41 M with hypercalcemia and hypotension

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HPI

- 41 M with history of paraplegia secondary to GSW at age 15 who was transferred from an outside hospital for septic shock
- Endocrinology consulted for slowly progressive hypercalcemia (12.3 uncorrected, 13.9 corrected)

Additional History

- Had presented to OSH 3 weeks prior to transfer with fevers, nausea, vomiting, groin excoriations
- Found to be in septic shock with MSSA pyelonephritis
- Had AKI requiring CRRT
- Episodes of bradycardia/hypotension and respiratory failure (possibly 2/2 HCAP) → intubated
- Outside imaging showed numerous bladder and right renal calculi, bone scan consistent with osteomyelitis related to sacral wounds

U of C course

- Briefly extubated, went to IR for nephrostomy tubes, then coded, resuscitated successfully
- Neuro status and renal function improving gradually (Cr now normal)
- Remained intubated at time of consult but awake and alert
- Calcium noted to be slowly trending up over several weeks

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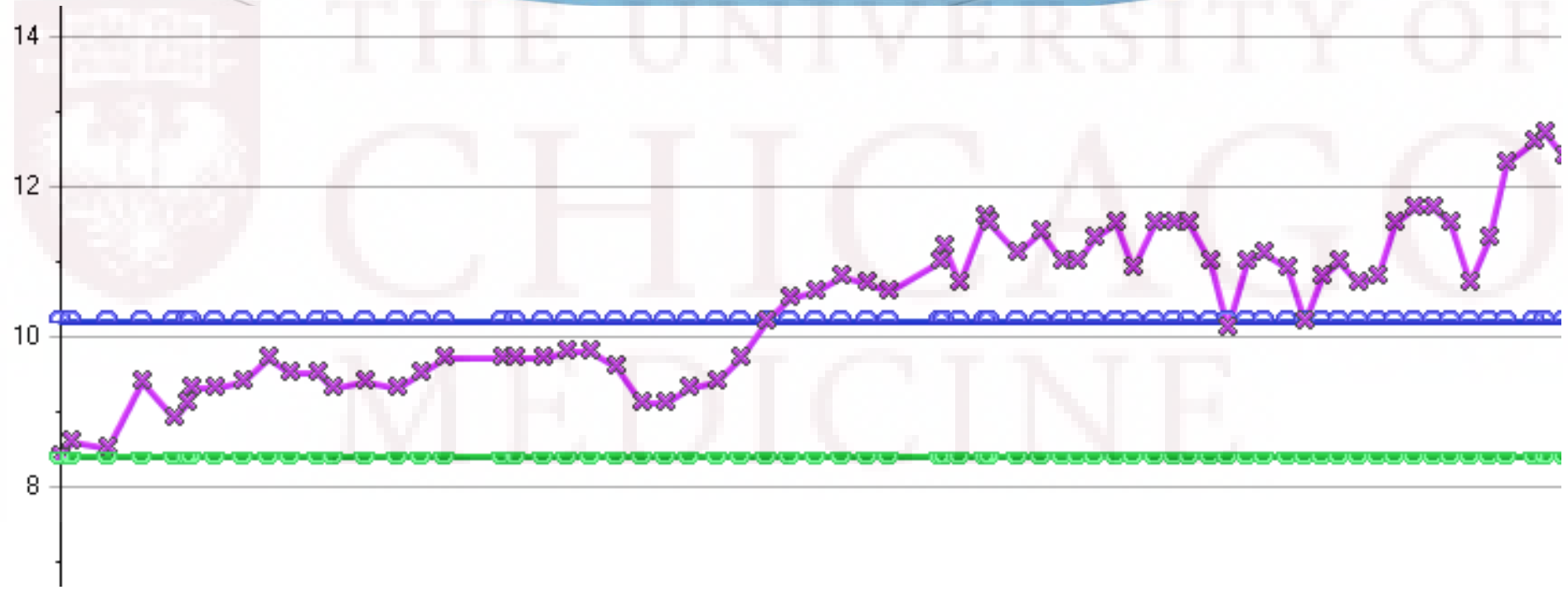
Calcium Trend since Admission



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Extended History

PMH: Paraplegia of LE, neurogenic bladder 2/2 GSW at age 15, recurrent UTI/urolithiasis, decubitus ulcers, pseudomonal infection of LE, Group B strep, hypotension

PSH: Suprapubic catheter, prior nephrostomy tubes

Social Hx: Lives at home with his father; mostly bed bound but can alter position using his arms

Family Hx: Non-contributory

Meds: Unknown

Exam

T 36.3, BP 125/96, P 97, R 22 SpO2 100%, Ht 152.4 cm (5'), Wt 43.7 kg (96 LB), BMI 18.8

Gen: Intubated, awake, alert,

HEENT: No thyromegaly, no lymphadenopathy but limited by ET tube and bandages around the neck. Temporal wasting

CV: Tachycardic but regular, no murmurs

Pulm: Mechanical breath sounds

Abd: Soft, non-tender

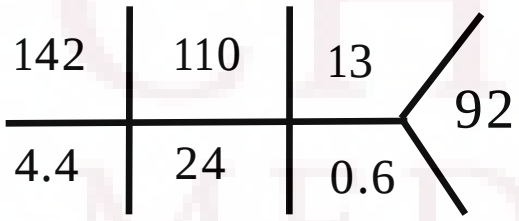
GU: Nephrostomy tubes with Foley bags

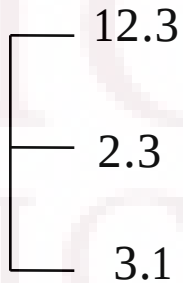
MSK: LE contractures, numerous wounds over the LE

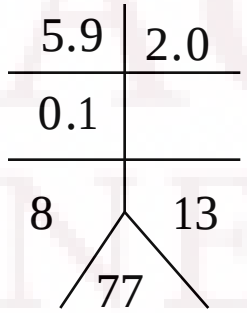
Neuro: Follows simple commands, nods head yes and no appropriately

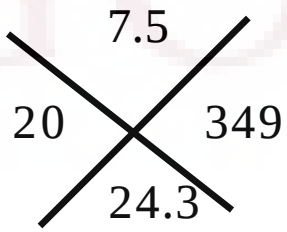
Psych: Not agitated

Labs









Admission Cortisol: 12.1
To be discussed!

What else do you want?

Further work-up

- Luckily, team had already sent:

25-OH Vitamin D: <7

1,25-OH Vitamin D: <8

PTH 6

PTHrp 17

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Imaging obtained prior

CXR: Left pleural effusion and opacities consistent with edema

CT Upper Abd and Pel WO

1. Bilateral pleural effusions left greater than right. Right basilar peribronchial airspace disease worrisome for pneumonia or possibly aspiration changes
2. Suprapubic Foley catheter with internal bladder stones and some moderate increased densities that may represent blood clots in the bladder. No evidence of extra bladder bleeding.
3. Diffuse edema with diffuse ascites and subcutaneous edema
4. Urinary tract stone disease with marked bilateral hydronephrosis
5. Bilateral hip dislocation and chronic hip flexion contractures

- What would you recommend to the team now?
  - Diagnostics?
  - Management?

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PTH related protein

- PTHrp is a normal gene product expressed in a variety of neuroendocrine, epithelial, and mesoderm-derived tissues
- Shares homology with PTH and can activate its receptor
- In a study of human volunteers, PTH and PTHrp displayed similar calcemic and phosphaturic effects, as well as similar effects on renal tubular calcium handling.
  - In contrast, PTH was selectively more effective than PTHrp in stimulating renal production of 1,25-OH Vitamin D

Horwitz et al. Direct comparison of sustained infusion of human parathyroid hormone-related protein (1-36) vs. hPTH (1-34) on serum calcium, plasma 1,25-dihydroxyvitamin D concentrations, and fractional calcium excretion in healthy human volunteers. JCEM 2003;88:1603-9.

PTHrp

- What cancers do we most frequently see elevated PTHrp?

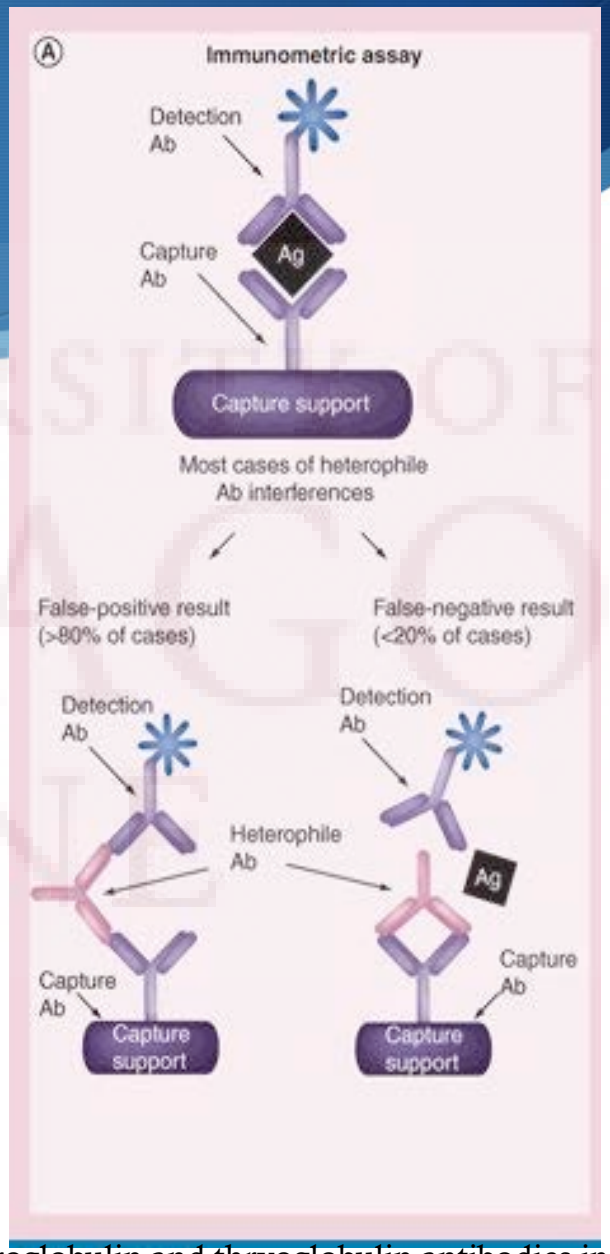
  Lung, renal, bladder, breast, ovarian, Non-Hodgkin lymphoma, CML, other leukemia or lymphoma

- What can cause elevated PTHrp besides malignancy?

  Heterophile antibodies (can affect any immunoassay) [false positive], pregnancy/lactating women, SLE, HIV-associated lymphadenopathy, lymphedema of chest or pleural cavities, benign tumors of the ovary/kidney/neuroendocrine, ??granuloma forming infections??

Heterophile Antibody

- Antibodies that can bind to animal antigens. In immunometric assays, these can interfere with measurements by forming a bridge between capture and detection antibody → falsely high or false positive
  - Can also bind to the capture/detection Ab in a way to hinder binding of the analyte → false negative
  - Most immunometric assays contain additives to reduce interference
  - If clinical concern, blocking agents can be added to the sample



Verberg FA et al. Heterophile antibodies rarely influence the measurement of thyroglobulin and thryoglobulin antibodies in differentiated thyroid cancer patients. Horm Metab Res 2010;42:736-39.

- What would you recommend to the team now?
  - Diagnostics?
  - Management?

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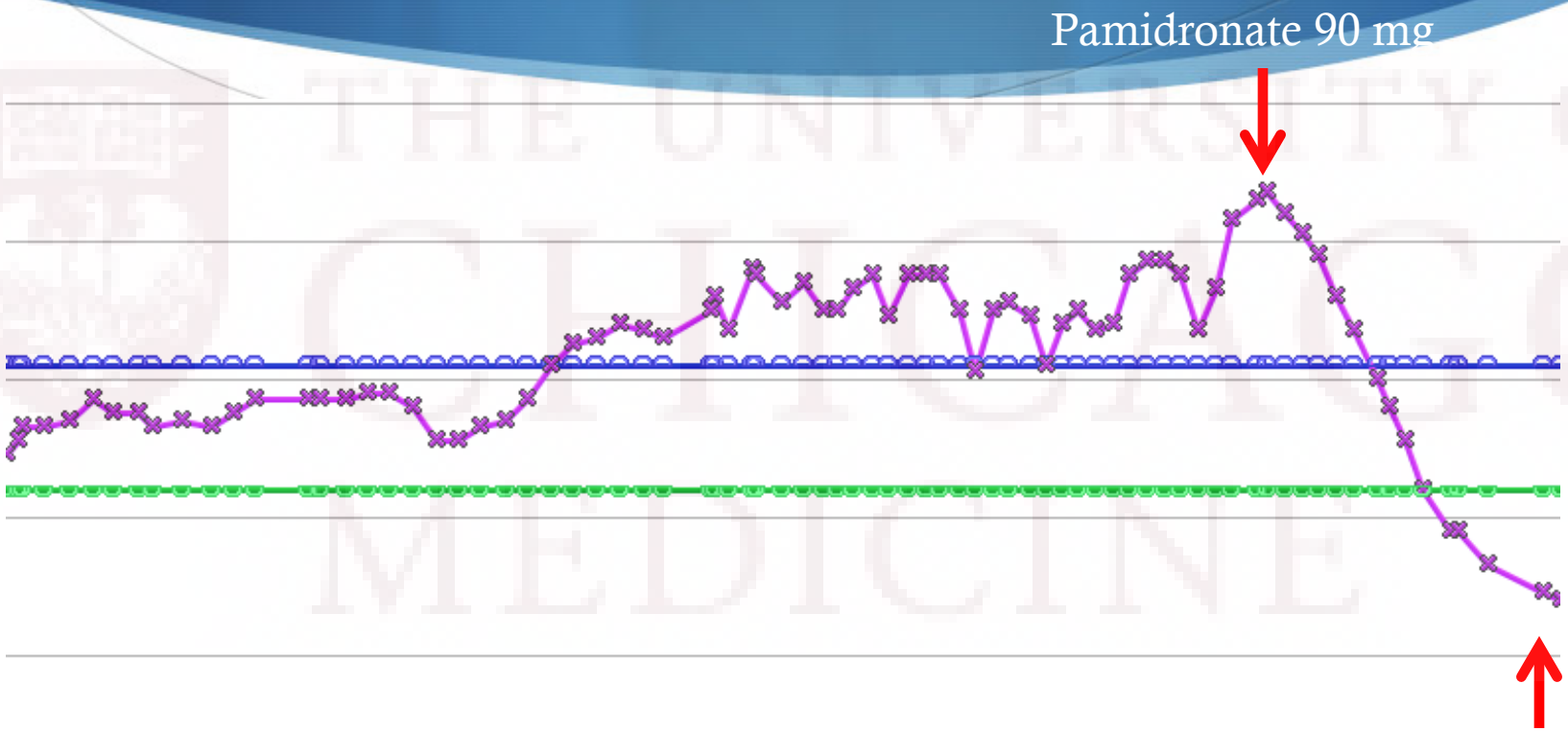
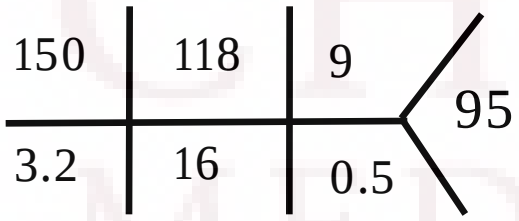
Management

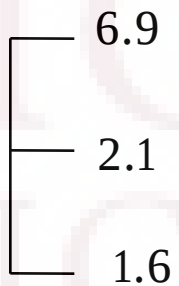
- We recommended a search for malignancy but ICU team chose not to do an aggressive workup 2/2 patient's overall status
- Also felt hypercalcemia of immobilization was playing a role
- We elected to give Ergocalciferol 50,000 IU x 3 days to avoid hypocalcemia from giving a bisphosphonate
- On Day 2, we recommended Pamidronate 60 mg IV; however, the team gave 90 mg IV
- Discussed with Mayo Lab, who ran heterophile antibody blocking reagents which did not change the PTHrp result, suggesting it was **NOT** present
- We also repeated the PTHrp – second value was 26

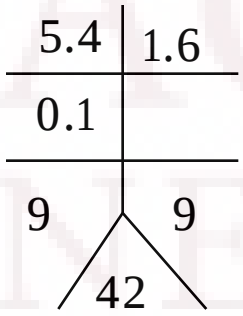
Calcium Trend



Labs







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Rapid declines in calcium

- Could the drop in calcium have lowered the seizure threshold?
- Rapid declines in calcium are mentioned as a precipitant for seizures in reviews and textbooks but there are not well-documented case reports of this
- Most case reports of hypocalcemic seizure are in the context of hypoparathyroidism

Is there evidence of bisphosphonates associated with seizures?

- Case report of 87 M with prostate cancer who got hypocalcemic to 3.6 (RR 8.1-10.4) four days after single dose of zoledronic acid (baseline Ca 8.3 one month prior)
  - Found to be Vitamin D deficient (25-OH D 13, RR 47.7-144), PTH 235
- There are also NON-hypocalcemia mediated cases of seizures.
  - E.g. one in a patient with known epilepsy who developed a fever (?acute phase reaction)

Navarro et al. Tonic-clonic seizure as the presentation symptom of severe hypocalcemia secondary to zoledronic acid administration. J Pall Med 2007;10(6):1226-7.
Tsourdi et al. Seizures associated with zoledronic acid for osteoporosis. JCEM 2011;96: 1955-59.

Management?

EKG did not show changed QTC

CT Head without contrast showed non-specific low-attenuation lesions on the white matter, EEG non-specific

- With hypocalcemic seizures, EEG can show slowing with generalized bursts of spikes

Neurology favored seizure as sequela of anoxic brain injury and started Keppra.

Changes in calcium and seizures

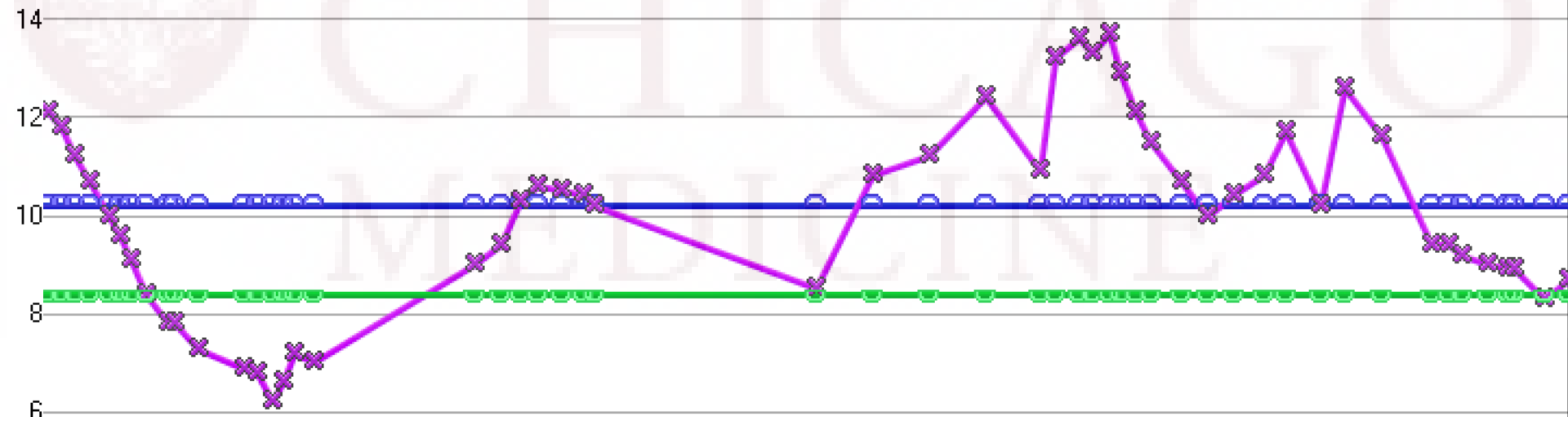
- Any further endocrine recommendations?

- We did not have high suspicion that hypocalcemia contributed but we elected to give calcium gluconate 1 g IV x 1

Follow-up

- Calciums would stabilize for ~1 week but then increase and require more pamidronate (eventually requiring 60 mg IV weekly), calcitonin, IV fluids, and lasix
- Patient would have significant issues with his G-tube, leakage. CT Abd/Pel with contrast showed extensive nodular circumferential bladder wall thickening and extensive abdominopelvic lymphadenopathy. Also with mucinous ascites. Did undergo paracentesis but cells were not diagnostic

Follow-up



Part 2: Adrenal insufficiency…?

- At admission (~2 weeks prior to consult), Cortisol was checked and was 12.1
- Primary team gave hydrocortisone 50 mg q8h IV x 3 days for "relative adrenal insufficiency" then stopped it and started midodrine
- 2 weeks later, when patient had a persistent pressor requirement, hydrocortisone was re-started by the primary team

Hydrocortisone 50 mg IV q8h started

07/10 0700 - 07/11 0659

Time:	0700	0730	0800	0811	0830	0900	0930	0932	0940	1000	1030	1050
Vital Signs												
Temp			36.5 (...									
Pulse	96	96	102	98	105	103	101			98	99	
Respirations	27	17	35	21	23	33	26			19	30	
MAP Method			Monitor			Monitor				Monitor		
Location ART #1			Arteri...			Arteri...				Arteri...		
ART #1 BP	100/53	114/64	112/62		98/49	107/56	111/59			114/57	117/63	
ART #1 MAP	70	85	81		64	74	78			76	84	
I/O Totals												
Total In												
Total Out												
I/O Net												
Drips												
norepinephrine D...	0.0391...		0.0391...					0 mcg/...				
vasopressin Dos...	0.04 U...		0.04 U...							0.04 U...		0.03 U...
Respiratory												

1100	1130	1133	1147	1200	1230	1300	1330	1400	1431
				36.6 (...					
100	98	97		104	103	104	107	111	
31	21	21		30	32	21	25	34	
Monitor				Monitor		Monitor		Monitor	
Arteri...				Arteri...		Arteri...		Arteri...	
121/63	121/62			123/65	110/54	119/62	103/47	90/39	
85	83			87	72	83	64	54	
0.03 U...			0.02 U...	0.02 U...					0.01 U...

Discussion

Initial thoughts and/or additional workup?

Unfortunately serum free cortisol could not be added on to prior labs.

Spinal Cord Injuries (SCI) and Blood pressure

- BP is typically low in individuals with SCI because of a reduction in sympathetic nervous system below the level of the injury
- Baroreflex control of vascular tone is often absent
- Therefore, hypotension and orthostatic hypotension are common
- We don't know this patient's baseline blood pressures!

Myers et al. Cardiovascular disease in spinal cord injury. Am J Phys Med Rehab 2007.

Hypoproteinemia & Cortisol levels

- Clinical problem: More than 90 percent of circulating cortisol is protein-bound and changes in binding proteins can alter total levels of cortisol without influencing free concentrations
- This was studied in 66 critically ill patients and 33 healthy volunteers who underwent measurement of baseline total and free cortisol and cosyntropin stimulated total and free cortisol.
- Of the 66 critically ill patients, 36 had albumin of 2.5 or lower

Hamrahian et al. Measurement of serum free cortisol in critically ill patients. NEJM 2004;350:1629-1638.

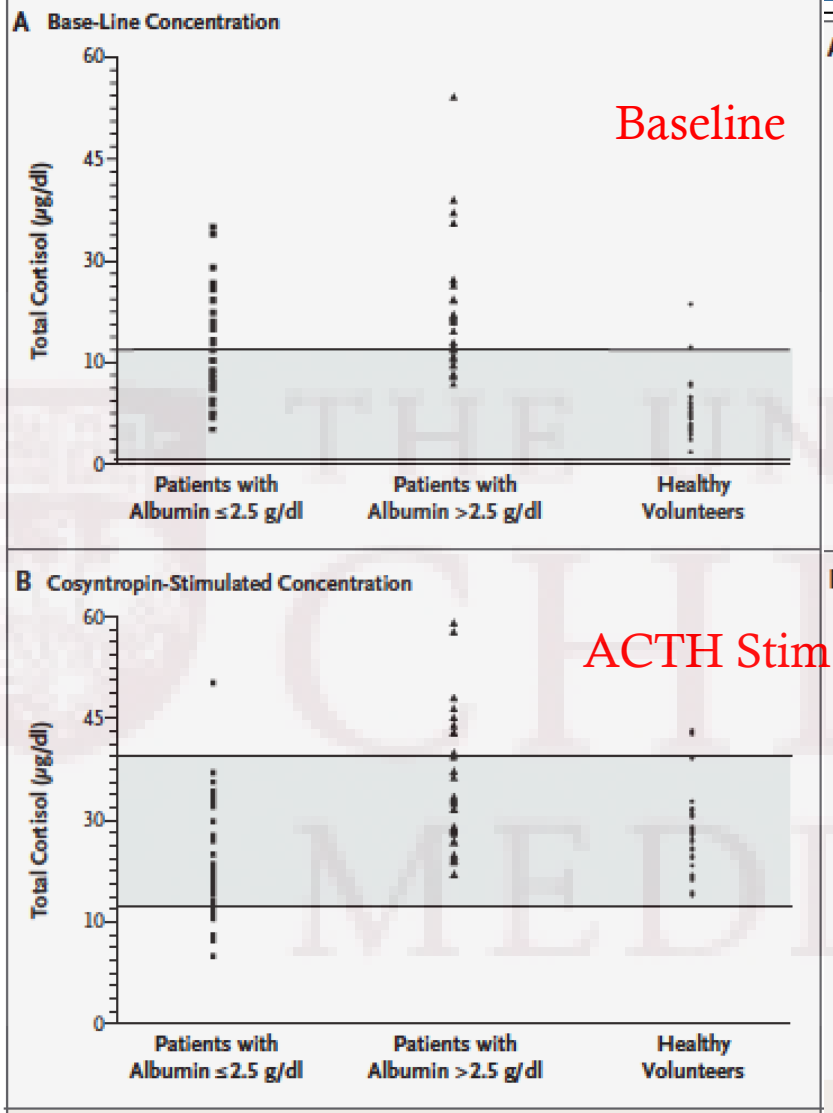
Table 1. Characteristics of Critically Ill Patients and Healthy Volunteers.*

Characteristic	Group 1 (N=36)	Group 2 (N=30)	Healthy Volunteers (N=33)
Age (yr)	65.2±14.2†	66.9±10.9†	54.6±16.6
Plasma corticotropin (ng/liter)‡	38.7±12.9§	37.8±18.8§	24.9±9.8
Corticosteroid-binding globulin (mg/liter)	17.7±5.9§¶	21.4±6.8§	26.0±3.8
Serum albumin (g/dl)	1.9±0.3§‖	3.1±0.4§	3.9±0.3
Total serum protein (g/dl)	4.7±0.8§**	6.0±1.0§	6.8±0.3
Duration of hospitalization before testing (days)	21.2±16.2**	6.4±5.6	NA
Severity-of-illness score	41.6±15.8	40.6±21.4	NA
No. died/no. survived	12/24	7/23	NA
Mean blood pressure (mm Hg)	78±9	81±11	82±5

Hamrahian et al. Measurement of serum free cortisol in critically ill patients. NEJM 2004;350:1629-1638.

Total Cortisol

Free Cortisol

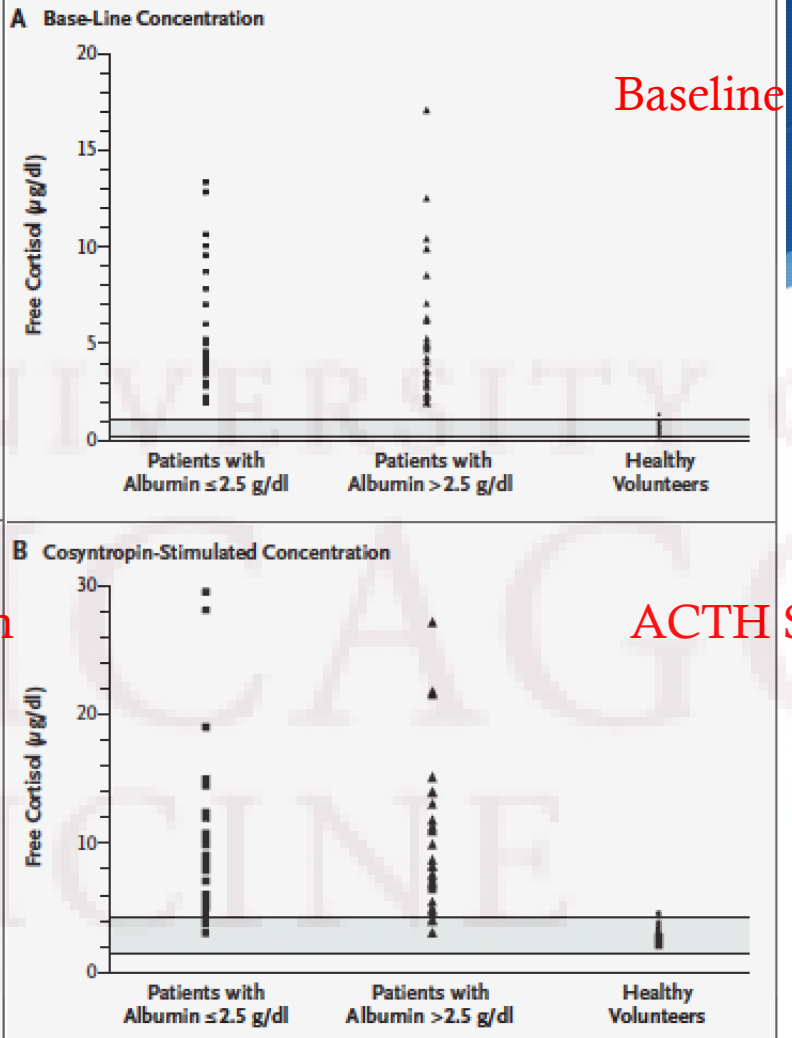


Baseline

ACTH Stim

Figure 1. Base-Line and Cosyntropin-Stimulated Serum Total Cortisol Concentrations in Two Groups of Critically Ill Patients and Healthy Volunteers.

The base-line concentrations (Panel A) and cosyntropin-stimulated concentrations (Panel B) were significantly lower in the group with albumin concentrations ≤2.5 g per deciliter than in the group with albumin concentrations >2.5 g per deciliter. The shaded area represents the mean ±2 SD from the mean in the group of healthy volunteers.



Baseline

ACTH Stim

Figure 2. Base-Line Serum Free Cortisol and Cosyntropin-Stimulated Serum Free Cortisol Concentrations in Two Groups of Critically Ill Patients and in Healthy Volunteers.

The base-line concentrations (Panel A) and cosyntropin-stimulated concentrations (Panel B) did not differ significantly between the two patient groups. However, the concentrations in the two patient groups were higher than the values in normal subjects. The shaded area represents the mean ±2 SD from the mean in the group of healthy volunteers.

Additional testing

- Of 14 patients with low total serum cortisol on ACTH stimulation testing, 6 were re-evaluated 6-10 weeks after hospital discharge at which point serum albumin had normalized. At this point, ACTH stimulation test repeated and showed normal total serum cortisol

Conclusion

- **Be wary of serum total cortisol when albumin is low!**

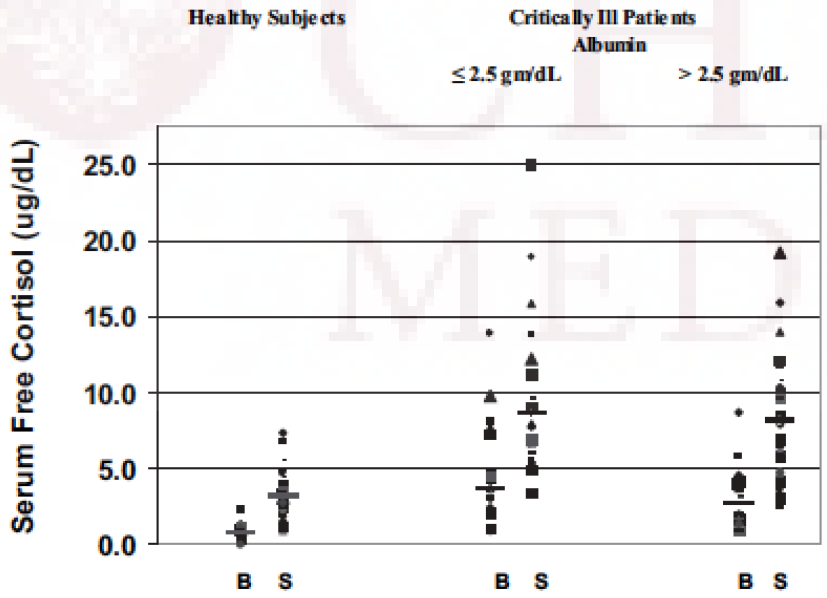
Alternative measures?

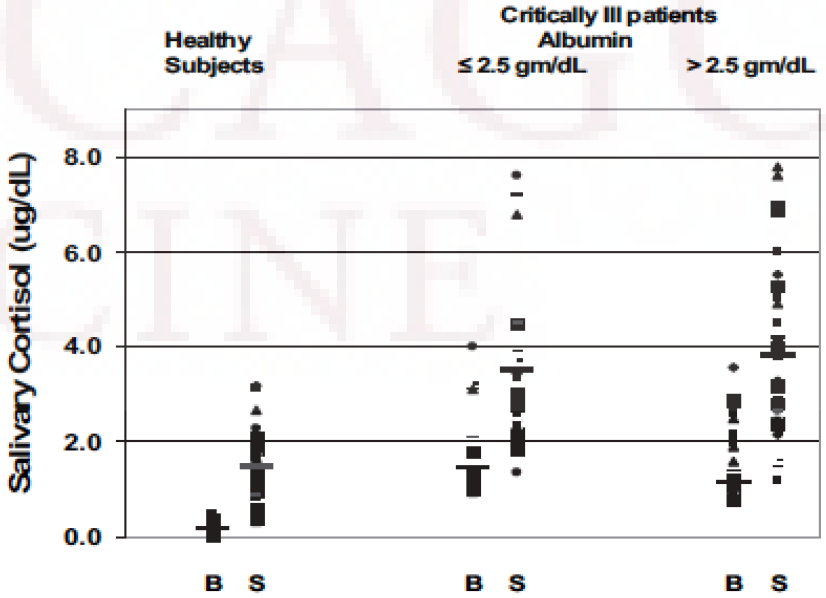
- Practical problem is that serum free cortisol takes awhile to come back
- The same group essentially repeated the previous experiment but now also looked at salivary cortisol at baseline and with ACTH stimulation

Measurement of Salivary Cortisol Concentration in the Assessment of Adrenal Function in Critically Ill Subjects: A Surrogate Marker of the Circulating Free Cortisol

Baha M. Arafah, Fumie J. Nishiyama, Haytham Tlaygeh, and Rana Hejal

51 critically ill patients underwent baseline/ACTH stimulated total cortisol, free cortisol, and salivary cortisol measurements.





Mean baseline salivary cortisol in healthy volunteers 5.1 nmol/L (185 ng/dL) vs 36.1 nmol/L (1308 ng/dL) in critically ill

- Any thoughts?
- Management?

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Management and Patient Course Continued…

- In conjunction with primary team concerns, we recommended hydrocortisone taper with plans to re-evaluate once hydrocortisone was stopped
- However, patient developed new issues (thrombocytopenia thought to be from Keppra, GI bleeding) that required stress dosing

Costs of Corticosteroids

- In a study of 100 trauma patients who received steroids (23 were for "adrenal insufficiency") vs. controls, there was higher risk of pneumonia (OR 2.64) and bloodstream infections (OR 3.25) in those who received steroids
- In a separate meta-analysis, use of steroids was associated with increased the risk of GI bleeding in hospitalized patients (OR 1.43)
- No substantial evidence that steroids help in sepsis or ARDS

Britt et al. Corticosteroid use in the ICU: at what cost? Arch Surg 2006;141:145-49
Narum et al. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open 2014;4:e004587.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

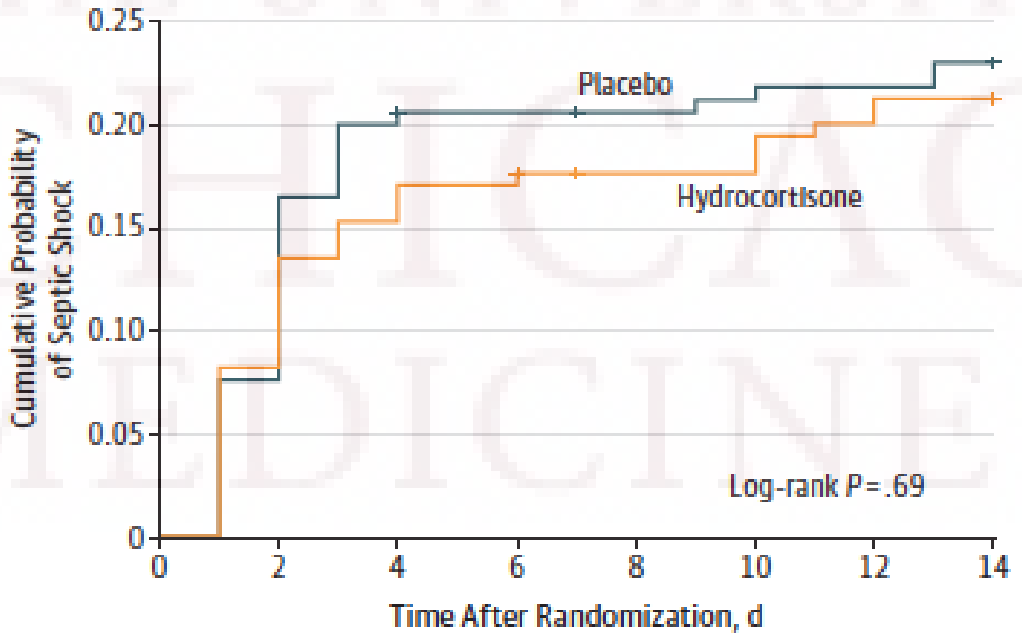
Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis

The HYPRESS Randomized Clinical Trial

- 380
  con
  foll
- No

days

Figure 2. Time to Septic Shock



No. at risk								
Placebo	176	161	139	136	134	131	130	128
Hydrocortisone	177	163	146	142	138	138	134	130

Tick marks on curves indicate censored data.

Table 3. Adverse Events in Safety Analysis Set

Adverse Event	Placebo (n = 189)	Hydrocortisone (n = 186)	Total (N = 375)	*P* Value[a]
Secondary infections, No. (%)	32 (16.9)	40 (21.5)	72 (19.2)	.26
MRC Scale for Muscle Strength score available, No. (%)	151 (79.9)	150 (80.6)	301 (80.3)	.86
Muscle weakness, No. (%)[b]	36 (23.8)	46 (30.7)	82 (27.2)	.18
Respiratory, No. (%)	24 (12.7)	24 (12.9)	48 (12.8)	.95
Weaning failure	16 (8.5)	16 (8.6)	32 (8.5)	.96
Respiratory failure	7 (3.7)	3 (1.6)	10 (2.7)	.34
Other	9 (4.8)	6 (3.2)	15 (4.0)	.45
Cardiovascular, No. (%)	19 (10.1)	17 (9.1)	36 (9.6)	.76
Arterial hypertension	1 (0.5)	5 (2.7)	6 (1.6)	.12
Other	18 (9.5)	14 (7.5)	32 (8.5)	.49
Abdominal, No. (%)	6 (3.2)	7 (3.8)	13 (3.5)	.76
Gastrointestinal bleeding	2 (1.1)	3 (1.6)	5 (1.3)	.68
Gastrointestinal ulcer	1 (0.5)	0	1 (0.3)	.99
Other	4 (2.1)	7 (3.8)	11 (2.9)	.35
Impaired wound healing, No. (%)	3 (1.6)	5 (2.7)	8 (2.1)	.50
Central nervous system, No. (%)	9 (4.8)	8 (4.3)	17 (4.5)	.83
Stroke, TIA, or convulsion	5 (2.6)	2 (1.1)	7 (1.9)	.45
Delirium	4 (2.1)	5 (2.7)	9 (2.4)	.75
Other	0	1 (0.5)	1 (0.3)	.50
Hypernatremia, No. (%)[c]	10 (5.3)	10 (5.4)	20 (5.3)	.97
Maximum sodium concentration, mean (SD), mEq/L	141 (6)	141 (5)	141 (6)	.29
Sodium concentration during study medication administration, mean (SD), mEq/L	140 (6)	141 (5)	141 (6)	.15
Hyperglycemia, No. (%)[d]	154 (81.5)	169 (90.9)	323 (86.1)	.009
Maximum glucose concentration, median (IQR), mg/dL	160 (134-196)	164 (145-204)	161 (140-201)	.04
Hyperglycemia during study medication administration, No. (%)	145 (76.7)	164 (88.2)	309 (82.4)	.004
Maximum glucose concentration during study medication administration, median (IQR), mg/dL	157 (133-198)	170 (147-208)	163 (141-201)	.006
Other, No. (%)	18 (9.5)	12 (6.5)	30 (8.0)	.27

Follow-up

- Despite stopping Keppra, patient's platelets remained low (<10) and refractory to transfusions
- G-tube problems persistent due to the mucinous ascites, eventually eroding through the abdominal wall
- Worsening hypotension and mental status
- Patient's family decided not to escalate care and patient passed away
- No autopsy was requested

References

- Horwitz et al. Direct comparison of sustained infusion of human parathyroid hormone-related protein (1-36) vs. hPTH (1-34) on serum calcium, plasma 1,25-dihydroxyvitamin D concentrations, and fractional calcium excretion in healthy human volunteers. JCEM 2003;88:1603-9.
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