Learning Goals

• To review pertinent Nephrology and Hypertension topics

• To provide an update on recent seminal studies
NO DISCLOSURES
Case #1

A 67-year-old man is seen for increase in serum creatinine level and abnormal urinalysis found during evaluation of monoclonal gammopathy of undetermined significance (MGUS). His evaluation revealed a M–protein spike of 1.5 g/dL, <10% clonal plasma cells on bone marrow biopsy, and no evidence of anemia, hypercalcemia or lytic bone lesions skeletal survey. Immunofixation revealed IgG as the monoclonal type. He has no constitutional symptoms, no other medical problems, and takes no medication.

On physical examination, vital signs are normal. Trace lower extremity edema is noted. The reminder of the examination is unremarkable.
Case #1

Laboratory studies:

- **Albumin**: 3.6 g/dL (36 g/L)
- **Creatinine**: 1.6 mg/dL (141.4 µmol/L)
- **Urinalysis**: pH 5.5; 2+ blood; 3+ protein; 5-8 erythrocytes/hpf
- **Urine albumin-creatinine ratio**: 400 mg/g
Case #1

Which of the following is the most appropriate next diagnosed test?

A. ANCA testing
B. $\beta_2$ microglobulin levels
C. Kidney biopsy
D. Serum free light chain
Case #1 Answer

• Monoclonal gammopathy of renal significance (MGRS) is diagnosed in patients who otherwise meet the criteria for MGUS but have an abnormal urine analysis and renal insufficiency; a kidney biopsy confirms the diagnosis.

• The diagnosis of MGRS renal disease can be challenging, because the spectrum of renal manifestations is very wide, and the detection of the pathogenic immunoglobulin can be difficult.

*Lymph node biopsy may be indicated if bone marrow aspirate/biopsy is negative and suspicion for lymphoma is high, especially if a monoclonal IgM is present.
MGRS-associated renal lesions

Organized deposits or inclusions
- Fibrils
  - Ig-related amyloidosis (AL, AHL, AH)
  - Fibrillary GN
- Microtubules
  - Immunotactoid GN/GOMMID
- Crystals or inclusions
  - Light chain proximal tubulopathy (with or without Fanconi syndrome)
  - Type 1 cryoglobulinemic GN
  - Crystal-storing histiocytosis

Non-organized deposits/inclusions
- Monoclonal immunoglobulin deposition disease (LCDD, LHCDD, HCDD)
- Proliferative GN with monoclonal Ig deposits (PGNMID)
- C3 glomerulopathy associated with monoclonal gammopathy
Case #2

A 38-year-old man is evaluated after passing his second kidney stone. History is significant for chronic pancreatitis secondary to a past history of alcohol abuse. Has 3-4 loose bowel movements each day. He reports no fever, flank pain, or dysuria. There is no family history of kidney disease, hyperparathyroidism, or nephrolithiasis. Current medications are pancreatic enzymes and multivitamins. Physical examination reveals a thin man. Vital signs and the remainder of examination are unremarkable.
Case #2

Laboratory studies:

Calcium 8.5 mg/dL (2.1 mmo/L)
Creatinine 0.7 mg/dL (61.9 µmol/L)

Electrolytes:
- Sodium 137 mEq/L (137 mmol/L)
- Potassium 3.5 mEq/L (3.5 mmol/L)
- Chloride 104 mEq/L (104 mmol/L)
- Bicarbonate 21 mEq/L (21 mmol/L)

Urinalysis: Specific gravity; pH 5.0; negative dipstick; positive for calcium oxalate crystals
Case #2

In addition to increasing fluid intake, which of the following is the most appropriate management?

A. Add allopurinol
B. Add potassium citrate
C. Add vitamin-C
D. Decrease calcium take
E. Increase protein intake
Case #2 Answer

- Potassium citrate can be used to help prevent calcium oxalate stones in patients with chronic diarrhea and malabsorption

- In the setting of diarrhea and metabolic acidosis, urine citrate, an inhibitor of crystallization, is often reduced and the calcium and oxalate concentration in the urine is increased due to dehydration

- In fat malabsorption calcium binds to fat as opposed to oxalate, leaving oxalate free to be absorbed and be excreted in the urine

Mechanisms of Stone Formation

Crystal

- Citrate
- Mg?
- pH

Inhibitors

RTA
PHP
CAI
*pH

Promoters

Nucleation
Growth
Aggregation

Crystals
Randall’s plaque

Modified from Pfau, A et al: AJKD, 2016
<table>
<thead>
<tr>
<th>Stone type</th>
<th>Morphology of Associated Crystals (Urine Microscopy)</th>
<th>Urinary Risk Factor</th>
<th>Clinical Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium oxalate monohydrate</td>
<td>Dumbell</td>
<td>Hypercalciuria</td>
<td>Hyperparathyroidism, immobilization, vitamin D excess, sarcoidosis, Cushing syndrome, high sodium intake, genetic disorders (eg, Dent disease), idiopathic, etc</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperoxaluria</td>
<td>• Increased oxalate absorption (eg, bowel pathologies)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Primary hyperoxaluria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Excess vitamin C intake</td>
</tr>
<tr>
<td>Calcium oxalate dihydrate</td>
<td>Envelope (Xl)</td>
<td>As outlined for calcium oxalate</td>
<td>As outlined for calcium oxalate monohydrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>monohydrate</td>
<td></td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>Flat shaped or wedge-shaped prisms; prisms often in rosettes</td>
<td>• Hypercalciuria • Hypocitraturia • Urine pH &gt; 7</td>
<td>• As outlined for calcium oxalate monohydrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Distal renal tubular acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Drugs with carbonic anhydrase inhibitory function (eg, topiramate, acetazolamide)</td>
</tr>
<tr>
<td>Struvite</td>
<td>Coffin-oid</td>
<td>High levels of ammonium and</td>
<td>Urinary tract infections with urease-splitting microorganisms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bicarbonate</td>
<td></td>
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<tr>
<td>Uric acid</td>
<td>Rhomboid/football-shaped; multiple forms possible; often yellow/brown</td>
<td>• Urine pH &lt; 5.5 • Hyperuricosuria</td>
<td>Patients with metabolic syndrome, insulin resistance, type-2 diabetes</td>
</tr>
<tr>
<td>Cystine</td>
<td>Hexagonal</td>
<td>Cystinuria</td>
<td>Genetic disorder</td>
</tr>
</tbody>
</table>

Case #3

A 48-year-old woman is evaluated in the emergency department for a 1-day history of hearing voices. History is significant for bipolar disorder. Medications are lithium carbonate and quetiapine. On physical examination, the patient is disheveled and looks chronically ill. She is alert oriented, but appears anxious. Blood pressure is 138/78 mmHg, and pulse rate is 80/min without orthostatic changes. There is no edema. The reminder of examination is normal.
Case #3

Laboratory studies:

BUN 6 mg/dL (2.1 mmo/L)
Creatinine 0.9 mg/dL (79.6 µmol/L)

Electrolytes:

- Sodium 126 mEq/L (126 mmol/L)
- Potassium 3.5 mEq/L (3.5 mmol/L)
- Chloride 94 mEq/L (94 mmol/L)
- Bicarbonate 26 mEq/L (26 mmol/L)

Glucose 156 mg/dL (8.7 mmol/L)

urine sodium 12 mEq/L (12 mmol/L)

urine osmolality 96 mOsm/Kg H₂O
Case #3

Which of the following is the most likely cause of this patient’s hyponatremia?

A. Hyperglycemia
B. Nephrogenic diabetes insipidus
C. Polydipsia
D. Syndrome of inappropriate antidiuretic hormone secretion
E. Volume depletion
Case #3 Answer

- Isovolemic hypotonic hyponatremia associated with urine osmolality < 100 Osm/Kg H₂O indicates excessive water intake, as seen with psychogenic polydipsia or poor solute intake.

- Isovolemic hypotonic hyponatremia secondary either to impaired dilution of urine or to water intake that exceeds the kidney’s ability to excrete diluted urine.
Hyponatremia

Measured serum osmolality 280-295 mosm/kg

Normal

Decreased

Increased

Isotonic hyponatremia

Hypotonic hyponatremia

Hypertonic hyponatremia

ECF volume status

Contracted

Normal

Expanded

Hypovolemic hypotonic hyponatremia

Euvolemic hypotonic hyponatremia

Hypervolemic hypotonic hyponatremia

Urine sodium & osmolality

Urine sodium

Urine osmolality

Osm >400 Na <20

Osm >400 Na >20

<100

>100

Extra renal losses

Renal losses

Primary polydipsia

beer potomania

reset osmostat

Adrenal insufficiency

hypothyroidism

cerebral salt wasting

SIADH

CHF, NS, cirrhosis

Renal failure

* UNa maybe < 20 mmo/L when low in diet

Modified from Reddy and Mooradian: Int J Clin Pract, 2009
Case #4

A 75-year-old woman is hospitalized for a 1-week history of dizziness, nausea, vomiting, increased urination, and decreased appetite. History is significant for hypertension treated with hydrochlorothiazide. She also takes calcium carbonate for bone health.

On physical examination, blood pressure is 150/85 mmHg supine and 122/70 mmHg standing, pulse rate 78/min supine in 100/min standing, and respiration rate is 18/min. There is no neck vein distention. Cardiac, pulmonary and abdominal examination is unremarkable there is no lower extremity edema.
Case #4

Laboratory studies:

Hematocrit 30%
Leukocyte count 3000/µL (3.0 x 10^9/L)
Platelet count 82,000/µL (82 x 10^9/L)
Calcium 12.8mg/dL (3.2 mmo/L)
Creatinine 3.7 mg/dL (327.1 µmol/L)

Electrolytes:
Sodium 132 mEq/L (132mmol/L)
Potassium 4.9 mEq/L (4.9mmol/L)
Chloride 115 mEq/L (115mmol/L)
Bicarbonate 17 mEq/L (17mmol/L)
Case #4

Laboratory studies:

Phosphorus 6.2 mg/dL (2 mmol/L)

Urine sodium 15 mg/L (15 mmol/L)

Urinalysis Specific gravity 1.018; trace protein, few erythrocytes/hpf, occasional leukocytes/hpf, few granular casts, numerous hyaline casts
Case #4

Which of the following is the most likely cause of this patient’s and acute kidney injury?

A. Hydrochlorothiazide therapy
B. Milk alkali syndrome
C. Multiple myeloma
D. Primary hyperparathyroidism
Case #4 Answer

• A diagnosis of multiple myeloma is suggested by the constellation of anemia, hypercalcemia, normal anion gap metabolic acidosis, and acute kidney injury.
Diagnostic Approach to Patients Presenting with Acute Kidney Injury and Suspected Myeloma
Case #5

A 25-year-old woman is evaluated in the emergency department after suicide attempt. History is significant for major depression. She takes no medication.

On physical examination temperature is normal, blood pressure is 142/92 mmHg, pulse rate 110/min, and his respiration rate 22/min. The patient is obtunded. The remainder of the exam is normal.
Case #5

Laboratory studies:

Blood urea nitrogen 28 mg/dL (10 mmol/L)
Creatinine 2.2 mg/dL (194.5 µmol/L)

Electrolytes:
- Sodium 136 mEq/L (136 mmol/L)
- Potassium 4.0 mEq/L (4.0 mmol/L)
- Chloride 100 mEq/L (100 mmol/L)
- Bicarbonate 12 mEq/L (12 mmol/L)

Ethanol Undetected
Glucose 90 mg/dL (5 mmol/L)

Osmolality 314 mOsm/Kg H₂O

Arterial blood gases
- pH 7.25
- PCO₂ 28 mmHg (3.7 kPa)
Case #5

Which of the following is the most appropriate management?

A. Activated charcoal gastric decontamination
B. Intravenous Ethanol
C. Intravenous hydration, fomepizole and hemodialysis
D. Intravenous sodium bicarbonate
Case #5 Answer

• Management of ethylene glycol toxicity in the context of organ-specific toxicity, severe acidemia, or with very large ingestions, includes aggressive fluid resuscitation, fomepizole and hemodialysis.

• Typical findings of ethylene glycol toxicity include CNS depression, an increased anion gap metabolic acidosis and an increase in osmolal gap.

• Osmolal gap is considered elevated when the measured osmolality exceeds the calculate osmolality by > 10 mOsm/Kg H₂O.

• Serum osmolality (mOsm/kg of H₂O)

  \[ \text{Serum osmolality} = 2\text{Na (mEq/L)} + \frac{\text{SUN (mg/dL)}}{2.8} + \frac{\text{glucose (mg/dL)}}{18} \]

Disorders Linked to High-Anion-Gap Metabolic Acidosis and an Increase in Serum Osmolal Gap

- Methanol intoxication
- Ethylene glycol intoxication
- Diethylene glycol intoxication
- Propylene glycol intoxication
- Isopropanol intoxication
- Lactic acidosis
- Alcoholic or diabetic ketoacidosis
- Acute kidney injury
- Salicylate intoxication

<table>
<thead>
<tr>
<th>High Anion Gap</th>
<th>Glycals</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>Oxoprolines</td>
</tr>
<tr>
<td>O</td>
<td>L-Lactate</td>
</tr>
<tr>
<td>L</td>
<td>D-Lactate</td>
</tr>
<tr>
<td>D</td>
<td>Methanol</td>
</tr>
<tr>
<td>M</td>
<td>Aspirin</td>
</tr>
<tr>
<td>A</td>
<td>Renal failure</td>
</tr>
<tr>
<td>R</td>
<td>Ketoacidosis</td>
</tr>
<tr>
<td>S</td>
<td>Sodium Thiosulfate</td>
</tr>
</tbody>
</table>
Disorders Linked to High-Anion-Gap Metabolic Acidosis and an Increase in Serum Osmolal Gap

- Increased serum osmolal gap with or without high-anion-gap metabolic acidosis can be an important clue to toxic alcohol intoxications
- The presence and magnitude of serum osmolal gap depends on several factors, including molecular weight of the offending alcohol, baseline serum osmolal gap, and state of metabolism of the parent alcohol
- Patients with toxic alcohol intoxications can present with an increase in serum osmolality alone, increased serum osmolality and high-anion-gap acidosis, or increased-anion-gap acidosis alone
- Rare cases in which both serum osmolality and anion gap are within reference ranges also might occur

Kraut, JA & Xing, SX: AJKD, 2011
Disorders Linked to High-Anion-Gap Metabolic Acidosis and an Increase in Serum Osmolal Gap

• Kidney failure, lactic acidosis, and diabetic ketoacidosis also can cause high-anion-gap metabolic acidosis associated with a large serum osmolal gap

• Given the potential severity of all these disorders, they should be excluded in all individuals presenting with serum osmolal gap, serum osmolal gap and high-anion-gap metabolic acidosis, or high-anion-gap metabolic acidosis alone
Case #6

A 68-year-old woman is evaluated during follow-up visit for 3-week history of nephrotic syndrome. She otherwise has been well and reports no additional symptoms. She has a 50-pack-year history of cigarette smoking with ongoing tobacco use. On physical examination, vital signs are normal. Pitting edema to the ankles is present. The reminder of the examination is unremarkable.
## Case #6

### Laboratory studies:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>2.9 g/dL (29 g/L)</td>
</tr>
<tr>
<td>C3</td>
<td>Normal</td>
</tr>
<tr>
<td>C4</td>
<td>Normal</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Normal</td>
</tr>
<tr>
<td>Rapid plasma reagin</td>
<td>Normal</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>Normal</td>
</tr>
<tr>
<td>Hepatitis B antibodies</td>
<td>Normal</td>
</tr>
<tr>
<td>Hepatitis C antibodies</td>
<td>Normal</td>
</tr>
<tr>
<td>24 hrs urine protein excretion</td>
<td>10000 mg/24hs</td>
</tr>
</tbody>
</table>
Case #6

Kidney ultrasound shows normal-appearing kidneys with no evidence of thrombus in the renal veins. Lower extremity Doppler ultrasounds showed no evidence of deep venous thrombosis. The kidney biopsy shows membranous glomerulopathy with negative staining for phospholipase A2 receptor (PLA2R) on immunofluorescence.
Case #6

Which of the following is the most appropriate management?

A. Age- and sex-appropriate cancer screening
B. Immunosuppression therapy
C. Prophylactic anticoagulation
D. Serologic testing for anti-PLA2R antibodies
Case #6 Answer

• The association between membranous nephropathy (MN) and cancer has been well documented.

• Approximately 75% of the cases of MN are idiopathic (+PLA2R), whereas the remainder are associated with infections, malignancies, autoimmune diseases and drug toxicity.

• Initial step in the management of newly diagnosed MN is to evaluate for secondary forms of the disease, which account for approximately 25% of the case.

Algorithm for centers preferentially performing immunofluorescence assays (IFAs)
Only for patients with normal renal function and absence of secondary causes of MN

Suspected MN

PLA2R IFA testing

PLA2R IFA+
- Perform ELISA
  - ELISA ≥ 2 RU/ml: Diagnose MN
  - ELISA < 2 RU/ml: May avoid renal biopsy if secondary causes are absent and renal function is preserved

PLA2R IFA−
- Perform renal biopsy (stain for PLA2R ag and THSD7A ag)
Algorithm for centers preferentially performing enzyme-linked immunosorbent assays (ELISAs) Only for patients with normal renal function and absence of secondary causes of MN

Increased rate of malignancy in THSD7A-associated MN
Case #7

A 52-year-old woman was hospitalized 3 days ago for laparoscopic resection of sigmoid colon secondary to recurrent diverticulitis. Diet has been advanced to a full diet. She has a 20 year history of hypertension, stage 3 chronic kidney disease, and migraine headaches. Medications are amlodipine, Heparin, Topiramate and as needed intravenous morphine.

On physical examination, vital signs are normal. Mild incisional tenderness is present. The remainder of the physical examination is unremarkable.
Case #7

Laboratory studies:

<table>
<thead>
<tr>
<th></th>
<th>On admission</th>
<th>Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>1.6mg/dL</td>
<td>1.9mg/dL</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>140 mEq/L</td>
<td>138 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.9 mEq/L</td>
<td>5.6 mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>102 mEq/L</td>
<td>110 mEq/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>25 mEq/L</td>
<td>20 mEq/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>116 mEq/L</td>
<td>128 mEq/L</td>
</tr>
</tbody>
</table>

Urine output during the past 24 hrs is 1400 mL
Case #7

Which of the following is the most likely cause of this patient’s elevated serum potassium?

A. Acute kidney injury
B. Heparin
C. Hyperglycemia
D. Metabolic acidosis
E. Topiramate
Case #7 Answer

- Hypoaldosteronism caused by heparin, inhibitors of the renin angiotensin system, type 4 RTA, or primary adrenal disease can cause hyperkalemia, specially patients with CKD or diabetes mellitus, home or in does take an ACE inhibitor or angiotensin receptor blocker
- Both unfractionated and LMW heparin use is associated with a decrease in aldosterone synthesis
Mechanisms of action of the development of hyperkalemia in patients with chronic kidney disease and associated comorbid conditions

Kovesdy, CP: Rev Endocr Metab Disord, 2017
Case #8

A 44-year-old male evaluated during a follow-up visit for treatment of persistent elevated blood pressure. He takes no medications.

Physical examination reveals a well-developed muscular man in no apparent distress. Blood pressure is of 165/98 mmHg, pulse rate 70/min, other vital signs are normal. BMI is 26. Jugular venous pressure is normal. Cardiac examination is unremarkable.
Case #8

Laboratory studies:

Bicarbonate  27mEq/L (27mmol/L)
Creatinine    1.3 mg/dL (114.9 µmol/L)
Potassium     4.5mEq/L (4.5mmol/L)
Estimated glomerular filtration rate  > 60mL/min/1.73m²
Urine toxicology screen  Negative

Electrocardiogram reveals normal sinus rhythm, voltage criteria for left ventricular hypertrophy are present.
Case #8

Which of the following is the most appropriate treatment?

A. Amlodipine/Benazepril combination once a daily

B. Doxazosin and metoprolol, each once daily

C. Hydralazine 3 times daily

D. Telmisartan and ramipril, each once daily
Case #8 Answer

<table>
<thead>
<tr>
<th>Blood Pressure Category</th>
<th>Systolic mm Hg (Upper Number)</th>
<th>Diastolic mm Hg (Lower Number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Less than 120</td>
<td>Less than 80</td>
</tr>
<tr>
<td>Elevated</td>
<td>120 – 129</td>
<td>Less than 80</td>
</tr>
<tr>
<td>High Blood Pressure (Hypertension) Stage 1</td>
<td>130 – 139</td>
<td>80 – 89</td>
</tr>
<tr>
<td>High Blood Pressure (Hypertension) Stage 2</td>
<td>140 or higher</td>
<td>90 or higher</td>
</tr>
<tr>
<td>Hypertensive Crisis (consult your doctor immediately)</td>
<td>Higher than 180</td>
<td>Higher than 120</td>
</tr>
</tbody>
</table>
Case #8 Answer

• The 2017 ACC/AHA blood pressure (BP) guidelines recommends combination therapy with 2 first-line antihypertensive drugs of different classes (separately or as a single dose pill) for adults with stage 2 hypertension and an average BP of 20/10 mmHg above blood pressure target.
BP thresholds and recommendations for treatment and follow-up

Normal BP (BP <120/80 mm Hg)
  - Promote optimal lifestyle habits
  - Reassess in 1 y (Class IIa)

Elevated BP (BP 120–129/<80 mm Hg)
  - Nonpharmacological therapy (Class I)
  - Reassess in 3–6 mo (Class I)

Stage 1 hypertension (BP 130–139/80–89 mm Hg)
  - Nonpharmacological therapy (Class I)
  - Reassess in 3–6 mo (Class I)

Clinical ASCVD or estimated 10-y CVD risk ≥10%*
  - No
  - Yes

Stage 2 hypertension (BP ≥140/90 mm Hg)
  - Nonpharmacological therapy and BP-lowering medication (Class I)
  - Nonpharmacological therapy and BP-lowering medication (Class I)
  - Reassess in 1 mo (Class I)

BP goal met
  - No
  - Yes
  - Assess and optimize adherence to therapy
  - Consider intensification of therapy
  - Reassess in 3–6 mo (Class I)

Case #9

A 36-year-old man is evaluated in the emergency department for renal colic. He is in otherwise good health and takes no medications. Physical examination reveals left carotid vertebral angle tenderness. The reminder of the examination is normal. Noncontrast helical CT scan shows an 11 mm stone at the left ureteral pelvic junction and mild left caliectasis. Analgesics are initiated.
Case #9

Which of the following is the most appropriate next step in management?

A. Extracorporeal shock wave lithotripsy
B. Forced diuresis with IV normal saline
C. Nifedipine
D. Tamsulosin
Case #9 Answer

• Urologic interventions is required in all patients with evidence of infection, acute kidney injury, intractable nausea pain, and stones that fall to pass or unlikely to pass

• Only 50% of stones >6 mm in size will pass spontaneously

• Shockwave lithotripsy can be used for stones in the renal pelvis and proximal ureter, but is less effective for stones located middle/distal ureter or lower pole calix, stones more than 15 mm and hard stones (calcium oxalate monohydrate are cystine)

• Medical expulsive therapy no longer recommended
Case #10

A 68-year-old woman is hospitalized for chest pain. History is significant for stage 3 chronic kidney disease. Hypertension, coronary artery disease, and type 2 diabetes mellitus. Medications are aspirin, losartan, basal and prandial insulin, metoprolol, nitroglycerin paste and unfractionated heparin. On physical examination, blood pressure is 130/80 mmHg, other vital signs are normal. S₁ and S₂ are normal. There is no S₃, lungs crackles or edema. Laboratory studies show serum creatinine level of 1.8 mg/dL (159.1μmol/L) and an elevated serum troponin level. EKG shows a 2-mm-ST segment depression in leads I, aVL and V₄ through V₆. Cardiac catheterization is planned.
Case #10

Which one of the following is the most appropriate procedure management?

A. Administer furosemide before cardiac catheterization

B. Administer intravenous isotonic fluids before and after cardiac catheterization

C. Administer oral sodium bicarbonate before cardiac catheterization

D. Initiate hemodialysis following cardiac catheterization
Case #10 Answer

- IV isotonic fluids are the mainstay in preventing contrast-induced nephropathy (CIN) in patients with CKD administered before and after cardiac catheterization.

- Furosemide before catheterization is incorrect because it can induce volume contraction and activate RAAS increasing the risk for CIN.

- Hemodialysis does not improve CIN outcomes, but rather may exacerbate acute kidney injury.

Fahling, M et al: Nat Rev Nephrol, 2017
Pathophysiology of Contrast-Induced Nephropathy

**Vasoconstriction**
- Ca$^{++}$ influx
- Endothelial release
- Selective vasoconstriction corticomedullary junction
- Impaired vasodilation
- Duration up to 4 hours

**Vasodilation**

**Direct tubular toxicity**

**Medullary hypoxia**
- PaO$_2$ 15-20 mm Hg

**Oxidative stress**
- OH$^-$ O$_2$ $^{••}$ free radicals

**↓ NO production**
Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine


ABSTRACT
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sodium Bicarbonate (N=2511)</th>
<th>Sodium Chloride (N=2482)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Acetylcysteine (N=2495)</th>
<th>Placebo (N=2498)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td>110 (4.4)</td>
<td>116 (4.7)</td>
<td>0.93 (0.72–1.22)</td>
<td>0.62</td>
<td>114 (4.6)</td>
<td>112 (4.5)</td>
<td>1.02 (0.78–1.33)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
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<tr>
<td>Contrast-associated acute kidney injury†</td>
<td>239 (9.5)</td>
<td>206 (8.3)</td>
<td>1.16 (0.96–1.41)</td>
<td>0.13</td>
<td>228 (9.1)</td>
<td>217 (8.7)</td>
<td>1.06 (0.87–1.28)</td>
<td>0.58</td>
</tr>
<tr>
<td>Death by 90 days</td>
<td>60 (2.4)</td>
<td>68 (2.7)</td>
<td>0.87 (0.61–1.24)</td>
<td>0.43</td>
<td>67 (2.7)</td>
<td>61 (2.4)</td>
<td>1.10 (0.78–1.57)</td>
<td>0.59</td>
</tr>
<tr>
<td>Need for dialysis by 90 days</td>
<td>32 (1.3)</td>
<td>29 (1.2)</td>
<td>1.09 (0.65–1.81)</td>
<td>0.73</td>
<td>30 (1.2)</td>
<td>31 (1.2)</td>
<td>0.97 (0.58–1.60)</td>
<td>0.90</td>
</tr>
<tr>
<td>Persistent kidney impairment by 90 days</td>
<td>28 (1.1)</td>
<td>25 (1.0)</td>
<td>1.10 (0.64–1.91)</td>
<td>0.71</td>
<td>26 (1.0)</td>
<td>27 (1.1)</td>
<td>0.96 (0.56–1.66)</td>
<td>0.89</td>
</tr>
<tr>
<td>Hospitalization with acute coronary syndrome, heart failure, or stroke by 90 days</td>
<td>272 (10.8)</td>
<td>251 (10.1)</td>
<td>1.08 (0.90–1.29)</td>
<td>0.40</td>
<td>244 (9.8)</td>
<td>279 (11.2)</td>
<td>0.86 (0.71–1.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>All-cause hospitalization by 90 days</td>
<td>1071 (42.7)</td>
<td>1052 (42.4)</td>
<td>1.01 (0.90–1.13)</td>
<td>0.85</td>
<td>1069 (42.8)</td>
<td>1054 (42.2)</td>
<td>1.03 (0.91–1.15)</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Conclusion

• Patients with high risk for renal complications who were undergoing angiography, there was no benefit of IV sodium bicarbonate over IV sodium chloride or of oral NAC over placebo for the prevention of death, RRT, or persistent decline in kidney function at 90 days or for the prevention of contrast-associated acute kidney injury.
Ultra-Low Contrast Volumes Reduce Rates of CIN in Patients With CKD Undergoing Coronary Angiography

Kane, G et al: JACC 2008
Case #11

A 45-year-old woman is evaluated for recent onset of resistant hypertension. During her last visit, chlorthalidone was added to her medication regimen. She reports no symptoms, and review of systems is otherwise unremarkable. Current medications are metoprolol, amlodipine, hydralazine, and chlorthalidone. Physical examination, blood pressure is 160/96 mmHg and pulse rate 65/min, other vital signs are normal. BMI is 24. There is no proptosis. The thyroid gland is not enlarged and the remainder of the examination is unremarkable.
Case #11

Laboratory studies:

- Bicarbonate: 34mEq/L (34mmol/L)
- Creatinine: 0.8 mg/dL (70.7 µmol/L)
- Potassium: 2.9mEq/L (2.9mmol/L)
- Urine albumin-creatinine ratio: 10mg/g
Case #11

Which one of the following is the most appropriate diagnostic tests to perform next?

A. Kidney ultrasonography with Doppler
B. Plasma aldosterone concentration/plasma renin activity ratio
C. Plasma fractionated metanephrines
D. Polysomnography
Case #11 Answer

• Calculation of PAC / PRA ratio is used to diagnose primary hyperaldosteronism (PH)

• Triad of resistant hypertension, metabolic alkalosis and hypokalemia followed addition of thiazide diuretic, raises suspicion for primary hyperaldosteronism

• Testing for PH recommended for resistant hypertension, hypokalemia, incidentally discovered adrenal mass, family history of early onset hypertension, stroke at age of < 40 y/o

Braam, B et al: CJAN, 2017
PAC/PRA ratio in Hypertension and Hypokalemia

Hypertension and hypokalemia

Plasma renin activity (PRA)
Plasma aldosterone concentration (PAC)

- ↓ PRA
- ↑ PAC
- PAC-PRA ratio ≥ 10
  - Investigate for causes of secondary hyperaldosteronism
    - Renovascular hypertension
    - Diuretic use
    - Renin-secreting tumor
    - Malignant hypertension
    - Coarctation of the aorta

- ↓ PRA
- ↑ PAC
- PAC-PRA ratio ≥ 20 and PAC ≥ 15 ng/dL (≥ 416 pmol/L)
  - Investigate for Primary aldosteronism

- ↓ PRA
- ↓ PAC
  - Investigate for
    - Congenital adrenal hyperplasia
    - Exogenous mineralcorticoid
    - DOC-producing tumor
    - Cushing's syndrome
    - 11-beta-HSD deficiency
    - Altered aldosterone metabolism
    - Liddle's syndrome
    - Glucocorticoid resistance

Modified from UpToDate
Primary Hyperaldosteronism Evaluation

- Must distinguish between (unilateral) aldosterone-producing adenoma and bilateral hyperplasia.
- Adrenal CT should be initial study for evaluation.
- However, CT findings can be misleading.
- Adrenal vein sampling should be performed.
  - Continuous cosyntropin (ACTH) infusion.
  - Measure aldosterone and cortisol levels from right adrenal vein, left adrenal vein, and IVC.
  - Cortisol-corrected aldosterone ratio
    - >4:1\(\) adenoma, <3:1\(\) bilateral hyperplasia.
Case #12

A 28-year-old woman is evaluated in the emergency department for muscle cramps and weakness. She notes a weight loss of 15 kg (33 lb) over the past 3 months, baseline weight was 115 kg (254 lb). She reports no abdominal pain or diarrhea. She has a 1 year history of type 2 diabetes mellitus, for which she takes metformin. On physical examination temperature is normal blood pressure is 122/72mmHg, pulse rate is 100/min and have respiration rate 18/min. BMI is 36. Muscle strength of the lower and upper extremities is 4/5. Other than weakness neurologic examination is normal.
## Case #12

**Laboratory studies:**

### Electrolytes:
- **Sodium**: 138 mEq/L (138 mmol/L)
- **Potassium**: 2.4 mEq/L (2.4 mmol/L)
- **Chloride**: 92 mEq/L (92 mmol/L)
- **Bicarbonate**: 34 mEq/L (34 mmol/L)

### Arterial blood gases:
- **pH**: 7.50
- **Pco₂**: 45 mm Hg (6.0 kPa)

### Urine:
- **Sodium**: 40 mEq/L (40 mmol/L)
- **Potassium**: 60 mEq/L (60 mmol/L)
- **Chloride**: 5 mEq/L (5 mmol/L)
Case #12

Which one of the following is the most likely diagnosis?

A. Cushing syndrome
B. Gitelman syndrome
C. Primary hyperaldosteronism
D. Surreptitious vomiting
Case #12 Answer

- Saline response metabolic alkalosis typically presents with hypovolemic and low urine chloride of < 15 mEq/L, the most common causes are vomiting, nasogastric catheter suction and diuretic use.
Diagnostic Guide for Chronic Hypokalemia

Chronic hypokalemia <3.2 mmol/L

High urinary chloride excretion (>60 mmol/L)

Diuretic abuse
- Metabolic alkalosis (often)
- Positive screen for diuretics of high chloride urinary samples

Gitelman’s syndrome
- Metabolic alkalosis
- Hypomagnesemia
- Hypocalciuria
- No diuretics demonstrable
- Mutations of the thiazide sensitive Na/Cl – cotransporter

Bartter’s syndrome
- Metabolic alkalosis
- No Hypomagnesemia
- No Hypocalciuria
- Distal fractional chloride reabsorption coefficient <0.6
- Mutation of a gene of the chloride reabortion mechanism of TALH

Renal tubular acidosis
- Metabolic alkalosis
- Deficiency of urinary acidification

Low urinary chloride excretion (<15 mmol/L)

Vomiting
- Metabolic alkalosis
- Hypochloremia
- Renal insufficiency

Diarrhea
- Metabolic alkalosis
- High 24 hr stool volumes

Previous diuretic abuse
- Metabolic alkalosis
- Positive screening of urine for diuretics may still be seen
Case #13

A 64-year-old man is evaluated for a 2-month history of increasing fatigue and bilateral swelling on the submandibular region. History is significant autoimmune pancreatitis treated with prednisone 2 years ago, hypertension, and allergic rhinitis. Medications are losartan and fluticasone propionate. On physical examination, blood pressure is 148/84mmHg, and pulse rate 78/min. There is no rash. Head and neck examination reveals bilateral submandibular gland swelling. Trace edema of the ankles is present. The remainder of the examination is normal.
Case #13

Laboratory studies:

Hemoglobin 12 g/dL (120g/L)
Leukocyte count 10,000/µL (10x10⁹/L)
  33% eosinophils
Platelet count 180,000/µL (180x10⁹/L)
C3 65mg/dL (650mg/L)
C4 7 mg/dL (70mg/L)
Creatinine 3.1mg/dL (274µmol/L);
  6 months ago: 1.8mg/dL (159.1µmol/L)
## Case #13

### Laboratory studies:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>2600mg/dL (26g/L)</td>
</tr>
<tr>
<td>IGE</td>
<td>500U/mL (500kU/L)</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>1:640</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Specific gravity 1010; trace protein; 6-10 leukocytes/hpf</td>
</tr>
</tbody>
</table>

Kidney ultrasound demonstrates bilateral markedly enlarged kidneys measuring 15cm in size with hyperechoic cortex and peripheral cortical nodules.
Case #13

Which of the following is the most likely diagnosis?

A. IgG 4-related disease
B. Lupus nephritis
C. Sarcoidosis
D. Sjogren syndrome
Case #13 Answer

- Tubulointerstitial nephritis is the most common kidney manifestation of IgG4-related disease and typically presented with pyuria, proteinuria and elevated serum IgG and IgE levels, on kidney imaging may show enlarged kidney or renal masses. Hypocomplementemia and allergy symptoms such as asthma and allergic rhinitis may be present IgG 4-related disease.
IgG4-related Kidney Disease

Saeki & Kawano; KI, 2014
Major Organ Manifestation of IgG-4 Related Disease

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Type 1 autoimmune pancreatitis</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Sialadenitis</td>
</tr>
<tr>
<td>Eye/orbit/lacrimal glands</td>
<td>Orbital inflammation/pseudotumor and dacryoadenitis</td>
</tr>
<tr>
<td>Aorta/artery/retroperitoneum periaortitis</td>
<td>Periaortitis/periarteritis and retroperitoneal fibrosis</td>
</tr>
<tr>
<td>Kidney</td>
<td>Tubulointerstitial nephritis and pyelitis</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Lung</td>
<td>Lung disease (inflammatory pseudotumor, alveolar interstitial disease, and pleuritis)</td>
</tr>
<tr>
<td>Biliary system</td>
<td>Sclerosing cholangitis and cholecystitis</td>
</tr>
<tr>
<td>Liver</td>
<td>Pseudotumor and hepatopathy</td>
</tr>
<tr>
<td>Central/peripheral nervous system</td>
<td>Pachymeningitis and infraorbital nerve swelling</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>Hypophysitis and thyroiditis</td>
</tr>
<tr>
<td>Others</td>
<td>Prostatitis, mastitis, mediastinitis, and pericarditis skin (nodules and papules)</td>
</tr>
</tbody>
</table>
IgG4-related Kidney Disease

- IgG4-related disease (IgG4-RD) is a systemic disease
- Diagnosis of IgG4-RD is based on characteristic pathology: a lymphoplasmacytic infiltrate enriched with IgG4+ plasma cells, and storiform fibrosis
- Serum IgG4 levels are elevated in most patients with IgG4-RD
- IgG4-related TIN is the most common form of IgG4-related kidney disease. The condition is characterized by unique findings on contrast-enhanced CT and the hallmark pathology of IgG4-RD
- Membranous glomerulonephropathy secondary to IgG4-RD is a rare manifestation and it is not associated PLA2r AB
- Steroids are the standard therapy for IgG4-RD
Case #14

A 42-year-old woman is evaluated during a routine visit. She recently had her blood pressure measured at the workplace, two measurements were taking and both were elevated. The patient feels well and review of system is unremarkable. Family history is significant for hypertension in her father, mother and two siblings. Her father had stroke and her mother had heart failure. She takes no medications. On physical examination average of three blood pressure measures is 128/78. BMI is 30 and the reminder for examination is normal.
Case #14

Laboratory studies:

- Bicarbonate: 24mEq/L (24mmol/L)
- Creatinine: 0.9mg/dL (79.6 µmol/L)
- Potassium: 4mEq/L (4mmol/L)
- Urine albumin-creatinine ratio: 10mg/g

EKG reveals normal sinus rhythm and positive voltage criteria for left ventricular hypertrophy.
Case #14

Which of the following is most appropriate test performed next?

A. 24-hr ambulatory blood pressure monitoring
B. Plasma aldosterone concentration/plasma renin activity ratio
C. Polysomnography
D. Thyroid-stimulating hormone measurement
Case #14 Answer

- Suspected masked hypertension (is defined as blood pressure that is normal in the office but elevated in the ambulatory setting) should be confirmed with ABPM on home blood pressure monitoring.
Detection of White Coat Hypertension or Masked Hypertension in Patients not on Drug Therapy

Office BP: ≥130/80 mm Hg but <160/100 mm Hg after 3 mo trial of lifestyle modification and suspected white coat hypertension

Daytime ABPM or HBPM
BP <130/80 mm Hg

Yes
White Coat Hypertension
- Lifestyle modification
- Annual ABPM or HBPM to detect progression (Class IIa)

No
Hypertension
Continue lifestyle modification and start antihypertensive drug therapy (Class IIa)

Office BP: 120–129/<80 mm Hg after 3 mo trial of lifestyle modification and suspected masked hypertension

Daytime ABPM or HBPM
BP ≥130/80 mm Hg

Yes
Masked Hypertension
Continue lifestyle modification and start antihypertensive drug therapy (Class IIa)

No
Elevated BP
- Lifestyle modification
- Annual ABPM or ABPM to detect masked hypertension or progression (Class IIa)

Detection of white coat effect or masked uncontrolled hypertension in patients on drug therapy

Office BP at goal

Increased CVD risk or target organ damage

Screen for masked uncontrolled hypertension with HBPM (Class IIb)

HBPM BP above goal

ABPM BP above goal

Masked uncontrolled hypertension: Intensify therapy (Class IIb)

Continue current therapy

Screening not necessary (No Benefit)

Office BP ≥5–10 mm Hg above goal on ≥3 agents

Screen for white coat effect with HBPM (Class IIb)

HBPM BP at goal

White coat effect: Confirm with ABPM (Class IIa)

Continue titrating therapy

Case #15

A 72-year-old woman evaluated during routine visit. History is significant for hypertension treated with amlodipine and losartan. She has no other medical problems. She remains physically active and routinely plays tennis and golf. On physical examination, blood pressure is 142/84mmHg, and pulse rate 72/min, other vital signs are normal. BMI is 24. The remainder of the examination is unremarkable.

Laboratory studies shows serum creatinine level of 0.8 mg/dL (70.7µmol/L) and serum potassium level of 4.0 mEq/L (4.0mmol/L)
Case #15

According to the target blood pressure goes recommended by the American College of physicians in the American academy of family physicians, which of the following would be most appropriate management?

A. Add chlorthalidone
B. Increase the amlodipine dose
C. Increase the losartan dose
D. Make no changes to antihypertensive medications
Case #15 Answer

• Based on evidence that the greatest absolute benefit of antihypertensive therapy is seen in patients with the highest blood pressure in cardiovascular risk, the American College of Physicians in American Academy of Family Physicians recommended antihypertensive drugs be initiated in patients ≥ 60 years old if BP is above 150/90 mmHg, with a goal of reducing systolic blood pressure less than < 150 mmHg. The ACC/AHH recommends a systolic blood pressure <130 mmHg in patients ≥ 65 years old.
Summary of the American College of Physicians and American Academy of Family Physicians Joint Guideline on Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Audience</td>
<td>All clinicians</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Adults aged ≥60 y with hypertension</td>
</tr>
<tr>
<td>Treatments Evaluated</td>
<td>Treatment to higher (&lt;150 mm Hg) vs. lower (≤140 mm Hg) SBP targets</td>
</tr>
<tr>
<td>Outcomes Evaluated</td>
<td>All-cause mortality, morbidity and mortality related to stroke, cardiac events, and harms</td>
</tr>
</tbody>
</table>
| Benefits | Incidence of stroke and cardiac events were reduced with treatment.  
Treating to 140 mm Hg did not have additional benefit. |
| Harms | Increased withdrawals due to adverse events with higher vs. lower BP targets |
| Adverse Effects | Some of the adverse effects associated with antihypertensive medications include (but are not limited to) the following:  
Thiazide-type diuretics: electrolyte disturbances, gastrointestinal discomfort, rashes and other allergic reactions, sexual dysfunction in men, photosensitivity reactions, and orthostatic hypotension  
ACEIs: cough and hyperkalemia  
ARBs: dizziness, cough, and hyperkalemia  
Calcium-channel blockers: dizziness, headache, edema, and constipation  
β-blockers: fatigue and sexual dysfunction |
| Recommendations | Recommendation 1: ACP and AAFP recommend that clinicians initiate treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg to achieve a target systolic blood pressure of less than 150 mm Hg to reduce the risk for stroke, cardiac events, and possibly mortality. (Grade: strong recommendation, high-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.  
Recommendation 2: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for recurrent stroke. (Grade: weak recommendation, moderate-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.  
Recommendation 3: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure of less than 140 mm Hg. (Grade: weak recommendation, low-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient. |
| Clinical Considerations | Accurate measurement of BP is important before initiating treatment for hypertension. Some patients may have elevated BP in clinical settings, and ambulatory measurement may be appropriate.  
Clinicians should consider treatment with nonpharmacologic options, including weight loss, dietary changes, and an increase in physical activity, initially or concurrently with pharmacologic treatment.  
Many older adults may be taking various medications. Clinicians should consider treatment burden and drug interactions when deciding on treatment options.  
When selecting pharmacologic therapy, clinicians should prescribe generic drugs where available.  
Evidence for adults who are frail or those with multimorbidity is limited. |
Case # 16

A 66-year-old woman was diagnosed with metastatic melanoma and initiated therapy every 3 weeks with pembroluzimab (PD-1 inhibitor). She is seen in consultation for acute kidney injury. She has been taking for several years Lisinopril, hydrochlorothiazide, citalopram and omeprazole. She has recently been noted to develop acute renal insufficiency and mild pancreatitis associated with a rash and mild elevated amylase and lipase. Her physical exam is remarkable for blood pressure of 136/83 mmHg, and heart rate is 98/min. Examination of the skin shows maculopapular exanthema. The remainder of the examination is unremarkable.
Case # 16

Laboratory studies:
sodium 136 mEq/L, potassium 5.1 mEq/L, chloride 108 mEq/L, Bicarbonate 19 mmol/L, BUN 48 mg/dl, creatinine 2.6 mg/dl (3 weeks ago was 1.2mg/dL and 6 weeks ago 0.9mg/dL),

Microscopic examination of the urinary sediment shows 1-3WBC/hpf and trace proteinuria
Case #16

Which of the following is the most likely cause of the acute kidney injury?

A. Omeprazole
B. Lisinorpi
C. Pembrolizumab
D. Hydrochlorothiazide
Case #16 Answer

• The most likely cause of her acute kidney injury is related to immune check point inhibitor (CPIs) therapy. By inhibition of negative co-stimulatory signaling through cytotoxic T lymphocyte associated protein 4 (CTLA-4) or programmed cell death protein-1/programmed cell death protein-ligand 1 (PD-1/PD-L1) on T cells, CPIs restore tumor-directed T-cell responses and are able to induce long-lasting responses in a subset of patients receiving these medications. However, this boost in T-cell reactivity is also the cause of the CPI-associated side effect, namely immune-related adverse events (iRAEs).
### Immune Checkpoint Inhibitors Approved by FDA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Non–small-cell lung cancer, urothelial carcinoma</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Merkel-cell carcinoma, urothelial carcinoma</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>Urothelial carcinoma</td>
</tr>
</tbody>
</table>

CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.
Organs Affected by Immune Checkpoint Blockade

- Encephalitis, aseptic meningitis
- Hypophysitis
- Uveitis
- Thyroiditis, hypothyroidism, hyperthyroidism
- Dry mouth, mucositis
- Pneumonitis
- Rash, vitiligo
- Thrombocytopenia, anemia
- Myocarditis
- Hepatitis
- Pancreatitis, autoimmune diabetes
- Adrenal insufficiency
- Nephritis
- Colitis
- Vasculitis
- Enteritis
- Arthralgia
- Neuropathy

Postow, MA et al: NEJM, 2018
Forest plot of included studies comparing the risk of AKI in patients treated with PD-1 inhibitors versus non-PD-1 inhibitors

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robert et al. (1)</td>
<td>Nivolumab</td>
<td>2.99</td>
<td>0.31</td>
<td>28.46</td>
<td>0.34</td>
</tr>
<tr>
<td>Weber et al.</td>
<td>Nivolumab</td>
<td>2.28</td>
<td>0.28</td>
<td>18.74</td>
<td>0.44</td>
</tr>
<tr>
<td>Ferris et al.</td>
<td>Nivolumab</td>
<td>0.24</td>
<td>0.02</td>
<td>2.57</td>
<td>0.24</td>
</tr>
<tr>
<td>Borghaei et al.</td>
<td>Nivolumab</td>
<td>6.54</td>
<td>0.81</td>
<td>52.78</td>
<td>0.08</td>
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<tr>
<td>Brahmer et al.</td>
<td>Nivolumab</td>
<td>2.46</td>
<td>0.48</td>
<td>12.57</td>
<td>0.28</td>
</tr>
<tr>
<td>Postow et al.</td>
<td>Nivolumab</td>
<td>0.49</td>
<td>0.03</td>
<td>7.65</td>
<td>0.61</td>
</tr>
<tr>
<td>Hodi et al.</td>
<td>Nivolumab</td>
<td>2.47</td>
<td>0.12</td>
<td>50.50</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.89</td>
<td>0.82</td>
<td>4.35</td>
<td>0.13</td>
</tr>
<tr>
<td>Bellmunt et al.</td>
<td>Pembrolizumab</td>
<td>2.05</td>
<td>0.85</td>
<td>4.96</td>
<td>0.11</td>
</tr>
<tr>
<td>Herbst et al.</td>
<td>Pembrolizumab</td>
<td>24.47</td>
<td>1.46</td>
<td>410.77</td>
<td>0.03</td>
</tr>
<tr>
<td>Reck et al.</td>
<td>Pembrolizumab</td>
<td>0.18</td>
<td>0.05</td>
<td>0.61</td>
<td>0.01</td>
</tr>
<tr>
<td>Ribas et al.</td>
<td>Pembrolizumab</td>
<td>4.79</td>
<td>0.23</td>
<td>99.42</td>
<td>0.31</td>
</tr>
<tr>
<td>Robert et al. (2)</td>
<td>Pembrolizumab</td>
<td>3.23</td>
<td>0.67</td>
<td>15.47</td>
<td>0.14</td>
</tr>
<tr>
<td>Langer et al.</td>
<td>Pembrolizumab</td>
<td>1.58</td>
<td>0.47</td>
<td>5.31</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
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<td>1.80</td>
<td>0.57</td>
<td>5.65</td>
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<td>1.86</td>
<td>0.95</td>
<td>3.64</td>
<td>0.07</td>
</tr>
</tbody>
</table>

The overall pooled RR of AKI in patients treated with PD-1 inhibitors versus control was 1.86 (95% CI 0.95–3.64; I² = 48%)
Questions & Discussion

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