceptual approach. New York: Churchill Livingstone, 1987.

Thadhani R, Pascual M, Bonventre JV. Acute renal failure. NEJM 1996;334:1448-1460.

U Urology

Matthew Lenardis and **Kai Yang,** chapter editors
Hassan Chaudhry and **Nardin Samuel,** associate editors
Alex Cressman and **Shany Gertzbein,** EBM editors
Dr. Sender Herschorn, Dr. Armando Lorenzo, staff editors

Acronyms

β-hCG	beta-human chorionic gonadotropin
ABx	antibiotics
AFP	alpha-fetoprotein
ART	assisted reproductive technologies
AUA	American Urology Association
BCG	Bacillus Calmette-Guérin
BPH	benign prostatic hyperplasia
CAH	congenital adrenal hyperplasia
CaP	prostatic carcinoma
CBI	continuous bladder irrigation
CFU	colony-forming unit
CHF	congestive heart failure
CIC	clean intermittent catheterization
CIS	carcinoma *in situ*
CMG	cystometrogram
CPPS	chronic pelvic pain syndrome
CTU	CT urography
CUA	Canadian Urological Association
CVA	costovertebral angle
d/c	discharge
DHT	dihydrotestosterone
DMSA	dimercaptosuccinic acid
DRE	digital rectal exam
DSD	detrusor sphincter dyssynergia
EBRT	external beam radiation therapy
ED	erectile dysfunction
EPS	expressed prostatic secretions
ESWL	extracorporeal shockwave lithotripsy
FNA	fine needle aspiration
GA	general anesthesia
GAG	glycosaminoglycan
HIFU	high-intensity focused ultrasound
HPF	high power field
HPTA	hypothalamic-pituitary-testicular axis
ICSI	intracytoplasmic sperm injection
IFN-α	interferon-alpha
IL-2	interleukin-2
IPSS	International Prostate Symptom Score
ISD	intrinsic sphincter deficiency
IUI	intrauterine insemination
IVF	*in vitro* fertilization
IVP	intravenous pyelogram
KUB	kidneys, ureters, bladder
LFT	liver function test
LMN	lower motor neuron
LUTS	lower urinary tract symptoms
MAG3	mercaptoacetyltriglycine
MET	medical expulsive therapy
MS	multiple sclerosis
NSGCT	non-seminomatous germ cell tumour
PCKD	polycystic kidney disease
PCNL	percutaneous nephrolithotomy
PDE	phosphodiesterase
PID	pelvic inflammatory disease
PMC	pontine micturition centre
POD	post-obstructive diuresis
PSA	prostate specific antigen
PUV	posterior urethral valve
PVD	peripheral vascular disease
PVR	post-void residual
QOL	quality of life
RCC	renal cell carcinoma
RFA	radio-frequency ablation
RP	radical prostatectomy
RPLND	retroperitoneal lymph node dissection
RTA	renal tubular acidosis
RUG	retrograde urethrogram
SA	semen analysis
SCC	squamous cell carcinoma
SUI	stress urinary incontinence
TMP/SMX	trimethoprim/sulfamethoxazole
TRUS	transrectal ultrasound
TUIP	transurethral incision of the prostate
TUNA	transurethral needle ablation
TURBT	transurethral resection of bladder tumour
TURP	transurethral resection of the prostate
U/A	urinalysis
U/O	urine output
U/S	ultrasound
UCC	urothelial cell carcinoma
UMN	upper motor neuron
UPJ	ureteropelvic junction
URS	ureteroscopy
UTI	urinary tract infection
UVJ	ureterovesicular junction
VB1	voided bladder, initial (urethra)
VB2	voided bladder, midstream (bladder)
VB3	voided bladder, post-massage/ digital rectal exam
VCUG	voiding cystourethrogram
VIU	visual internal urethrotomy
VUR	vesicoureteral reflux

Basic Anatomy Review

- recall that the anatomical position of the penis is erect; therefore, the anatomical ventral side of the penis appears to be the dorsal side of the flaccid penis

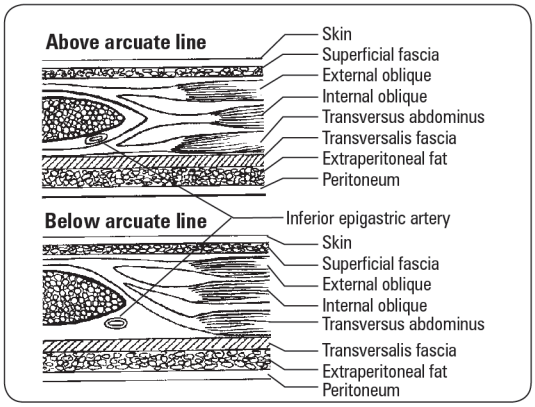


Figure 1. Midline cross-section of abdominal wall

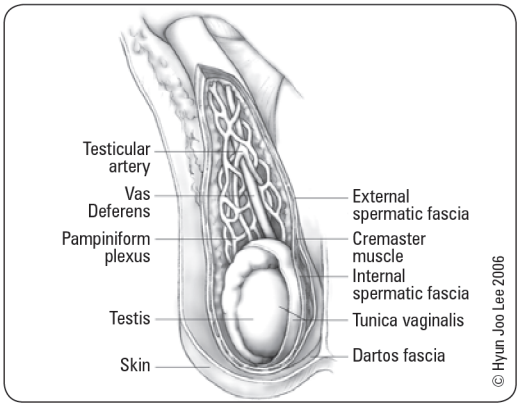


Figure 2. Anatomy of scrotum

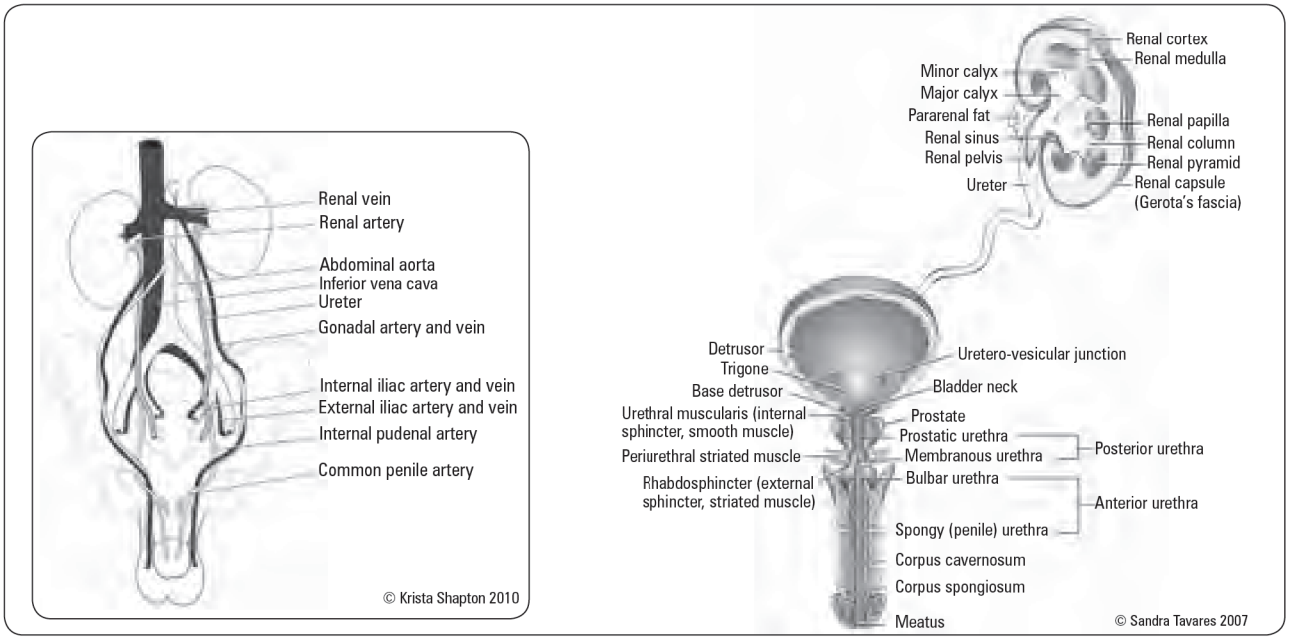


Figure 3. Essential male genitourinary tract anatomy

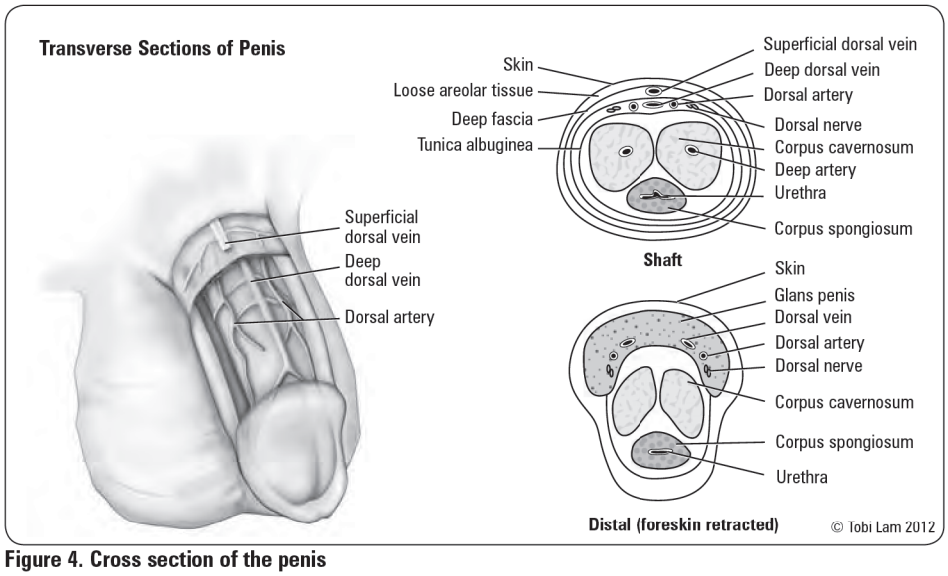


Figure 4. Cross section of the penis

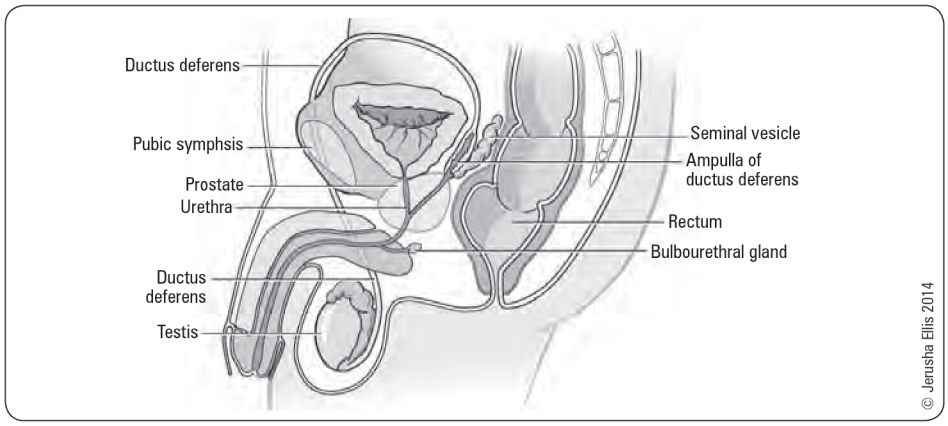


Figure 5. Median sagittal section of the male pelvis and perineum

Urologic History

- follow the OPQRSTUVW approach
  - note that pain may not be limited to the genital region (e.g. lower abdomen, CVA)
- inquire about risk factors: past urologic disease (e.g. UTI, stones, STI, cancers, anatomic abnormalities, family Hx, medications, lifestyle factors, trauma, previous surgical procedures)
- urinary habits
  - frequency of voiding, quality of urine, volume of voids, incontinence, nocturia
  - specific urinary symptoms include
    - storage symptoms: frequency, nocturia, urgency
    - voiding symptoms: straining, hesitancy, dysuria, intermittency, post-void dribbling, reduced stream, feeling of incomplete voiding
    - hematuria: part of stream during which bleeding occurs, blood clots
    - incontinence: rushing to washroom (urge); leakage with coughing, sneezing, laughing (stress); constant dribbling (overflow)
- sexual function
  - scrotal mass: see *Scrotal Mass*, U29
  - ED: see *Erectile Dysfunction*, U30
  - infertility: see *Infertility*, U34
- risk factors
  - past urologic disease (e.g. UTI, stones, cancers, STI), anatomic abnormalities, trauma, previous surgical procedures, medications, family Hx, lifestyle factors
- associated symptoms
  - N/V
  - bowel dysfunction
- constitutional symptoms
  - fever, chills, unintentional weight loss, night sweats, fatigue, malaise

Always ask about sexual function on history. Change in erectile function can be one of the first symptoms that there is concomitant vascular disease. If there is new onset ED, consider screening for DM and CAD risk factors

Hematuria (Blood in the Urine)

Macroscopic (Gross) Hematuria

Definition
- blood in the urine that can be seen with the naked eye

Classification
- see Nephrology, NP20

Etiology

Table 1. Etiology by Age Group

Age (yr)	Etiology	
0-20	UTI, glomerulonephritis, congenital abnormalities	
20-40	UTI, stones, bladder tumour	
40-60	Male: bladder tumour, stones, UTI	Female: UTI, stones, bladder tumour
>60	Male: BPH, bladder tumour, UTI, RCC	Female: bladder tumour, UTI, RCC

Table 2. Etiology by Type

Pseudohematuria	Infectious/ Inflammatory	Malignancy	Benign	Structural	Hematologic
Vaginal bleeding Dyes (beets, rhodamine B in candy and juices) Hemoglobin (hemolytic anemia) Myoglobin (rhabdomyolysis) Drugs (rifampin, phenazopyridine, phenytoin) Porphyria Laxatives (phenolphthalein)	Pyelonephritis Cystitis Urethritis Glomerulonephritis Interstitial nephritis Tuberculosis	RCC (mainly in adult population) UCC Wilms' tumour (mainly in pediatric population) Leukemia	BPH Polyps Exercise-induced	Stones Trauma Foreign body Urethral stricture Polycystic kidneys Arteriovenous malformation Infarct	Anticoagulants Coagulation defects Sickle cell disease Thromboembolism

Gross, painless hematuria in adults is bladder cancer until proven otherwise

Common Urologic Causes of Hematuria can be Classified as:

TICS
Trauma/**T**umour/**T**oxins
Infection/**I**nflammatory
Calculi/**C**ysts
Surgery/**S**ickle cell and other hematological causes

History
- inquire about timing of hematuria in urinary stream
  - initial: anterior urethra
  - terminal: bladder neck and prostatic urethra
  - total: bladder and/or above

Investigations
- CBC (rule out anemia, leukocytosis), electrolytes, Cr, BUN, INR, PTT
- urine studies
  - U/A, C&S, cytology
- imaging
  - CT (with contrast) has largely replaced IVP to investigate upper tracts
    - consider contraindications to contrast: allergy, renal insufficiency
    - U/S alone is not sufficient
  - cystoscopy to investigate lower tract (possible retrograde pyelogram)

Upper Tract Imaging Options

CT Urography (CTU): Optimal test for renal parenchyma, calculi, and infections. Involves exposure to radiation and IV contrast. Assess kidney function, allergies prior to use of contrast

U/S: Superior to IVP for evaluation of renal parenchyma and renal cysts. Limited sensitivity for UCC and small renal masses. U/S alone is not sufficient for upper tract imaging

Intravenous Pyelogram (IVP): Traditional option but rarely used (replaced by CTU). Reasonable sensitivity for UCC, but poor sensitivity for RCC

Acute Management of Severe Bladder Hemorrhage
- manual irrigation via catheter with normal saline to remove clots
- CBI using large (22-26 Fr) 3-way Foley to help prevent clot formation
- cystoscopy if active bleeding
  - identify resectable tumours
  - coagulate obvious sites of bleeding
- refractory bleeding
  - intravesical agents
    - continuous intravesical irrigation with 1% aluminum potassium sulfate solution as needed
    - intravesical instillation of 1% silver nitrate solution
    - intravesical instillation of 1-4% formalin (requires GA and pre-procedure cystogram to rule out reflux)
  - embolization or ligation of iliac arteries
  - cystectomy and diversion (rarely performed)

Microscopic Hematuria

Definition
- blood in the urine that is not visible to the naked eye
- >3 RBCs/HPF on urinalysis of at least two separate samples

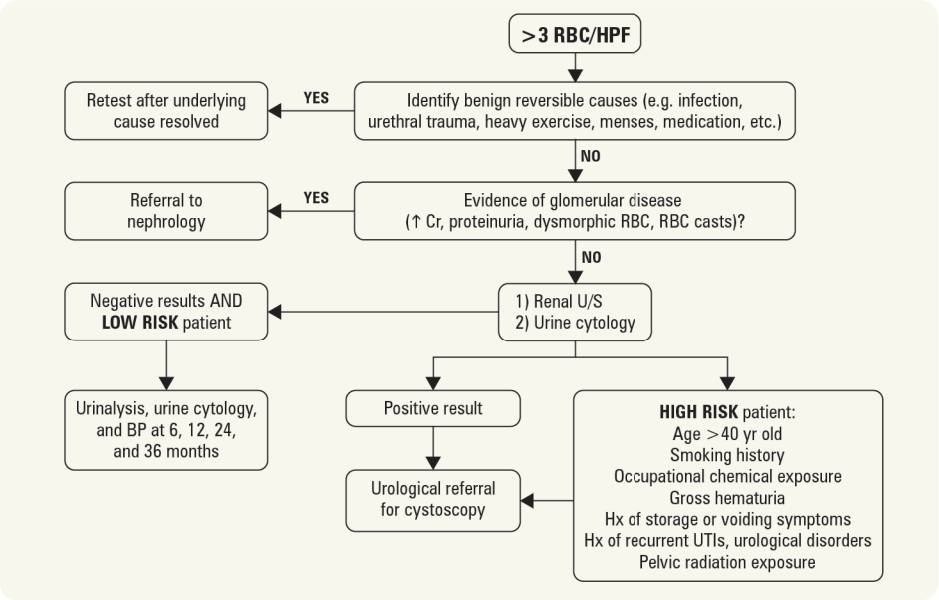


Figure 6. Workup of asymptomatic microscopic hematuria
Based on CUA Guidelines. Alternatively, the AUA recommends cystoscopy and CT urogram for all patients with confirmed microscopic hematuria; follow-up for negative workup is urinalysis yearly for two years, with repeat anatomic evaluation if microscopic hematuria persists

Lower Urinary Tract Dysfunction

- see Gynecology, GY37 for relevant female topics

Voiding

- two phases of lower urinary tract function
  1. storage phase (bladder filling and urine storage)
     - accommodation and compliance
     - no involuntary contraction
  2. voiding phase (bladder emptying)
     - coordinated detrusor contraction
     - synchronous relaxation of outlet sphincters
     - no anatomic obstruction
- voiding dysfunction can therefore be classified as
  - failure to store: due to bladder or outlet
  - failure to void: due to bladder or outlet
- three types of symptoms
  - storage (formerly known as irritative)
  - voiding (formerly known as obstructive)
  - post-voiding

Urinary Incontinence

Definition
- involuntary leakage of urine

Etiology
- urgency incontinence
  - detrusor overactivity
    - CNS lesion, inflammation/infection (cystitis, stone, tumour), bladder neck obstruction (tumour, stone), BPH, idiopathic

Lower Urinary Tract Symptoms (LUTS)

Storage (FUND)
Frequency
Urgency
Nocturia
Dysuria

Voiding (SHED)
Stream changes
Hesitancy
Incomplete **E**mptying
Dribbling

  - decreased compliance of bladder wall (inability to store urine)
    - CNS lesion, fibrosis
    - sphincter/urethral problem
- stress urinary incontinence (SUI)
  - common in women; seen in men after prostate cancer treatment or pelvic operations
  - urethral hypermobility
    - weakened pelvic floor and musculofascial urethral and vaginal supporting mechanisms allows bladder neck and urethra to descend with increased intra-abdominal pressure
    - urethra is pulled open by greater motion of posterior wall of outlet relative to anterior wall
    - associated with childbirth, pelvic surgery, aging, levator muscle weakness, obesity
  - intrinsic sphincter deficiency (ISD): weakness of the urethra and associated smooth and striated muscle elements
    - pelvic surgery, neurologic problem, aging and hypoestrogen state
  - ISD and urethral hypermobility can co-exist
- mixed incontinence
  - combination of stress and urgency incontinence
- overflow incontinence
  - is a term sometimes used to describe urinary incontinence as a complication of urinary retention; for causes of urinary retention see Table 4
  - use of the term should be accompanied by the associated pathophysiology (e.g. BPH with overflow incontinence)

Causes of Reversible Urinary Incontinence

DIAPERS
Delirium
Inflammation/**I**nfection
Atrophic vaginitis/urethritis
Pharmaceuticals/**P**sychological
Excess U/O
Restricted mobility/**R**etention
Stool impaction

Epidemiology
- variable prevalence in women: 25-45%
- F:M = 2:1
- more frequent in the elderly, affecting 5-15% of those living in the community and 50% of nursing home residents

Table 3. Urinary Incontinence: Types and Treatments

Type	Urgency	Stress	Mixed
Definition	Involuntary leakage of urine preceded by a strong, sudden urge to void	Involuntary leakage of urine with sudden increases in intra-abdominal pressure	Urinary leakage associated with urgency and increased intra-abdominal pressure
Etiology	Bladder (detrusor overactivity)	Urethra/sphincter weakness, post-partum pelvic musculature weakness	Combination of bladder and sphincter issues
Diagnosis	Hx Urodynamics	Hx Urodynamics Stress test (have patient bear down/cough)	Hx Urodynamics Stress test
Therapy	Lifestyle changes (fluid alterations, diet, etc.) Bladder habit training Anticholinergics β3 agonist Neuromodulation Botulinum toxin A	Weight loss Kegel exercises Bulking agents Surgery (slings, tension-free vaginal tape, transobturator tape, artificial sphincters)	Combination of management of urge and stress incontinence

Urgency is the symptom of a strong need to void; it is not necessarily associated with incontinence

Urinary Retention

Table 4. Etiology of Urinary Retention

Outflow Obstruction	Bladder Innervation	Pharmacologic	Infection
• Bladder neck or urethra: calculus, clot, foreign body, neoplasm, neurological (DSD) • Prostate: BPH, prostate cancer • Urethra: stricture, phimosis, traumatic disruption • Miscellaneous: constipation, pelvic mass	• Intracranial: CVA, tumour, Parkinson's, cerebral palsy • Spinal cord: injury, disc herniation, MS • DM • Post-abdominal or pelvic surgery	• Anticholinergics • Narcotics • Antihypertensives (ganglionic blockers, methyldopa) • OTC cold medications containing ephedrine or pseudoephedrine • Antihistamines • Psychosomatic substances (e.g. ecstasy)	• GU: UTI, prostatitis, abscess, genital herpes • Infected foreign body • Varicella zoster

Acute vs. Chronic Retention

Acute retention is a medical emergency characterized by suprapubic pain and anuria with normal bladder volume and architecture

Chronic retention can be painless with greatly increased bladder volume and detrusor hypertrophy followed by atony (late)

If a trauma patient is unable to void, has blood at urethral meatus, a scrotal hematoma, or a high riding prostate, there is urethral injury until proven otherwise so catheterization is CONTRAINDICATED unless performed by urology staff or resident

Clinical Features
- suprapubic pain
- palpable and/or percussible bladder (suprapubic)
- possible purulent/bloody meatal discharge
- increased size of prostate or reduced anal sphincter tone on DRE
- neurological: presence of abnormal or absent deep tendon reflexes, reduced "anal wink", saddle anesthesia

Investigations
- CBC, electrolytes, Cr, BUN, U/A and urine C&S, U/S, cystoscopy, urodynamic studies, PVR

Patients with ascites may have a falsely elevated PVR measured by bladder scan

Treatment
- treat underlying cause
- catheterization
  - acute retention
    - immediate catheterization to relieve retention; leave Foley in to drain bladder; follow-up to determine cause; closely monitor fluid status and electrolytes (risk of POD)
  - chronic retention
    - intermittent catheterization by patient may be used; definitive treatment depends on etiology
- suprapubic tube placement
- for post-operative patients with retention:
  - encourage ambulation
  - α-blockers to relax bladder neck outlet
  - may need catheterization
  - definitive treatment will depend on etiology

Benign Prostatic Hyperplasia

Definition
- periurethral hyperplasia of stroma and epithelium in prostatic transition zone
- prostatic smooth muscle cells play a role in addition to hyperplasia

Etiology
- etiology unknown
  - DHT required (converted from testosterone by 5-α reductase)
  - possible role of impaired apoptosis, estrogens, other growth factors
  - genetic: increased risk in 1st degree relatives and twin studies

Epidemiology
- age-related, extremely common (50% of 50 yr olds, 80% of 80 yr olds)
- 25% of men will require treatment

Clinical Features
- result from outlet obstruction and compensatory changes in detrusor function
- voiding and storage symptoms
- DRE
  - prostate is smooth, rubbery, and symmetrically enlarged
- complications
  - retention
  - overflow incontinence
  - hydronephrosis
  - renal insufficiency
  - infection
  - gross hematuria
  - bladder stones

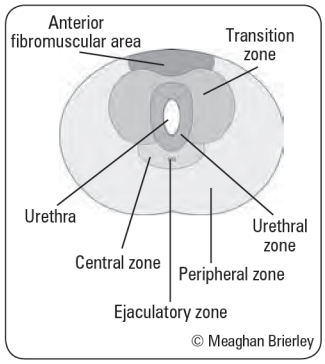


Figure 7. Cross-section of prostate

Prostate size does not correlate well with symptoms in BPH

Approximate Prostate Sizes
- 20 cc – chestnut
- 25 cc – plum
- 50 cc – lemon
- 75 cc – orange
- 100 cc – grapefruit

Investigations
- Hx, assessing LUTS and impact on QOL
  - may include self-administered questionnaires (IPSS or AUA symptom index for severity, progression, and treatment response)
- P/E, including DRE
- U/A to exclude UTI
- Cr to assess renal function
- renal U/S to assess for hydronephrosis
- PSA to rule out malignancy (see *Prostate Cancer Screening*, U25)
- uroflowmetry to measure flow rate (optional)
- PVR (optional)
- consider cystoscopy or transrectal ultrasound prior to potential surgical management to evaluate outlet and prostate volume
- biopsy if suspicious for malignancy, i.e. elevated PSA or abnormal DRE

AUA BPH Symptom Score

FUNWISE
Frequency
Urgency
Nocturia
Weak stream
Intermittency
Straining
Emptying, incomplete feeling of

Each symptom graded out of 5
0-7: Mildly symptomatic
8-19: Moderately symptomatic
20-35: Severely symptomatic

Note: dysuria not included in score but is commonly associated with BPH

Treatment

Table 5. Treatment of BPH

	Conservative	Medical	Surgical	Minimally Invasive Surgical Therapies
When to use	Asymptomatic patients	Moderate to severe symptoms that are distressing for patient	Significant symptom burden, acute urinary retention, refractory hematuria, recurrent infections	Patients who wish to avoid or may not tolerate surgery
Options	• Watchful waiting: 50% of patients improve spontaneously • Lifestyle modifications (e.g. evening fluid restriction, planned voiding)	• α-adrenergic antagonists: reduce stromal smooth muscle tone • 5-α reductase inhibitor: block conversion of testosterone to DHT; act to reduce prostate size • Combination is synergistic • Anti-cholinergic agents (for storage LUTS, without elevated PVR)	• TURP (see U42) • Laser ablation • TUIP (prostate <30 g) • Open prostatectomy	• Microwave therapy • TUNA • Prostatic stent (not commonly used)

Men with planned cataract surgery should avoid starting α-adrenergic antagonists until after their surgery due to the risk of intraoperative floppy iris syndrome

BPH Surgery
Absolute Indication
- Renal failure with obstructive uropathy
- Refractory urinary retention

Relative Indications
- Recurrent UTIs
- Recurrent hematuria refractory to medical treatment
- Renal insufficiency (rule out other causes)
- Bladder stones

Finasteride for Benign Prostatic Hyperplasia
Cochrane DB Syst Rev 2010;10:CD006015
Purpose: To examine the effectiveness and safety of finasteride versus placebo or other active controls for the treatment of urinary tract symptoms.
Summary of Findings:
1. Finasteride improved urinary symptoms more than placebo in trails >1 yr duration and significantly lowered the risk of BPH progression.
2. Compared with α-blockers, finasteride was less effective than either doxazosin or terazosin, but equally as effective as tamsulosin.
3. Symptom improvement with finasteride + doxazosin is equal to doxazosin alone.
4. Finasteride treatment resulted in an increased risk of ejaculation disorder, impotence and lowered libido compared with placebo.
5. Compared with doxazosin and terazosin, finasteride had a lower risk of asthenia, dizziness, and postural hypotension.

Microwave Thermotherapy for Benign Prostatic Hyperplasia
Cochrane DB Syst Rev 2012;9:CD004135
Purpose: To evaluate the efficacy and safety of microwave thermotherapy for the treatment of benign prostatic obstruction.
Selection Criteria: RCTs evaluating transurethral microwave therapy (TUMT) for men with symptomatic BPH with multiple comparison groups.
Results: 15 studies, 1,585 patients, mean age 66.8 yr, 3-60 mo duration. Mean urinary symptom scores decreased by 65% with TUMT and 77% with TURP. The pooled mean peak urinary flow increased by 70% with TUMT and 119% with TURP. Compared with TURP, TUMT was associated with decreased risks for retrograde ejaculation, treatment for strictures, hematuria, blood transfusions and transurethral resection syndrome, but increased risk for dysuria, urinary retention and retreatment for BPH symptoms.
Conclusions: Overall, microwave thermotherapy techniques are effective alternatives to TURP and α-blockers for treating symptomatic BPH, although less effective than TURP in improving symptom score and urinary flow.

Urethral Stricture

Definition
- decrease in urethral calibre due to scar formation in urethra (may also involve corpus spongiosum)
- M>F

Etiology
- congenital
  - failure of normal canalization (i.e. posterior urethral valves)
- trauma
  - instrumentation/catheterization (most common)
  - external trauma (e.g. burns, straddle injury)
  - foreign body
- infection
  - long-term indwelling catheter
  - STI (gonococcal or chlamydial disease)
- inflammation
  - balanitis xerotica obliterans (BXO; lichen sclerosis or chronic progressive sclerosing dermatosis of the male genitalia) causing meatal and urethral stenosis

Clinical Features
- voiding symptoms
- urinary retention
- hydronephrosis
- related infections: recurrent UTI, secondary prostatitis/epididymitis

Investigations
- laboratory findings
  - flow rates <10 mL/s (normal ~20 mL/s) on uroflowmetry
  - urine culture usually negative, but U/A may show pyuria
- radiologic findings
  - RUG and VCUG will demonstrate location
- cystoscopy

Treatment
- urethral dilatation
  - temporarily increases lumen size by breaking up scar tissue
  - healing will often reform scar tissue, recurrence of stricture
- visual internal urethrotomy (VIU)
  - endoscopically incise stricture
  - equal success rates to dilation with mid bulbar strictures <2 cm
  - high rate of recurrence (30-80%), avoid in younger patients
- open surgical reconstruction
  - complete stricture excision with anastomosis, ± urethroplasty depending on location and size of stricture

Neurogenic Bladder

Definition

- malfunctioning urinary bladder due to deficiency in some aspect of its innervation

Neurophysiology

Table 6. Efferent Sympathetic, Parasympathetic, and Somatic Nerve Supply

Nerve Fibres	Nerve Roots	Neurotransmitter/Receptor	Target
Sympathetic	T10-L2	NA/Adrenergic	Trigone, internal sphincter, proximal urethra (α) Bladder body (β)
Somatic (Pudendal)	S2-4	ACh/Nicotinic	External sphincter
Parasympathetic	S2-4	ACh/Muscarinic (M2, M3)	Detrusor

Nerve roots in micturition:
"S2-3-4 keeps the urine off the floor"

- stretch receptors in the bladder wall relay information to PMC and activate micturition reflex (normally inhibited by cortical input)
  - micturition
    - stimulation of parasympathetic neurons (bladder contraction)
    - inhibition of sympathetic and somatic neurons (internal and external sphincter relaxation, respectively)
  - urine storage
    - opposite of micturition
- voluntary action of external sphincter (pudendal nerve roots S2-S4) can inhibit urge to urinate
- cerebellum, basal ganglia, thalamus, and hypothalamus all have input at PMC in the brainstem

Classification of Neurologic Voiding Dysfunction

"Spinal shock", initially manifests as atonic bladder

- neuropathic detrusor overactivity (formerly termed detrusor hyperreflexia)
  - lesion above PMC (e.g. stroke, tumour, MS, Parkinson's disease)
  - loss of voluntary inhibition of voiding
  - intact pathway inferior to PMC maintains coordination of bladder and sphincter
- detrusor sphincter dyssynergia (DSD)
  - suprasacral lesion of spinal cord (e.g. trauma, MS, arteriovenous malformation, transverse myelitis)
  - loss of coordination between detrusor and sphincter (detrusor contracts on closed sphincter and vice versa)
  - component of detrusor overactivity as well
- detrusor atony/areflexia
  - lesion of sacral cord or peripheral efferents (e.g. trauma, DM, disc herniation, MS, congenital spinal cord abnormality, post abdominoperineal resection)
  - flaccid bladder which fails to contract
  - may progress to poorly compliant bladder with high pressures
- peripheral autonomic neuropathy
  - deficient bladder sensation → increasing residual urine → decompensation (e.g. DM, neurosyphilis, herpes zoster)
- muscular lesion
  - can involve detrusor, smooth/striated sphincter

Neuro-Urologic Evaluation

- Hx and P/E (urologic and general neurologic)
- U/A, renal profile
- imaging
  - IVP (less used), U/S to rule out hydronephrosis and stones
- cystoscopy
- urodynamic studies
  - uroflowmetry to assess flow rate, pattern
  - filling CMG to assess capacity, compliance, detrusor overactivity
  - voiding CMG (pressure-flow study) to assess bladder contractility and extent of bladder outflow obstruction
  - video study to visualize bladder/bladder neck/urethra during CMG using x-ray contrast
  - EMG ascertains presence of coordinated or uncoordinated voiding, allows accurate diagnosis of DSD

Treatment

- goals of treatment
  - prevent renal failure
  - prevent infections
  - achieve social continence

- clean intermittent catheterization (CIC)
- treatment options depend on status of bladder and urethra
  - bladder hyperactivity → anticholinergic medications to relax bladder (see *Urinary Incontinence*, U5)
    - if refractory
      - botulinum toxin injections into bladder wall
      - occasionally augmentation cystoplasty (enlarging bladder volume and improving compliance by grafting section of detubularized bowel onto the bladder)
      - occasionally urinary diversion (ileal conduit or continent diversion) in severe cases if bladder management unsuccessful
  - flaccid bladder → CIC

Dysuria

Definition
- painful urination

Etiology

Table 7. Differential Diagnosis of Dysuria

Infectious	Cystitis, urethritis, prostatitis, epididymitis/orchitis (if associated with lower tract inflammation), cervicitis, vulvovaginitis, perineal inflammation/infection, TB, vestibulitis
Neoplasm	Kidney, bladder, prostate, penis, vagina/vulva, BPH
Calculi	Bladder stone, urethral stone, ureteral stone
Inflammatory	Seronegative arthropathies (reactive arthritis: arthritis, uveitis, urethritis), drug side effects, autoimmune disorders, chronic pelvic pain syndrome (CPPS), interstitial cystitis
Hormonal	Endometriosis, hypoestrogenism
Trauma	Catheter insertion, post-coital cystitis (honeymoon cystitis)
Psychogenic	Somatization disorder, depression, stress/anxiety disorder
Other	Contact sensitivity, foreign body, radiation/chemical cystitis, diverticulum

Investigations
- focused Hx and P/E to determine cause (fever, d/c, conjunctivitis, CVA tenderness, back/joint pain)
  - any d/c (urethral, vaginal, cervical) should be sent for gonococcus/chlamydia testing; wet mount if vaginal d/c
  - U/A and urine C&S
  - if suspect infection, may start empiric ABx treatment (see Table 8, U11)
  - ± imaging of urinary tract (tumour, stones)

Hydronephrosis

Definition
- dilation of the renal pelvis and calyces caused by the impairment in antegrade urine flow

Etiology
- mechanical
  - congenital: see *Congenital Abnormalities*, U35
  - acquired
    - intrinsic: trauma, inflammation and bleeding, calculi, urologic neoplasms, BPH, urethral stricture, phimosis, previous urological surgery
    - extrinsic: trauma, neoplasms (uterine fibroid; colorectal, uterine, and cervical malignancies; lymphoma), aortic aneurysm, pregnancy (gravid uterus)
- functional
  - neuropathic: neurogenic bladder, diabetic neuropathy, spinal cord disease
  - pharmacologic: anticholinergics, α-adrenergic agonists
  - hormonal: pregnancy (progesterone decreases ureteral tone)

Investigations
- focused Hx, inquiring about pain (flank, lower abdomen, testes, labia), U/O, medication use, pregnancy, trauma, fever, Hx of UTIs, calculi, and PID and urological surgery

- CBC, electrolytes, Cr, BUN, U/A, C&S
- imaging studies (U/S is >90% sensitive and specific)
  - MAG3 diuretic renogram: evaluates differential renal function and demonstrates if functional obstruction exists

Treatment
- hydronephrosis can be physiologic
- treatment should be guided at improving symptoms, treating infections, or improving renal function
- urgent treatment may require percutaneous nephrostomy tube or ureteral stenting to relieve pressure

Post-Obstructive Diuresis

Definition
- polyuria resulting from relief of severe chronic obstruction
- >3 L/24 h or >200 cc/h over each of two consecutive hours

Pathophysiology
- **physiologic POD** secondary to excretion of retained urea, Na^+, and H_2O (high osmotic load) after relief of obstruction
  - self-limiting; usually resolves in 48 h with PO fluids but may persist to pathologic POD
- **pathologic POD** is a Na^+-wasting nephropathy secondary to impaired concentrating ability of the renal tubules due to
  - decreased reabsorption of NaCl in the thick ascending limb and urea in the collecting tubule
  - increased medullary blood flow (solute washout)
  - increased flow and solute concentration in the distal nephrons

Management
- admit patient and closely monitor hemodynamic status and electrolytes (Na^+ and K^+ q6-12h and replace prn; follow Cr and BUN to baseline)
- monitor U/O q2h and ensure total fluid intake <U/O by replacing every 1 mL U/O with 0.5 mL 1/2 NS IV (PO fluids if physiologic POD)
- avoid glucose-containing fluid replacement (iatrogenic diuresis)

Overactive Bladder

Definition
- a symptom complex that includes urinary urgency with or without urgency incontinence, urinary frequency (voiding >8 times in a 24 hr period), and nocturia (awakening two or more times at night to void)

Etiology
- etiology unknown
- symptoms usually associated with involuntary contractions of the detrusor muscle. The overactivity of the muscle could be neurogenic, myogenic or idiopathic

Epidemiology
- F:M= 1:1
- prevalence increases with age. 42% in males 75 years old or older; 31% in females 75 years old or older

Diagnosis
- the diagnostic process should document symptoms and signs that define overactive bladder and exclude other disorders that could cause of the patient's symptoms
- minimal requirements for the process consist of
  - focused history including past genitourinary disorders and conditions outlined in Table 8, questionnaires of LUTS for women and diaries of urination frequency, volume and pattern
  - P/E including genitourinary, pelvic and rectal examination
  - urinalysis to rule out hematuria and infection
- in some patients, the following investigations could be considered
  - bladder scan for residual urine in patients with risk factors of urinary retention
  - cystoscopy to rule out recurrent infections, carcinoma in situ and other intravesical abnormalities
    - urodynamics to rule out obstruction in older men

Treatment

- non-pharmacological: behaviour therapies such as bladder training, bladder control strategies, pelvic floor muscle training, fluid management, and avoidance of caffeine
- pharmacological
  - anti-muscarinics such as oxybutinin hydrochloride, tolterodine, solifenacin, fesoterodine, or trospium
  - β3-adrenoceptor agonist such as mirabegron
- refractory patients may be treated with
  - neuromuscular-junction inhibition such as botulinum toxin bladder injection
- other interventional procedures include
  - posterior tibial nerve stimulation (not used commonly in Canada)
  - sacral neuromodulation

Table 8. Conditions that could contribute to symptoms of Overactive Bladder

Lower urinary tract conditions	UTI, obstruction, impaired bladder contractility
Neurological conditions	Stroke, MS, dementia, diabetic neuropathy
Systemic diseases	CHF, sleep disorders (primarily nocturia)
Functional and behavioral	Excessive caffeine and alcohol, constipation, impaired mobility
Medication	Diuretics, anticholinergic agents, narcotics, calcium-channel blocker, cholinesterase inhibitors

Infectious and Inflammatory Diseases

Table 8. Antibiotic Treatment of Urological Infections

Condition	Drug	Duration
Urethritis	Non-Gonococcal	
	azithromycin (1 g PO)	x 1
	OR	
	doxycycline (100 mg PO bid)	7 d
	Gonococcal	
	ceftriaxone (250 mg IM) AND treat for *Chlamydia trachomatis*	x 1
Simple, Uncomplicated UTI	TMP-SMX (160 mg/800 mg PO bid)	3 d
	OR	
	nitrofurantoin (100 mg PO bid)	5 d
Complicated UTI (see *Classification*, U13 for features)	ciprofloxacin (1 g PO daily OR 400 mg IV q12h)	up to 2-3 wk
	OR	
	ampicillin (1 g IV q6h) + gentamicin (1 mg/kg IV q8h)	up to 2-3 wk
	OR	
	ceftriaxone (1-2 g IV q24h)	up to 2-3 wk
Recurrent/Chronic Cystitis	rophylactic treatment	
	Continuous: TMP-SMX (40 mg/200 mg PO qd OR 3x/wk)	6-12 mo
	OR	
	nitrofurantoin (50-100 mg PO qd)	6-12 mo
	Post-Coital: TMP-SMX (40 mg/200 mg-80 mg/400 mg)	within 2 h of coitus
	OR	
	nitrofurantoin (50-100 mg PO qd)	within 2 h of coitus
Acute Prostatitis	ciprofloxacin (500-750 mg PO bid)	2-4 wk
	OR	
	TMP-SMX (160 mg/800 mg PO bid)	4 wk
	OR	
	IV therapy with gentamicin and ampicillin, penicillin with β-lactamase inhibitor, 3rd gen cephalosporin, OR a fluoroquinolone	4 wk total (IV and oral step-down)
Chronic Prostatitis	ciprofloxacin (500 mg PO bid)	4-6 wk
Epididymitis/Orchitis	<35 yr	
	ceftriaxone (200 mg IM)	x 1
	AND	
	doxycycline (100 mg PO bid)	10 d
	≥35 yr	
	ofloxacin (300 mg PO bid)	10 d
Acute Uncomplicated Pyelonephritis	ciprofloxacin (500 mg PO bid)	7 d
	± ceftriaxone (1 g IV) OR ciprofloxacin (400 mg IV)	x 1
	OR	
	IV therapy with a fluoroquinolone, gentamicin and ampicillin, extended spectrum cephalosporin, extended spectrum penicillin, OR a carbapenem	14 d total (IV and oral step-down)

Antibiotic therapy should always be based on local resistance patterns and adjusted according to culture and sensitivity results

Cystitis: Common Pathogens

KEEPS
K*lebsiella sp.*
E. *coli* (90%), other Gram-negatives
E*nterococci*
P*roteus mirabilis*, ***P****seudomonas*
S. *saprophyticus*

Acute uncomplicated pyelonephritis: suspected or confirmed enterococcus infection requires treatment with ampicillin

Urinary Tract Infection

- for UTIs during pregnancy, see Obstetrics, OB29

Definition
- symptoms suggestive of UTI + evidence of pyuria and bacteriuria on U/A or urine C&S
  - if asymptomatic + 100,000 CFU/mL = asymptomatic bacteriuria; only requires treatment in certain patients (e.g. pregnancy)

Classification
- uncomplicated: lower UTI in a setting of functionally and structurally normal urinary tract
- complicated: structural and/or functional abnormality, male patients, immunocompromised, diabetic, iatrogenic complication, pregnancy, pyelonephritis, catheter-associated
- recurrent: see *Recurrent/Chronic Cystitis*

Risk Factors
- stasis and obstruction
  - residual urine due to impaired urine flow e.g. PUVs, reflux, medication, BPH, urethral stricture, cystocele, neurogenic bladder
- foreign body
  - introduce pathogen or act as nidus of infection e.g. catheter, instrumentation
- decreased resistance to organisms
  - DM, malignancy, immunosuppression, spermicide use, estrogen depletion, antimicrobial use
- other factors
  - trauma, anatomic abnormalities, female, sexual activity, fecal incontinence

Prevention of UTIs
- Maintain good hydration (try cranberry juice)
- Wipe from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse

Clinical Features
- storage symptoms: frequency, urgency, dysuria
- voiding symptoms: hesitancy, post-void dribbling
- other: suprapubic pain, hematuria, foul-smelling urine
- pyelonephritis – if present: typically presents with more severe symptoms (e.g. fever/chills, CVA tenderness, flank pain)

Organisms
- typical organisms
- atypical organisms
  - tuberculosis (TB)
  - *Chlamydia trachomatis*
  - Mycoplasma (*Ureaplasma urealyticum*)
  - fungi (*Candida*)

Indications for Investigations
- pyelonephritis
- persistence of pyuria/symptoms following adequate antibiotic therapy
- severe infection with an increase in Cr
- recurrent/persistent infections
- atypical pathogens (urea splitting organisms)
- Hx of structural abnormalities/decreased flow

Investigations
- U/A, urine C&S
  - UA: leukocytes ± nitrites ± hematuria
  - C&S: midstream, catheterized, or suprapubic aspirate
- if hematuria present, retest post-treatment, if persistent need hematuria workup (see *Microscopic Hematuria*, U5)
- U/S, CT scan if indicated

Treatment
- see Table 8 for approach to ABx therapy
- if febrile, consider admission with IV therapy and rule out obstruction

Recurrent/Chronic Cystitis

Definition
- ≥3 UTIs/yr

Etiology
- bacterial reinfection (80%) vs. bacterial persistence (relapse)
  - **bacterial reinfection**
    - recurrence of infection with either 1) a different organism, 2) the same organism if cultured >2 wk following therapy, or 3) with any organism with an intermittent sterile culture
  - **bacterial persistence**
    - same organism cultured within 2 wk of sensitivity-based therapy

Investigations
- assess predisposing factors as described above
- investigations may include cystoscopy, U/S, CT

Treatment
- lifestyle changes (limit caffeine intake, increase fluid/H_2O intake)
- ABx: continuous vs. post-coital
- post-menopausal women: consider topical or systemic estrogen therapy
- no treatment for asymptomatic bacteriuria except in pregnant women or patients undergoing urinary tract instrumentation

Interstitial Cystitis (Painful Bladder or Bladder Pain Syndrome)

Definition
- bladder pain, chronic urgency and frequency without other reasonable causation

Classification
- non-ulcerative (more common)
- ulcerative

Etiology
- unknown
  - theories: increased epithelial permeability, autoimmune, neurogenic, defective GAG layer overlying mucosa
  - associations: severe allergies, IBS, fibromyalgia

Epidemiology
- prevalence: 20/100,000
- 90% of cases are in females
- mean age at onset is 40 yr (non-ulcerative tends to affect a younger to middle-aged population, while ulcerative tends to be seen in middle-aged to older)

Cystoscopic evaluation is not necessary to make a diagnosis

Clinical Features
- pain associated with the bladder
- glomerulations (submucosal petechiae) or Hunner's lesions (ulcers) on cystoscopic examination
- urinary urgency
- negative U/A, urine C&S, and urine cytology

Four Symptom Scores Exist to Evaluate and Monitor Patients with Interstitial Cystitis
- Interstitial Cystitis Symptom Index (ICSI)
- Interstitial Cystitis Problem Index (ICPI)
- Wisconsin Interstitial Cystitis (UW-IC) Scale
- Pain, Urgency and Frequency (PUF) Score

Differential Diagnosis
- UTI, vaginitis, bladder tumour
- radiation/chemical cystitis
- eosinophilic/TB cystitis
- bladder calculi

Treatment
- first-line: patient empowerment (diet, lifestyle, stress management), pain management
- second-line
  - oral: pentosan polysulfate sodium, amitriptyline, cimetidine, hydroxyzine
  - intravesical: dimethylsulfoxide (DMSO), heparin, lidocaine
- third-line: cystoscopy with bladder hydrodistention (traditionally diagnostic) under GA, treat Hunner's lesions if present
- other: neuromodulation, cyclosporine A, intradetrusor botulinum toxin
- surgery (last resort): augmentation cystoplasty, or urinary diversion ± cystectomy

Acute Pyelonephritis

Definition
- infection of the renal parenchyma with local and systemic manifestations
- clinical diagnosis of flank pain, fever and elevated WBC

Etiology
- ascending (usually GN bacilli) or hematogenous route (usually GP cocci)
- causative microorganisms
  - gram positives: *Enterococcus faecalis, S. aureus, S. saphrophyticus*
  - gram negatives: *E. coli* (most common), *Klebsiella, Proteus, Pseudomonas, Enterobacter*
- common underlying causes of pyelonephritis
  - stones, strictures, prostatic obstruction, vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, PCKD, immunosuppression, post-renal transplant, instrumentation, pregnancy

Clinical Features
- rapid onset (<24 h)
- LUTS including frequency, urgency, hematuria; NOT dysuria unless concurrent cystitis
- fever, chills, nausea, vomiting, myalgia, malaise
- CVA tenderness or exquisite flank pain

Investigations
- U/A, urine C&S
- CBC and differential: leukocytosis, left shift
- imaging indicated if suspicious of complicated pyelonephritis or symptoms do not improve with 48-72 h of treatment
  - abdominal/pelvic U/S
  - CT
- nuclear medicine: DMSA scan can be used to help secure the diagnosis
  - a photopenic defect indicates active infection or scar; if normal alternative diagnoses should be considered

Treatment
- hemodynamically stable
  - outpatient oral ABx treatment ± single initial IV dose (see Table 9)
- severe or non-resolving
  - admit, hydrate, and treat with IV ABx (see Table 9)
- emphysematous pyelonephritis
  - percutaneous nephrostomy tube and antibiotics first line
  - consider early nephrectomy after IV ABx started and patient stabilized
- renal obstruction
  - admit for emergent stenting or percutaneous nephrostomy tube

Nitrofurantoin has poor tissue penetration and therefore is not used to treat pyelonephritis (requires post-renal uroconcentration)

Prostatitis/Prostatodynia

Epidemiology
- most common urologic diagnosis in men <50 yr
- prevalence 2-12%

Classification

Table 10. Comparison of the Three Types of Prostatitis

	Category I: Acute Bacterial Prostatitis	Category II: Chronic Bacterial Prostatitis	Category III: Chronic Pelvic Pain Syndrome (CPPS) (Abacterial)
Etiology	Ascending urethral infection with KEEPS (see U12 sidebar): 80% *E. coli* Often associated with outlet obstruction, recent cystoscopy, prostatic biopsy Most infections occur in the peripheral zone (see Figure 7, U7)	Recurrent exacerbations of acute prostatitis-like signs and symptoms Recurrent UTI with same organism	Divided into inflammatory (IIIA) and non-inflammatory (IIIB) Intraprostatic reflux of urine ± urethral hypertonia Multifactorial (immunological, neuropathic, neuroendocrine, psychosocial)
Clinical Features	Acute onset fever, chills, malaise Rectal, lower back, and perineal pain LUTS	Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain	Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain
Investigations	P/E: abdomen, external genitalia, perineum, prostate U/A Blood CBC, C&S Transrectal U/S if non-resolving/ suspect prostatic abscess	P/E: as per Category I + pelvic floor Urine C&S: 4-glass test VB1 (voided bladder): initial (urethra) VB2: midstream (bladder) EPS (expressed prostatic secretions): not usually performed VB3: post-massage/DRE	Same as per Category II NIH-CPSI score* Consider psychological assessment
Treatment	Supportive measures PO or IV ABx depending how sick (see Table 9) May consider catheterization in patients with severe obstructive LUTS or retention I&D of abscess if present	ABx (see Table 9) Consider addition of an α-blocker	Supportive measures Trial of ABx therapy if newly diagnosed Multimodal treatment strategy may include: α-blocker Anti-inflammatories Phytotherapy (quercetin, cernilton)

*NIH-CPSI: National Institute of Health Chronic Prostatitis Symptom Index

4-Glass Test: Prostatic source is suggested when colony counts in EPS and VB3 exceed those of VB1 and VB2 by 10x

It is not recommended to do a serum PSA during acute bacterial prostatitis

Prostatic massage may cause extreme tenderness and increased risk of inducing sepsis, abscess, or epididymo-orchitis

Epididymitis and Orchitis

Etiology
- common infectious causes
  - <35 yr: *N. gonorrhoeae* or *Chlamydia trachomatis*
  - ≥35 yr or penetrative anal intercourse: GI organisms (especially *E. coli*)
- other causes
  - mumps infection may involve orchitis, post-parotitis
  - TB
  - syphilis
  - granulomatous (autoimmune) in elderly men
  - amiodarone (involves only head of epididymis)
  - chemical: reflux of urine into ejaculatory ducts

Risk Factors
- UTI
- unprotected sexual contact
- instrumentation/catheterization
- increased pressure in prostatic urethra (straining, voiding, heavy lifting) may cause reflux of urine along vas deferens → sterile epididymitis
- immunocompromise

Clinical Features
- sudden onset scrotal pain and swelling ± radiation along cord to flank
- scrotal erythema and tenderness
- fever
- storage symptoms, purulent d/c
- reactive hydrocele

Prehn's Sign: pain may be relieved with elevation of testicles in epididymitis but not in testicular torsion (poor sensitivity, especially in children)

Investigations
- U/A, urine C&S
- ± urethral d/c: Gram stain/culture
- if diagnosis uncertain, must do
  - colour-flow Doppler U/S to rule out testicular torsion

If unsure between diagnoses of epididymitis and torsion, always go to OR

Remember: torsion >6 h has poor prognosis

Treatment
- rule out torsion (see *Investigations* Table 24, U29)
- see Table 9 for ABx therapy
- scrotal support, bed rest, ice, analgesia

Complications
- if severe → testicular atrophy
- 30% have persistent infertility problems

Inadequately treated acute epididymitis may lead to chronic epididymitis or epididymo-orchitis

Urethritis

Etiology
- infectious or inflammatory (e.g. reactive arthritis)

Reactive Arthritis (formerly known as Reiter's syndrome)
Urethritis, uveitis (or conjunctivitis), and arthritis
(can't pee, can't see, can't climb a tree)

Table 11. Infectious Urethritis: Gonococcal vs. Non-Gonococcal

	Gonococcal	Non-Gonococcal
Causative Organism	*Neisseria gonorrhoeae*	Usually *Chlamydia trachomatis*
Diagnosis	Hx of sexual contact, thick, profuse, yellow-grey purulent d/c, LUTS Gram stain (GN diplococci), urine PCR and/or culture from urethral specimen	Hx of sexual contact, mucoid whitish purulent d/c, ± storage LUTS Gram stain demonstrates >4 PMN/oil immersion field, no evidence of *N. gonorrhoeae*, urine PCR and/or culture from urethral specimen
Treatment	See Table 9	See Table 9

If culture negative or unresponsive to treatment consider: *Ureaplasma urealyticum, Mycoplasma genitalium, Trichimonas vaginalis*, HSV, or adenovirus

Stone Disease

Epidemiology
- prevalance of 2-3%
- M:F = 3:1
- peak incidence 30-50 yr of age
- recurrence rate: 10% at 1 yr, 50% at 5 yr, 60-80% lifetime

Risk Factors
- hereditary: RTA, Glucose-6-phosphate dehydrogenase deficiency, cystinuria, xanthinuria, oxaluria, etc.
- lifestyle: minimal fluid intake; excess vitamin C, oxalate, purines, calcium
- medications: loop diuretics (furosemide, bumetanide), acetazolamide, topiramate, and zonisamide
- medical conditions: UTI (with urea-splitting organisms: *Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus*), myeloproliferative disorders, IBD, gout, DM, hypercalcemia disorders (hyperparathyroidism, tumour lysis syndrome, sarcoidosis, histoplasmosis), obesity (BMI >30)

Key Points in Stone Hx
- Diet (especially FLUID INTAKE)
- Predisposing medical conditions
- Predisposing medications
- Previous episodes/investigations/treatments
- Family Hx (1st degree relative)

Clinical Features
- urinary obstruction → upstream distention → pain
  - flank pain from renal capsular distention (non-colicky)
  - severe waxing and waning pain radiating from flank to groin, testis, or tip of penis due to stretching of collecting system or ureter (ureteral colic)
- writhing, never comfortable, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- bladder stones result in: storage and voiding LUTS, terminal hematuria, suprapubic pain
- if fever, rule out concurrent pyelonephritis and/or obstruction

The four narrowest passage points for upper tract stones are:
- UPJ
- Pelvic brim
- Under vas deferens/broad ligament
- UVJ

Table 12. Differential Diagnosis of Renal Colic

GU	Abdominal	Neurological
• Pyelonephritis • Ureteral obstruction from other cause: UPJ obstruction, clot colic secondary to gross hematuria, sloughed papillae • Gynecological: ectopic pregnancy, torsion/rupture of ovarian cyst, PID	• AAA • Bowel ischemia • Pancreatitis • Other acute abdominal crisis	• Radiculitis (L1): herpes zoster, nerve root compression

Location of Stones
- calyx: may cause flank discomfort, persistent infection, persistent hematuria, or remain asymptomatic
- pelvis: tend to cause obstruction at UPJ, may cause persistent infection
- ureter: <5 mm diameter will pass spontaneously in 75% of patients

	Radiopaque	Radiolucent
KUB	Calcium Struvite Cystine	Uric acid Indinavir Atazanavir
CT	Calcium Struvite Cystine Uric acid	Indinavir Atazanavir

Stone Pathogenesis
- supersaturation of stone constituents (at appropriate temperature and pH)
- stasis, low flow, and low volume of urine (dehydration)
- crystal formation and stone nidus
- loss of inhibitory factors
  - citrate (forms soluble complex with calcium)
  - magnesium (forms soluble complex with oxalate)
  - pyrophosphate
  - Tamm-Horsfall glycoprotein

Approach to Renal Stones

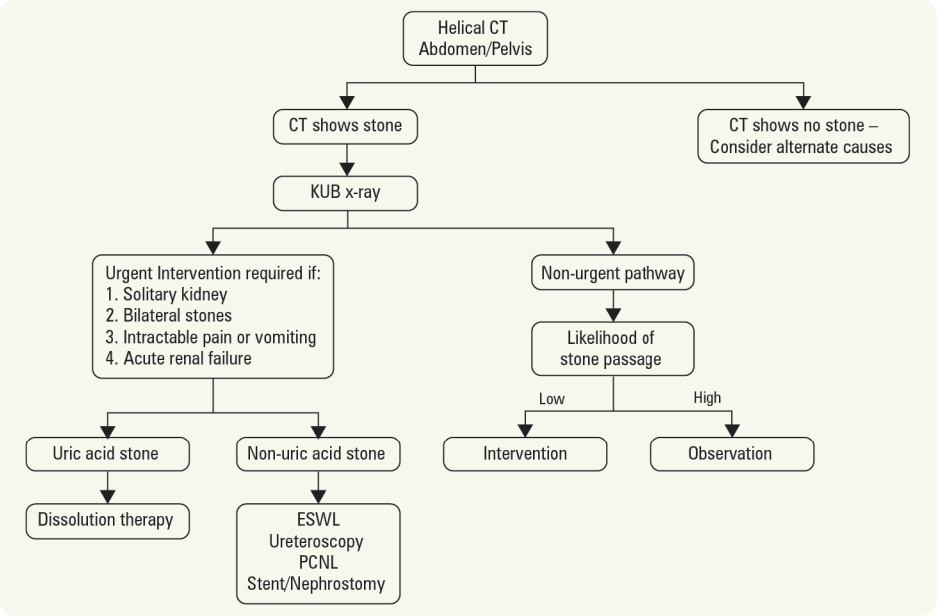


Figure 8. Approach to renal stone

Although hypercalciuria is a risk factor for stone formation, decreasing dietary calcium is NOT recommended to prevent stone formation. Low dietary calcium leads to increased GI oxalate absorption and higher urine levels of calcium oxalate

Stones and Infection
If septic, urgent decompression via ureteric stent or percutaneous nephrostomy is indicated. Definitive treatment of the stone should be delayed until the sepsis has cleared

Indications for PCNL
- Size >2 cm
- Staghorn
- UPJ obstruction
- Calyceal diverticulum
- Cystine stones (poorly fragmented with ESWL)
- Anatomical abnormalities
- Failure of less invasive modalities

Investigations

Table 13. Investigations for Renal Stones

	CBC, Uric Acid, U/A, Urine C&S	KUB x-ray	CT Scan	Abdominal Ultrasound	Cystoscopy	PTH, 24 h urine x 2 for volume, Cr, Ca^{2+}, Na^{+}, PO_4^{3-}, Mg^{2+}, oxalate, citrate, ± cystine
Who gets it?	Everyone	Most	First episode renal colic	Pediatric cases or those concerning for obstruction	± Those concerning for bladder stone	Recurrent Ca^{2+} stone formers ± pediatric cases
Why is it done?	May show signs of infection, ± sensitivities	90% of stones are radiopaque Good for follow-up	Distinguish radiolucent stone from soft tissue filling defect X-ray comparison	Identify and follow-up stone without radiation exposure Visualize hydronephrosis	Visualize bladder	Need to rule out metabolic cause for stones
Cautions	–	Do not mistake phleboliths for stones!	Radiation (especially if female of child bearing age) Must be a non-contrast scan	Not good at visualizing stones in ureter	–	–

Treatment – Acute

- medical
  - analgesic ± antiemetic
  - NSAIDs help lower intra-ureteral pressure
  - medical expulsion therapy (MET)
    - α-blockers: increase rate of spontaneous passage in distal ureteral stones
    - calcium channel blockers
  - ± Abx for bacteriuria
  - IV fluids if vomiting (note: IV fluids do NOT promote stone passage)
- interventional
  - required if obstruction endangers patient, e.g. sepsis, renal failure
  - first line: ureteric stent (via cystoscopy)
  - second line: image-guided percutaneous nephrostomy
- admit if necessary
  - *Indications for Admission to Hospital*

24 h urine collections must be done AFTER discontinuing stone preventing/promoting medications

Indications for Admission to Hospital
- Intractable pain
- Intractable vomiting
- Fever (suggests infection)
- Compromised renal function (including single kidney, bilateral obstructing stone)
- Pregnancy

Treatment – Elective

- medical
  - likely conservative if ureteral stone <10 mm or kidney stone <5 mm and no complications/symptoms well controlled
    - stones <5 mm especially likely to pass spontaneously
  - PO fluids to increase urine volume to >2 L/d (3-4 L if cystine) and MET
  - specific to stone type (see Table 14)
  - periodic imaging to monitor stone position and assess for hydronephrosis
  - progress to interventional stone removal methods if symptoms worsen or fail to improve (indicating stone passage)

Detailed metabolic studies are NOT recommended unless complex patient (recurrent stone formers, pregnancy, pediatrics, strong family Hx, underlying kidney or systemic disease, etc.)

- interventional
  - kidney
    - may stent prior to ESWL if stone is 1.5-2.5 cm
    - ESWL if stone <2 cm
    - PCNL if stone >2 cm
  - ureteral stones >10 mm
    - ESWL and URS are both first line treatment modalities for all locations
      - URS has significantly greater stone-free rates for stones at all locations in ureter, but also has higher complication rates (ureter perforation, stricture formation, etc.)
    - PCNL is second line treatment
    - laparoscopic or open stone removal (very rare)
  - bladder
    - transurethral stone removal or cystolitholapaxy
    - remove outflow obstruction (TURP or stricture dilatation)

Prevention

- dietary modification
  - increase fluid (>2 L/d), K^+ intake
  - reduce animal protein, oxalate, Na^+, sucrose, and fructose intake
  - avoid high-dose vitamin C supplements
- medications
  - thiazide diuretics for hypercalciuria
  - allopurinol for hyperuricosuria
  - potassium citrate for hypocitraturia, hyperuricosuria

Alpha-blockers as Medical Expulsive Therapy for Ureteral Stones
Cochrane DB Syst Rev 2014;4:CD008509
Purpose: To determine whether or not alpha blockers compared with other pharmacological treatments or placebo improve stone clearance rates and other clinically relevant outcomes in patients presenting with symptoms of stones less than 10mm confirmed by imaging.
Results/Conclusions: 32 RCTs, 5,864 participants. Although patients using alpha-blockers were more likely to experience adverse effects compared to standard therapy, stone-free rates were significantly higher in the alpha-blocker group (RR 1.48, 95% CI 1.33-1.64), expulsion time was 2.91 days shorter, and there was a reduction in the number of pain episodes (MD -0.48, 95% CI -0.94 to -0.01), the need for analgesic medication (MD -38.17, 95% CI -74.93 to -1.41), and hospitalization (RR 0.35, 95% CI 0.13-0.97). Alpha blockers should therefore be offered as a primary treatment modality for ureteral stones.

Consideration must be given to monitoring stone formers with periodic imaging (i.e. at year 1 and then q2-4yr based on likelihood of recurrence)

Table 14. Stone Classification

Type of Stone	Calcium (75-85%)	Uric Acid (5-10%)	Struvite (5-10%)	Cystine (1%)
Etiology	Hypercalciuria Hyperuricosuria (25% of patients with Ca^{2+} stones) Hyperoxaluria (<5% of patients) Hypocitraturia (12% of patients) Other causes: • Hypomagnesemia – associated with hyperoxaluria and hypocitraturia • High dietary Na^+ • Decreased urinary proteins • High urinary pH, low urine volume (e.g. GI water loss) • Hyperparathyroidism, obesity, gout, DM	Uric acid precipitates in low volume, acidic urine with a high uric acid concentration: • Hyperuricosuria alone • Low urinary pH, low urine volume (e.g. GI water loss) • Drugs (ASA, thiazides) • Diet (purine rich red meats) • Hyperuricosuria with hyperuricemia • Gout • High rate of cell turnover or cell death (leukemia, cytotoxic drugs)	Infection with urea-splitting organisms (*Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus*) results in alkaline urinary pH and precipitation of struvite (magnesium ammonium phosphate)	Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in "COLA" in urine (cystine, ornithine, lysine, arginine)
Key Features	Radiopaque on KUB Reducing dietary Ca^{2+} is NOT an effective method of prevention/ treatment	Radiolucent on KUB Radiopaque on CT Acidic urine, pH <5.5 (NOT necessarily elevated urinary uric acid)	Perpetuates UTI because stone itself harbours organism Stone and all foreign bodies must be cleared to avoid recurrence Associated with staghorn calculi Positive urine dip and cultures Note: *E. coli* infection does not cause struvite stones M:F = 3:1, UTI more common in female	Aggressive stone disease seen in children and young adults Recurrent stone formation, family Hx Often staghorn calculi Faintly radiopaque on KUB Positive urine sodium nitroprusside test, urine chromatography for cystine
Treatment Medical if stone <5 mm and no complications Procedural/Surgical treatment if stone >5 mm or presence of complications (see U17 for treatment)	Fluids to increase urine volume to >2 L/d For calcium stones: cellulose phosphate, orthophosphate for absorptive causes Calcium oxalate: thiazides, ± potassium citrate, ± allopurinol Calcium struvite: ABx (stone must be removed to treat infection)	Increased fluid intake Alkalinization of urine to pH 6.5 to 7 (bicarbonate, potassium citrate) ± allopurinol	Complete stone clearance ABx for 6 wk Regular follow-up urine cultures	Increased fluid intake (3-4 L of urine/d) Alkalinize urine (bicarbonate, potassium citrate), Penicillamine/ α-MPG or Captopril (form complex with cystine) ESWL not effective

Urological Neoplasms

Approach to Renal Mass

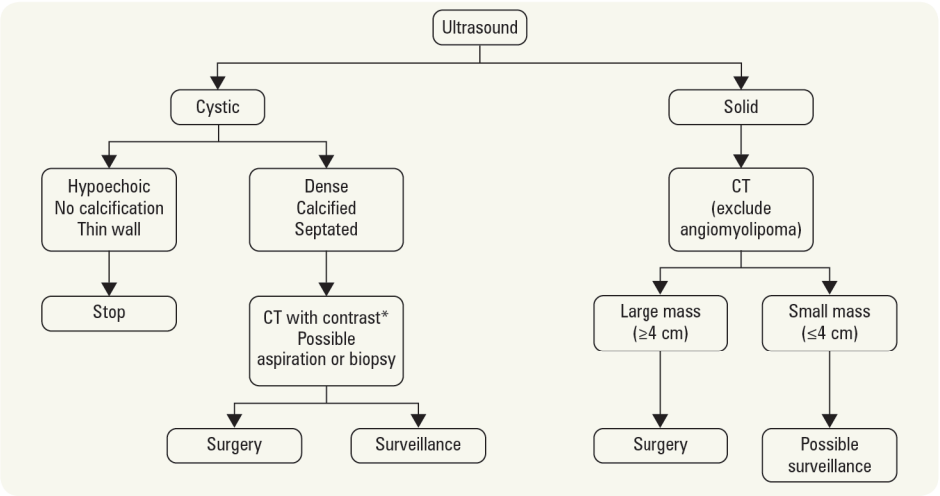


Figure 9. Workup of a renal mass
*Imaging modality may be different in cases of contrast allergy or elevated creatinine

There is controversy over optimal m[illegible]ement of small renal masses

Benign Renal Neoplasms

CYSTIC KIDNEY DISEASE

- **simple cysts**: usually solitary or unilateral
  - very common: up to 50% at age 50
  - usually incidental finding on abdominal imaging
  - **Bosniak Classification** is used to stratify for risk of malignancy based on cyst features from contrast CT
- **polycystic kidney disease**
  - autosomal recessive: multiple bilateral cysts, often leading to early renal failure in infants
  - autosomal dominant: progressive bilateral disease leading to HTN and renal failure, adult-onset
- **medullary sponge kidney**: cystic dilatation of the collecting ducts
  - usually benign course, but patients are predisposed to stone disease
- **von Hippel-Lindau syndrome**: multiple bilateral cysts or clear cell carincomas (50% incidence of RCC)
  - renal cysts, cerebellar, spinal and retinal hemangioblastomas, pancreatic and epididymal cysts, pheochromocytomas

Table 15. Bosniak Classification of Renal Cysts

Class	Description	Features	Risk of Malignancy	Management Plan
I	Simple cyst	Round, no septations, no calcifications, no solid component	Near zero	Follow-up usually not required
II	Simple cyst	A few thin septa, no true enhancement, well-marginated, uniform high attenuation, <3 cm	Minimal	Follow-up usually not required
IIF	Minimally complex cyst with extra features that require follow-up	Still well-marginated and non-enhancing, but now multiple thin septa or some thickening/ calcification of septa/wall, >3 cm	5-20%	Requires follow-up with imaging q6-12mo If the lesion evolves, may require surgical resection
III	Complex cyst	Thicker or more irregular walls with measurable enhancement	>50%	Requires surgical resection
IV	Clearly malignant	Class III + enhancing soft-tissue components	>90%	Requires surgical resection

Table 16. Benign Renal Masses

	Angiomyolipoma (Renal Hamartoma)	Renal Oncocytoma	Renal Adenoma
Epidemiology	<1% of adult renal tumours F>M 20% associated with tuberous sclerosis (especially if multiple, recurrent)	3-7% of renal tumours M>F Oncocytomas also found in adrenal, thyroid and parathyroid glands	Most common benign renal neoplasm M:F = 3:1 Incidence increases with age Found in 7-23% of all autopies
Characteristics	Clonal neoplasm consisting of blood vessels (angio-), smooth muscle (-myo-), and fat (-lipoma) May extend into regional lymphatics and other organs and become symptomatic	Spherical, capsulated with possible central scar Histologically organized aggregates of eosinophilic cells originating from intercalated cells of collecting duct	Small cortical lesions <1 cm Majority are solitary but can be multifocal
Diagnosis	Incidental finding on CT Negative attenuation (-20 HU) on CT is pathognomonic Rare presentation of hematuria, flank pain, and palpable mass (same as RCC)	Incidental finding on CT Difficult to distinguish from RCC on imaging – treated as RCC until proven otherwise Biopsy may be performed to rule out malignancy	Incidental finding on CT Rarely symptomatic Controversy as to whether this represents benign or pre-malignant neoplasm
Management	May consider surgical excision or embolization if symptomatic (pain, bleeding) or higher risk of bleeding (e.g. pregnancy) Potential role for mTOR inhibitors in unresectable/ metastatic disease Follow with serial U/S	Partial/radical nephrectomy for large masses HIFU or RFA for smaller masses	If mass >3 cm, likely not a benign adenoma; will require partial/radical nephrectomy due to increased likelihood of malignancy

Malignant Renal Neoplasms

RENAL CELL CARCINOMA

Etiology
- cause unknown
- originates from proximal convoluted tubule epithelial cells in clear cell subtype (most common)
- hereditary forms seen with von Hippel-Lindau syndrome and hereditary papillary renal carcinoma

Epidemiology
- 8th most common malignancy (accounts for 3% of all newly diagnosed cancers)
- 85% of primary malignant tumours in kidney
- M:F = 3:2
- peak incidence at 50-60 yr of age

Pathology
- histological subtypes: clear cell (75-85%), papillary (10-15%), chromophobic (5-10%), collecting duct
- sarcomatoid elements in any subtype is a poor prognostic factor

Risk Factors
- top 3 risk factors: smoking, HTN, obesity
- miscellaneous: horseshoe kidney, acquired renal cystic disease
- role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

Clinical Features
- usually asymptomatic: frequently diagnosed incidentally by U/S or CT
- poor prognostic indicators: weight loss, weakness, anemia, bone pain
- classic "too late triad" found in 10-15%
  - gross hematuria 50%
  - flank pain <50%
  - palpable mass <30%
- was called the "internist's tumour" because of paraneoplastic symptomatology – now called the "radiologist's tumour" because of incidental diagnosis via imaging
- metastases: seen in 1/3rd of new cases; additional 20-40% will go on to develop metastases
  - bone, brain, lung and liver most common site
  - may invade renal veins and inferior vena cava lumen. This may result in ascites, hepatic dysfunction, right atrial tumour, and pulmonary emboli

Investigations
- routine labs for paraneoplastic syndromes (CBC, ESR, LFTs, extended electrolytes)
- U/A (60-75% have hematuria)
- renal U/S: solid vs. cystic lesion

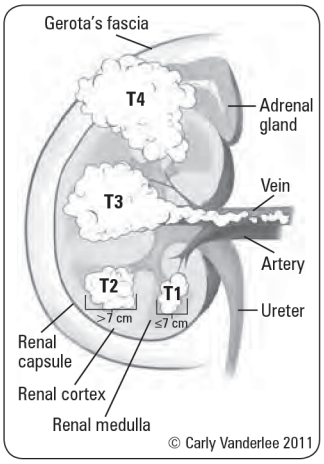


Figure 10. RCC staging

Role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

RCC Systemic Effects: paraneoplastic syndromes (10-40% of patients)
- Hematopoietic disturbances: anemia, polycythemia, raised ESR
- Endocrinopathies: hypercalcemia (increased vitamin D hydroxylation), erythrocytosis (increased erythropoietin), HTN (increased renin), production of other hormones (prolactin, gonadotropins, TSH, insulin, and cortisol)
- Hepatic cell dysfunction or Stauffer syndrome: abnormal LFTs, decreased WBC count, fever, areas of hepatic necrosis; no evidence of metastases; reversible following removal of primary tumour
- Hemodynamic alterations: systolic HTN (due to AV shunting), peripheral edema (due to caval obstruction)

- contrast-enhanced CT: higher sensitivity than U/S for detection of renal masses and for staging purposes
- MRI: useful for evaluation of vascular extension
- renal biopsy: to confirm diagnosis if considering observation or other non-surgical therapy

Tumour may invade renal veins and inferior vena cava lumen. This may result in ascites, hepatic dysfunction, right atrial tumour, and pulmonary emboli

Staging
- involves CT, CXR, liver enzymes and LFTs, bone/head imaging (if symptoms dictate)

Table 17. 2010 TNM Classification of Renal Cell Carcinoma

T	N	M
T1: tumour <7 cm, confined to renal parenchyma **T1a**: <4 cm **T1b**: 4-7 cm **T2**: tumour >7 cm, confined to renal parenchyma **T2a**: tumour >7 cm but ≤10 cm in greatest dimension, limited to the kidney **T2b**: tumour >10 cm, limited to the kidney **T3**: tumour extends into major veins or perinephric tissues, but NOT into ipsilateral adrenal or beyond Gerota's fascia **T3a**: into renal vein or sinus fat **T3b**: into infradiaphragmatic IVC **T3c**: into supradiaphragmatic IVC **T4**: tumour extends beyond Gerota's fascia including extension into ipsilateral adrenal	**N0**: no regional nodes **N1**: metastasis to a single node, <2 cm **N2**: metastasis to a single node between 2-5 cm or multiple nodes <2 cm **N3**: node >5 cm	**M0**: no evidence of metastasis **M1**: presence of distant metastasis

Treatment
- surgical
  - radical nephrectomy: en bloc removal of kidney, tumour, ipsilateral adrenal gland (in upper pole tumours) and intact Gerota's capsule and paraaortic lymphadenectomy
  - partial nephrectomy (parenchyma-sparing): small tumour (roughly <4 cm) or solitary kidney/bilateral tumours
  - surgical removal of solitary metastasis may be considered
- ablative techniques (cryoablation, RFA)
- palliative radiation to painful bony lesions
- therapy for advanced stage
  - tyrosine kinase inhibitors for metastatic disease (e.g. sunitinib, sorafenib)
  - anti-angiogenesis/anti-VEGF (e.g. bevacizumab)
  - mTOR inhibitors (e.g. temsirolimus, everolimus)
  - high-dose IL-2 (high toxicity but able to induce long-term cure in 5-7% of patients)
  - IFN α: monotherapy has been largely replaced by molecularly targeted agents listed above

Sorafenib in Advanced Clear-Cell Renal Cell Carcinoma – TARGET Trial
NEJM 2007;356:125-134
Study: Phase III, double-blind RCT comparing multikinase inhibitor, sorafenib, with placebo in treatment of advanced clear-cell renal cell carcinoma.
Methods: Patients with clear cell renal cell carcinoma, resistant to standard therapy. The main intervention and outcome were sorafenib and overall survival, respectively.
Results: Progression-free survival in intervention group was 5.5 mo, compared with 2.8 mo in the placebo group. The survival improvement was associated with an increased number of adverse events.

Prognosis
- stage at diagnosis most important prognostic factor
  - T1: 90-100% 5 yr survival
  - T2-T3: 60% 5 yr survival
  - metastatic disease: <5% 10 yr survival

Axitinib vs. Sorafenib as Second-Line Treatment for Advanced Renal Cell Carcinoma: Overall Survival Analysis and Updated Results from a Randomized Phase 3 Trial
Lancet Oncol 2013;14:552-562
Study: Phase 3 trial of patients with clear cell metastatic renal cell carcinoma randomized to receive axitinib 5 mg twice daily (n=361) or sorafenib 400 mg twice daily (n=362).
Results: Median overall survival was 20.1 mo with axitinib (16.7 -23.4) and 19.2 monwith sorafenib (17.5-22.3) (HR 0.969, 95% CI 0.800-1.174). Median progression-free survival was 8.3 months with axitinib (6.7-9.2) and 5.7 mo with sorafenib (4.7-6.5) (HR 0.656, 95% CI 0.552-0.779).
Conclusions: Axitinib should be a second-line treatment option for patients with metastatic renal cell carcinoma.

Carcinoma of the Renal Pelvis and Ureter

Etiology
- risk factors include
  - smoking
  - chemicals/dietary exposures (industrial dyes and solvents; aristolochic acid)
  - analgesic abuse (acetaminophen, ASA, and phenacetin)
  - Balkan nephropathy

Epidemiology
- rare: accounts for 5% of all urothelial cancers
- frequently multifocal, 2-5% are bilateral
- M:F = 3:1
- relative incidence: bladder:renal:ureter = 100:10:1

Radiotherapy With or Without Chemotherapy in Muscle-Invasive Bladder Cancer
NEJM 2012;366:1477-1488
Study: Phase 3 trial with random assignment of 360 patients with muscle-invasive bladder cancer to radiotherapy with or without chemotherapy.
Results: At 2 yr, rates of locoregional disease-free survival were 67% in the chemoradiotherapy group and 54% in the radiotherapy group (HR 0.68, 95% CI 0.48-0.96). Five year overall survival rates were 48% in the chemoradiotherapy group and 35% in the radiotherapy group (HR 0.82, 95% CI 0.63-1.09).
Conclusions: Chemotherapy with fluorouracil and mitomycin C in combination with radiotherapy improves locoregional control of bladder cancer compared to radiotherapy alone, with no significant increase in adverse events.

Pathology
- 85% are papillary urothelial cell carcinoma; others include SCC and adenocarcinoma
- UCC of ureter and renal pelvis are histologically similar to bladder UCC

Clinical Features
- gross/micrscopic hematuria
- flank pain
- storage or voiding symptoms (dysuria only if lower urinary tract involved)
- flank mass ± hydronephrosis (10-20%)

Investigations
- IVP/CT urogram
- cystoscopy and retrograde pelogram

Treatment
- radical nephroureterectomy with cuff of bladder
- distal ureterectomy for distal ureteral tumours
- emerging role for endoscopic laser ablation in patients with low grade disease, poor baseline renal health

Differential Diagnosis of Filling Defect
- Urothelial carcinoma (differentiate via cytology and CT scan)
- Uric acid stone (differentiate via cytology and CT scan)
- Blood clot
- Pyelitis cystica
- Papillary necrosis
- Fungus ball
- Gas bubble from gas producing organisms

Bladder Carcinoma

Etiology
- unknown, but environmental risk factors include
  - smoking (main factor – implicated in 60% of new cases)
  - aromatic amines: naphthylamines, benzidine, tryptophan, phenacetin metabolites
  - cyclophosphamide
  - prior Hx of radiation treatment to the pelvis
  - *Schistosoma hematobium* infection (associated with SCC)
  - chronic irritation: cystitis, chronic catheterization, bladder stones (associated with SCC)
  - aristolochic acid: associated with Balkan Nephropathy (renal failure, upper tract urothelial cancer) and Chinese Herbal Nephropathy

Epidemiology
- 2nd most common urological malignancy
- M:F = 3:1, more common among whites than blacks
- mean age at diagnosis is 65 yr

Pathology
- classification
  - UCC >90%
  - SCC 5-7%
  - adenocarcinoma 1%
  - others <1%
- stages and prognoses of urothelial carcinoma at diagnosis
  - non-muscle invasive (75%) → >80% overall survival
    - 15% of these will progress to invasive UCC
    - the majority of these patients will have recurrence
  - invasive (25%) → 50-60% 5 yr survival
    - 85% have no prior Hx of superficial UCC (i.e. *de novo*)
    - 50% have occult metastases at diagnosis, and most of these will develop overt clinical evidence of metastases within 1 yr – lymph nodes, lung, peritoneum, liver
- carcinoma *in situ* → flat, non-papillary erythematous lesion characterized by dysplasia confined to urothelium
  - more aggressive, worse prognosis
  - usually multifocal
  - may progress to invasive UCC

The "field defect" theory helps to explain why UCC has multiple lesions and has a high recurrence rate. The entire urothelium (pelvis to bladder) is bathed in carcinogens

Clinical Features
- asymptomatic (20%)
- hematuria (key symptom: 85-90% at the time of diagnosis)
- pain (50%) → location determined by size/extent of tumour (i.e. flank, suprapubic, perineal, abdominal, etc.)
- clot retention (17%)
- storage urinary symptoms → consider carcinoma *in situ*
- palpable mass on bimanual exam → likely muscle invasion
- obstruction of ureters → hydronephrosis and uremia (nausea, vomiting, and diarrhea)

The ENTIRE urinary tract must be evaluated in patients with hematuria unless there is clear evidence of glomerular bleeding (e.g. red cell casts, dysmorphic RBCs, etc.)

Investigations
- U/A, urine C&S, urine cytology
- U/S
- CT scan with contrast → look for filling defect
- cystoscopy with biopsy (gold standard)
- biopsy to establish diagnosis and to determine depth of penetration
- specific bladder tumour markers (e.g. NMP-22, BTA, Immunocyt, FDP)

Cystoscopy is the initial procedure of choice for the diagnosis and staging of urothelial malignancy

Unexplained hematuria in any individual >40 yr old must be investigated to rule out a malignancy

Grading
- low grade: <=10% invasive, 60% recur
- high grade: 50-80% are invasive or should progress to invasive over time

Tumour grade is the single most important prognostic factor for progression

Staging
- for invasive disease: CT or MRI, CXR, LFTs, extended electrolytes (Ca^{2+}, Mg^{1+}, PO_4^{3-}) (metastatic workup)

Table 18. 2010 TNM Classification of Bladder Carcinoma

T	N	M
TX: Primary tumour cannot be assessed	**NX:** Lymph nodes cannot be assessed	**M0:** No distant metastasis
T0: No evidence of primary tumour	**N0:** No lymph node metastasis	**M1:** Distant metastasis
Ta: Noninvasive papillary carcinoma	**N1:** Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)	
Tis: Carcinoma *in situ*: "flat tumour"	**N2:** Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)	
T1: Tumour invades subepithelial connective tissue	**N3:** Lymph node metastasis to the common iliac lymph nodes	
T2: Tumour invades muscularis propria		
pT2a: Tumour invades superficial muscularis propria (inner half)		
pT2b: Tumour invades deep muscularis propria (outer half)		
T3: Tumour invades perivesical tissue		
pT3a: Microscopically		
pT3b: Macroscopically (extravesical mass)		
T4: Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall		
T4a: Tumour invades prostatic stroma, uterus, vagina		
T4b: Tumour invades pelvic wall, abdominal wall		

Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer
NEJM 2003;349:859-866
Study: Randomized clinical trial.
Patients: 317 patients with transitional-cell carcinoma of the bladder (T2N0M0 to T4aN0M0).
Intervention: Randomized to undergo radical cystectomy or to receive three cycles of combined chemotherapy (methotrexate, vinblastine, doxorubicin, and cisplatin) followed by radical cystectomy.
Main Outcome: Survival. Secondary objective was to quantify down-staging of tumour following chemotherapy.
Results: At 5 yr after treatment initiation, 57% of the combination-therapy group vs. 43% of the cystectomy group were alive (p=0.06). In the combination-therapy group, 38% of the patients were pathologically free of cancer at the time of cystectomy vs. 15% of the cystectomy-only group at the time of surgery (p<0.001).
Conclusions: For locally advanced bladder carcinoma, neoadjuvant chemotherapy significantly reduces tumour volume and also improves survival.

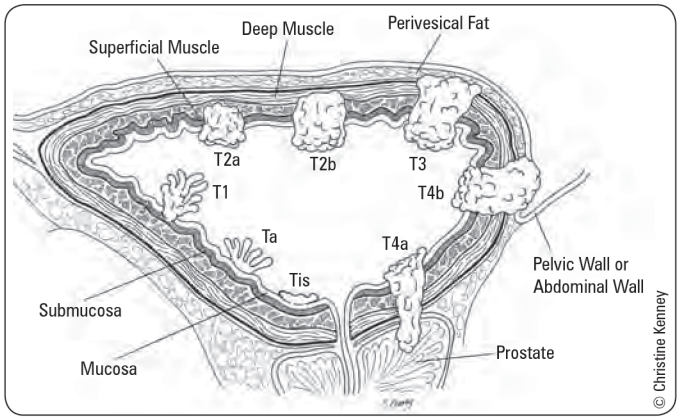


Figure 11. Urothelial carcinoma of bladder

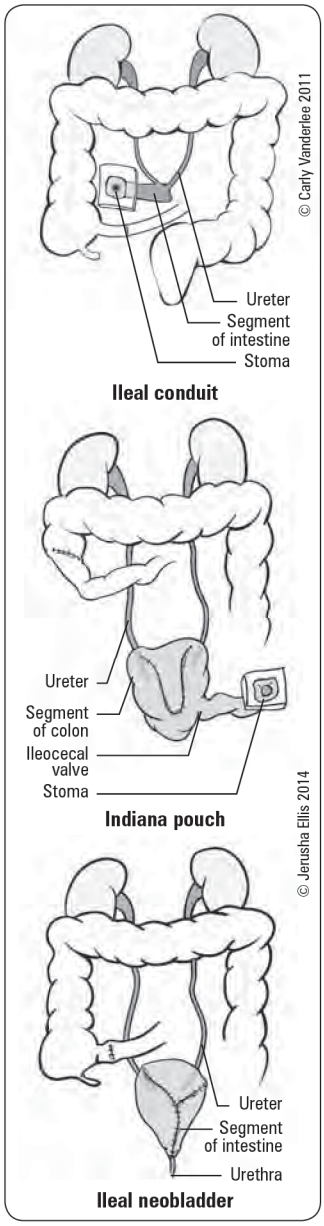


Figure 12. Ileal conduit, Indiana pouch, ileal neobladder

Treatment

- superficial (non-muscle invasive) disease: Tis, Ta, T1
  - low-grade disease
    - single dose mitomycin c within 24 hours of resection reduces recurrence rates
  - high-grade
    - TURBT ± intravesical chemo/immuno-therapy (e.g. BCG, mitomycin C) to decrease recurrence rate
    - maintenance with intravesical chemotherapy with BCG for 3 cycles every 3 mo, may be continued for 2-3 yr
- invasive disease: T2a, T2b, T3
  - radical cystectomy + pelvic lymphadenectomy with urinary diversion (e.g. ileal conduit, Indiana pouch, ileal neobladder) or TURBT + chemo-radiation (bladder sparing) for small tumours with non-obstructed ureters
  - neo-adjuvant chemotherapy prior to cystectomy may also be done
  - use of adjuvant chemotherapy after definitive local treatment is controversial
- advanced/metastatic disease: T4a, T4b, N+, M+
  - initial combination of systemic chemotherapy ± irradiation ± surgery

Prognosis

- depends on stage, grade, size, number of lesions, recurrence and presence of CIS
  - T1: 90% 5 yr survival
  - T2: 55% 5 yr survival
  - T3: 20% 5 yr survival
  - T4/N+/M+: <5% 5 yr survival

Prostate Cancer

Etiology

- not known
- risk factors
  - increased incidence in persons of African descent
  - high dietary fat = 2x risk

- family Hx
  - 1st degree relative = 2x risk
  - 1st and 2nd degree relatives = 9x risk

Epidemiology
- most prevalent cancer in males
- 3rd leading cause of male cancer deaths (following lung and colon)
- up to 50% risk of CaP at age 50
- lifetime risk of death from CaP is 3%
- 75% diagnosed between ages of 60 and 85; mean age at diagnosis is 72

Pathology
- adenocarcinoma
  - >95%, often multifocal
- urothelial carcinoma of the prostate (4.5%)
  - associated with UCC of bladder; does NOT follow TNM staging below; not hormone-responsive
- endometrial (rare)
  - carcinoma of the utricle

Anatomy (see Figure 7, U7)
- 60-70% of nodules arise in the peripheral zone
- 10-20% arise in the transition zone
- 5-10% arise in the central zone

Clinical Features
- usually asymptomatic
- most commonly detected by DRE, elevated PSA, or as an incidental finding on TURP
  - DRE: hard irregular nodule or diffuse dense induration involving one or both lobes
  - PSA: see *Prostate Cancer Screening*, U26
- locally advanced disease
  - storage and voiding symptoms, ED (all uncommon without spread)
- metastatic disease
  - bony metastases to axial skeleton common
  - visceral metastases are less common (liver, lung, and adrenal gland most common sites)
  - leg pain and edema with nodal metastases obstructing lymphatic and venous drainage

Methods of Spread
- local invasion
- lymphatic spread to regional nodes
  - obturator > iliac > presacral/para-aortic
- hematogenous dissemination occurs early

Investigations
- DRE
- PSA elevated in the majority of patients with CaP
- TRUS-guided needle biopsy
- bone scan may be omitted in untreated CaP with PSA <10 ng/mL
- CT scanning to assess metastases
- MRI: being investigated for possible role in detection, staging, MRI-guided biopsying and active surveillance

Table 19. 2010 TNM Classification of Prostate Carcinoma

T	N	M
T1: clinically undetectable tumour, normal DRE and TRUS **T1a**: tumour incidental histologic finding in <5% of tissue resected **T1b**: tumour incidental histologic finding in >5% of tissue resected **T1c**: tumour identified by needle biopsy (due to elevated PSA level) **T2**: palpable, confined to prostate **T2a**: tumour involving ≤ one half of one lobe **T2b**: tumour involving > one half of one lobe, but not both lobes **T2c**: tumour involving both lobes **T3**: tumour extends through prostate capsule **T3a**: extracapsular extension (unilateral or bilateral) **T3b**: tumour invading seminal vesicle(s) **T4**: tumour invades adjacent structures (besides seminal vesicles)	**NX**: regional lymph nodes were not assessed **N0**: no regional lymph node metastasis **N1**: spread to regional lymph nodes	**M0**: no distant metastasis **M**: distant metastasis **M1a**: nonregional lymph nodes **M1b**: bone(s) **M1c**: other site(s) with or without bone disease

Table 20. Prostate Cancer Mortality Risk

	Low Risk	Intermediate Risk (if any of following)	High Risk (if any of following)
PSA	<10	10-20	>20
Gleason Score	<7	7	8-10
Stage	pT1-2a	pT2b-T2c	pT3/4

Treatment
- T1/T2 (localized, low-risk)
  - if adequate life expectancy or no other significant comorbidities, consider active surveillance vs. definitive local treatment (RP, brachytherapy, or EBRT)
  - no difference in cure rate between definitive treatment modalities
  - in older population: watchful waiting + palliative treatment for symptomatic progression
- T1/T2 (intermediate or high-risk)
  - definitive therapy over active surveillance
- T3, T4
  - EBRT + androgen deprivation therapy or RP + adjuvant EBRT
- N >0 or M >0
  - requires hormonal therapy/palliative radiotherapy for metastases; may consider combined androgen blockade
  - bilateral orchiectomy – removes 90% of testosterone
  - GnRH agonists (e.g. leuprolide, goserelin)
  - GnRH antagonist (e.g. degarelix)
  - estrogens (e.g. diethylstilbestrol [DES])
  - antiandrogens (e.g. bicalutamide)
  - local irradiation of painful secondaries or half-body irradiation
- hormone-refractory prostate cancer
  - chemotherapy: docetaxel, cabazitaxel, sipuleucel-T

Table 21. Treatment Options for Localized Prostate Cancer

Modality	Population Considered	Limitations
Watchful Waiting	Short life expectancy (<5-10 yr); will likely only receive non-curative hormonal therapy if disease progresses	Disease progression
Active Surveillance (serial PSA, DRE, and biopsies)	Low grade disease, good follow-up; is still considering more curative treatment if disease progresses	Disease progression; decrease in QOL associated with serial testing; risks associated with biopsies; no optimal monitoring schedule has been defined to date
Brachytherapy	Low volume, low PSA (<10), low grade	ED (50%), long-term effectiveness not well-established
EBRT	Locally advanced disease, older patients	Radiation proctitis (5%), ED (50%), risk of rectal cancer
RP	Young patients (<75 yr), high-risk disease	Incontinence (10%), ED (30-50%)

*Other options include cryosurgery, HIFU, hormonal ablation

Radical Prostatectomy vs. Watchful Waiting in Early Prostate Cancer (Scandinavian Prostate Cancer Group Study)
NEJM 2011;364:1708-1717
Study: Randomized clinical trial comparing watchful waiting with radical prostatectomy for localized prostate cancer.
Methods: 695 men from 14 centres in Finland, Sweden, and Iceland with newly diagnosed, localized prostate cancer were included in this study.
Main Outcomes: Mortality, distant metastases, local progression.
Results: For men with low-risk prostate cancer (PSA<10, Gleason score<7), at 15 yr after treatment initiation, the relative risk of death due to prostate cancer in the radical prostatectomy group versus watchful waiting was 0.62 (p=0.01). The cumulative incidence of death from prostate cancer after radical prostatectomy was high as compared with other studies.
Conclusions: Radical prostatectomy was associated with reduced rate of death due to prostate cancer.

Radical Prostatectomy vs. Observation for Localized Prostate Cancer (Prostate Cancer Intervention vs. Observation Trial (PIVOT) Study Group)
NEJM 2012;367:203-213
Study: Randomized clinical trial comparing observation with radical prostatectomy for localized prostate cancer.
Methods: 731 men at 52 United States centres with localized prostate cancer participated.
Main Outcomes: Mortality, bone metastases, surgical morbidity.
Results: Radical prostatectomy did not reduce all-cause or prostate cancer mortality relative to observation (relative risk 0.60, p=0.09), through at least 12 yr of follow-up.
Conclusions: Observation is recommended for localized prostate cancer, especially in men with low PSA and low-risk disease.

Prognosis
- T1-T2: comparable to normal life expectancy
- T3-T4: 40-70% 10-yr survival
- N+ and/or M+: 4 % 5 yr survival
- prognostic factors: tumour stage, tumour grade, PSA value, PSA doubling time

Prostate Cancer Screening

Digital Rectal Exam
- should be included as part of initial screening
- suspicious findings: abnormal feeling, nodularity, focal lesion, discrete change in texture/fullness/symmetry

Prostate Specific Antigen
- glycoprotein produced by epithelial cells of prostate gland
- leaks into circulation in setting of disrupted glandular architecture
- value of <4 ng/mL traditionally considered as cut-off to differentiate normal from pathologic value, but no single justifiable cutpoint
- measured serum PSA is a combination of free (15%) and bound PSA (85%)
- PSA velocity, PSA density, and free:total PSA: all intended to increase sensitivity and specificity of serum PSA values
  - association of increased CaP rates with decreased free are total PSA, elevated PSA velocity and density

Causes of Increased PSA
BPH, prostatitis, prostatic ischemia/infarction, prostate biopsy/surgery, prostatic massage, acute urinary retention, urethral catheterization, cystoscopy, TRUS, strenuous exercise, perineal trauma, ejaculation, acute renal failure, coronary bypass graft, radiation therapy

PSA is specific to the PROSTATE, but NOT to prostate cancer

Screening Recommendations
- conflicting evidence regarding mortality reduction with PSA-based screening and debate regarding overdiagnosis/overtreatment

- Long-Term Care and United States Preventative Services Task Force all recommend against PSA testing as a population-wide screening tool
- however, serum PSA screening recommended in any man with >10 yr life-expectancy and any of the following
  - suspicious finding on DRE
  - moderate-severe LUTS
  - high risk individuals
  - investigating secondary carcinoma of unknown origin to rule out CaP as primary

Canadian Urological Association Guidelines (2011) re: CaP Screening
- harms and benefits of PSA testing must be explained to the patient and an informed, shared decision to test must be established
- initial screening should include both serum PSA and DRE
- all men should be offered screening at age 50 if >10 yr life-expectancy
- high-risk individuals (family Hx of CaP or African ancestry) should be offered screening at age 40 if >10 yr life-expectancy
- standard has been annual screening, but q2-4yr screening acceptable
- no strict cutpoint for when to biopsy. Decision to biopsy should be based on more than a single PSA value

*new guidelines under development, however, AUA guidelines recommend against universal routine PSA screening for CaP

Screening for Prostate Cancer
Cochrane DB Syst Rev 2013;1:CD004720
Background: Screening for prostate cancer has an unclear benefit for reducing prostate cancer-specific mortality and morbidity.
Study: Systematic review of randomized clinical trials of screening vs no screening. A total of 31 trials were retrieved for this review.
Results: A meta-analysis of 5 RCTs with 341,342 participants was done. Collectively, there was no significant reduction in prostate cancer-specific mortality within 10 yr of follow-up. Screening procedures and biopsies were commonly associated with bleeding, bruising, and short-term anxiety; subsequent over-diagnosis and overtreatment resulted in additional harms, some severe.
Conclusions: Men who have a life expectancy less than 10-15 yr should be informed that screening for prostate cancer is unlikely to be beneficial. Significant harms are associated with screening, over-diagnosis, and overtreatment.

Testicular Tumours

Etiology/Risk Factors
- cryptorchidism, atrophy, sex hormones, HIV infection, infertility, family Hx, past Hx of testicular cancer

Epidemiology
- rare, but most common solid malignancy in young males 15-34 yr
- any solid testicular mass or acute hydrocoele in young patient – must rule out malignancy
- slightly more common in right testis (corresponds with slightly higher incidence of right-sided cryptorchidism)
- 2-3% bilateral (simultaneously or successively)

Pathology
- primary
  - 1% of all malignancies in males
  - cryptorchidism has increased risk (10-40x) of malignancy
  - 95% are germ cell tumours (all are malignant)
    - seminoma (35%) → classic, anaplastic, spermatocytic
    - NSGCT → embryonal cell carcinoma (20%), teratoma (5%), choriocarcinoma (<1%), yolk sac (<<1%), mixed cell type (40%)
  - 5% are non-germ cell tumours (usually benign) → Leydig (testosterone, precocious puberty), Sertoli (gynecomastia, decreased libido)
- secondary
  - male >50 yr
  - usually lymphoma or metastases (e.g. lung, prostate, GI)

Clinical Features
- **painless** testicular enlargement (painful if intratesticular hemorrhage or infarction)
- dull, heavy ache in lower abdomen, anal area or scrotum
- associated hydrocele (10%)
- coincidental trauma (10%)
- infertility (rarely presenting complaint)
- gynecomastia due to secretory tumour effects
- supraclavicular and inguinal lymphadenopathy
- abdominal mass (retroperitoneal lymph node mets)

Methods of Spread
- local spread follows lymphatics
  - right → medial, paracaval, anterior and lateral nodes
  - left → left lateral and anterior paraaortic nodes
  - "cross-over" metastases from right to left are fairly common, but no reports from left to right
- hematogenous most commonly to lung, liver, bones, and kidney

Investigations
- diagnosis is established by pathological evaluation of specimen obtained by radical inguinal orchidectomy
- tumour markers (β-hCG, LDH, AFP)
  - β-hCG and AFP are positive in 85% of non-seminomatous tumours
  - elevated marker levels return to normal post-operatively if no metastasis
  - β-hCG positive in 7% of pure seminomas, AFP never elevated with seminoma
- testicular U/S (hypoechoic area within tunica albuginea = high suspicion of testicular cancer)
- evidence of testicular microlithiasis is not a risk factor for testicular cancer
- needle aspiration contraindicated

Testes and scrotum have different lymphatic drainage, therefore trans-scrotal approach for biopsy or orchiectomy should be avoided

Staging
- Clinical: CXR (lung mets), markers for staging (β-hCG, AFP, LDH), CT abdomen/pelvis (retroperitoneal lymphadenopathy)
  - Stage I: disease limited to testis, epididymis, or spermatic cord
  - Stage II: disease limited to the retroperitoneal nodes
  - Stage III: disease metastatic to supradiaphragmatic nodal or visceral sites

Table 22. 2010 TNM Classification of Testicular Carcinoma

T	N	M
Tis: intratubular germ cell neoplasia **T1**: limited to testis and epididymis without vascular/lymphatic invasion **T2**: limited to testis and epididymis with vascular/lymphatic invasion **T3**: invasion of the spermatic cord ± vascular/lymphatics **T4**: invasion of the scrotum ± vascular/lymphatics	**N** status: same as RCC	**M0**: no distant mets **M1**: distant mets **M1a**: nonregional lymph node(s) or pulmonary mets **M1b**: distant mets other than to regional lymph nodes and lung

Management
- orchiectomy through inguinal ligament for all stages
- consider sperm banking, testicular prosthesis
- adjuvant therapies

Orchiopexy
Surgical descent (orchiopexy) of undescended testis does not eliminate the risk of malignancy, but allows for earlier detection by self-examination and reduces the risk of infertility

Prognosis
- 99% cured with stage I and II disease
- 70-80% complete remission with advanced disease

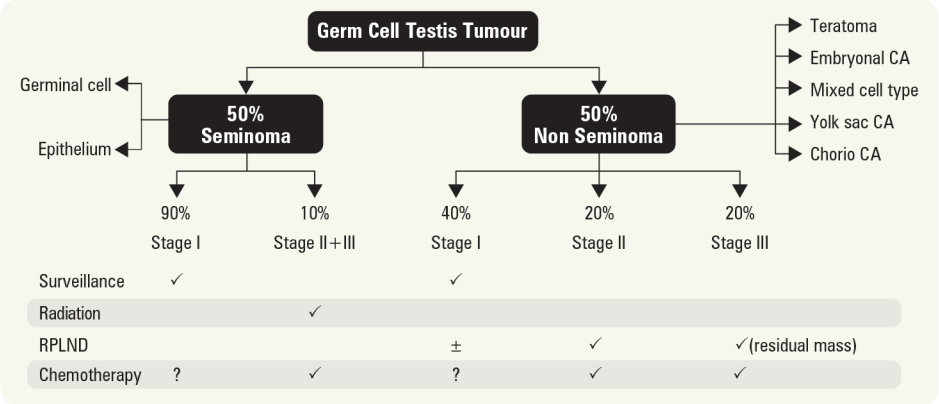


Figure 13. Adjuvant management of testicular cancer post-orchiectomy
Adapted from Dr. MAS Jewett

Penile Tumours

Epidemiology
- rare (<1% of cancer in males in U.S.)
- most common in 6th decade

Benign
- cyst, hemangioma, nevus, papilloma

Pre-Malignant
- balanitis xerotica obliterans, leukoplakia, Buschke-Lowenstein tumour (large condyloma)

Pre-invasive Cancer
- carcinoma *in situ*
  - Bowen's disease → crusted, red plaques on the shaft
  - erythroplasia of Queyrat → velvet red, ulcerated plaques on the glans
  - treatment options: local excision, laser, radiation, topical 5-fluorouracil

Malignant
- risk factors
  - chronic inflammatory disease
  - STI
  - phimosis
  - uncircumcised penis
- 2% of all urogenital cancers
- SCC (>95%), basal cell, melanoma, Paget's disease of the penis (extremely rare)
- definitive diagnosis requires full thickness biopsy of lesion
- lymphatic spread (superficial/deep inguinal nodes → iliac nodes) >> hematogenous

Treatment
- wide surgical excision with tumour-free margins (dependent on extent and area of penile involvement) ± lymphadenectomy
- consider less aggressive treatment modalities in CIS (cryotherapy, laser therapy, etc.) if available

Scrotal Mass

Table 23. Differentiating between Scrotal Masses

Condition	Pain	Palpation	Additional Findings
Torsion	+	Diffuse tenderness Horizontal lie of testicle	Absent cremaster reflex, negative Prehn's sign
Epididymitis (U16)	+	Epididymal tenderness	Present cremaster reflex, positive Prehn's sign
Orchitis (U16)	+	Diffuse tenderness	Present cremaster reflex, positive Prehn's sign
Hematocele	+	Diffuse tenderness	No transillumination
Hydrocele	–	Testis not separable from hydrocele, cord palpable	Transillumination, Hx of trauma
Spermatocele	–	Testis separable from spermatocele, cord palpable	Transillumination
Varicocele	–	Bag of worms	No transillumination, increases in size with Valsalva, decrease in size if supine
Indirect Inguinal	– (+ if strangulated)	Testis separable from hernia, cord not palpable, cough impulse may transmit, may be reducible	No transillumination
Tumour	– (+ if hemorrhagic)	Hard lump/nodule	
Generalized/ Dependant edema	–	Diffuse swelling	Often post-operative or immobilized, check for liver dysfunction
Idiopathic	–		

Varicocele Grading
- Grade 1: Palpable only with Valsalva manoeuvre
- Grade 2: Palpable without Valsalva
- Grade 3: Visible through scrotal skin

Suspect a Retroperitoneal Mass/ Process in a Patient with a Varicocele if
- Acute onset
- Right sided (isolated)
- Palpable abdominal mass
- Does not reduce while supine

Indications for Treatment of Varicocele
- Impaired sperm quality or quantity
- Pain or dull ache affecting QOL
- Affected testis fails to grow in adolescents
- Cosmetic indications (especially in adolescents)

Table 24. Benign Scrotal Masses

Type	Varicocele	Spermatocele	Hydrocele	Testicular Torsion	Inguinal Hernia
Definition	Dilatation and tortuosity of pampiniform plexus	A benign, sperm filled epididymal retention cyst	Collection of serous fluid that results from a defect or irritation in the tunica vaginalis	Twisting of the testicle causing venous occlusion and engorgement as well as arterial ischemia and infarction	Protrusion of abdominal contents through the inguinal canal into the scrotum
Etiology	15% of men Due to incompetent valves in the testicular veins 90% left sided	Multiple theories, including: Distal obstruction Aneurysmal dilations of the epididymis Agglutinated germ cells	Usually idiopathic Found in 5-10% testicular tumours Associated with trauma/ infection Communicating: patent processus vaginalis, changes size during day (peds) Non-communicating: non-patent processus vaginalis (adult)	Trauma Cryptorchidism "Bell clapper deformity" Many occur in sleep (50%) Necrosis of glands in 5-6 h	Indirect (through internal ring, often into scrotum): congenital Direct (through external ring, rarely into scrotum): abdominal muscle weakness
Hx/P/E	"Bag of worms" Often painless Pulsates with Valsalva	Non-tender, cystic mass Transilluminates	Non-tender, intrascrotal mass Cystic Transilluminates	Acute onset severe scrotal pain, swelling GI upsets cases Retracted and transverse testicle (horizontal lie) Negative Phren's sign Absent cremasteric reflex	A small bulge in the groin that may increase in size with Valsalva and disappear when lying down Can present as a swollen or enlarged scrotum Discomfort or sharp pain – especially when straining, lifting, or exercising
Investigations	P/E Valsava	P/E U/S to rule out tumour	U/S to rule out tumour	U/S with colour flow Doppler probe over testicular artery Decrease uptake on ^{99m}Tc-pertechnetate scintillation scan (doughnut sign)	Hx and P/E Invagination of the scrotum Valsalva
Treatment	Conservative Surgical ligation of testicular veins Percutaneous vein occlusion (balloon, sclerosing agents) Repair may improve sperm count/ motility 50-75%	Conservative Avoid needle aspiration as it can lead to infection, reaccumulation and spilling of irritating sperm within scrotum Excise if symptomatic	Conservative Needle drainage Surgical	**Emergency surgical exploration and bilateral orchiopexy** Orchiectomy if poor prognosis	Surgical repair

TORSION OF TESTICULAR APPENDIX
- twisting of testicular/epididymal vestigial appendix

Signs and Symptoms
- clinically similar to testicular torsion, but vertical lie and cremaster reflex preserved
- "blue dot sign"
  - blue infarcted appendage seen through scrotal skin (can usually be palpated as small, tender lump)

Treatment
- analgesia – most will subside over 5-7 d
- surgical exploration and excision if refractory pain

HEMATOCELE
- trauma with bleed into tunica vaginalis
- U/S helpful to exclude fracture of testis which requires surgical repair

Treatment
- ice packs, analgesics, surgical repair

Acute scrotal swelling/pain in young boys is torsion until proven otherwise

Transillumination refers to if light is able to transmit through tissue (i.e. due to excess fluid)

Differential of a Benign Scrotal Mass

HIS BITS
Hydrocele
Infection (epididymitis/orchitis)
Sperm (spermatocele)
Blood (hematocele)
Intestines (hernia)
Torsion
Some veins (varicocele)

Penile Complaints

Table 25. Penile Complaints

Type	Peyronie's Disease	Priapism	Paraphimosis	Phimosis	Premature Ejaculation
Definition	Benign curvature of penile shaft secondary to fibrous thickening of tunica albuginea	Prolonged erection lasting >4 h in the absence of sexual excitement/desire	Foreskin caught behind glans leading to edema → inability to reduce foreskin	Inability to retract foreskin over glans penis	Ejaculation prior to when one or both partners desire it, either before or soon after penetration
Etiology	Etiology unknown Trauma/repeated inflammation Familial predisposition Associated with DM, vascular disease, autoimmunity, Dupuytren's contracture, erectile dysfunction	50% idiopathic Ischemic (common) • Thromboembolic (sickle cell) Non-Ischemic • Trauma • Medications • Neurogenic	Iatrogenic (post cleaning/instrumentation) Trauma Infectious (balanitis, balanopsthitis)	Congential (90% natural separation by age 3) Balanitis Poor Hygiene	Psychological factors Primary: no period of acceptable control Secondary: symptoms after a period of control, not associated with general medical condition
Hx/P/E	Penile curvature/shortening Pain with erection Poor erection distal to plaque	Painful erection ± signs of necrosis	Painful, swollen glans penis, foreskin Constricting band proximal to corona Dysuria, decreased urinary stream in children	Limitation and pain when attempting to retract foreskin Balanoposthitis (infection of prepuce)	Ejaculatory latency ≥1 min Inability to control or delay ejaculation Psychological distress
Investigations	Hx and P/E	Hx and P/E Cavernosal blood gas analysis	Hx and P/E	Hx and P/E	Hx and P/E Testosterone levels if in conjunction with impotence
Treatment	Watchful waiting (spontaneous resolution in up to 50%) Intralesional or topical verapamil Incision/excision of plaque Shortening of less affected side ± penile prosthesis	Treat reversible causes High-flow: • Self-limited • Consider arterial embolization Low-flow: • Needle aspirated decompression • Phenylephrine intracorporeal injection q3-5min • Surgical shunt no response within 1 h	Manual pressure (with analgesia) Dorsal slit Circumcision (urgent or electively to prevent recurrence)	Proper hygiene Topical corticosterioids Dorsal slit Circumcision	rule out medical condition Address psychiatric concerns, counselling Medication: • SSRI or clomipramine • Topical lidocaine, prilocaine

Erectile Dysfunction

Definition
- consistent (>3 mo duration) or recurrent inability to obtain or maintain an adequate erection for satisfactory sexual performance

Physiology
- erection involves the coordination of psychologic, neurologic, hemodynamic, mechanical, and endocrine components
- nerves: sympathetic (T11-L2), parasympathetic (S2-4), somatic (dorsal penile/pudendal nerves [S2-4])

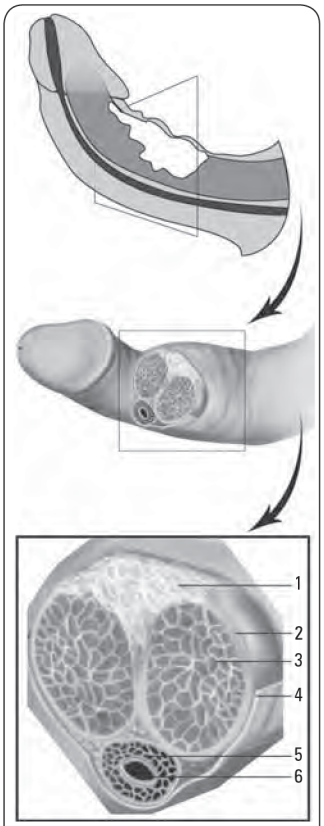
- erection ("POINT")
  - parasympathetics → release of nitric oxide (NO) → increased cGMP levels within corpora cavernosa leading to:
    1. arteriolar dilatation
    2. sinusoidal smooth muscle relaxation → increased arterial inflow and compression of penile venous drainage (decreased venous outflow)
- emission ("SHOOT")
  - sensory afferents from glans
  - secretions from prostate, seminal vesicles, and ejaculatory ducts enter prostatic urethra (sympathetics)
- ejaculation ("SHOOT")
  - bladder neck closure (sympathetic)
  - spasmodic contraction of bulbo-cavernosus and pelvic floor musculature (somatic)
- detumescence
  - sympathetic nerves, norepinephrine, endothelin-1 → arteriolar and sinusoidal constriction → penile flaccidity

Erections POINT AND SHOOT
parasympathetics = **point**; and
sympathetics/**s**omatics = **shoot**

Classification

Table 26. Classification of Erectile Dysfunction

	Psychogenic	Organic
Proportion	10%	90%
Onset	Sudden	Gradual
Frequency	Sporadic	All circumstances
Variation	With partner and circumstance	No
Age	Younger	Older
Organic Risk Factors (HTN, DM, dyslipidemia)	No organic risk factors	Risk factors present
Nocturnal/AM Erection	Present	Absent



1. Fibrous plaque
2. Tunica albuginea
3. Corpus cavernosum
4. Buck's fascia
5. Corpus spongiosum
6. Urethra

Figure 14. Peyronie's disease

Etiology ("IMPOTENCE")

- **I**atrogenic: pelvic surgery, pelvic radiation
- **M**echanical: Peyronie's, post-priapism
- **P**sychological: depression, stress, anxiety, PTSD, widower syndrome
- **O**cclusive vascular: arterial HTN, DM, smoking, hyperlipidemia, PVD, venous (impaired veno-occlusion)
- **T**rauma: penile/pelvic, bicycling
- **E**xtra factors: renal failure, cirrhosis, COPD, sleep apnea, malnutrition
- **N**eurogenic: CNS (e.g. Parkinson's, MS, spinal cord injury, Guillain-Barré, spina bifida, stroke), PNS (e.g. DM, peripheral neuropathy)
- **C**hemical: antihypertensives, sedatives, antidepressants, antipsychotics, anxiolytics, anticholingerics, antihistamines, anti-androgens (including 5-α reductase inhibitors), statins, GnRH agonists, illicit drugs
- **E**ndocrine: DM, hypogonadism, hyperprolactinemia, hypo/hyperthyroid

Diagnosis

- complete Hx (include sexual, medical, and psychosocial aspects)
- self-administered questionnaires (e.g. International Index of Erectile Function, Sexual Health Inventory for Men Questionnaire, ED Intensity Scale, ED Impact Scale)
- focused P/E, including vascular and neurologic examinations, secondary sexual characteristics
- lab investigations, dependent on clinical picture
  - risk factor evaluation: fasting blood glucose or HbA1c, cholesterol profile
  - optional: TSH, CBC, U/A, testosterone (free and total), prolactin, LH
- specialized testing including nocturnal penile tumescence monitoring usually unnecessary
- psychological/psychiatric assessment could be considered to rule out performance anxiety
- evaluation of penile vasculature only relevant with past history of trauma (i.e. pelvic fracture)

Penile vascular abnormalities may be a marker of risk for CV disease. Young men with vascular ED have 50x higher risk of having a CV event

Testosterone deficiency is an uncommon cause of ED

Treatment

- can often be managed by family doctor, see sidebar for when to refer
- must fully inform patient/partner of options, benefits and complications
- non-invasive
  - lifestyle changes (alcohol, smoking), psychological (sexual counseling and education)
  - change precipitating medications
  - treat underlying causes (DM, CVD, HTN, endocrinopathies)

When to Consider Referral

FAT PEN
Failed medical therapy
penile **A**natomic abnormality
pelvic/perineal **T**rauma
Psychogenic cause
Endocrinopathy
vascular/**N**eurologic assessment

- minimally invasive
  - oral medication (see *Common Medications*, U43)
    - sildenafil, tadalafil, vardenafil, avanafil: inhibits PDE-5 to increase intracavernosal cyclic GMP levels
      - all four have similar effectiveness, but tadalafil has certain advantages: earlier onset, longer half-life, no cyanopsia, can be taken on empty or full stomach (others better on empty stomach)
  - vacuum devices: draw blood into penis via negative pressure, then put ring at base of penis once erect
  - MUSE: male urethral suppository for erection – vasoactive substance (PGE1) capsule inserted into urethra
- invasive
  - intracavernous vasodilator injection/self-injection
    - triple therapy (papaverine, phentolamine, PGE1) or PGE1 alone
    - complications: priapism (overdose), thickening of tunica albuginea at site of repeated injections (Peyronie's plaque) and hematoma
- surgical
  - penile implant (last resort): malleable or inflatable
  - penile artery reconstruction (in young men with isolated vascular lesion – investigational)

PDE-5 inhibitors are contraindicated in patients on nitrates/nitroglycerin due to severe hypotension

Initial trial of MUSE® or intracavernosal injection should be done under medical supervision

Trauma

- see Emergency Medicine, ER41

Renal Trauma

Classification According to Severity
- minor
  - contusions and superficial lacerations/hematomas: 90% of all blunt traumas, surgical exploration seldom necessary
- major
  - laceration that extends into medulla and collecting system, major renal vascular injury, shattered kidney

Etiology
- 80% blunt (MVC, assaults, falls) vs. 20% penetrating (stab wounds and gunshots)

Clinical Features
- mechanism of injury raises suspicion
- can be hemodynamically unstable secondary to renal vascular injury and/or other sustained injuries: ABCs
- upper abdominal tenderness, flank tenderness, flank contusions, lower rib/vertebral transverse process fracture

Investigations
- U/A
  - hematuria: requires workup but degree does not correlate with the severity of injury
- imaging
  - CT (contrast, triphasic) if patient stable: look for renal laceration, extravasation of contrast, retroperitoneal hematoma, and associated intra-abdominal organ injury

Staging (does not necessarily correlate well with clinical status)
- I: contusion/hematoma
- II: <1 cm laceration without urinary extravasation
- III: >1 cm laceration without urinary extravasation
- IV: urinary extravasation
- V: shattered kidney or avulsion of pedicle

Treatment
- microscopic hematuria + isolated well-staged minor injuries → no hospitalization
- gross hematuria + contusion/minor lacerations → hospitalize, bedrest, repeat CT if bleeding persists
- surgical intervention/minimally invasive angiography and embolization
  - absolute indications
    - hemorrhage and hemodynamic instability

  - relative indications
    - non-viable tissue and major laceration
    - urinary extravasation
    - vascular injury
    - expanding or pulsating peri-renal mass
    - laparotomy for associated injury
- follow-up with U/S or CT before discharge, and at 6 wk

Complications
- HTN in 5% of renal trauma

Bladder Trauma

Classification
- contusions: no urinary extravasation, damage to mucosa or muscularis
- intraperitoneal ruptures: often involve the bladder dome
- extraperitoneal ruptures: involve anterior or lateral bladder wall in full bladder

Etiology
- blunt (MVC, falls, and crush injury) vs. penetrating trauma to lower abdomen, pelvis, or perineum
- blunt trauma is associated with pelvic fracture in 97% of cases

Clinical Features
- abdominal tenderness, distention, peritonitis, and inability to void
- can be hemodynamically unstable secondary to pelvic fracture, other sustained injuries: ABCs
- suprapubic pain

Investigations
- U/A: gross hematuria in 90%
- imaging (including CT cystogram and post-drainage films for extravasation)

Treatment
- penetrating trauma → surgical exploration
- contusion → urethral catheter until hematuria completely resolves
- extraperitoneal bladder perforations → typically non-operative with foley insertion, and follow with cystograms
  - surgery if: infected urine, rectal/vaginal perforation, bony spike into bladder, laparotomy for concurrent injury, bladder neck involvement, persistent urine leak and failed conservative management
- intraperitoneal rupture usually requires surgical repair and suprapubic catheterization

Complications
- complications of bladder injury itself are rare
- mortality is around 20%, and is usually due to associated injuries rather than bladder rupture

Urethral Injuries

Etiology
- posterior urethra
  - common site of injury is junction of membranous and prostatic urethra due to blunt trauma, MVCs, pelvic fracture
  - shearing force on fixed membranous and mobile prostatic urethra
- anterior urethra
  - straddle injury can crush bulbar urethra against pubic rami
- other causes
  - iatrogenic (instrumentation, prosthesis insertion), penile fracture, masturbation with urethral manipulation
- always look for associated bladder rupture

Clinical Features
- blood at urethral meatus
- high-riding prostate on DRE
- swelling and butterfly perineal hematoma
- penile and/or scrotal hematoma
- sensation of voiding without U/O
- distended bladder

Investigations
- must perform RUG or cystoscopy prior to catheterization

All patients with suspected urethral injury should undergo RUG

Treatment
- simple contusions
  - no treatment
- partial urethral disruption
  - very gentle attempt at catheterization by urologist
  - with no resistance to catheterization → Foley x 2-3 wk
  - with resistance to catheterization → suprapubic cystostomy or urethral catheter alignment in OR
- periodic flow rates/urethrograms to evaluate for stricture formation
- complete disruption
  - immediate repair if patient stable, delayed repair if unstable (suprapubic tube in interim)

Complications
- stricture

Infertility

Definition
- failure to conceive after one year of unprotected, properly timed intercourse
- incidence
  - 15% of all couples
  - ~ 35-40% female, 20% male, 25-30% combined problem

Female Factors

- see Gynecology, GY23

Male Factors

Male Reproduction
- hypothalamic-pituitary-testicular axis (HPTA)
  - pulsatile GnRH from hypothalamus acts on anterior pituitary stimulating release of LH and FSH
  - LH acts on Leydig (interstitial) cells → testosterone synthesis and secretion
  - FSH acts on Sertoli cells → structural and metabolic support to developing spermatogenic cells
  - FSH and testosterone support germ cells (responsible for spermatogenesis)
  - sperm route: epididymis → vas deferens → ejaculatory ducts → prostatic urethra

Etiology
- idiopathic (40-50% infertile males)
- testicular
  - varicocele (35-40% infertile males)
  - tumour
  - congenital (Klinefelter's triad: small, firm testes, gynecomastia, and azoospermia)
  - post-infectious (epididymo-orchitis, STIs, mumps)
  - uncorrected torsion
  - cryptorchidism (<5% of cases)
- obstructive
  - iatrogenic (surgery: see below)
  - infectious (gonorrhea, chlamydia)
  - trauma
  - congenital (absence of vas deferens, CF)
  - bilateral ejaculatory duct obstruction, epididymal obstructions
  - Kartagener's syndrome (autosomal recessive disorder causing defect in action of cilia)
- endocrine (see Endocrinology, E48)
- HPTA (2-3%) e.g. Kallmann's syndrome (congenital hypothalamic hypogonadism), excess prolactin, excess androgens, excess estrogens
- other
  - retrograde ejaculation secondary to surgery
  - medications
  - drugs: marijuana, cocaine, tobacco, alcohol
  - increased testicular temperature (sauna, hot baths, tight pants or underwear)
  - chronic disease: e.g. liver, renal
  - unexplained infertility

Male Infertility Factors

SPERM COUNT
Systemic factor/**S**moking
Psychological illness
Endocrinopathy
Retrograde ejaculation
Medications

Chronic disease
Obstructive
Unexplained
Narcotics
Testicular

History
- age of both partners
- medical: past illness, DM, trauma, CF, genetic syndromes, STIs, cryptorchidism
- surgical: vasectomy, herniorrhaphy, orchidopexy, prostate surgery
- fertility: pubertal onset, previous pregnancies, duration of infertility, treatments
- sexual: libido, erection/ejaculation, timing, frequency
- family Hx
- medications: cytotoxic agents, GnRH agonists, anabolic steroids, nitrofurantoin, cimetidine, sulfasalazine, spironolactone, α-blockers
- social Hx: alcohol, tobacco, cocaine, marijuana
- occupational exposures: radiation, heavy metals

Physical Exam
- general appearance: sexual development, gynecomastia, obesity
- scrotal exam: size, consistency, and nodularity of testicles; palpation of cord for presence of vas deferens; DRE; Valsalva for varicocele

Investigations
- semen analysis (SA) at least 2 specimens, collected 1-2 weeks apart
  - delivery to lab within 1 hour, 2-7 days of abstinence prior to collection
- hormonal evaluation
  - indicated with abnormal SA (rare to be abnormal with normal SA)
  - testosterone and FSH
  - serum LH and prolactin are measured if testosterone or FSH are abnormal
- genetic evaluation
  - chromosomal studies (Klinefelter's syndrome – XXY)
  - genetic studies (Y-chromosome microdeletion, CF gene mutation)
- immunologic studies (antisperm antibodies in ejaculate and blood)
- testicular biopsy
- scrotal U/S (varicocele, testicular size)
- vasography (assess patency of vas deferens)

Common Terminology on SA
- Teratospermia: Abnormal morphology
- Asthenospermia: Abnormal motility
- Oligospermia: Decreased sperm count
- Azoospermia: Absent sperm in semen
- Mixed types: i.e. oligoasthenospermia

Mutation of cystic fibrosis transmembrane conductance regulator (CFTR) gene is associated with congenital bilateral absence of vas deferens and epididymal cysts, even if patient manifests no symptoms of CF

Treatment
- assessment of partner
- lifestyle
  - regular exercise, healthy diet
  - eliminate alcohol, tobacco and illicit drugs
- medical
  - endocrine therapy (see Endocrinology, E49)
  - treat retrograde ejaculation
  - discontinue anti-sympathomimetic agents, may start α-adrenergic stimulation (phenylpropanolamine, pseudoephedrine, or ephedrine)
  - treat underlying infections
- surgical
  - varicocelectomy (if indicated)
  - vasovasostomy (vasectomy reversal) or epididymovasostomy
  - transurethral resection of blocked ejaculatory ducts
- assisted reproductive technologies (ART)
  - refer to infertility specialist
  - sperm washing + intrauterine insemination (IUI)
  - *in vitro* fertilization (IVF)
  - intracytoplasmic sperm injection (ICSI) after CF screening of patient and partner in patients with congenital bilateral absence of vas deferens

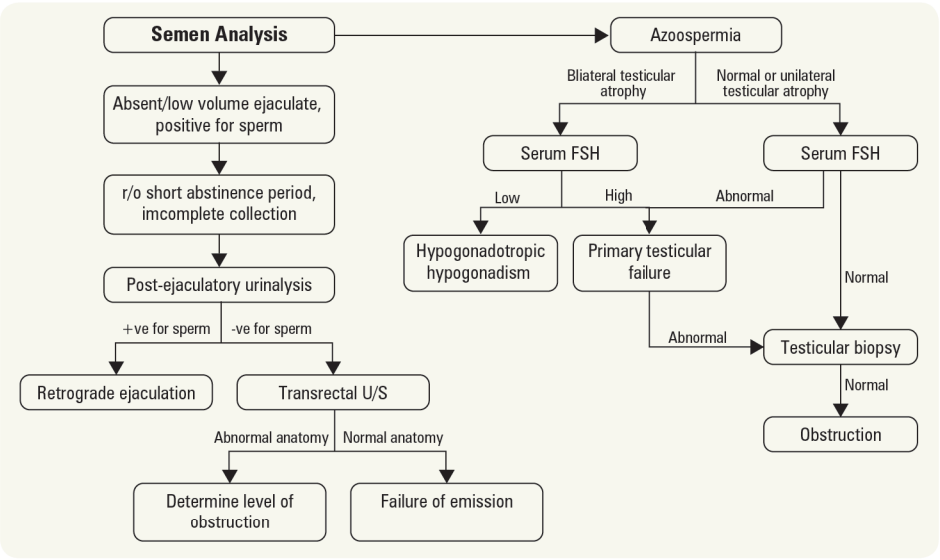


Figure 15. Infertility work up

WHO Guidelines
Normal Semen Values
- Volume: 2-5 mL
- Concentration: >15 million sperm/mL
- Morphology: 30% normal forms
- Motility: >40% adequate forward progression
- Liquefaction: complete in 20 min
- pH: 7.2-7.8
- WBC: <10/HPF or $<10^6$ WBC/mL semen

Pediatric Urology

Congenital Abnormalities

- not uncommon; 1/200 have congenital abnormalities of the GU tract
- six common presentations of congenital urological abnormalities

1. ANTENATAL HYDRONEPHROSIS

Majority of antenatal hydronephroses resolve during pregnancy or within the first year of life

Epidemiology
- 1-5% fetal U/S, detectable as early as first trimester
- most common urological consultation in perinatal period and one of most common U/S abnormalities of pregnancy

Differential Diagnosis
- UPJ or UVJ obstruction
- multi-cystic dysplastic kidney
- VUR
- PUVs (only in boys)
- duplication anomalies
- ureterocele
- ectopic ureter

Treatment
- antenatal *in utero* intervention rarely indicated unless evidence of PUVs with oligohydramnios

2. POSTERIOR URETHRAL VALVES

Epidemiology
- the most common congenital obstructive urethral lesion in male infants

Pathophysiology
- abnormal mucosal folds at the distal prostatic urethra causing varying degrees of obstruction

Clinical Presentation
- dependent on age
  - antenatal: bilateral hydronephrosis, distended bladder, oligohydramnios
  - neonatal (recognized at birth): palpable abdominal mass (distended bladder, hydronephrosis), ascites (transudation of retroperitoneal urine), respiratory distress (pulmonary hypoplasia from oligohydramnios), weak urinary stream
  - neonatal (not recognized at birth): within weeks present with urosepsis, dehydration, electrolyte abnormalities, failure to thrive

  - toddlers: UTIs or voiding dysfunction
  - school-aged boys: voiding dysfunction → urinary incontinence
- associated findings include renal dysplasia and secondary VUR

Investigations
- most commonly recognized on prenatal U/S → bilateral hydronephrosis, thickened bladder, dilated posterior urethra ("keyhole sign"), oligohydramnios in a male fetus
- VCUG → dilated and elongated posterior urethra, trabeculated bladder, VUR

Treatment
- immediate catheterization to relieve obstruction, followed by cystoscopic resection of PUV when baby is stable
- if resection of PUV is not possible, vesicostomy is indicated

3. URETEROPELVIC JUNCTION OBSTRUCTION

Etiology
- unclear: adynamic ureteral segment, stenosis, strictures, extrinsic compression, stenosis, strictures, aberrant blood vessels
- can rarely be secondary to tumour, stone, etc, in children

Epidemiology
- the most common congenital defect of the ureter
- M:F = 2:1
- up to 40% bilateral, which may be associated with worse prognosis

Clinical Presentation
- symptoms depend on severity and age at diagnosis (mostly asymptomatic finding on antenatal U/S)
  - infants: abdominal mass, urinary infection
  - children: pain, vomiting, failure to thrive
- some cases are diagnosed after puberty and into adulthood
  - in adolescents and adults, the symptoms may be triggered by episodes of increased diuresis, such as following alcohol ingestion (Dietl's crisis)

Investigations
- antenatal U/S most common, Doppler U/S (rare), IVP (rare), and renal scan ± furosemide

Treatment
- surgical correction (pyeloplasty), consider nephrectomy if <15% differential renal function

4. VESICOURETERAL REFLUX

Definition
- retrograde passage of urine from the bladder, through the UVJ, into the ureter

Classification
- primary reflux: incompetent or inadequate closure of UVJ
  - lateral ureteral insertion, short submucosal segment
- secondary reflux: abnormally high intravesical pressure resulting in failure of UVJ closure
  - often associated with anatomic (PUV) or functional (neuropathic) bladder obstruction

Epidemiology
- estimated ~1% of newborns, but not well known
- incidence and clinical relevance higher in children with febrile UTIs and prenatal hydronephrosis
- risk factors: race (white > black), female gender, age (<2 yr), genetic predisposition

Investigations
- focused Hx, particularly of voiding dysfunction (frequency, urgency, diurnal enuresis, constipation, encopresis)
  - also screen for signs of infection (UTI, pyelonephritis, urosepsis) and renal failure (uremia, HTN)
- initial evaluation of renal status, growth parameters, and blood pressure is warranted in any child with VUR due to high incidence of renal scarring
  - height, weight, blood pressure
  - Cr
  - U/A, C&S
  - renal U/S
  - DMSA renal scan if at high risk (greater sensitivity in detecting structural defects associated with dysplasia, renal scarring or pyelonephritis; entails radiation exposure)
  - family screening is controversial

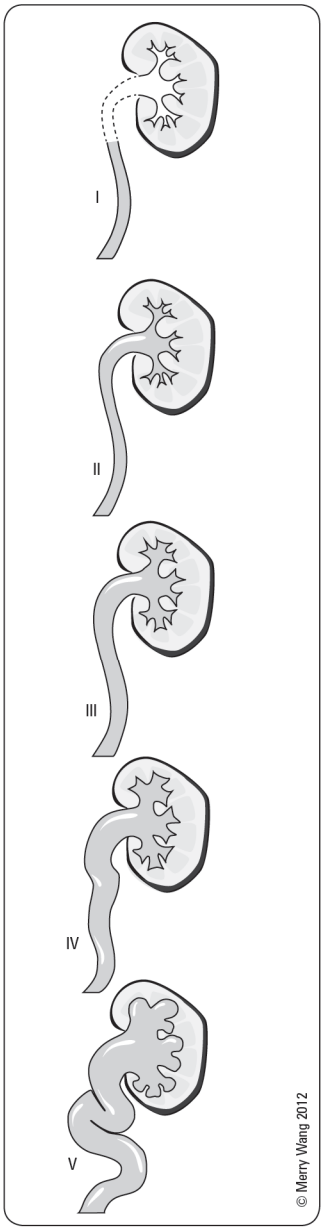


Figure 16. VUR grading
(based on cystogram)

Treatment
- spontaneous resolution in 60% of primary reflux
  - in lower grades (I-III), goal is to prevent infection or renal damage via medical treatment and monitoring
- medical treatment: daily ABx prophylaxis at half the treatment dose for acute infection (see Table 9 - TMP/SMX, trimethoprim, amoxicillin, or nitrofurantoin)
- surgical treatment: ureteral reimplantation ± ureteroplasty, or subureteral injection with bulking agents (Deflux® or Macroplastique®)
  - indications include failure of medical management, renal scarring (e.g. renal insufficiency, HTN), breakthrough UTIs, persistent high grade (IV or V) reflux

VUR Grading (based on cystogram)
- **Grade I:** ureters only fill
- **Grade II:** ureters and pelvis fill
- **Grade III:** ureters and pelvis fill with some dilatation
- **Grade IV:** ureters, pelvis, and calyces fill with significant dilatation
- **Grade V:** ureters, pelvis, and calyces fill with major dilatation and tortuosity

5. HYPOSPADIAS

Definition
- a condition in which the urethral meatus opens on the ventral side of the penis, proximal to the normal location in the glans penis
- depending on severity, may result in difficulty directing urinary stream, having intercourse or depositing sperm in vagina

Defer circumcision in patients with hypospadias

Epidemiology
- very common; 1/300 live male births
- distal hypospadias more common than proximal
- white >> black
- may be associated with ventral penile curvature, disorders of sexual differentiation, undescended testicles or inguinal hernia

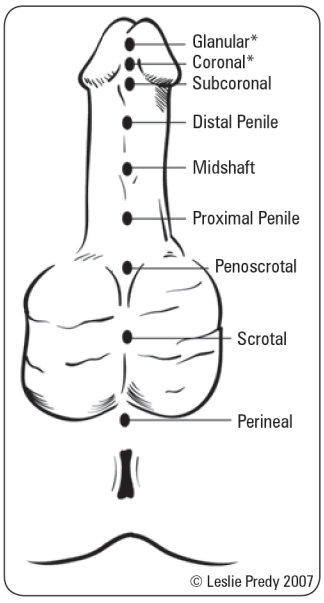


Figure 17. Classification of hypospadias (*account for 75%)

Treatment
- early surgical correction; optimal repair before 2 yr
- neonatal circumcision should be deferred because the foreskin may be utilized in the correction

6. EPISPADIAS-EXSTROPHY COMPLEX

Definition
- a spectrum of defects depending on the timing of the rupture of the cloacal membrane
  - bladder exstrophy: congenital absence of a portion of lower abdominal and anterior bladder wall, with exposure of the bladder lumen
  - cloacal exstrophy
    - exposed bladder and bowel with imperforate anus
    - associated with spina bifida in >50%
  - epispadias (least severe)
    - urethra opens on dorsal aspect of the penis, often associated with penile curvature

Etiology
- represents failure of closure of the cloacal membrane, resulting in the bladder and urethra opening directly through the abdominal wall

Epidemiology
- rare: incidence 1/30,000, M:F = 3:1 predominance
- high morbidity → multiple reconstructive surgeries, incontinence, infertility, reflux

Treatment
- surgical correction at birth
- later corrections for incontinence, VUR, and low bladder capacity may be needed

Nephroblastoma (Wilms' Tumour)

Etiology
- arises from abnormal proliferation of metanephric blastema

Epidemiology
- 5% of all childhood cancers, 5% bilateral
- most common primary malignant renal tumour of childhood
- average age of incidence is 3 yr

Clinical Features
- abdominal mass: large, firm, unilateral (80%)
- HTN (25%)
- flank tenderness
- microscopic hematuria
- nausea/vomiting

Treatment
- always investigate contralateral kidney and renal vein (for tumour thrombus)
- unilateral disease: radical nephrectomy ± radiation ± chemotherapy
- bilateral disease: nephron-sparing surgery following neoadjuvant chemotherapy

Prognosis
- 5 yr survival 80%

Cryptorchidism/Ectopic Testes

Definition
- abnormal location of testes somewhere along the normal path of descent (external inguinal ring > inguinal canal > abdominal)
- ectopic testis (testis found outside its normal path of descent) is most commonly located within a superficial pouch between the external oblique fascia and Scarpa's fascia (Denis Browne pouch)
- differential diagnosis:
  - retractile testes
  - atrophic testes
  - disorders of sexual differentiation (bilateral impalpable gonads)

Normal Testicular Development and Descent *in Utero*

2nd month: Testicle begins to form

4th month: Begins to take on its normal appearance and migrates from its origin at the kidney to the internal inguinal ring

7th month: The testis, surrounded in peritoneal covering, begins to descend through the internal ring, inguinal canal and external ring to terminate in the scrotum

Epidemiology
- 2.7% of full term newborns
- 0.7-0.8% at 1 yr

Treatment
- orchiopexy
- hormonal therapy not proven to be of benefit over standard surgical treatment

Prognosis
- reduction in fertility
  - untreated bilateral cryptorchidism: ~100% infertility
  - paternity rates: 53%, 90%, and 93% in formerly bilateral cryptorchid, formerly unilateral cryptorchid, and normal men, respectively
- increased malignancy risk
  - intraabdominal > inguinal
  - surgical correction facilitates testicular monitoring and may reduce malignancy risk
- increased risk of testicular torsion (reduced by surgical correction)

Disorders of Sexual Differentiation

Definition
- formerly known as intersex disorders
- abnormal genitalia for chromosomal sex due to the undermasculinization of males or the virilization of females
- considered a social emergency

Classification
1. 46 XY DSD
   - defect in testicular synthesis of androgens
   - androgen resistance in target tissues
   - palpable gonad
2. 46 XX DSD
   - most due to CAH (21-hydroxylase deficiency most common enzymatic defect) → shunt in steroid biosynthetic pathway leading to excess androgens
   - undiagnosed and untreated CAH can be associated with life-threatening electrolyte abnormalities in the newborn (salt-wasting CAH)
3. ovotesticular DSD
4. mixed gonadal dysgenesis (46 XY/45 XO most common karyotype)
   - presence of Y chromosome → partial testis determination to varying degrees

A phenotypic male newborn with bilateral non-palpable testicles should be considered 46XX with salt-wasting CAH and must undergo proper evaluation prior to discharge

Diagnosis
- thorough family Hx noting any consanguinity
- maternal Hx, especially medication/drug use during pregnancy (maternal hyperandrogenemia)
- P/E: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, HTN, stretched phallus length, position of urethral meatus
- laboratory tests
  - plasma 17-OH-progesterone (after 36 h of life) → increased in 21-hydroxylase deficiency (CAH)
  - plasma 11-deoxycortisol → increased in 11-β-hydroxylase deficiency
  - basal adrenal steroid levels
  - serum testosterone and DHT pre- and post-hCG stimulation (2,000 IU/d for 4 d)
  - serum electrolytes
  - chromosomal evaluation including sex karyotype
- U/S of adrenals, gonads, uterus, and fallopian tubes
- endoscopy and genitography of urogenital sinus

Treatment
- steroid supplementation as indicated (e.g. CAH)
- sex assignment after extensive family consultation
  - must consider capacity for sexually functioning genitalia in adulthood, fertility potential, and psychological impact
- reconstruction of external genitalia between 6 and 12 mo
- long-term psychological guidance and support for both patient and family

Enuresis

- see Pediatrics, P9

Selected Urological Procedures

Bladder Catheterization

- catheter size measured by the French (Fr) scale – circumference in mm
- each 1 mm increase in diameter = approximately 3 Fr increase (standard size 16-18 Fr)
- should be removed as soon as possible to reduce the risk of UTI

Continuous Catheterization
- indications
  - accurate monitoring of U/O
  - relief of urinary retention due to medication, neurogenic bladder, or intravesical obstruction
  - temporary therapy for urinary incontinence
  - perineal wounds
  - clot prevention (24-28 Fr) for CBI
  - post-operative

Alternatives to Continuous Catheterization
- intermittent catheterization
  - PVR measurement
  - to obtain sterile diagnostic specimens for U/A, urine C&S
  - management of neurogenic bladder or chronic urinary retention
- condom catheter
- suprapubic catheter

Causes of Difficult Catheterizations and Treatment
- patient discomfort → use sufficient lubrication (± xylocaine)
- collapsing catheter → lubrication as above ± firmer or larger catheter (silastic catheter)
- meatal/urethral stricture → dilate with progressively larger catheters/balloon catheter
- BPH → use coudé catheter as angled tip can help navigate around enlarged prostate
- urethral disruption/obstruction → filiform and followers or suprapubic catheterization
- anxious patient → anxiolytic medication

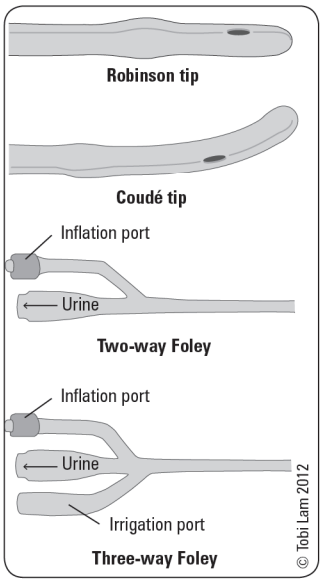


Figure 18. Transurethral (Foley) catheters

Complications of Catheterization
- infection: UTI
- meatal/urethral trauma

Contraindications
- urethral trauma: blood at the meatus of the urethra, scrotal hematoma, pelvic fracture, and/or high riding prostate

Circumcision

Definition
- removal of some or all of the foreskin from the penis

Epidemiology
- 30% worldwide
- frequency varies depending on geographic location, religious affiliation, socioeconomic classification

Medical Indications
- phimosis and recurrent paraphimosis
- recurrent UTIs (particularly in infants and in association with other urinary abnormalities)
- balanitis xerotica obliterans or other chronic inflammatory conditions

Contraindications
- unstable or sick infant
- congenital genital abnormalities (hypospadias)
- family Hx of bleeding disorders warrants laboratory investigation prior to circumcision

Complications
- bleeding
- infection
- penile entrapment, skin bridges
- fistula
- glans injury
- penile sensation deficits

Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men
Cochrane DB Syst Rev 2009;2:CD003362
Purpose: To evaluate the effectiveness and safety of male circumcision for preventing acquisition of HIV in heterosexual men.
Methods: The analyzed data is from three randomized controlled trials to assess the efficacy of male circumcision for preventing HIV acquisition in men in Africa.
Results: Medical male circumcision reduces the acquisition of HIV by heterosexual men (38%-66% over 24 mo).

Circumcision Status and Risk of HIV and Sexually Transmitted Infections among Men who have Sex with Men: A Meta-Analysis
JAMA 2008;300:1674-1684
Purpose: To describe the association between male circumcision and HIV infection and other sexually transmitted infections (STIs) among men who have sex with men (MSM).
Methods: Meta-analysis of 15 studies (n=53,567)
Results: The associations between circumcision and HIV-positive and STIs were not statistically significant. Male circumcision had a protective association with HIV in studies of MSM conducted before the introduction of highly active anti-retroviral therapy.
Conclusions: There is insufficient evidence to support that male circumcision protects against HIV infection or other STIs.

Cystoscopy

Objective
- endoscopic inspection of the lower urinary tract (urethra, prostate, bladder, and ureteral orifices), samples for cytology
- scopes can be flexible or rigid

Indications
- gross hematuria
- LUTS (storage or voiding)
- urethral and bladder neck strictures
- bladder stones
- bladder tumour surveillance
- evaluation of upper tracts with retrograde pyelography (ureteric stents, catheters)

Complications
- during procedure
  - bleeding
  - anesthetic-related
  - perforation (rare)
- post-procedure (short-term)
  - infections, e.g. epididymo-orchitis (rare)
  - urinary retention
- post-procedure (long-term)
  - stricture

Male Circumcision
Pediatrics 2012;130:e756-e785
Study: Guidelines by the American Academy of Pediatrics (AAP).
Recommendations: The American Academy of Pediatrics radically changed their position on male circumcision in 2012. The report from the AAP now states that the preventative health benefits outweigh the risks of the procedure and that the procedure is well-tolerated with adequate pain management and sterility. Stated benefits include the prevention of urinary tract infection, penile cancer, transmission of some sexually transmitted infections, including HIV. There is believed to be no effect on penile sexual function, sensitivity or sexual satisfaction. Acute complications are rare and more common if the procedure is done by an untrained provider.
Note: The Canadian Pediatric Society (CPS) has not yet updated their position on male circumcision since 1996, which stated that the CPS is opposed to routine circumcision. A new statement is expected soon.

Radical Prostatectomy

Objective
- the removal of the entire prostate and prostatic capsule via a lower midline abdominal incision, laparoscopically or robotically
  - internal iliac and obturator vessel lymph nodes may also be dissected and sent for pathology (dependent on risk: clinical stage, grade, PSA)
  - seminal vesicle vessels are also partially or completely removed

Indications
- treatment for localized prostate cancer

Complications
- immediate (intraoperative)
  - blood loss
  - rectal injury (extremely rare)
  - ureteral injury (extremely rare)
- perioperative
  - lymphocele formation
- late
  - moderate to severe urinary incontinence (3-10%)
  - mild urinary incontinence (20%)
  - ED (~50%, depending on whether one, both, or neither of the neurovascular bundles are involved in extracapsular extension of tumour)

Retropubic, Laparoscopic, and Robot-Assisted Radical Prostatectomy: A Critical Review of Outcomes Reported by High-Volume Centres
J Endourology 2010;24:2003-2015
Study: A systematic review to compare perioperative outcomes, positive surgical margin (PSM) rates, and functional outcomes in retropubic radical prostatectomy (RRP) laparoscopic RP (LRP) and robot-assisted radical prostatectomy (RARP).
Methods: Medline database was searched. Weighted means (based on number of participants in each study) were calculated for all outcomes.
Results: 58 articles were reviewed. LRP and RARP were associated with better perioperative outcomes compared to RRP. RRP, LRP, and RARP had similar post-operative complication rates ranging from 10.3-10.98%. RARP had a lower overall PSM rate than LRP, and RRP. RARP had the highest continence rate and mean potency rates.
Conclusion: In high-volume centers, RRP, LRP and RARP are safe options for treating patients with localized prostate cancer. LRP and RARP are associated with better perioperative outcomes and RARP showed lower PSM rates, higher potency and continence compared to RRP and LRP.

Transurethral Resection of the Prostate

Objective
- to partially resect the periurethral portion of the prostate (transition zone) to decrease symptoms of urinary tract obstruction
- accomplished via a transurethral (cystoscopic) approach using an electrocautery loop, irrigation (glycine), and illumination

Indications
- obstructive uropathy (large bladder diverticula, renal insufficiency)
- refractory urinary retention
- recurrent UTIs
- recurrent gross hematuria
- bladder stones
- intolerance/failure of medical therapy

Complications
- acute
  - intra- or extraperitoneal rupture of the bladder
  - rectal perforation
  - incontinence
  - incision of the ureteral orifice (with subsequent reflux or ureteral stricture)
  - hemorrhage
  - epididymitis
  - sepsis
  - transurethral resection syndrome (also called "post-TURP syndrome")
    - caused by absorption of a large volume of the hypotonic irrigation solution used, usually through perforated venous sinusoids, leading to a hypervolemic hyponatremic state
    - characterized by dilutional hyponatremia, confusion, nausea, vomiting, HTN, bradycardia, visual disturbances, CHF, and pulmonary edema
    - treat with diuresis and (if severe) hypertonic saline administration
- chronic
  - retrograde ejaculation (>75%)
  - ED (5-10% risk increases with increasing use of cautery)
  - incontinence (<1%)
  - urethral stricture
  - bladder neck contracture

Extracorporeal Shock Wave Lithotripsy

Objective
- to treat renal and ureteral calculi (proximal, middle or distal) which cannot pass through the urinary tract naturally
- shockwaves are generated and focused onto stone → fragmentation, allowing stone fragments to pass spontaneously and less painfully

Indications
- potential first-line therapy for renal and ureteral calculi <2.5 cm
- individuals with calculi in solitary kidney
- individuals with HTN, DM or renal insufficiency

*patient preference and wait-times play a large role in stone management

Contraindications
- acute UTI or urosepsis
- bleeding disorder or coagulopathy
- pregnancy
- obstruction distal to stone

Complications
- bacteriuria
- bacteremia
- post-procedure hematuria
- ureteric obstruction (by stone fragments)
- peri-nephric hematoma

A Comparison of Treatment Modalities for Renal Calculi Between 100 and 300 mm^2: Are Shockwave Lithotripsy, Ureteroscopy, and Percutaneous Nephrolithotomy Equivalent?
J Endourol 2011;25:481-485

Purpose: To describe the outcomes of a series of patients who underwent shockwave lithotripsy (SWL), ureteroscopy (URS) or percutaneous nephrolithotomy (PCNL).

Methods: Patients treated for intermediate-sized upper tract calculi (100-300 mm^2) at a single tertiary centre were included. Demographic and clinical data were collected from a prospectively maintained database.

Results: Of 137 patients, 38.7%, 29.9%, and 31.4% were treated with SWL, URS, and PCNL, respectively. Stone-free rate (95.3%) and single treatment success rate (95.3%) were highest for PCNL compared to SWL and URS ($p<0.001$). When allowing for up to two SWL treatments, success rates became equivalent for the three treatment groups ($p=0.66$). Auxiliary treatments were more frequent after SWL compared to URS and PCNL. Clavien grade complications did not differ between the three groups.

Conclusion: Up to two SWL treatments have equivalent success rate as compared to URS and PCNL. Hence, multiple SWL treatments may be a reasonable therapeutic option for patients who prefer SWL or who are not good candidates for alternative therapies.

Common Medications

Table 27. Erectile Dysfunction Medications

Drug	Class	Mechanism	Adverse Effects
sildenafil tadalafil vardenafil (PDE5s for use when some erection present)	Phosphodiesterase 5 inhibitor	Selective inhibition of PDE5 (enzyme which degrades cGMP) Leads to sinusoidal smooth muscle relaxation and erection	Severe hypotension (very rare) Contraindicated if Hx of priapism, or in conditions predisposing to priapism (leukemia, myelofibrosis, polycythemia, sickle cell disease) Contraindicated with nitrates
alprostadil (MUSE®), PGE_1 + phentolamine + papaverine mixture	Prostaglandin E_1	Activation of cAMP, relaxing sinusoidal smooth muscle Local release (capsule inserted into urethra)	Penile pain Presyncope
alprostadil, papaverine (intracavernosal injection) triple therapy also used: papaverine, phentolamine, PGE_1	See above	See above	Thickening of tunica albuginea at site of repeated injections (Peyronie's plaque) Painful erection Hematoma Contraindicated if Hx of priapism, or in conditions predisposing to priapism

Table 28. Benign Prostatic Hyperplasia Medications

Drug	Class	Mechanism	Adverse Effects
terazosin doxazosin tamsulosin alfuzosin silodosin	α_1 blockers α_{1A} selective	α-adrenergic antagonists reduce stromal smooth muscle tone Reduce dynamic component of bladder outlet obstruction	Presyncope Leg edema Retrograde ejaculation Headache Asthenia Nasal congestion
finasteride dutasteride	5-α reductase inhibitor	Blocks conversion of testosterone to DHT Reduces static component of bladder outlet obstruction Reduces prostatic volume	Sexual dysfunction PSA decreases

Table 29. Prostatic Carcinoma Medications (N>0, M>0)

Drug	Class	Mechanism	Adverse Effects
leuprolide, goserelin	GnRH agonist	Initially stimulates LH, increasing testosterone and causing "flare" (initially increases bone pain) Later causes low testosterone	Hot flashes Headache Decreased libido
*diethylstilbestrol (DES)	Estrogens	Inhibit LH and cytotoxic effect on tumour cells	Increased risk of cardiovascular events (no longer available commercially in North America)
*cyproterone acetate	Steroidal antiandrogen	Competes with DHT for intracellular receptors: 1. Prevent flare produced by GnRH agonist 2. Use for complete androgen blockade 3. May preserve potency	
flutamide, bicalutamide	Non-steroidal antiandrogen	As above	Hepatotoxic: AST/ALT monitoring
*ketoconazole, spironolactone	Steroidogenesis inhibitors	Blocks multiple enzymes in steroid pathway, including adrenal androgens	GI symptoms Hyperkalemia Gynecomastia

*Very rarely used

Table 30. Continence Agents and Overactive Bladder Medications

Drug	Class	Mechanism	Indication	Adverse Effects
oxybutynin	Antispasmotic	Inhibits action of ACh on smooth muscle Decreases frequency of uninhibited detrusor contraction Diminishes initial urge to void	Overactive bladder Urge incontinence + urgency + frequency	Dry mouth Blurred vision Constipation Supraventricular tachycardia
oxybutynin, tolterodine, trospium, solifenacin, darifenacin fesoterodine	Anticholinergic	Muscarinic receptor antagonist Selective for bladder Increases bladder volume Decreases detrusor pressure	Overactive bladder Urge incontinence + urgency + frequency	As above
mirabegron	β3 agonist	Beta sympathetic receptor blocker in the bladder; relaxes bladder during storage phase	Overactive bladder Urge incontinence + urgency + frequency	Blood pressure should be monitored
imipramine	Tricyclic antidepressant	Sympathomimetic effects: urinary sphincter contraction Anticholinergic effects: detrusor relaxation	Stress and urge incontinence	As above Weight gain Orthostatic hypotension Prolonged PR interval

Note: All anti-cholinergics are equally effective and long-acting formulations are better tolerated. Newer muscarinic M3 receptor specific agents (solifenacin, darifenacin) are equally efficacious as older drugs, however, RCTs based on head-to-head comparison to long acting formulations are lacking.

References

General Information

American Urological Association. Available from: http://www.auanet.org/guidelines/.
Canadian Urological Association. Available from: http://www.cua.org/guidelines_e.asp.
Ferri F. Practical guide to the care of the medical patient, 6th ed. St. Louis: Mosby, 2006.
Goldman L, Ausiello D. Cecil textbook of medicine, 23rd ed. Philadelphia: WB Saunders, 2007.
Macfarlane MT. House officer series: urology, 3rd ed. Philadelphia: Lippincott, 2001.
Montague DK, Jarow J, Broderick GA, et al. Guideline on the management of priapism. American Urological Association Education and Research, Inc. ©2003. Available from: http://www.auanet.org/education/guidelines/priapism.cfm.
Tanagho EA, McAninch JW. Smith's general urology, 17th ed. New York: McGraw-Hill, 2007.
Wein AJ, Kavoussi LR, Novick AC, et al. Campbell's urology, 10th ed. Philadelphia: WB Saunders, 2011.
Wieder JA. Pocket guide to urology, 4th ed. Oakland: Wieder, 2010.

Common Presenting Problems

Bremnor JD, Sadovsky R. Evaluation of dysuria in adults. Am Fam Phys 2002;65:1589-1597.
Cohen RA, Brown RS. Microscopic hematuria. NEJM 2003;348:2330-2338.
Morton AR, Iliescu EA, Wilson JWL. Nephrology: investigation and treatment of recurrent kidney stones. CMAJ 2002;166:213-218.
Teichman JMH. Acute renal colic from ureteral calculus. NEJM 2004;350:684-693.

Overactive Bladder

Ouslander JG. Management of overactive bladder. NEJM 2004: 250(8):786-799.

Benign Renal Neoplasm

Israel GM, Bosniak MA. An update of Bosniak renal cyst classification system, Urology 2005;66:484-488.

Urological Emergencies

Galejs LE. Diagnosis and treatment of the acute scrotum. Am Fam Phys 1999;5:817-824.

Medications

Bill-Axelson A, Holmberg L, Ruutu M, et al, SPCG-4 Investigators. Radical prostatectomy versus watchful waiting in early prostate cancer. NEJM 2011;364:1708-1717.
Compendium of Pharmaceuticals and Specialties. Available from: http://www.e-therapeutics.ca.
Micromedex health care series. Available from: http://www.micromedex.com.
Rini B, Halabi S, Rosenberg J, et. al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206 trial. J Clin Oncol 2008;26:5422-5428.

EBM

Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. NEJM 2011;364:1708-1717.
Campschroer T, Zhu Y, Duijvesz D, et al. Alpha-blockers as medical expulsive therapy for ureteral stones. Cochrane DB Syst Rev 2014;4:CD008509.
Coelho RF, Rocco B, Patel MB, et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a critical review of outcomes reported by high-volume centers. J Endourol 2010;24:2003-2015.
Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. NEJM 2007;356:125-134.
Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. NEJM 2003;349:859-866.
Hoffman RM, Monga M, Elliott SP, et al. Microwave thermotherapy for benign prostatic hyperplasia. Cochrane DB Syst Rev 2012;9:CD004135.
Ilic D, O'Connor D, Green S, et al. Screening for prostate cancer. Cochrane DB Syst Rev 2013;1:CD004720.
James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. NEJM 2012;366:1477-1488.
Kim SC, Seo KK. Effacacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind, placebo controlled study. J Urol 1998;159:425-427.
McDonnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. NEJM 2003;349:2387-2398.
Millett GA, Flores SA, Marks G, et al. Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. JAMA 2008;300:1674-1684.
Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomized phase 3 trial. Lancet Oncol 2013;14:552-562.
Outerbridge E, Canadian Paediatric Society, Fetus and Newborn Committee. Position statement: neonatal circumcision revisited. CMAJ 1996;154:769-780.
Parsons JK, Hergan LA, Sakamoto K, et al. Efficacy of alpha-blockers for the treatment of ureteral stones. J Urol 2007;177:983-987.
Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. NEJM 2009;360:1320-1328.
Siegfried N, Muller M, Deeks JJ, et al. Male circumcision for prevention of heterosexual acquisition of HIV in men. Cochrane DB Syst Rev 2009;2:CD003362.
Tacklind J, Fink HA, Macdonald R, et al. Finasteride for benign prostatic hyperplasia. Cochrane DB Syst Rev 2010;10:CD006015.
Wiesenthal JD, Ghiculete D, D'A Honey RJ, et al. A comparison of treatment modalities for renal calculi between 100 and 300 mm^2: are shockwave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy equivalent? J Endourol 2011;25:481-485.
Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. NEJM 2012;367:203-213.