Brigham and Women's Hospital
Founding Member, Mass General Brigham

Brigham Renal Board Review

Q&A Session

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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  - Clinical focus: ESRD
  - Research focus: Cardiovascular disease in CKD

Disclosures

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- Consulting: Advanced Medical and GSK

Question 1

Administration of amiloride may be beneficial for which of the following situations?

A. Genetic defect for the Thick Ascending Limb luminal potassium channel ROMK

B. Genetic defect for the epithelial sodium channel (inactivating mutation)

C. Genetic defect for 11B-hydroxysteroid dehydrogenase

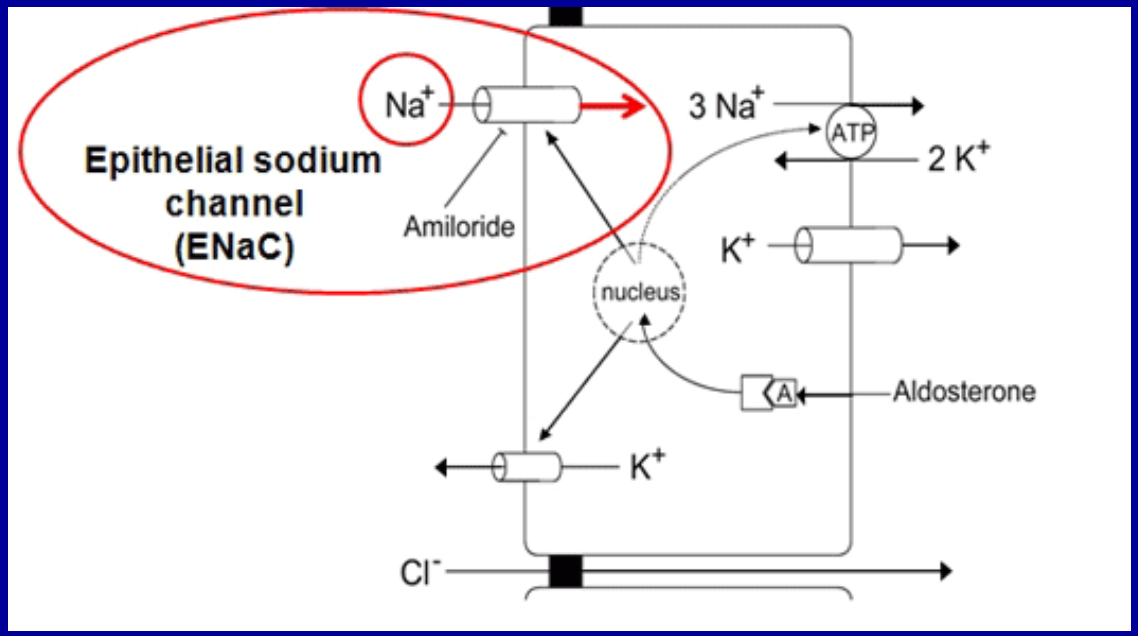
D. Genetic defect from fusion of portions of the 11B-hydroxylase gene and the aldosterone synthase gene

E. Genetic defect for the epithelial sodium channel (activating mutation)

Answer 1

E. Genetic defect for the epithelial sodium channel (activating mutation)

ENaC and distal tubule function (Principal cells)



Answer 1

Liddles' syndrome

- Activating mutation of the epithelial sodium channel in the collecting duct
- Autosomal dominant trait
- Early onset of hypertension
- Hypokalaemia and metabolic alkalosis

Question 2

Which of the following set of laboratory findings is consistent with Liddle's syndrome?

A. Low renin; low aldosterone; high potassium

B. Low renin; high aldosterone; low potassium

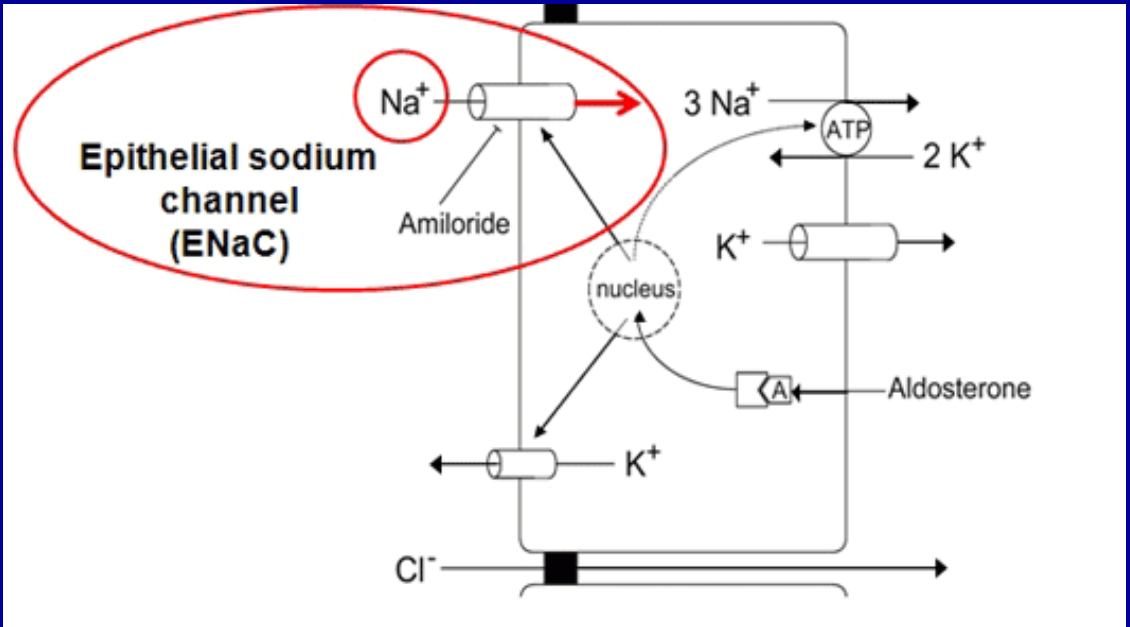
C. High renin; low aldosterone; high potassium

D. High renin; high aldosterone; low potassium

E. Low renin; low aldosterone; low potassium

Answer 2

E. Low renin; low aldosterone; low potassium



Hypertensive renal potassium wasting

High renin
- Renovascular disease
- Malignant hypertension
- Renin-secreting tumour
- Some forms of Cushing's disease

Low renin
- Conn's syndrome
- Bilateral adrenal hyperplasia
- Glucocorticoid-remediable hyperaldosteronism
- Apparent mineralocorticoid excess syndrome
- Licorice ingestion
- Liddle syndrome

Question 3

A 61 year old man with ESKD secondary to type 2 diabetes mellitus experiences large inter-dialytic weight gains and recurrent episodes of intra dialytic hypotension in his outpatient unit. Strategies proven to mitigate against intra-dialytic hypotension include all of the following, EXCEPT …..?

A. Lowering of the dialysate temperature below body temperature

B. Use of dialysate sodium modeling

C. Use of lower dialysate calcium concentration

D. Administration of hypertonic mannitol

Answer 3

C. Use of lower dialysate calcium concentration

Intra-dialytic hypotension can be defined as an intra-dialytic decline in SBP of 20 mmHg accompanied by patient symptoms.

It is estimated to complicate up to one third of outpatient treatments.

Various strategies have been proven to reduce IDH, including sodium modeling, cooled dialysate, isolated UF, hypertonic fluid administration, vasopressin infusions and ***higher*** dialysate calcium.

Question 4

Which of the following statements regarding cooled dialysate is TRUE?

A. Cooling the dialysate increases stroke volume.

B. Cooling the dialysate increases systemic vascular resistance.

C. Cooling the dialysate is associated with decreased circulating norepinephrine concentrations.

D. Cooling the dialysate is associated with reduced dialysis adequacy.

E. Cooling the dialysate is associated with post-dialysis hyperkalaemia.

Answer 4

B. Cooling the dialysate increases systemic vascular resistance.

Cooled dialysate has been shown to increase systemic vascular resistance, thereby promoting blood pressure stability during haemodialysis.

Despite concerns of centralization of blood flow, previous studies did not note any decrease in dialysis adequacy.

Small studies in outpatients have noted reduced frequency of myocardial wall motion abnormalities and reduced frequency of cerebral white matter changes associated with cooled dialysate use. The major patient symptoms with this strategy were shivering.

Question 5

A 45 year-old man has been vomiting for 2 days and has orthostatic hypotension and a serum K of 2.9 mEq/L. The blood pH is 7.54. Urine pH is 6.8. Which of the following statements is FALSE?

A. The urine [Na+] is >25 mEq/L

B. The urine [K+] is >15 mEq/L

C. The urinary anion gap is positive

D. The hypokalaemia is mostly due to gastric losses

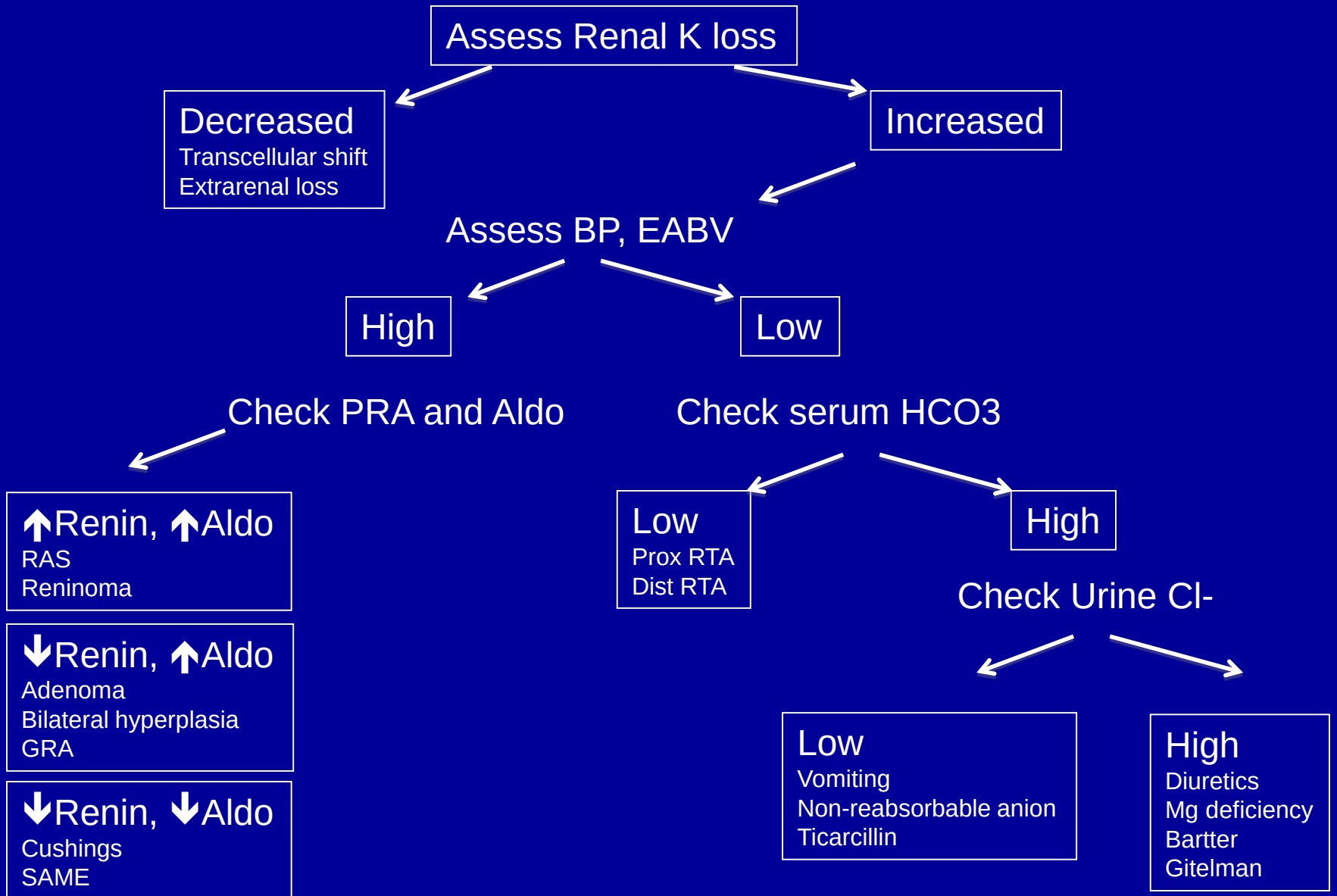
E. The serum bicarbonate is >30mEq/L

Answer 5

D. The hypokalaemia is mostly due to gastric losses - FALSE

Vomiting and serum K

- K concentration in gastric fluid only 5-10mEq/L
- The loss of large amounts of HCl leads to:
  - Metabolic alkalosis (bicarbonaturia, pulls K with it)
  - Volume depletion (activation of RAAS)
  - Secondary hyperaldosteronism
- Secondary hyperaldosteronism promotes K secretion via
  - Increased activity of H+K+ATPase
  - Increased activity of ENaC
- Bicarbonaturia draws Na+ ions to maintain electroneutrality
  - Therefore UNa may be higher than expected
  - Check the Urine Cl level


Assess Renal K loss
Decreased
Transcellular shift
Extrarenal loss
Increased
Assess BP, EABV
High
Low
Check PRA and Aldo
Check serum HCO3
↑Renin, ↑Aldo
RAS
Reninoma
↓Renin, ↑Aldo
Adenoma
Bilateral hyperplasia
GRA
↓Renin, ↓Aldo
Cushings
SAME
Liddle
11β OH deficiency
17α OH deficiency
Low
Prox RTA
Dist RTA
High
Check Urine Cl-
Low
Vomiting
Non-reabsorbable anion
Ticarcillin
High
Diuretics
Mg deficiency
Bartter
Gitelman

Evaluation of urine K^+ wasting

- History
- 24 hour collections are the most accurate
  - Urine K conservation can lower renal losses to 25-30mEq/day
- Spot samples
  - Minimum K concentration achievable is 5-15 mEq/L
  - Must be interpreted in association with urinary volume
  - Alternative is the urine K/Cr ratio – values less than 13mEq/g suggest non-renal losses
- TTKG
  - TTKG = UK/SK * POsm/UOsm
  - UNa should be >25 so K secretion is not limited by distal Na delivery
  - Urine Osm should be greater than POsm

Question 6

A 32 year-old male with a known history of alcoholism and substance abuse is brought to the ED. He has been drinking heavily for the last week and admits to several episodes of vomiting per day for the last three days. He is hypoglycaemic on admission and is treated with normal saline, thiamine and glucose. Four hours later he developed a generalized tonic-clonic seizure.

Question 6

Which is the most likely cause of this event?

A. Hypernatraemia from saline infusion.

B. Lowering of ionized calcium as his metabolic alkalosis corrects.

C. Hyperglycaemia from administered glucose solutions.

D. Hyperkalaemia from correction of metabolic alkalosis.

E. Hypophosphataemia from stimulation of insulin release.

Answer 6

E. Hypophosphataemia from stimulation of insulin release.

- This patient likely developed severe hypophosphataemia as a result of insulin release in response to the administered glucose.
- His underlying acid-base disturbance was most likely a metabolic alkalosis from vomiting, with concomitant low/low-normal potassium from secondary hyperaldosteronism. Restoration of volume status with normal saline and correction of alkalosis (with bicarbonaturia) may exacerbate the low potassium, in addition to the effects of insulin release.
- Correction of an alkalosis will increase ionized calcium levels.
- He is unlikely to develop hypernatraemia form normal saline infusion.

Re-feeding Syndrome

Characterized by hypophosphataemia, hypokalaemia, hypomagnesaemia, vitamin and trace mineral deficiency and volume overload/oedema.

Total body phosphate depletion is exacerbated by the administration of carbohydrate, which leads to insulin release. This drives intracellular uptake of phosphate and stimulation of ATP and 2,3-DPG production.

Severe hypophosphataemia can lead to impaired myocardial, skeletal muscle and diaphragmatic contractility, rhabdomyolysis, bradycardia, abnormal LFTs and seizures.

Caloric intake should be increased gradually and electrolyte abnormalities corrected before institution of the re-feeding process.

Question 7

Which of the following statements regarding the use of vasopressin receptor antagonists is FALSE?

A. The anti-diuretic response of vasopressin receptor antagonists is mediated primarily via the V2 receptors.

B. Upon initiation of vasopressin antagonists, strict free water intake restrictions must be maintained.

C. Conivaptan must be administered intravenously.

D. Tolvaptan use should be avoided in patients with liver failure.

E. Conivaptan blocks both V2 and V1a receptors.

Answer 7

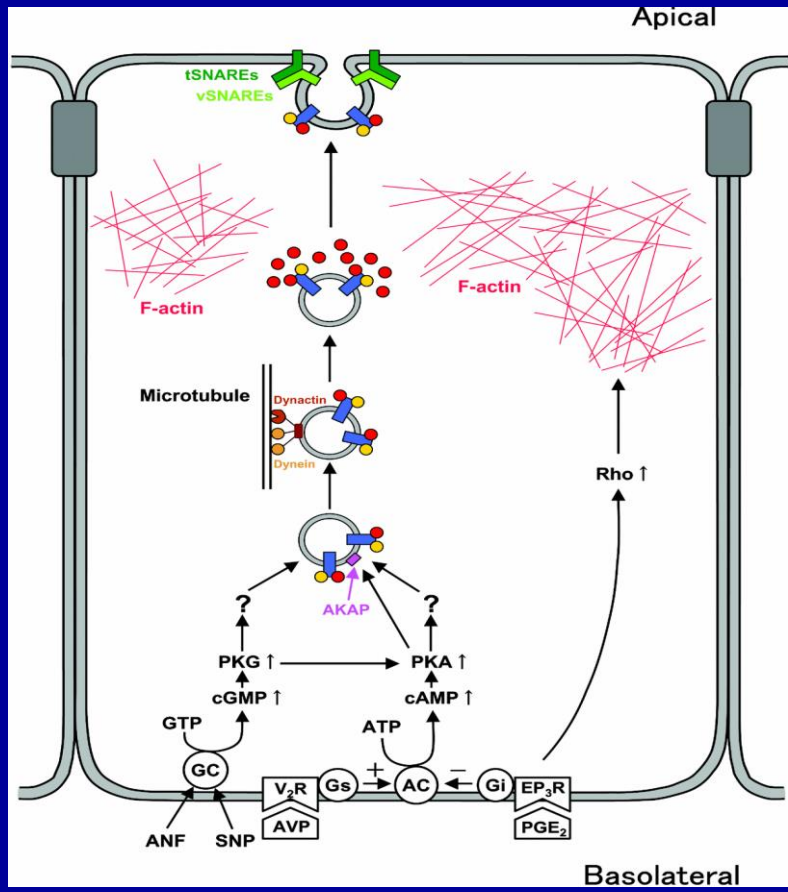
B. Upon initiation of vasopressin antagonists, strict free water intake restrictions must be maintained.

V1a - Vasoconstriction

V1b - ACTH release

V2 - Anti-diuresis

- V2 receptor antagonists (vaptans) should not be used in hypovolaemic patients.
- Recent concerns have limited tolvaptan use to a maximum of 30 days and advised avoidance in patients with liver disease.



Question 8

A 52-year-old Caucasian female is referred for evaluation of dipstick albuminuria. Her medical history is notable for long-standing pain in her hands and feet, worse with exercise and hot weather. She denies smoking, alcohol intake or illicit drug use. She takes no regular medications at present and has no allergies.

On physical examination, her blood pressure is 108/68 mmHg with a heart rate of 72 bpm. The pulse is regular and she appears euvolaemic. Inspection of the skin reveals several 1-2mm reddish-purple macules around her umbilicus and lower abdomen which she claims are unchanged and there as long as she can remember.

Urinalysis reveals specific gravity of 1.010, negative haem and 2+ albumin.

Question 8

Which of the following is the next MOST appropriate diagnostic test to perform?

A. Measurement of alpha-galactosidase A activity in peripheral blood leucocytes.

B. Plasma anti-PLA2R antibodies.

C. Kidney biopsy.

D. Bidirectional sequence analysis of the GLA gene.

E. Fasting plasma glucose.

Answer 8

D. Bidirectional sequence analysis of the GLA gene.

This presentation should raise the concern for Fabry's disease, an X-linked multisystem disorder.

Mutation in the GLA gene coding for the alpha-galactosidase enzyme leads to accumulation of globotriasoylceramide in cells

Presentation includes acroparaesthesiae, autonomic neuropathy, stroke, left ventricular hypertrophy, proteinuria, chronic kidney disease, GI symptoms, angiokeratoma, corneal whorls and impaired sweating.

Females can have varying degrees of involvement depending on the proportions of affected versus unaffected X chromosomes - the next recommended step involves mutational analysis of the GLA gene.

Answer 8

The neuropathy would not be typically associated with membranous nephropathy.

A kidney biopsy would not be the next most appropriate step, as there are other less invasive methods of accurately making the diagnosis of Fabry's disease.

While the presence of neuropathy and proteinuria could be consistent with diabetes, this would be less likely in an otherwise healthy female with no other symptoms of this disease. Rather, the combination of patient history and physical findings suggest an inherited disorder.

Question 9

With regard to the clinical use of diuretics, which of the following statements is FALSE?

A. Hypoglycaemia is a common complication of thiazide diuretics

B. Bumetanide exhibits less intra- and inter-patient differences in oral bioavailability than furosemide

C. Hyponatraemia is more common with thiazide diuretics than loops

D. Acetazolamide may be helpful for treating a diuretic-associated metabolic alkalosis

E. Eplerenone has greater specificity for the mineralocorticoid receptor and therefore has a weaker association with gynaecomastia

Answer 9

A. Hypoglycaemia is a common complication of thiazide diuretic therapy

Thiazide diuretics are associated with several electrolyte complications, including hyperglycaemia, hyperlipidaemia, hyperuricaemia, hypercalcaemia, hyponatraemia and hypokalaemia

Loops diuretics are associated with hypocalcaemia, hypokalaemia and hypomagnesaemia

Thiazide diuretics are more likely to associate with hyponatraemia than loops, as the medullary concentrating gradient remains intact, allowing a continually favourable gradient for water to be reabsorbed in the collecting tubule

Question 10

Regarding the use of eculizumab, which one of the following statements is TRUE?

A. Eculizumab is most efficacious if given immediately before plasma exchange

B. Eculizumab is not indicated for the treatment of paroxysmal nocturnal haemoglobinuria

C. Supplemental dosing is not required for patients receiving fresh frozen plasma

D. Patients receiving Eculizumab should be vaccinated against meningococcus.

E. Eculizumab is a humanized monoclonal IgG antibody that binds to complement protein C3

Answer 10

D. Patients receiving Eculizumab should be vaccinated against meningococcus.

Eculizumab is a humanized monoclonal IgG antibody that binds to complement protein C5, thereby preventing cleavage to C5a and C5b and ultimately inhibiting formation of the membrane attack complex

It is FDA-approved for the treatment of PNH and aHUS

Several reports of meningococcal disease have been reported in association with it's use; vaccination is recommended at least two weeks prior to use

Eculizumab is rapidly cleared by plasma exchange and should not be given prior to this treatment; supplemental dosing is recommended for patients receiving FFP

Question 11

A 70 year old male was diagnosed with an ST elevation MI, requiring deployment of a drug-eluting stent in the LAD artery. His EF was reduced to 15% and he developed severe pulmonary oedema requiring treatment with IV furosemide. Three days later he developed a diffuse maculopapular rash. Which of the following is the next most reasonable step to take?

A. Switch IV furosemide to oral furosemide

B. Switch IV furosemide to IV bumetanide

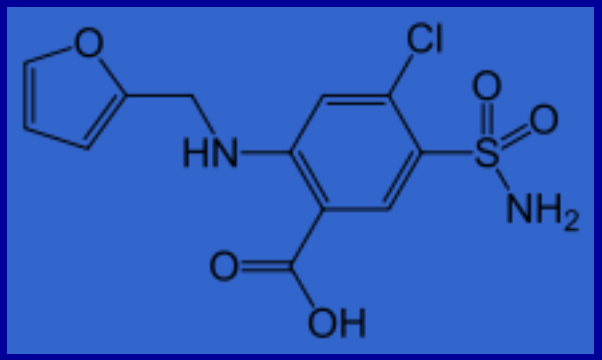
C. Switch IV furosemide to IV chlorothiazide

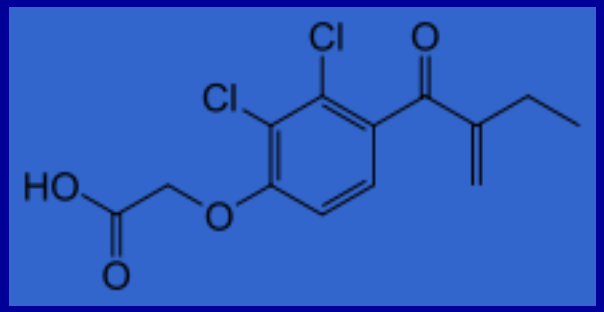
D. Switch IV furosemide to IV ethacrynic acid

E. Stop diuretics and begin extracorporeal ultrafiltration

Answer 11

D. Switch IV furosemide to IV ethacrynic acid





- Furosemide and it's related molecules contain a sulpha group.
- The original loop diuretic ethacrynic acid does not contain a sulpha group and so should not cause problems for patients with sulpha allergies.
- A thiazide diuretic is unlikely to be efficacious enough in this situation.
- Ultrafiltration is more invasive when other more conservative measures could be considered first.

Question 12

Midodrine is increasingly used (off-label) to reduce the frequency of intra dialytic hypotensive events. Which of the following statements is TRUE regarding this medication?

A. Midodrine is highly protein bound.

B. The active metabolite (desglymidodrine) is an alpha-1 agonist, which causes an increase in arteriolar and venous tone.

C. The peak onset of action is within ten minutes of oral administration.

D. Midodrine is associated with a reflex tachycardia.

E. The oral bioavailability is poor and it should not be administered with food.

Answer 12

B. The active metabolite (desglymidodrine) is an alpha-1 agonist, which causes an increase in arteriolar and venous tone.

- Midodrine is rapidly absorbed from the GI tract and is highly bioavailable (93%). The bioavailability of desglymidodrine is similar with oral and intravenous administration, and is not affected by food.
- It is poorly protein bound.
- Elevation of systemic pressure may associate with a reflex bradycardia.
- The major side-effect is supine hypertension, with around 13% of individuals experiencing SBP's >200 mmHg. Other side-effects include urinary retention, paraesthesiae, pruritis and piloerection.

Question 13

A 54 year-old African American woman with ESKD secondary to hypertensive nephrosclerosis has developed painful skin lesions on the lower abdomen and upper thigh. Biopsy was consistent with calcific uremic arteriopathy and she was commenced on sodium thiosulphate (STS) therapy. Which of the following statements regarding this treatment is FALSE?

A. STS is associated with development of a metabolic alkalosis.

B. STS may be associated with excess sodium loading during HD.

C. Headache is a common side effect.

D. STS is dialyzable and should only be given towards the end of dialysis.

E. STS can be injected intra-lesionally to minimize systemic side-effects.

Answer 13

A. STS is associated with development of a metabolic alkalosis.

- STS therapy has several proposed mechanisms in the treatment of calciphylaxis lesions, including complexing with lesional calcium and anti-oxidant activity.
- Accumulation of thiosulphuric acid can lead to a raised anion gap acidosis, which may necessitate changes in the dialysate prescription.
- Administration of 25g of STS results in administration of around 7.3 g of sodium, which may associate with greater thirst, IDWG and SBP.

Question 14

Regarding autosomal dominant polycystic kidney disease, which of the following statements is FALSE?

A. Defects in the gene PKD1 are responsible for 85-90% of clinically detected cases
B. Polycystin 1 plays an important role in intracellular calcium homeostasis in primary cilia
C. PKD1 gene is located on chromosome 4
D. The frequency of renal stone disease is increased compared with the general population
E. Polycystic liver disease is the most common extra-renal manifestation of ADPKD

Answer 14

C. PKD1 is located on chromosome 4

- ADPKD affects between 1 in 100 and 1 in 1000 individuals
- PKD1 is located on chromosome 16 and codes for polycystin 1
- PKD2 is located on chromosome 4 and codes for polycystin 2
- Both are present in primary cilia and are thought to regulate calcium flux in response to mechanical stimuli
- Renal stone disease is estimated to occur in 20% of patients
- Hepatic cysts increase in frequency with age – 20% in third decade to 75% by seventh decade, with females>males
- Intracranial aneurysm ~8%; MVP ~25%; HTN ~ 75% (prior to ESKD)

Question 15

Regarding Alport's Syndrome, which of the following statements is FALSE?

A. It is caused by a defect in the genes coding for α-3, α-4 or α-5 chains of collagen

B. Ocular manifestations may include anterior lenticonus

C. The autosomal dominant form has a faster rate of progression than the X-linked form

D. Anti-glomerular basement membrane antibodies may develop post-transplant, but are typically not directed against the Goodpasture antigen

E. Lamellation of the glomerular basement membrane may be found on electron microscopy evaluation of a renal biopsy

Answer 15

C. The autosomal dominant form has a faster rate of progression than the X-linked form

- 80% X linked (mutations in COL4A5 gene)
- 15% Autosomal recessive (mutations in COL4A3 or COL4A4 genes)
- 5% Autosomal dominant (mutations in COL4A3 or COL4A4 genes)
  - Slower progression than X-linked Alport's
- Co-distribution of collagen α-3, α-4 & α-5 chains in the cochlea and eye can lead to presence of hereditary deafness and anterior lenticonus
- EM shows irregular diameter of the GBM with splitting and a multilaminated appearance of the lamina densa (basket weaving)
- Occurrence of anti-GBM disease occurs in ~5% of those receiving renal transplants; more common in those with extensive deletion of COL4A5

Question 16

Which of the following statements is FALSE regarding arginine vasopressin (AVP)?

A. AVP is manufactured in the paraventricular and supraoptic nuclei of the posterior pituitary gland

B. AVP may have pressor-like effects via binding to V1a receptors in the vasculature

C. The stimulus for AVP release is greater for relative volume depletion than for increased plasma osmolality

D. Cortisol inhibits the secretion of AVP from the paraventricular nuclei

E. Copeptin is a cleavage product of AVP that tends to be more biochemically stable

Answer 16

A. AVP is manufactured in the paraventricular and supraoptic nuclei of the posterior pituitary gland - FALSE

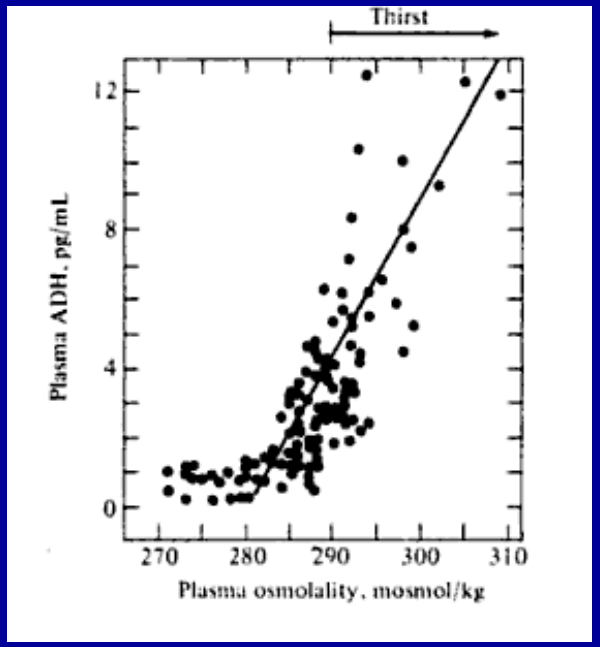
- AVP is manufactured in the PVN and SO nuclei of the hypothalamus and transported to the posterior pituitary for release.

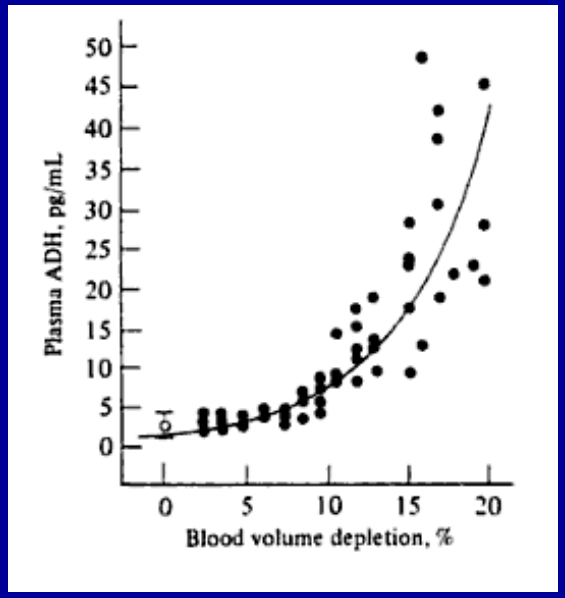
- AVP release may be stimulated by stress (pain), pregnancy, hypoglycaemia, nicotine, morphine and may be inhibited by ethanol and phenytoin.

- Pre-pro-AVP is cleaved to vasopressin, neurophysin II and copeptin during transport from the hypothalamus to the posterior pituitary.

Answer 16

- V1a - Vasoconstriction
- V1b - ACTH release
- V2 - Anti-diuresis





Adapted from Clinical physiology of acid-base and electrolyte disroders

Question 17

75 yo AA male with ESRD presumed secondary to DM2. He has been on HD for 2 years and has a background notable for DM2, HTN, PVD and gout. Pre dialysis SBP ~ 140-150 mmHg. Calculated LDL 134 mg/dL; TG 264 mg/dL. His current medications include aspirin, metoprolol, insulin, multivitamin, warfarin, famotidine, sevelamer hydrochloride and calcitriol.

Question 17

According to the 2013 KDIGO recommendations, the patient should be prescribed which of following:

A. Atorvastatin 20 mg daily

B. Rosuvastatin 10 mg daily

C. Ezetemibe 10 mg daily

D. Fenofibrate 160 mg daily

E. No pharmacological lipid lowering therapy

Answer 17

E. No pharmacological lipid lowering therapy

- 4-D Study
  - Die Deutsche Diabetes Dialyse
  - 1255 DM2 patients with elevated baseline LDL
  - Atorvastatin 20 mg vs. placebo
  - Median follow-up of 4 yrs:
    - No difference in primary outcome of CV death, nonfatal MI or stroke (RR 0.92, 95%CI 0.77-1.10)
    - Reduction in cardiac events (RR 0.82, 95%CI 0.68-0.99)
    - Paradoxical increase in stroke risk (RR 2.03, 95%CI 1.05-3.93)
    - Reduction in primary outcome in those with baseline LDL > 145 mg/dL (not a pre-specified primary outcome)

Answer 17

- AURORA
  - A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
  - 2776 HD patient not previously on a statin
  - Rosuvastatin 10 mg/day vs. Placebo
  - Median follow-up of 3.8 years:
    - No difference in primary outcome of composite of CV death, nonfatal MI, stroke (HR 0.96, 95%CI 0.84-1.11)
    - Sub-group of diabetics potential benefit (HR 0.68, 95%CI 0.51-0.90)
    - Higher incidence of haemorrhagic stroke (12 vs 2 patients)

Answer 17

- SHARP
  - Study of Heart and Renal Protection trial
  - 3023 HD patients (1/3 of total sample) with no history of MI or coronary revascularization
  - Simvastatin 20mg + ezetemibe 10mg vs. placebo
  - Median of 4.9 years follow up:
    - No significant effect on incidence of atherosclerotic CV events (RR 0.95, 95%CI 0.78-1.15)
    - However, this study was not powered for the sub-group of HD patients

Answer 17

- KDIGO 2013 guideline 2.3.1
  - In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated. (2A)
- KDIGO 2013 guideline 2.3.2
  - In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued. (2C)
- NB – for hypertriglyceridaemia KDGIO recommends non-pharmacological therapy for fasting TG > 500mg/dL and consideration of drug therapy only for TG > 1000mg/dL

Question 18

41 year old woman presents with a 3-4 month history of fatigue, dyspnea and muscle aches. A work-up reveals a high serum ACE and hilar lymphadenopathy and a LN biopsy confirms the diagnosis of sarcoid. Her labs were notable for:

- Serum: Na 159 mmol/L, K 3.3 mmol/L, Cl 123 mmol/L, CO2 22 mmol/L, BUN 24 mg/dl, Creat 0.93 mg/dl, Osm 321 mosm/kg.
- Urine: Na 146 mmol/L, K 75.8 mmol/L, Cl 189 mmol/L, Osm 1103 mosm/kg.

What is the most likely cause for her hypernatremia?

A. Nephrogenic diabetes insipidus due to hypercalcemia
B. SIADH
C. Central diabetes insipidus
D. Central Hypodipsia
E. Overdose of Sodium Chloride tablets

Answer 18

D. Central Hypodipsia

- The absence of thirst suggests a central problem – it can be managed by regular prescription of free water
- High UOsm indicates a maximally concentrated urine, ruling out DI
- SIADH is associated with hyponatraemia
- An overdose of sodium chloride tablets could lead to severe hypernatremia in the absence of appropriate thirst and free water intake
- The commonest causes of central hypodipsia are tumours (particularly craniopharyngiomas), anterior communicating artery aneurysms and sarcoidosis

Question 19

A 35yr old man with a history of ESRD secondary to ADPKD and a renal transplant 2 years ago presents to the ED with diarrhoea for the past 5 days. His current medications include tacrolimus, MMF, loperamide and TMP/SMX. On admission, he is euvolaemic and normotensive. His admission labs reveal a creatinine of 2.0 mg/dL (baseline 1.2 mg/dL) and tacrolimus levels of 21

What is the mechanism for the transient increase in tacrolimus levels seen in this patient?

A. Poor medication compliance
B. Drug interaction with loperamide
C. Decreased activity of liver CYP3A4
D. Decreased activity of P-glycoprotein in the intestinal mucosa
E. Decreased gut transit time due to diarrheal illness

Answer 19

- **D. Decreased activity of P-glycoprotein in the intestinal mucosa**

Tacrolimus has a low oral bioavailability and approximately 20% reaches the bloodstream. There are 3 reasons for this:

- Significant first-pass metabolism in the liver by cytochrome p450 system
- Metabolism by CYP3A4 in the intestinal mucosa
- Transport out of intestinal cells into the lumen by P-glycoprotein

In patients with inflammatory diarrhea, the latter processes are downregulated in enterocytes allowing for both increased absorption and decreased gut metabolism of tacrolimus. This causes increased drug levels despite higher gut transit times related to the diarrheal illness.

After resolution of the diarrhea, these mechanisms reconstitute and the drug levels return to normal.

Question 20

A 29yo woman with a history of polysubstance abuse and epilepsy presented in status epilepticus. Phenytoin and propofol (5mg/kg/hr) were commenced; she was intubated and ventilated. On hospital day 4 her labs were as follows:

CPK 100,000 u/L, BUN 22 mg/dl, Creatinine 1.8 mg/dl, Na 136 mmol/L, K 5.4 mmol/L, Cl 100 mmol/L, HCO3 8 mmol/L, Lactate 8 mmol/L, pH 7.20.
BP 130/60, HR 85, Temp 98F; ECG revealed new Right Bundle Branch Block

Question 20

What is the most likely diagnosis?

A. Seizure-induced rhabdomyolysis
B. Propofol-infusion syndrome
C. Septic Shock
D. Neuroleptic Malignant Syndrome
E. Phenytoin-induced rhabdomyolysis

Answer 20

B. Propofol-infusion syndrome

Propofol at high doses (>4mg/kg/hr) and for prolonged periods (>24-48hr) can inhibit the mitochondrial electron-transport chain, leading to impaired oxygen utilization and the build-up of toxic fatty-acid metabolites.

The diagnosis is made in the presence of three of: Lactic Acidosis, Rhabdomyolysis, Cardiac dysfunction, AKI and Hyperlipidemia, within 3 days.

Overall incidence <1% but mortality is up to 30%; Risk factors include prolonged use at high doses, exogenous catecholamines and corticosteroids and poor carbohydrate intake.

Treatment involves stopping propofol. Prolonged HD/CVVH may be necessary to clear the drug as it is generally poorly cleared by dialysis.

Suggested Reading

- McIntyre, C. W. (2010). "Haemodialysis-induced myocardial stunning in chronic kidney disease - a new aspect of cardiovascular disease." Blood Purif **29(2): 105-110.**
- Germain, DP: Fabry disease. *Orphanet J Rare Dis,* 5**:** 30, 2010.
- Okuda, S: Renal involvement in Fabry's disease. *Intern Med,* 39**:** 601-2, 2000.
- Zuber, J et al. (2012). "Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies." Nat Rev Nephrol **8(11): 643-657.**

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