**Hypercalcemia in Pediatrics**

**Physiology of Calcium Homeostasis**

* Calcium (Ca) is maintained primarily by parathyroid hormone (PTH) and calcitriol (1,25 dihydroxyvitamin D) through actions on the bone, kidney, and GI tract
* PTH:
	+ Secreted in response to low Ca (sensed by Calcium-sensing Receptor on parathyroid cells).
	+ Actions:
		- Bone: PTH mobilizes Ca stores and promotes bone resorption by osteoclasts
		- Kidney: PTH increases Ca reabsorption in distal tubule, increases Phosphorus (Phos) excretion, and activates 1-alpha hydroxylase to convert 25-hydroxyvitamin D to 1,25-vitamin D
		- Net effect = Increased serum Ca, decreased serum Phos
* Calcitriol:
	+ GI tract (primary source of calcium): calcitriol enhances intestinal Ca and Phos absorption
	+ Net effect = Increase serum Ca and serum Phos



serum Ca and Phos

**Hypercalcemia**: Defined as [Ca] 2 standard deviations above mean (for age) adjusted for albumin

* Symptoms/Signs: “bones/stones” (nephrolithiasis, bone pain, polyuria), “groans” (abdominal pain, constipation), “psychic overtones” (fatigue, irritability, behavior change, depression, memory loss), failure to thrive, hypotonia, dehydration
* History**:** dietary assessment, medications (including OTC), family history of hypercalcemia
* Physical Exam: dysmorphic features, bony abnormalities
* Lab Evaluation: total Ca,albumin, ionized Ca, Phos, magnesium, PTH, 25-hydroxyvitamin D
	+ Also consider: 1,25-hydroxyvitamin D, urine calcium/creatinine
* Differential diagnosis:
	+ *PTH-Independent Hypercalcemia (more common)*
		- Milk-alkali syndrome
		- Hypervitaminosis D: Vitamin D toxicity, CYP24A1 mutation
		- Immobilization
		- Hypervitaminosis A
		- Granulomatous disorder: subcutaneous fat necrosis of the newborn, TB, sarcoid
		- Endocrinopathies: hyperthyroidism, adrenal insufficiency, pheochromocytoma, severe congenital hypothyroidism
		- Inborn errors of metabolism
		- Williams Syndrome: infantile hypercalcemia
		- Medications: thiazide
		- Phosphate depletion in neonates
		- Hypercalcemia of malignancy (uncommon): PTHrP-mediated, osteolysis, 1-25-mediated
	+ *PTH-depending Hypercalcemia (less common)*
		- **Primary hyperparathyroidism**
			* Labs: high Ca, low Phos, high PTH
			* Evaluation: Sestamibi, thyroid US to localize enlarged gland(s)
			* Causes (neonatal): maternal hypocalcemia
			* Causes (children): genetic tumors/hyperplasia (MEN1, MEN2A, MEN3, MEN4, HPT-JT), non-syndromic (FIHP), PTH/PTHrP receptor activating mutations, carcinoma, lithium
		- Tertiary Hyperparathyroidism (from chronic renal disease or hypophosphatemic rickets)
		- **Familial hypocalciuric hypercalcemia**
			* Labs: high Ca, normal/high PTH, Ca/Cr clearance < 0.01
			* No symptoms of high PTH (no nephrolithiasis, bone loss)
			* No treatment needed
* Management:
	+ Based on underlying etiology
	+ If symptomatic:
		- IVF hydration (with NS)
		- Loop diuretics (enhance urinary Ca excretion but require caution given resulting volume contraction)
		- Calcitonin (short window of effectiveness due to tachyphylaxis)
		- IV bisphosphonates
	+ If granulomatous disorder: glucocorticoids
	+ If primary hyperparathyroidism: parathyroidectomy, cinacalcet

 Available resources/References

1. Sperling, Mark A. Pediatric Endocrinology 4th Edition.