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**Case 1 - congestive heart failure - AKI**

John Heartly is a regular patient of your clinic. He has had congestive cardiac failure for the last 10 years and this was caused by long standing cardiac hypertrophy due to aortic stenosis.

1. **Define ejection fraction and what is a normal range**
* Ejection fraction (EF) is a measurement, expressed as a percentage, of how much blood the left ventricle pumps out with each contraction.
* An ejection fraction of 60 percent means that 60 percent of the total amount of blood in the left ventricle is pushed out with each heartbeat.
* This indicates how well your heart is pumping out blood and can help to diagnose and track heart failure.
* A normal range is usually between 50 to 70%
1. **What do HFrEF and HFpEF mean and what is the pathophysiology of both?**
* **HFrEF** **= Heart failure with REDUCED ejection fraction**
	+ Also known as systolic HF
	+ Most common
	+ Reduced ejection fraction AND stroke volume
	+ Underlying mechanisms:
		- **Reduced contractility:** Damage and loss of myocytes reduce ventricular contractility and stroke volume.
		- **Increased afterload:** increase in mean aortic pressure, outflow obstruction
		- **Increased preload:** ventricular volume overload
		- **Cardiac arrhythmias**
		- **High-output conditions** - secondary HF - conditions that lead to increased cardiac demand i.e. anemia, hyperthyroidism, pregnancy etc.
* **HFpEF = Heart failure with PRESERVED ejection fraction**
	+ Also known as diastolic HF
	+ Reduced stroke volume but normal ejection fraction
	+ Related to aging
	+ Underlying mechanisms:
		- **Decreased ventricular compliance:** increased stiffness or impaired relaxation of the ventricle → reduced ventricular filling and increased diastolic pressure → decreased cardiac output
		- **Increased afterload;** increase in pulmonary artery pressure
		- **Increased preload;** ventricular volume overload

John has come to your clinic today complaining of urinary infrequency and even when he is able to go he produces a small volume of urine. You order some blood tests and the results show the following:

* Elevated creatinine (Cr)
* Elevated urea
* BUN:Cr > 20
* FENa < 1%
* Urine Osmolarity > 500
1. **Given his history of heart failure what is the most likely diagnosis? Briefly explain**
* Pre-renal Acute Renal Injury (AKI)
* Decreased blood supply to kidneys (due to hypovolemia - decreased circulating volume); → decreased GFR → activation of renin-angiotensin system → increased aldosterone release → increased reabsorption of Na+, H2O → increased urine osmolality → secretion of antidiuretic hormone → increased reabsorption of H2O and urea
* \*\*\*Also note FENa isn’t as important to know examwise but is good to know clinically
	+ FENa = fractional excretion of sodium
	+ percentage of the glomerular filtered sodium that is excreted in the urine.
	+ Used to determine the cause of acute kidney injury. While a FENa < 1% is consistent with prerenal AKI, a FENa > 1% suggests intrinsic AKI.
1. **Why is a BUN:Cr ratio used in kidney disease and what is the normal range**
* The BUN/Creatinine ratio is useful in the differential diagnosis of acute or chronic renal disease. BUN/Creatinine ratio test results have been proven to be one of the best ways to diagnose acute or chronic renal disease, gastrointestinal bleeding, and urinary tract blockages.
* Reduced renal perfusion, e.g., congestive heart failure, or recent onset of urinary tract obstruction will result in an increase in BUN/Creatinine ratio.
* Increased urea formation also results in an increase in the ratio, e.g., gastrointestinal bleeding, trauma, etc.
* When there is decreased formation of urea as seen in liver disease, there is a decrease in the BUN/Creatinine ratio.
* In most cases of chronic renal disease the ratio remains relatively normal.
* Normal range is usually between 15:1 to 20:1
1. **Outline the pathophysiological mechanism for increased BUN:Cr ratio in patients with pre-renal AKI**
* Less blood flow to kidney → RAAS activates → more water reabsorption from aldosterone’s action → this is coupled with enhanced proximal tubular reabsorption of urea, which is disproportionate to creatinine reabsorption → elevated BUN:Cr
1. **Briefly explain how the following would also lead to pre-renal AKI: pulmonary embolism, tension pneumothorax, anaphylaxis**
* Prerenal causes include any condition leading to **decreased renal perfusion.**
* **Pulmonary embolism**
	+ pulmonary blood vessels obstructed → less blood flow to left side of heart → less blood ejected to systemic circulation AND
	+ PE causes right heart failure → further exacerbates lack of blood flow
* **Tension pneumothorax** -
	+ kinking of veins returning into right atrium → same as above
* **Anaphylaxis** -
	+ widespread oedema leads to increased volume in interstitium and hence decreased volume in plasma

John comes back a few weeks later still not well and the tests are redone which show the following

* BUN:Cr <15
* FENa > 2%
* Urine osmolarity < 500
* Muddy brown granular casts in urine
1. **What is most likely the new diagnosis given the results above and what has caused this?**
* John now has INTRA-renal AKI (also known as “intrinsic” AKI), in particular he has **acute tubular necrosis** - which is the most common cause of intra-renal AKI
* Prolonged prerenal failure leads to intra-renal failure because decreased renal perfusion causes tubular necrosis
* \*\*key concept is intra-renal AKI is commonly preceded by pre-renal AKI
* The main causes of acute tubular necrosis are
	+ **Ischemic:** Injury occurs secondary to decreased renal blood flow
	+ **Toxic:** Injury occurs directly due to nephrotoxic substances
	+ **Other:** sepsis, infection
1. **Explain the difference in John’s FENa and urine osmolality compared the his initial visit and why he now has casts in his urine**
* In pre-renal AKI, there is **no** damage to the renal tubules.
* In **acute tubular necrosis**,
	+ necrosis or apoptosis of tubular cells → decreased reabsorption capacity of electrolytes (e.g., Na+), water, and/or urea; → increased Na+ and H2O in the urine → decreased urine osmolality and high FENa
	+ Casts are from dead tubular epithelial cells sloughing into tubular lumen

It has been 4 months since you last saw John and you order blood tests which show his kidney function has continued to deteriorate and he now has chronic kidney disease (CKD).

1. **List the clinical features of Chronic kidney disease**
* A good mnemonic for Chronic Kidney disease is **“MAD HUNGER”**
	+ **M**etabolic **A**cidosis
	+ **D**yslipidemia (especially high triglycerides)
	+ **H**igh Potassium
	+ **U**remia - clinical syndrome marked by
		- Nausea, anorexia
		- Pericarditis
		- Asterixis
		- Encephalopathy
		- Platelet dysfunction
	+ **N**a+/H2O retention (HF, pulmonary oedmea, hypertension)
	+ **G**rowth retardation and developmental delay
	+ **E**rythropoietin failure (anemaia)
	+ **R**enal osteodystrophy
* Less advanced stages usually asymptomatic
* Oliguria - Urine output < 400mL in 24 hour
* ↑ fluid volume → Peripheral oedema, pulmonary oedema
* Skin → Uremic pruritus, excoriations
* GI tract → Ulcerations, bleeding, diarrhea, vomiting
* Azotemia/uremia/Encephalopathy → Fatigue, somnolence, appetite loss, asterixis, confusion, seizures, paresthesias, uremic pericarditis
* Hyperkalemia → Cardiac arrhythmias
* Anemia → Low erythropoietin production by kidneys
	+ ↑ Risk of infection
	+ ↑ Bleeding tendency secondary to platelet dysfunction
* Chronic kidney disease-mineral and bone disorder (CKD-MBD): abnormalities of mineral or bone metabolism in the setting of chronic renal disease
* \*\*Side note\*\* a Mnemonic for Uremia is **“RESIN & 8P's”**
	+ R- Retinopathy
	+ E- Excoriations (scratch marks)
	+ S- Skin is yellow
	+ I- Increased blood pressure
	+ N- Nails are brown
	+ P- Pallor
	+ P- Purpura and bruises
	+ P- Pericarditis and cardiomegaly
	+ P- Pleural effusions
	+ P- Pulmonary oedema
	+ P- Peripheral oedema
	+ P- Proximal myopathy
	+ P- Peripheral neuropathy
1. **Explain the mechanism of hyperparathyroidism in CKD?**
* It is secondary to derangements in the homeostasis of calcium, phosphate, and vitamin D
* Decreased hydroxylation of vit D → less intestinal Ca2+ absorption → decreased serum calcium → increased parathyroid hormone
* Also decreased excretion of phosphorus → increased serum phosphorus → decreased serum calcium → increased parathyroid hormone

**Case 2 -**

You are on the renal ward at GCUH. You have a few patients who have various kidney diseases each presenting with symptoms of the nephrotic syndrome.

1. **What are the components of the filtration barrier in the kidney?**
* FenestratedCapillary endothelium
* Glomerular Basement membrane (GBM)
* Foot processes of podocytes
1. **What are the differences in presentation and overall pathophysiology of nephrotic syndrome vs nephritic syndrome**

|  |  |  |
| --- | --- | --- |
|  | **Nephrotic Syndrome** | **Nephritic Syndrome** |
| **Presentation**  | Heavy proteinuria (> 3.5 g/day)HypoalbuminemiaGeneralized oedemaHyperlipidemia and fatty casts in urine → frothy urineHypertension↑ Risk of thromboembolism: (via loss of antithrombin III)↑ Risk of infection | Proteinuria (< 3.5 g/day) (can be in nephrotic range in severe cases )Hematuria with acanthocytesRBC casts in urineMild to moderate oedemaOliguriaAzotemiaHypertensionSterile pyuria |
| **Pathophysiology**  | Damage to podocytes → structural damage of glomerular filtration barrier → massive renal loss of protein | Inflammatory response within glomeruli → GBM disruption → loss of renally excreted RBCs (acanthocytes) and ↓ GFR → hematuria, oliguria, azotemia, and ↑ renin → edema and hypertensionDamage to podocytes → structural damage of glomerular filtration barrier → massive renal loss of protein |

1. **Explain the mechanism leading to each of the following symptoms of the nephrotic syndrome.**
* **Proteinuria**
* **Peripheral oedema**
* **Hyperlipidemia and fatty casts in urine**
* **Decreased prothrombin time**
* **Increased risk of infection**
* **Proteinuria**
	+ Derangement of the kidney filtration barrier leading to increased permeability.
	+ This can be due to immune mechanisms or non immune mechanisms.
	+ This leads to loss of protein and lipids into filtrate
* **Peripheral oedema**
	+ Loss of albumin/protein from blood = ↓ plasma oncotic pressure = fluid movement to interstitial fluid
* **Hyperlipidemia and fatty casts in urine**
	+ In response to low protein, the liver upregulates all protein and lipid production leading to hyperlipidaemia.
	+ Fatty casts are due to loss of these lipids via urine, due to damage to the filtration barrier.
* **Decreased prothrombin time**
	+ Loss of anticoagulant proteins (such as antithrombin III) in the urine
* **Increased risk of infection**
	+ Due to loss of IgG and tissue oedema which compromises the local blood supply and immune response
1. **Briefly fill out the below table in regards to the different causes of nephrotic syndrome**

\*\*know the basics don't need to know all details listed - comprehensive answers provided to give a better understanding\*\*

|  |  |  |  |
| --- | --- | --- | --- |
| **Disease** | **Epidemiology**  | **Associations**  | **Treatment**  |
| Minimal change disease | Most common cause of nephrotic syndrome in children | Often idiopathicSecondary causes (rare)* Immune stimulus (e.g., infection, immunization)
* Tumors (e.g., Hodgkin lymphoma)
* Certain drugs (e.g., NSAIDs)
 | Responds well to prednisoneGood prognosis |
| Focal segmental glomerulosclerosis | Most common cause of nephrotic syndrome in adults, especially in African American and Hispanic populations | Can be idiopathicHeroin useHIV infectionSickle cell diseaseMassive obesityInterferon treatmentCongenital malformations (e.g., Charcot-Marie-Tooth syndrome) | Prednisone (often shows poor response)If necessary, PLUS other immunosuppressants (e.g., cyclosporine, tacrolimus)RAAS inhibitorsUsually leads to end stage renal disease if left untreated |
| Membranous nephropathy | Most common cause of nephrotic syndrome in adults of European, Middle Eastern, or North African descent | **Primary:** anti-PLA2R antibodies**Secondary:**Infections (HBV, HCV, malaria, syphilis)Autoimmune diseases (e.g., SLE)Tumors (e.g., lung cancer, prostate cancer)Medications (e.g., NSAIDs, penicillamine, gold) | RAAS inhibitorsPrednisone (often shows poor response)PLUS other immunosuppressants (e.g., cyclophosphamide) in severe diseaseUsually leads to end stage renal disease if left untreated |
| Diabetic nephropathy | Leading cause of end stage renal failure in high-income countries | Usually additional signs of other organ system complications (e.g., retinopathy, neuropathy) | Stringent glycemic controlRAAS inhibitors |
| Amyloid nephropathy | More commonly seen in elderly patients | The kidney is the most commonly affected organ in systemic amyloidosis.Other organs might be involved simultaneously (e.g., the heart).Multiple myeloma (AL amyloidosis)Chronic inflammatory disease, e.g., tuberculosis, rheumatoid arthritis (AA amyloidosis) | Melphalan, corticosteroidsTreatment of underlying disease (e.g., bone marrow transplantation may be used for multiple myeloma) |

Table adapted from Amboss - nephrotic syndrome

1. **Some of these patients go on to develop various other complications. Explain the mechanism of the following signs and symptoms for THESE patients.**
2. **Unilateral calf pain and swelling**
3. **Dyspnoea, stony dull percussion note and decreased breath sounds at the base of the lungs bilaterally**
4. **Sudden onset flank pain with an acute decline in GFR**
5. **Unilateral calf pain and swelling**
* Patient has a DVT
* Increased clotting factor production and loss of antithrombin III = hypercoagulable state = predisposed to DVT.
* Patient is also in hospital (likely on bed rest) so there is likely a stasis of blood.
* Increased risk of endothelial damage due to hyperlipidaemia as a result of nephrotic syndrome.
1. **Dyspnoea, stony dull percussion note and decreased breath sounds at the base of the lungs bilaterally**
* Patient has pleural effusion, due to loss of protein from blood - Loss of albumin/protein from blood = ↓ plasma oncotic pressure = fluid movement to interstitial fluid
* Here, prompt discussion of exudate vs transudative pleural effusions – use this table as a guide: (table from amboss - pleural effusion)
1. **Sudden onset flank pain with an acute decline in GFR**
* Renal vein thrombosis, caused by hypercoagulable state (as per DVT answer above)

**Stand alone questions...**

1. **What if another patient (not necessarily with nephrotic syndrome) presented with the following findings on urine dipstick analysis? Indicate whether they are normal found in urine or not, and indicate a possible cause (other than filtration barrier problems or medications)?**
* **Bilirubin** - No - Post-hepatic causes of jaundice (eg, bile duct obstruction)
* **Urobilinogen** - Yes - low concentrations of urobilinogen is normally excreted in urine
* **Glucose** - No - Diabetes mellitus
* **Haemoglobin** - No - Haemolysis, cancer, pyelonephritis
1. **Another patient presents with suprapubic pain, dysuria, urinary urgency and frequency. Their urine dipstick is positive for nitrites and leukocytes. Explain why.**
* Cystitis - UTI involving bladder and urethra
* Likely caused by E. coli, because E. coli has an enzyme that converts nitrates to nitrites
	+ If no nitrites present, UTI likely due to non-E coli bacteria.
* Leukocytes present due to infection

**Please provide feedback for this case at:** [**https://docs.google.com/forms/d/1KmfO3yIEpnCBxAX8Q4alZIqdYBDVZaltx98rPMi63cs/edit**](https://docs.google.com/forms/d/1KmfO3yIEpnCBxAX8Q4alZIqdYBDVZaltx98rPMi63cs/edit)