Clinical Chemistry
Trainee Council

PEARLS OF LABORATORY MEDICINE

Hyperkalemia

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Roy Peake, PhD, FRCPath, DABCC
Department of Laboratory Medicine
Boston Children's Hospital

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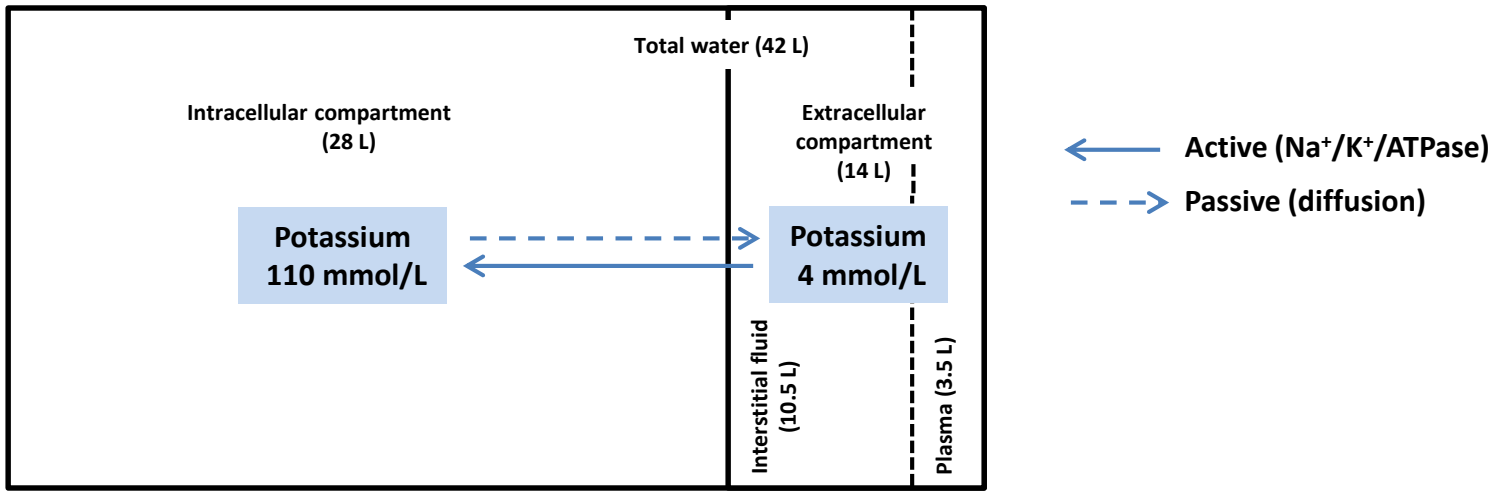
Potassium distribution

- Potassium (K^+) is the most abundant cation in the body
- Vast majority is found in the intracellular compartment (~2% is extracellular)



- K^+ is maintained inside the cell by the Na^+/K^+/ATPase
- Serum adult reference interval: ~3.5 to 5.5 mmol/L
- Disturbances in K^+ distribution resulting in an increase in extracellular K^+ concentration is defined as hyperkalemia

Hyperkalemia

- Serum [K^+] > 5.5 mmol/L
- Clinical symptoms depend upon the serum/plasma [K^+]
- Clinical symptoms also depend upon the underlying cause

    - [K^+] 5.6 to 6.5 mmol/L - Usually asymptomatic
    - [K^+] > 6.5 mmol/L - May result in cardiac arrhythmias and ventricular tachycardia

- In addition to clinical symptoms, characteristic ECG changes may be observed (peaked T waves, broadening of QRS complex, ST depression)
- Marked hyperkalemia is a life-threatening emergency
- May result in cardiac arrest
- **Clinical laboratories should have a clear policy in place for telephoning elevated serum/plasma K^+ results**

Investigation: Points to Consider

- How elevated is the serum [K^+]?
- Clinical information?
- Comparison with previous results where available
- Acute or chronic?
- Source of the request (e.g. inpatient/outpatient/renal unit)

- Could the result be artifactual?
  - Hemolysis
  - Time taken for sample to get to the laboratory
  - Contamination of sample
  - Pseudohyperkalemia resulting from elevated platelets or leucocytes

- Renal function?
- Drug history?

Investigation of Hyperkalemia 1

HYPERKALEMIA

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Causes of elevated [K^+] → **Eliminate artifactual causes**

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1. **Hemolysis**
2. **Delays in centrifugation**
3. **Contamination**
4. **Elevated platelets or leukocytes**

Very important that the laboratory works to identify artifactual causes of hyperkalemia

Artifactual Causes

- Sample Hemolysis
  - Sample hemolysis (*in vitro*) is caused by mechanical trauma to red blood cells during collection
  - K^+ released from intracellular compartment
  - The degree of K^+ increase is dependent on the extent of hemolysis
  - Very common, especially in samples from certain patient groups (e.g. neonates) or wards (Emergency Room)
- Delays in Sample Centrifugation
  - Over time, K^+ leaks from cells
  - Delays in centrifugation can result in falsely increased serum [K^+]
  - This is a particular problem in samples received from primary care where long distances may be involved in transporting samples
  - This effect is temperature-dependent (more K^+ leaks from cells at low temperatures due to inactivity of the Na^+/K^+/ATPase)

Artifactual Causes

- Contamination of specimen with K^+/EDTA
  - Occurs when blood is drawn into a CBC vacutainer followed by a serum vacutainer tube, resulting in contamination of the serum sample with K^+/EDTA
  - Typically causes a grossly increased serum K^+ concentration
  - EDTA is a chelator of divalent cations such as calcium, magnesium, and zinc
  - In a sample contaminated with EDTA, calcium concentration is abnormally decreased
  - Alkaline phosphatase (ALP) activity is also typically decreased since the chelated magnesium and zinc ions are important co-factors for this enzyme
  - Therefore, if K+/EDTA contamination is suspected, calcium and ALP analysis on that sample may help confirm this suspicion

Case A

- Routine pre-chemotherapy bloods from hematology clinic:

Sodium	140	mmol/L	(137 – 144)
Potassium	11.0	mmol/L	(3.5 – 4.9)
Chloride	109	mmol/L	(98 – 106)
Urea	11.4	mmol/L	(3.4 - 7.0)
Creatinine	76	µmol/L	(84 - 116)
Calcium (Adjusted)	1.40	mmol/L	(2.20 – 2.26)
Albumin	3.6	g/dL	(3.7 – 4.9)
Bilirubin	5	µmol/L	(1 – 22)
ALT	21	U/L	(<40)
ALP	41	U/L	(45 – 105)

- Sample was NOT hemolysed and no delay in sample centrifugation
- Grossly increased K^+ and decreased calcium and Alkaline phosphatase
- Results consistent with contamination with K^+/EDTA from CBC tube
- On repeat blood draw, K^+ (3.8 mmol/L); Calcium (2.19 mmol/L); ALP (95 U/L)

Artifactual Causes

- Contamination of specimen from I.V. fluid
  - Contamination from intravenous fluid containing potassium
  - K^+ is often given with dextrose
  - A markedly elevated glucose result may raise the index of suspicion
- Elevated platelets or leucocytes
  - May be observed in serum samples from patients with thrombocytosis or leukocytosis
  - In thrombocytosis, platelets are released during the clotting process resulting in pseudohyperkalemia (this is not a true indicator of physiological blood K^+ concentration)
  - Pseudohyperkalemia observed in a serum sample caused by elevated platelets can be resolved by measuring K^+ in a plasma sample (no clotting) instead

Case B

- Post-operative bloods from a patient on a general surgery ward

Sodium	136	mmol/L	(137 – 144)
Potassium	7.0	mmol/L	(3.5 – 4.9)
Chloride	96	mmol/L	(98 – 106)
Urea	6.2	mmol/L	(3.4 - 7.0)
Creatinine	47	µmol/L	(84 - 116)

- Hyperkalemia on a non-hemolysed specimen
- Patient was clinically well with no ECG changes (results did not fit clinically)
- Platelet count was noted to be elevated: 1428 $x10^9$/L (140 – 400$x10^9$/L)
- The medical team were contacted and another sample was drawn from the patient collected into a lithium heparin plasma tube
- Plasma K^+ result returned was 4.4 mmol/L
- Pseudohyperkalemia confirmed due to thrombocytosis

Case C

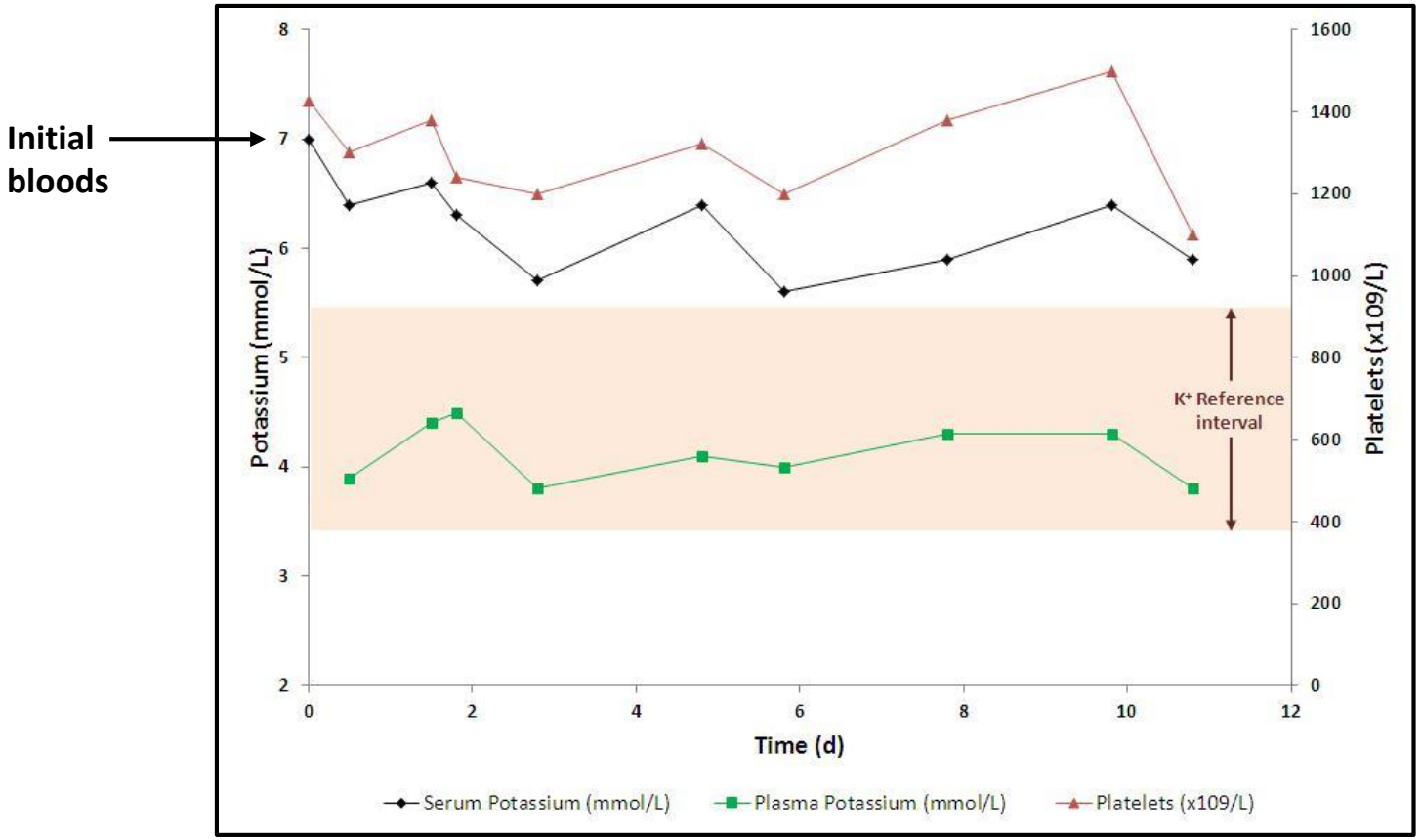

Figure 1: Variation of plasma and serum potassium in a patient with thrombocytosis

Investigation of Hyperkalemia 2

HYPERKALEMIA

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Causes of elevated [K^+] → **Eliminate artifactual causes**

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1. Hemolysis
2. Delay in centrifugation
3. Contamination
4. Elevated platelets or leukocytes

Renal Retention

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1. Acute renal failure
2. Chronic renal failure
3. Hypoadrenalism (e.g. adrenal failure)

Renal Retention

- Renal Failure
  - Hyperkalemia occurs in chronic renal failure as a result of decreased Glomerular Filtration Rate and subsequent increase in renal K^+ retention
  - Commonly encountered in dialysis patients
  - In acute renal failure, there may be K^+ release from the intracellular compartment as a result of acute tubular necrosis
  - Metabolic acidosis in renal failure may also drive hyperkalemia
- Hypoadrenalism
  - Decreased aldosterone production by the adrenal cortex results in renal K^+ retention and subsequent hyperkalemia
  - May occur in primary or secondary adrenal failure

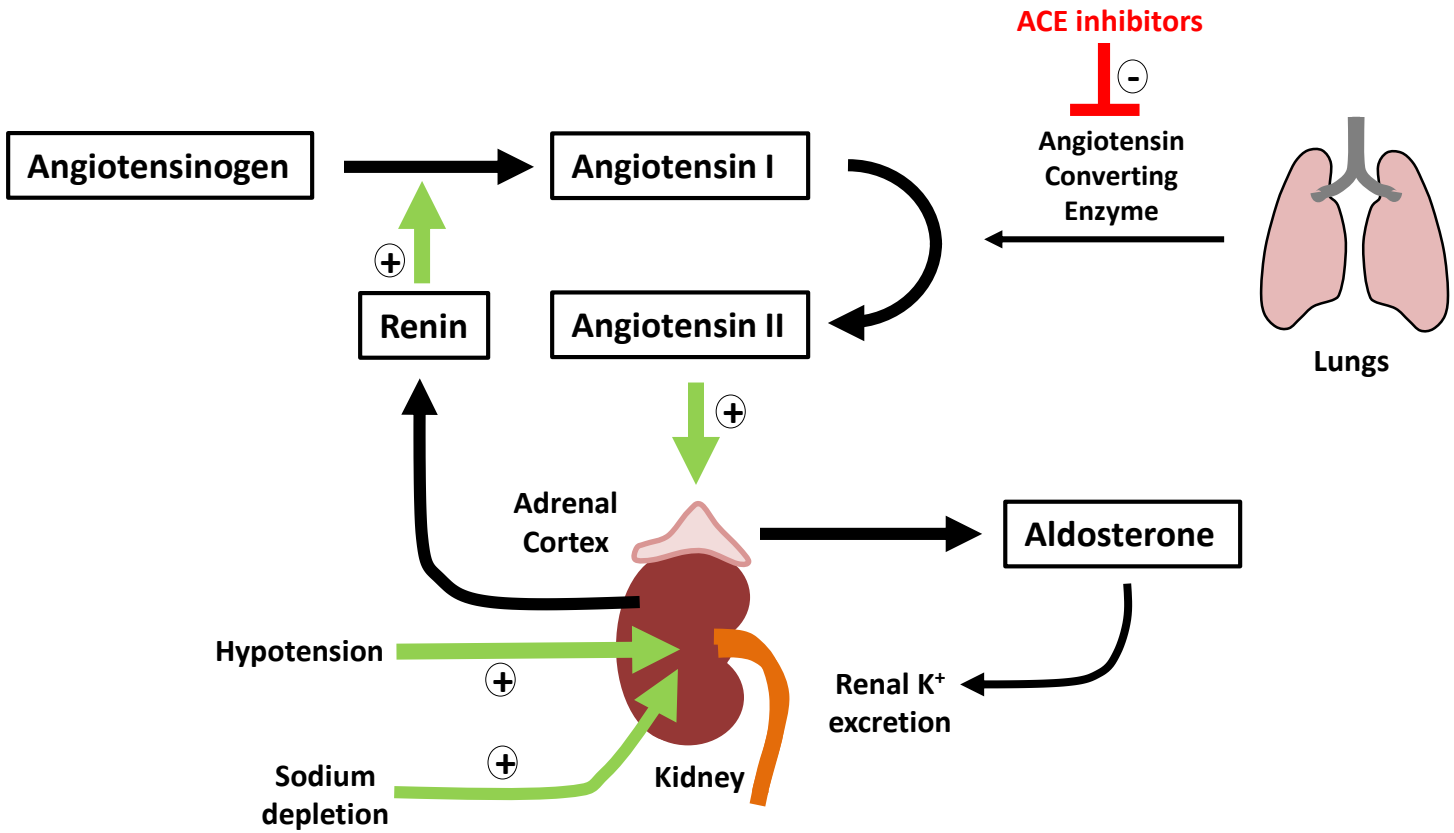
Case C

- A 38 year old female presents to the ER complaining of general malaise, vomiting and abdominal pain. The following bloods were taken around 8am:

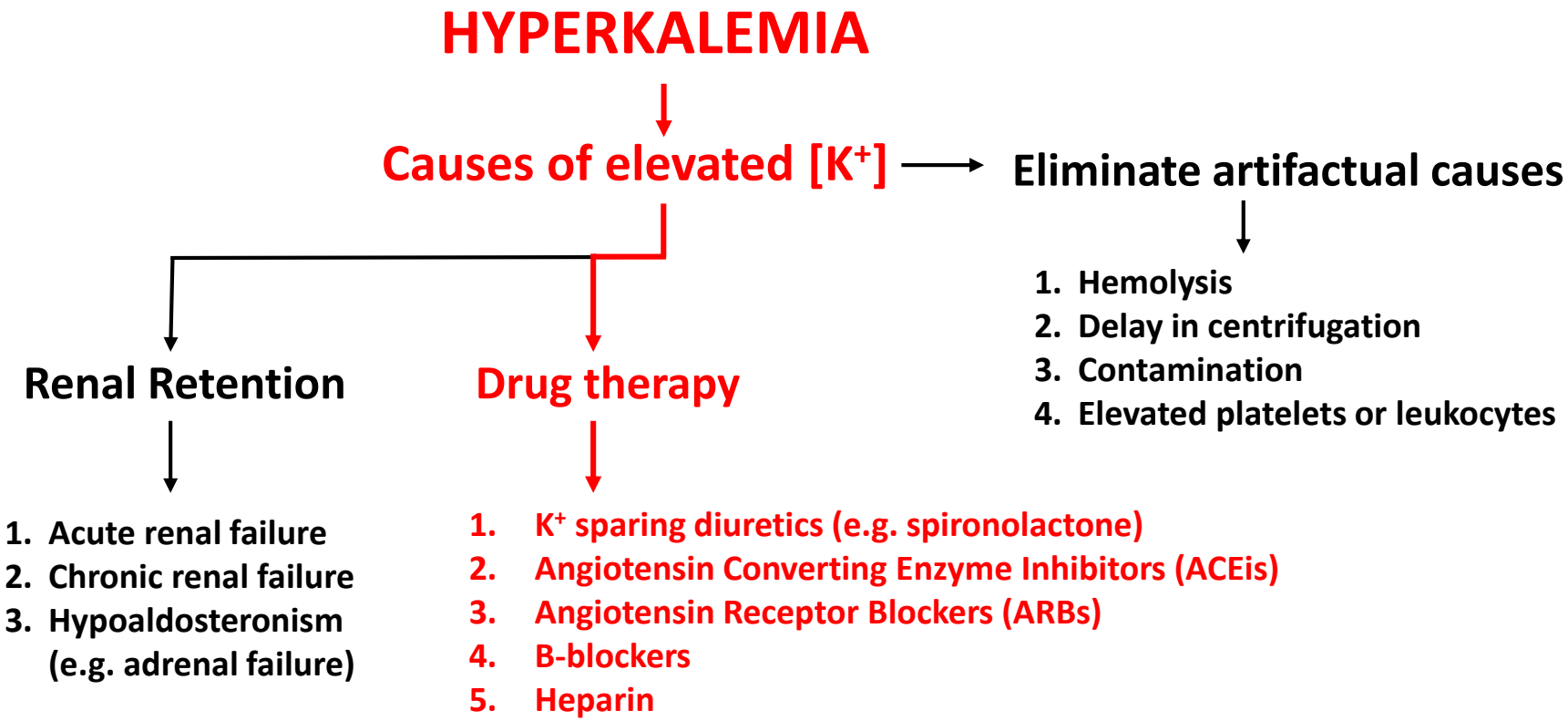
Sodium	121	mmol/L	(137 – 144)
Potassium	5.8	mmol/L	(3.5 – 4.9)
Chloride	99	mmol/L	(98 – 106)
Urea	13.0	mmol/L	(3.4 - 7.0)
Creatinine	88	µmol/L	(84 - 116)
Cortisol	<50	nmol/L	

- In addition to the hyperkalemia, the results show an inappropriately low 8am cortisol value, hyponatremia and pre-renal uraemia
- This patient has primary adrenal failure (Addison's Disease)
- Decreased aldosterone production by the adrenal cortex results in renal K^+ retention and subsequent hyperkalemia

Case C


ACE inhibitors
Angiotensinogen
Angiotensin I
Angiotensin Converting Enzyme
Lungs
Renin
Angiotensin II
Adrenal Cortex
Aldosterone
Hypotension
Renal K+ excretion
Sodium depletion
Kidney

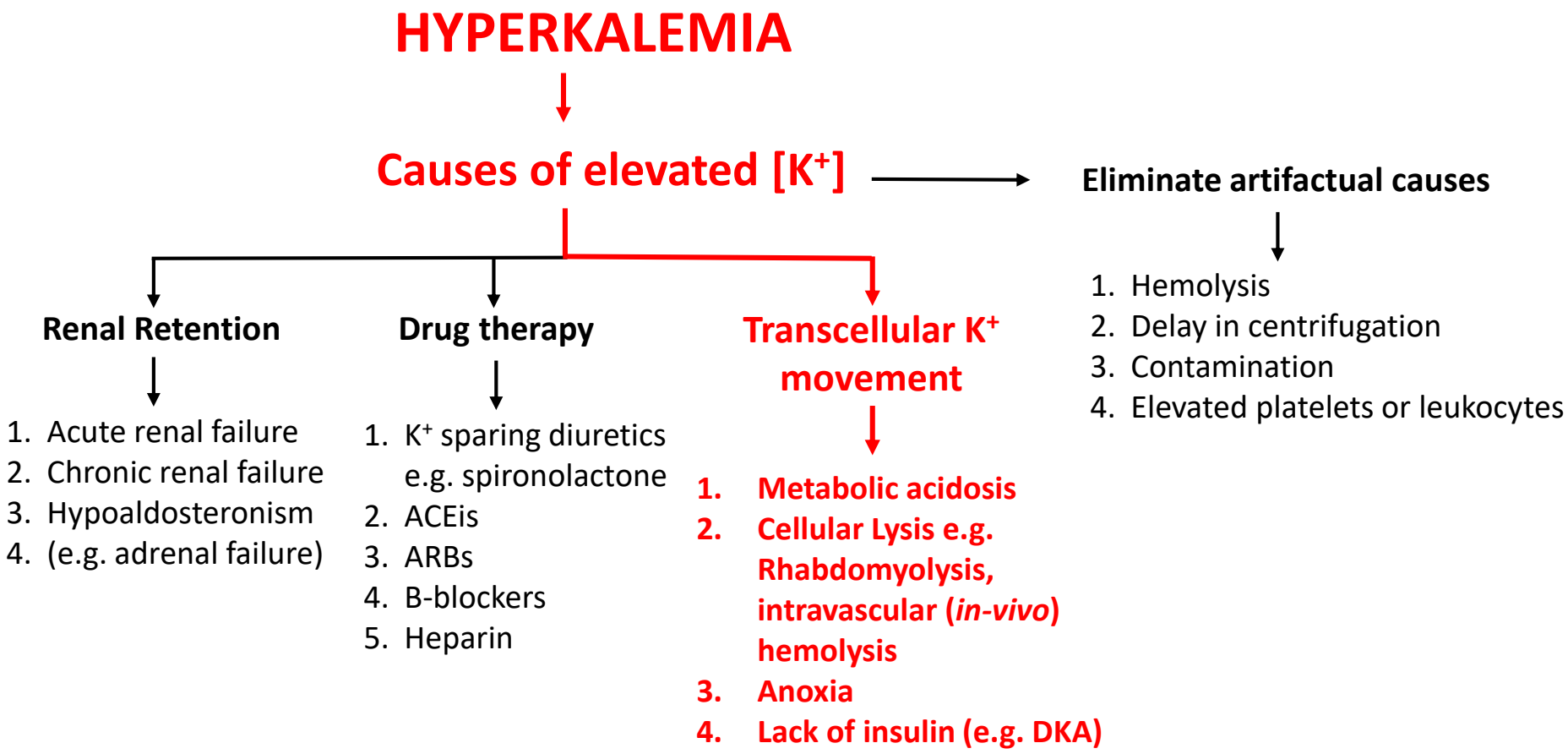
Investigation of Hyperkalemia 3



Drug therapy

- Potassium-sparing diuretics
  - E.g. Spironolactone and Amiloride
  - These drugs are K^+ sparing diuretics traditionally prescribed for heart failure and hypertension
  - Spironolactone is an aldosterone antagonist which inhibits sodium reabsorption at the collecting duct with concurrent K^+ retention
  - Amiloride is used as an blocks the epithelial sodium channel promoting sodium and water loss with K^+ retention
- Angiotensin Converting Enzyme Inhibitors (ACEis)
  - E.g. Ramipril and Lisinopril
  - ACEis are commonly prescribed for hypertension
  - Act on the Renin-Angiotensin system and inhibit aldosteronism promoting renal K^+ excretion
  - ACEis are recommended for use in patients with CKD

Investigation of Hyperkalemia 4



Transcellular K^+ "Shifting"

- Metabolic Acidosis
  - In acidosis states there is an increase in extracellular [H^+]
  - To maintain electroneutrality, H^+ ions will diffuse or "shift" across the cell membrane from the extracellular to the intracellular compartment
  - In exchange, K^+ ions will move in the opposite direction from the intracellular to extracellular compartment, causing hyperkalemia
- Cell Lysis
  - K^+ release from the intracellular compartment e.g. Rhabdomyolysis or acute intravascular hemolysis (*in vivo* hemolysis)
- Lack of Insulin
  - Insulin is required to "shift" K^+ into the cell
  - States of hypoinsulinemia (e.g. DKA) may result in hyperkalemia

Management of Hyperkalemia

- Urgent potassium reduction
  - Required if [K^+] > 7.0 mmol/L
  - Required if there are significant ECG changes
  - Typically by slow IV infusion of insulin/dextrose (lowers serum [K+] by shifting K^+ into the intracellular compartment)
  - Calcium gluconate may also be given intravenously in order to stabilize the myocardium
- Less urgent potassium reduction
  - Typically when [K^+] between 6.5 and 7.0 mmol/L
  - No significant ECG changes
  - Ion exchangers may be used (e.g. Resonium – lowers [K+] by exchanging sodium for K^+)

Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

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- **Patents:** None declared

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