Endocrine Management in Critically Ill Patients

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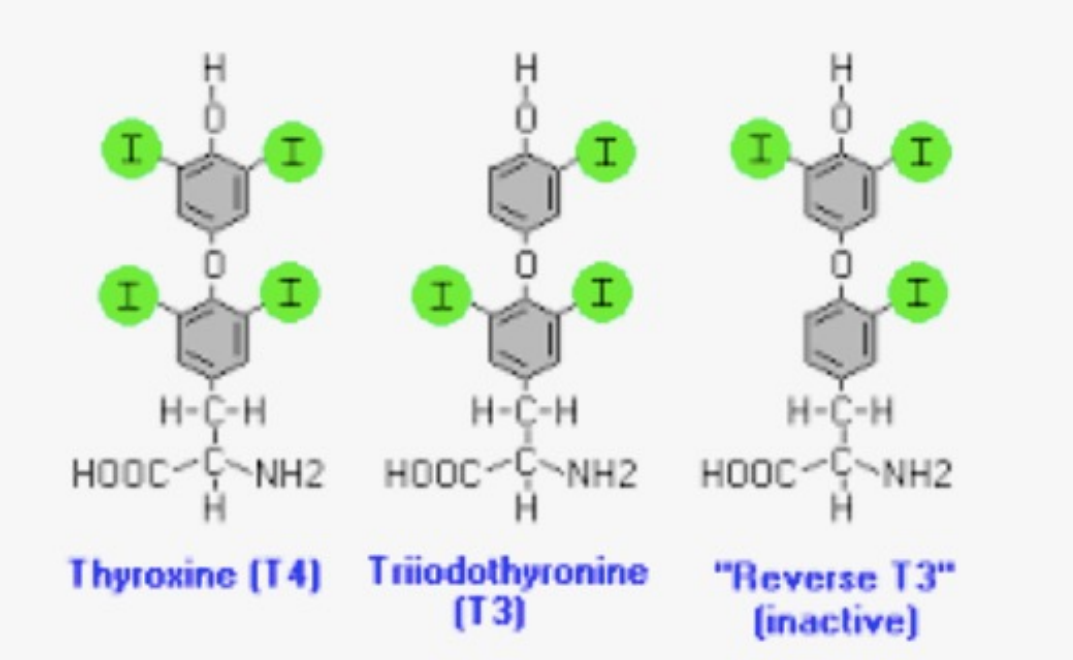
Disclosures

- Nothing to disclose

Topics

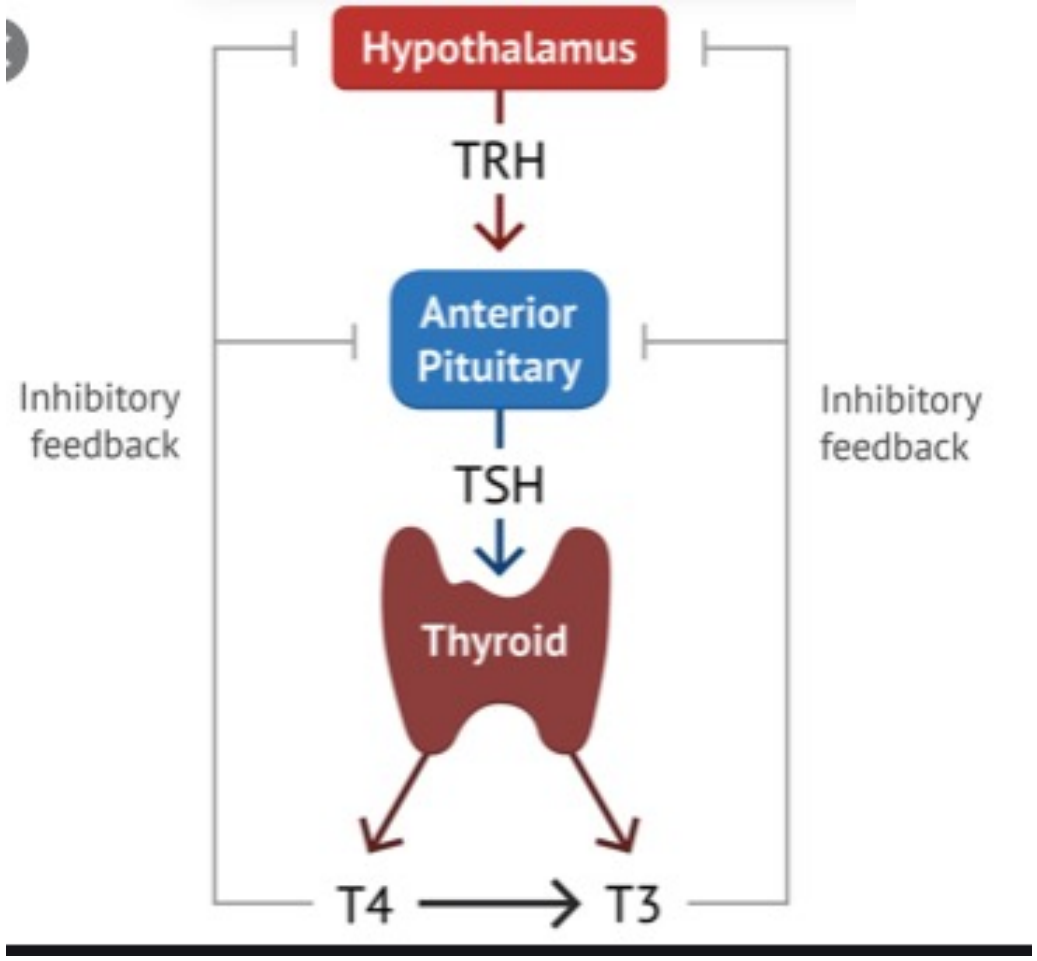
- Thyroid Function Tests in the ICU: Non-Thyroidal Illness Syndrome (NTIS)
- Diagnosing and Treating Adrenal insufficiency in the ICU
- Managing Glucose in the ICU

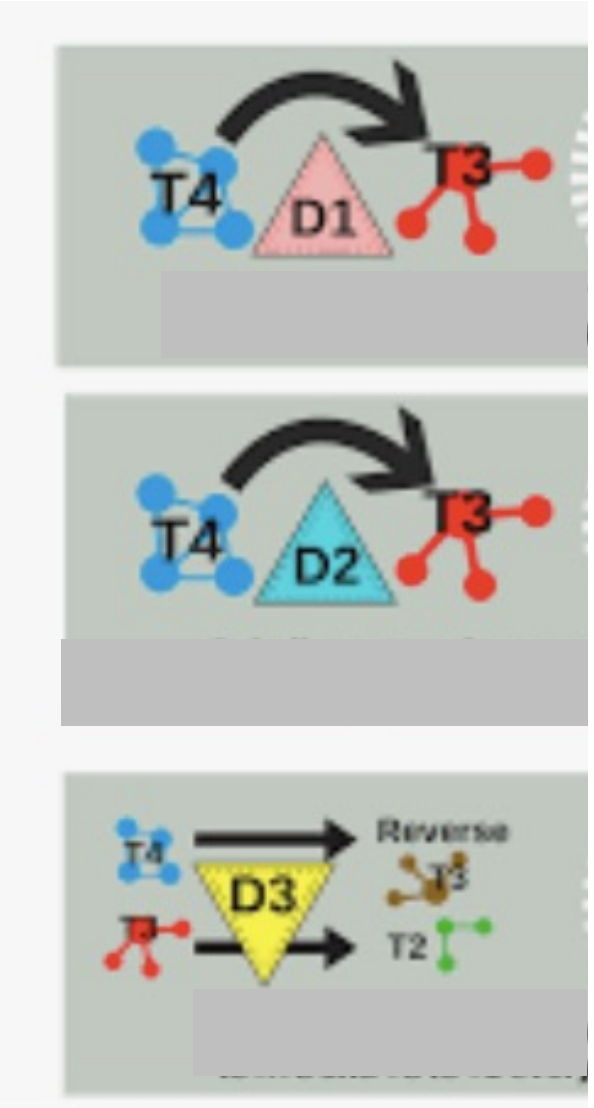
Thyroid Hormones: The Players



- Thyroid hormones circulate bound to proteins
- Changes in levels of binding proteins can impact measured total levels
- Measuring free levels can overcome this issue
- Commercial assays for free T4 are generally accurate
- Assays for free T3 are not as accurate and so total T3 is still the standard

Hypothalamic-Pituitary-Thyroidal Axis

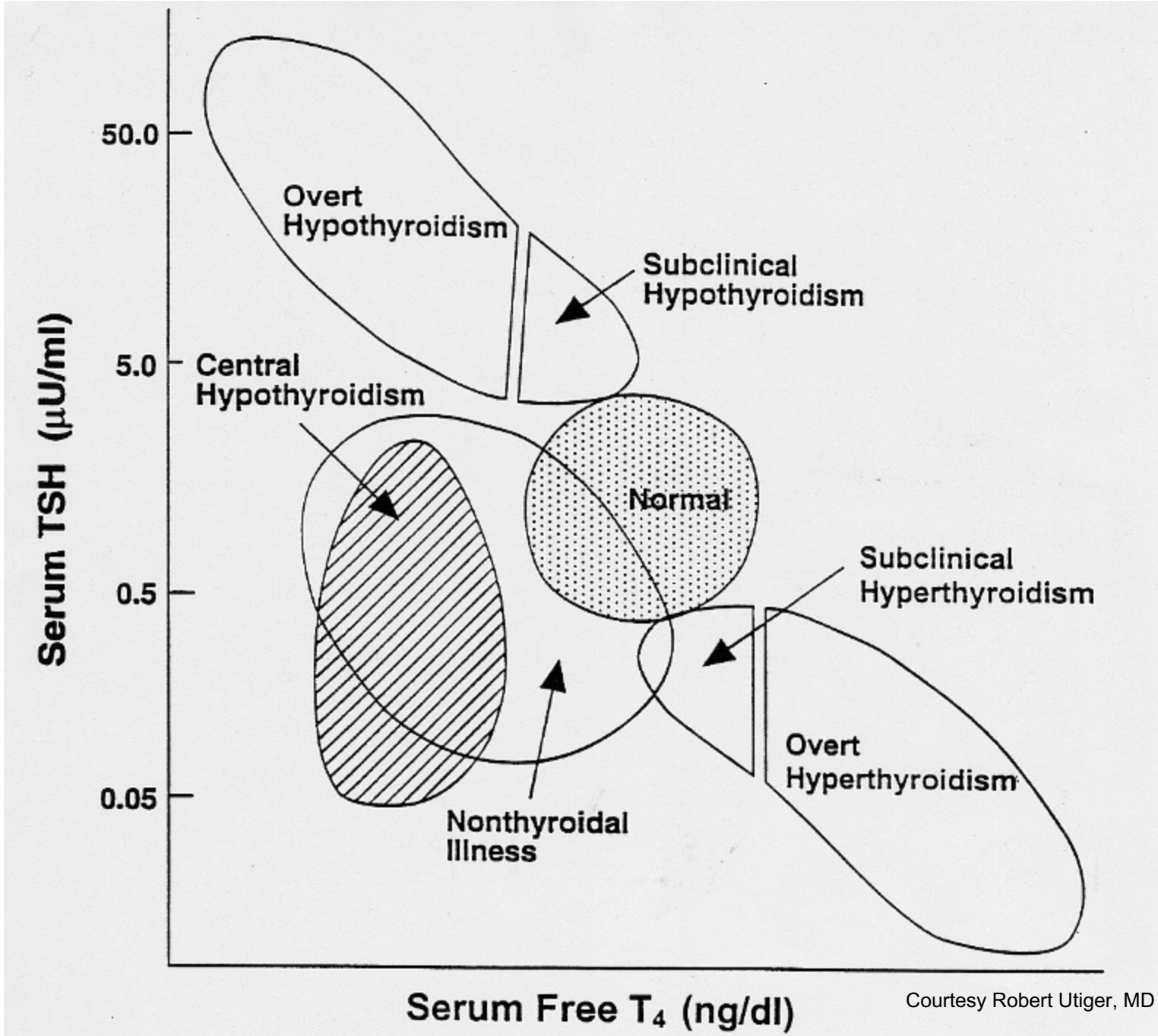




De-iodinase enzymes
D1,D2 and D3 convert T4
To T3 or rT3
T3 is “activated”
rT3 is “de-activated”

Thyroid Function Tests in the ICU

Diagnosis	TSH	Free T4	Total T3
1° Hyperthyroidism	↓↓↓	↑	↑
1° Hypothyroidism	↑	↓	↔↓
2° Hypothyroidsm	↔↓	↓	↔↓
Non-thyroidal illness syndrome	↔↓	↔↓	↓↓↓



Courtesy Robert Utiger, MD

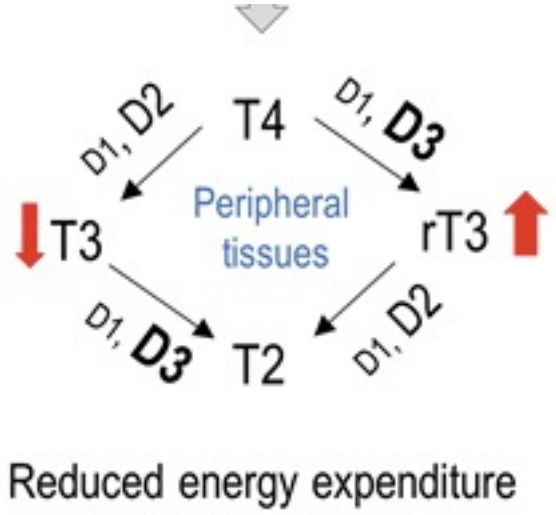
NTIS

- In critical illness and starvation, T3 and T4 levels drop
- Failure of hypothalamus to respond to low T3 and T4
- Mortality inversely correlates with thyroid hormone levels in NTIS
- Pathogenesis: Why does feedback seem to fail?
- Is this adaptive or maladaptive?

Lancet Diabetes Endocrinol. 2015 October ; 3(10): 816–825
Journal of Clinical Endocrinology and Metab 105:2830, 2020

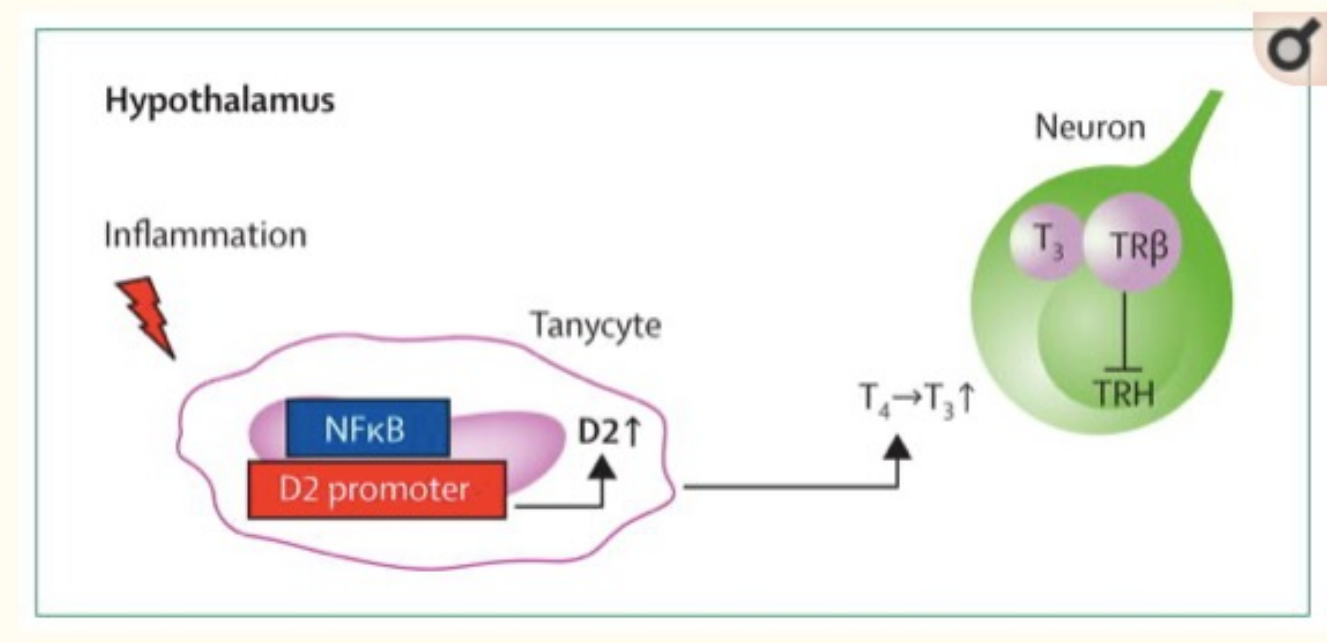
Sequence in NTIS

Inflammation and malnutrition impact de-iodinases: ↑D3 and ↓D2 peripherally



Journal of the Endocrine Society, Volume 3, Issue 12, December 2019, Pages 2313–2325

But centrally D2 is increased so T3 levels increase



Lancet Diabetes Endocrinol. 2015 Oct; 3(10): 816–825.

Pathogenesis: summary

- T4 is converted to T3(active form) by enzymes D1(liver) or D2(other tissues)
- T4 is converted to rT3(inactive form) by D3
- Hypoxia, ischemia, inflammation and malnutrition lower D1 and D2 activity and increase D3 activity resulting in lower T3 and higher rT3
- However, in hypothalamus D2 activity is increased(hypothesized) by inflammation and so more T3 is produced locally decreasing TRH which may be why TSH secretion is not increased in presence of low peripheral levels of T3

Courtesy of Ann Marie Zavacki, PhD

Time to Think

- A 60 year old woman with no prior history of thyroid dysfunction has been in the ICU intubated with respiratory failure for 10 days. She develops atrial fibrillation with rate approx. 100, BP 110/70 and temp 38.2 As part of the evaluation, thyroid function tests are ordered.
- Labs show: TSH 0.4 mIU/ml(nl 0.5-5)
- Free T4 0.7 ng/dl (nl 0.8-1.7)
- Total T3 50 ng/dl (nl 60-180)
- What would you do?
  - Start methimazole 10mg po
  - Start Levothyroxine 75 mcg iv
  - No specific therapy for thyroid hormone abnormalities

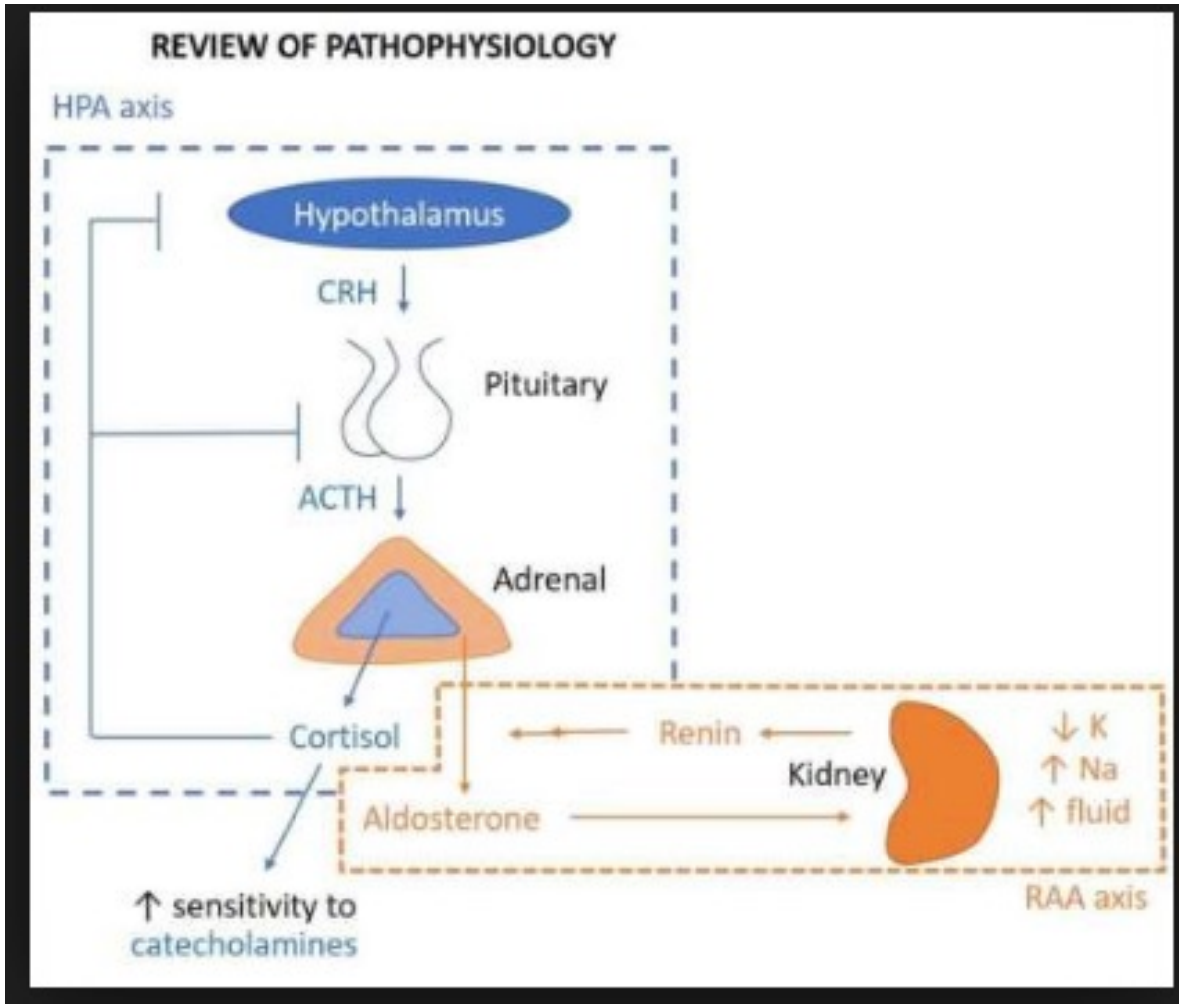
Is there a role for replacing T4 or T3?

- Multiple clinical trials have shown discrepant results with replacing thyroid hormone in NTIS
- Studies have varied by
  - Study design(RCT or not RCT)
  - Thyroid hormone used(T4 or T3)
  - Type of patients recruited
- Some studies have shown benefit(heart failure); some no effect
- No harm has been shown BUT
- No evidence-based guidelines or consensus statements advocate use of thyroid hormones in critically ill patients with NTIS

Front. Endocrinol. 13:850328, 2022

Lancet Diabetes Endocrinol. 2015 Oct; 3(10): 816–825.

Hypothalamic/Pituitary/Adrenal Axis



- 90% of cortisol circulates bound to cortisol binding globulin(CBG)
- 10% of cortisol circulates as free cortisol
- Only free cortisol is able to bind its receptor and initiate action
- Common assays measure total cortisol not free

Basicmedical Key

Steroid Action

- Some effects of cortisol
  - Maintain blood pressure by sensitizing vascular smooth muscle to catecholamine pressor effects
  - Antagonize effect of ADH on free water excretion and suppress ADH secretion
  - Increase hepatic gluconeogenesis
- Effects of aldosterone
  - Na retention
  - Potassium excretion
  - Maintain extracellular volume
  - Increase vascular resistance

Types of Adrenal Insufficiency

- Primary adrenal insufficiency
  - Destruction of the adrenal glands
  - Cortisol and aldosterone will be deficient
- Secondary adrenal insufficiency
  - Pituitary, hypothalamic disease or *chronic steroid use*
  - Adrenal glands are not destroyed
  - Aldosterone axis will remain intact
  - Cortisol producing cells will atrophy over time

Definition of Acute Adrenal crisis: 3 components required

- Symptoms/signs of Adrenal crisis
  - Fatigue/lethargy/nausea
  - Fever
  - Hypotension
  - Labs: hyponatremia, hypoglycemia, hyperkalemia
- Low cortisol level
- Clinical improvement in response to parenteral glucocorticoid(hydrocortisone)

Ther Adv Endocrinol Metab
2019, Vol. 10: 1–12

Precipitants of acute adrenal crisis

- Acute stress in patient with undiagnosed chronic adrenal insufficiency (infection or dehydration)
- Primary adrenal insufficiency
  - Bilateral adrenal hemorrhage
  - Autoimmune destruction
  - Infiltrative(TB, bilateral metastasis)
- Secondary Adrenal insufficiency
  - Abrupt cessation of glucocorticoids or failure to increase dose in setting of stress
  - Pituitary infarction, mass, hypophysitis
- Medications inhibiting cortisol production:
  - Etomidate, ketoconazole, megestrol

ACTH Stim Test for Diagnosis of Adrenal Insufficiency

- Baseline ACTH level if available
- Measure cortisol and aldosterone level at baseline
- Give 250 µg cosyntropin(synthetic ACTH) iv
- Measure cortisol and aldosterone between 30 and 60 minutes
- ACTH stim can be done any time of the day

BMJ Open. 2018; 8(5): e019273

Testing the HPA axis

STATIC TEST

- Morning cortisol (**and ACTH**)
- An "appropriate" AM cortisol should ideally be >13-14 µg/dL, reflecting a morning peak, but values > 10 µg/dL when pre-test probability is low

- An AM cortisol <5 mcg/dL is highly suggestive of adrenal insufficiency
- AM cortisol levels between 5-13 can be difficult to interpret and can be repeated

PROVOCATIVE TEST

- 250 µg cosyntropin stimulation test
- Stimulated cortisol <14* mcg/dL highly suggestive of primary adrenal insufficiency

*18 mcg/dL is the traditional cutoff. New cortisol immunoassays and LC-MS/MS assays have lower thresholds

Slide courtesy of Anand Vaidya, MD

Acute Adrenal Insufficiency: Primary or Secondary?

Primary:

- Increased ACTH
- Low aldosterone and no response to ACTH

Secondary

- Normal or low ACTH
- Normal K levels
- Increase in aldosterone level to ACTH stim

Measuring steroids

- Cortisol levels may be falsely elevated by cross-reactivity with administered drugs
  - Steroids which will cross-react
    - Hydrocortisone
    - Prednisolone, prednisone (to a moderate degree)
  - Steroid which does not cross-react in assays
    - Dexamethasone
    - Give dexamethasone if necessary while performing ACTH stim testing

Acute Adrenal Insufficiency: Treatment during stress (surgery, sepsis etc)

- Infuse normal saline or D5NS 1-3 liters over 12-24 hours
- Hydrocortisone 100 mg iv bolus X 1
- 200 mg iv continuous infusion of hydrocortisone q 24 hours tapered to physiologic replacement as indicated or 50 mg iv hydrocortisone q 6 hours
- Saline will be adequate to replace mineralocorticoid needs acutely until diagnosis established
- Average maintenance dose
  - Hydrocortisone 10-15 mg qam and 5-10 mg qpm
  - Fludrocortisone .1 mg qd (if there is mineralocorticoid deficiency)

Anesthesia 75: 654-663, 2020
JCEM 105:2262-2274, 2020

Time to Think

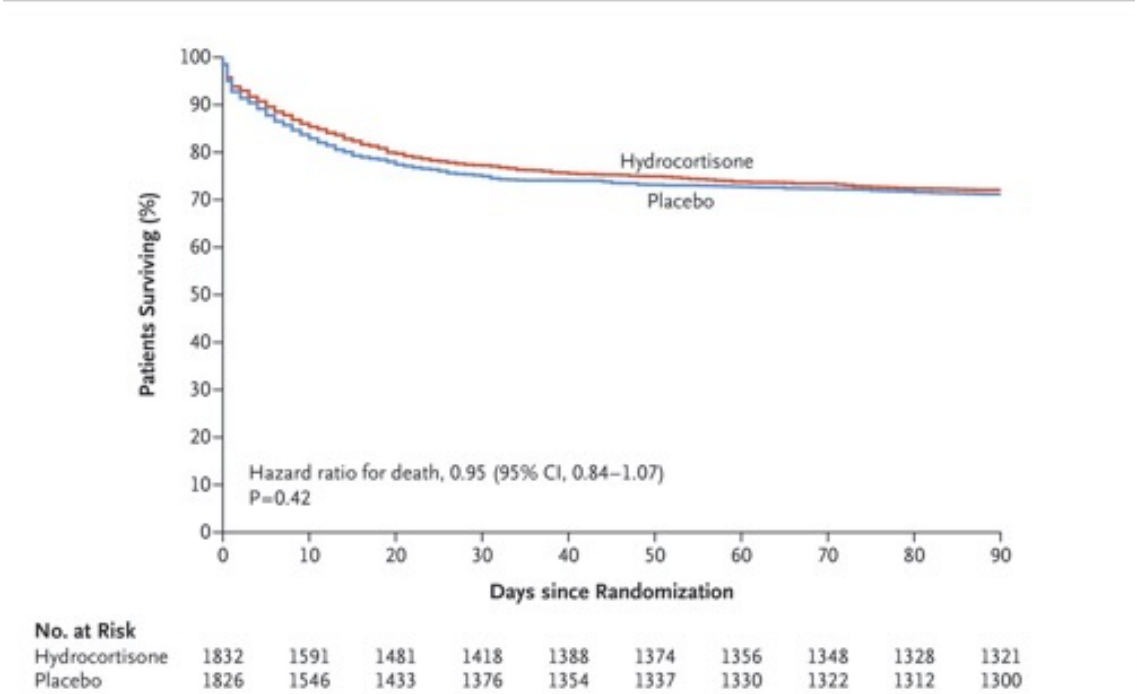
- 60 year old woman previously healthy but now with UTI and presumed sepsis is admitted to ICU with refractory hypotension despite significant fluid resuscitation.
- ACTH stim test is done
  - Baseline cortisol level is 20 µg/dl
  - 30 minute cortisol is 24 µg/dl
- What would you do?
  - Give hydrocortisone 100 mg iv bolus
  - Start pressors
  - Increase fluids

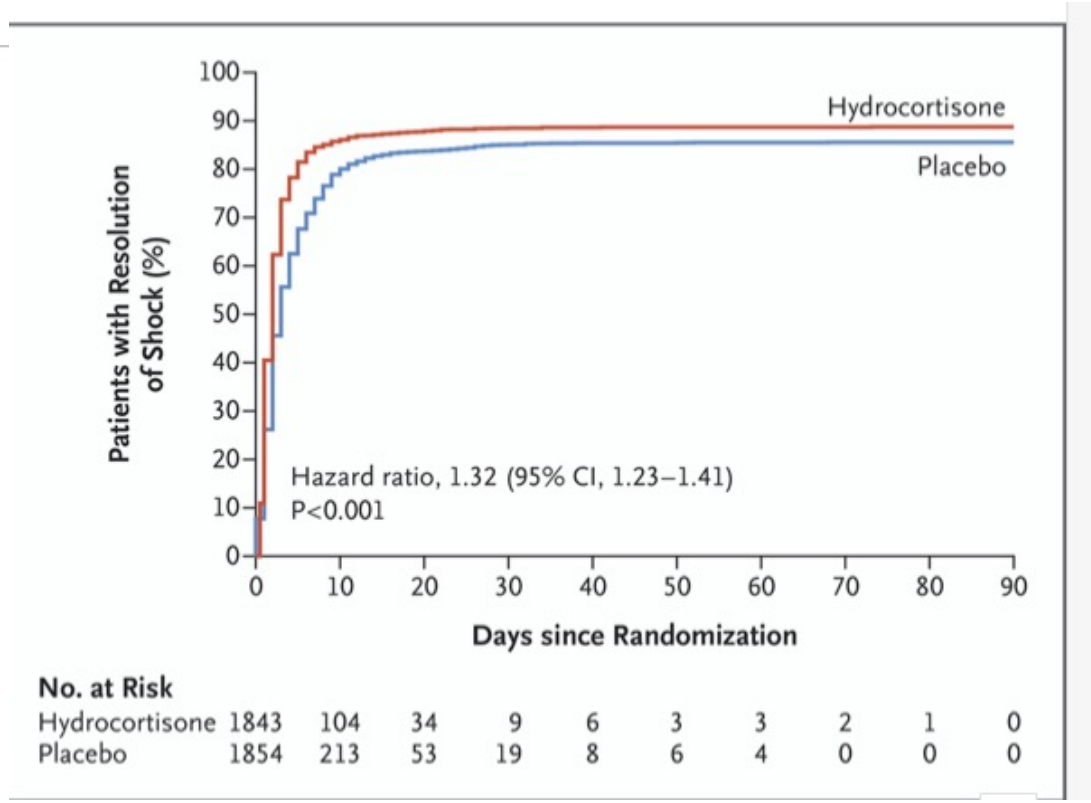
“Relative Adrenal Insufficiency” In Sepsis and Critical Illness

- Concept has been that despite “normal” levels of cortisol during stress that this may not be adequate
- A study found that incremental response of cortisol of less than 9µg/dl (even with levels otherwise considered adequate) to ACTH stim predicted higher mortality in sepsis patients
- This has not been consistently replicated
- No clear diagnostic criteria have been accepted for this condition

JAMA 2000;**283:** 1038–45.

Does treating septic patients with 200mg a day of hydrocortisone help?





N Engl J Med 2018; 378:797-808

Use of Hydrocortisone in Sepsis: Surviving Sepsis Guideline

- IV hydrocortisone is not recommended routinely in septic shock
- Fluid resuscitation and vasopressor therapy are recommended to restore hemodynamic stability
- If that fails, iv hydrocortisone 200 mg/day can be used(weak quality of evidence for this)
- Use hydrocortisone for patients with “conventional” adrenal insufficiency

Intensive Care Med **43,** 304–377 (2017)
Semin Respir Crit Care Med 40:594,2019

Glucose Management In the ICU: Definition of Terms

- Hospital hyperglycemia: Any BG > 140 mg/dl (7.8 mmol/L)
- Stress hyperglycemia: Elevations in blood glucose levels that occur in patients with no prior history of diabetes and A1c levels that are not significantly elevated (<6.5%)
- A1c value equal to or above 6.5% in patients with hyperglycemia suggests a prior history of diabetes
- Hypoglycemia:
  - Level 1 Glucose 54-70 mg/dl
  - Level 2 Glucose < 54 mg/dl
  - Level 3 A severe event characterized by altered mental or physical status requiring assistance

Diabetes Care 2021 Jan; 44 (Supplement 1): S1 211-S220.

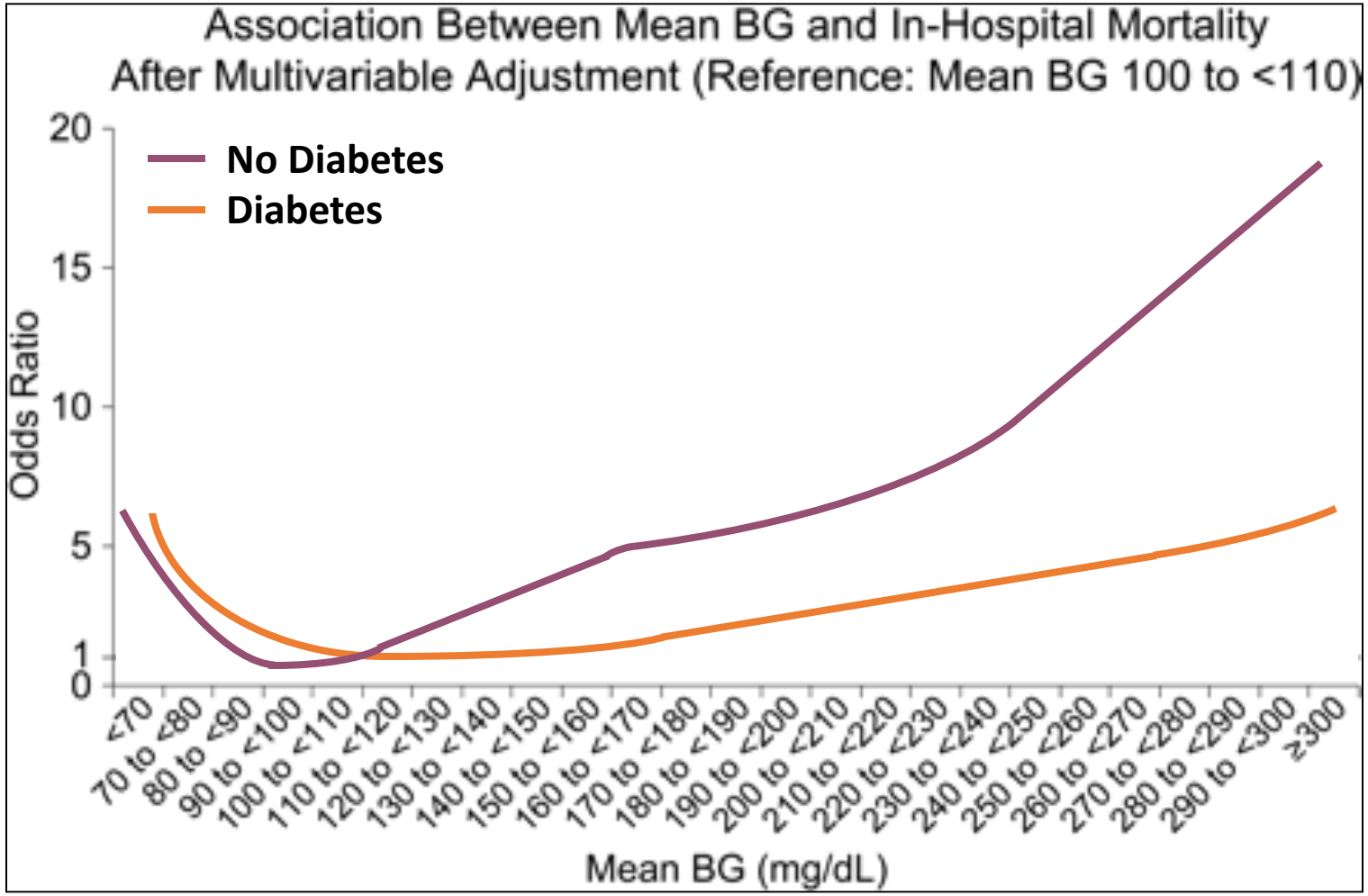
Scope of the Problem of Hyperglycemia in the Hospital

- 26% of all inpatients have known diabetes
- 12% of all admissions have previously unrecognized diabetes or stress hyperglycemia
- 70% of MI patients are hyperglycemic
- 60-90% of patients with diabetes are hyperglycemic after cardiac surgery
- 60% of patients without diabetes are hyperglycemic after cardiac surgery

Umpierrez,JCEM87:978,2002

Endocrinology Metab Clin North Am. 2018 Mar;47(1):203-222

Why Control Glucose Levels? Results in MI



Kosiborod et al Circulation 117:1018-1027, 2008

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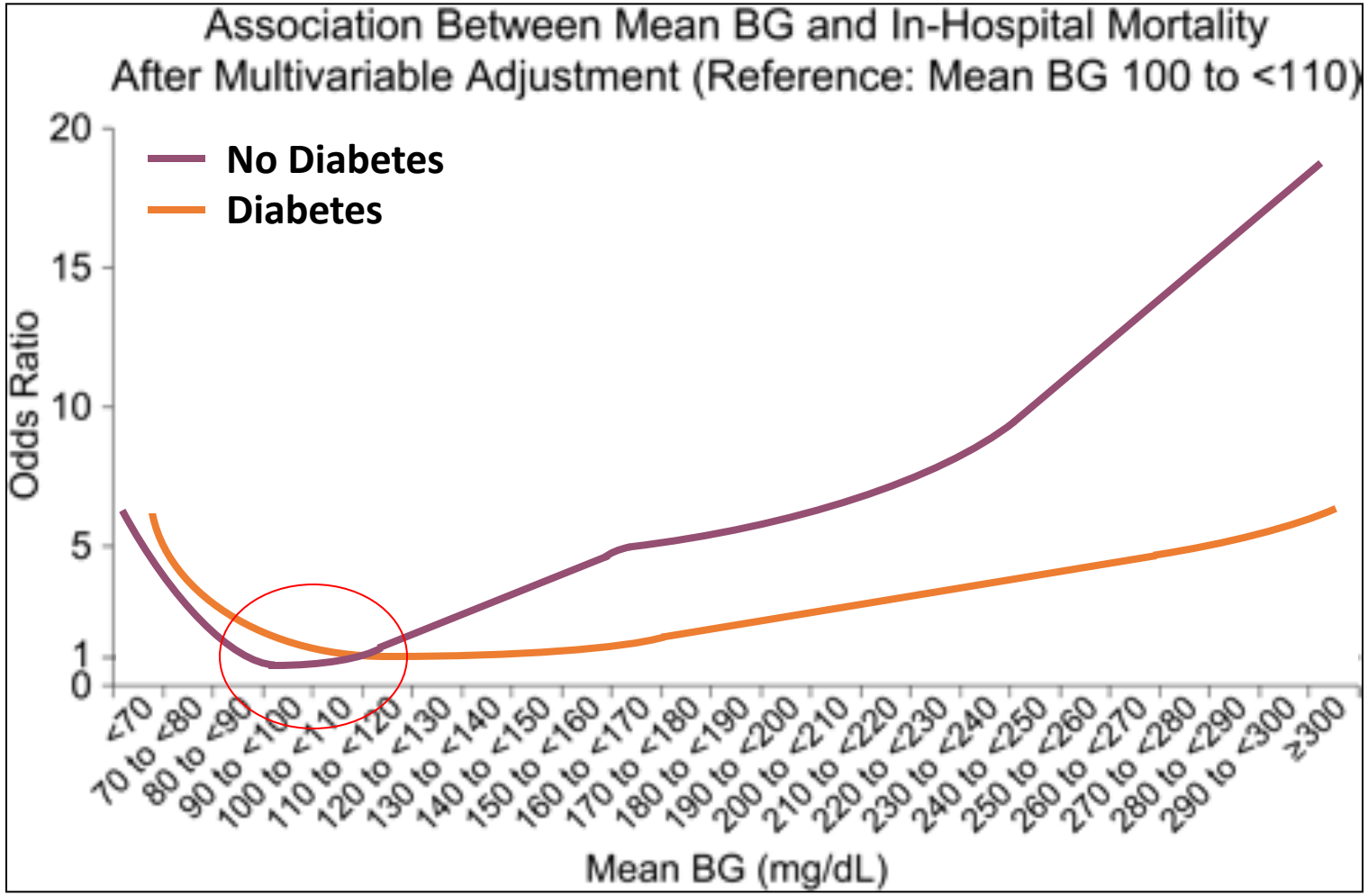
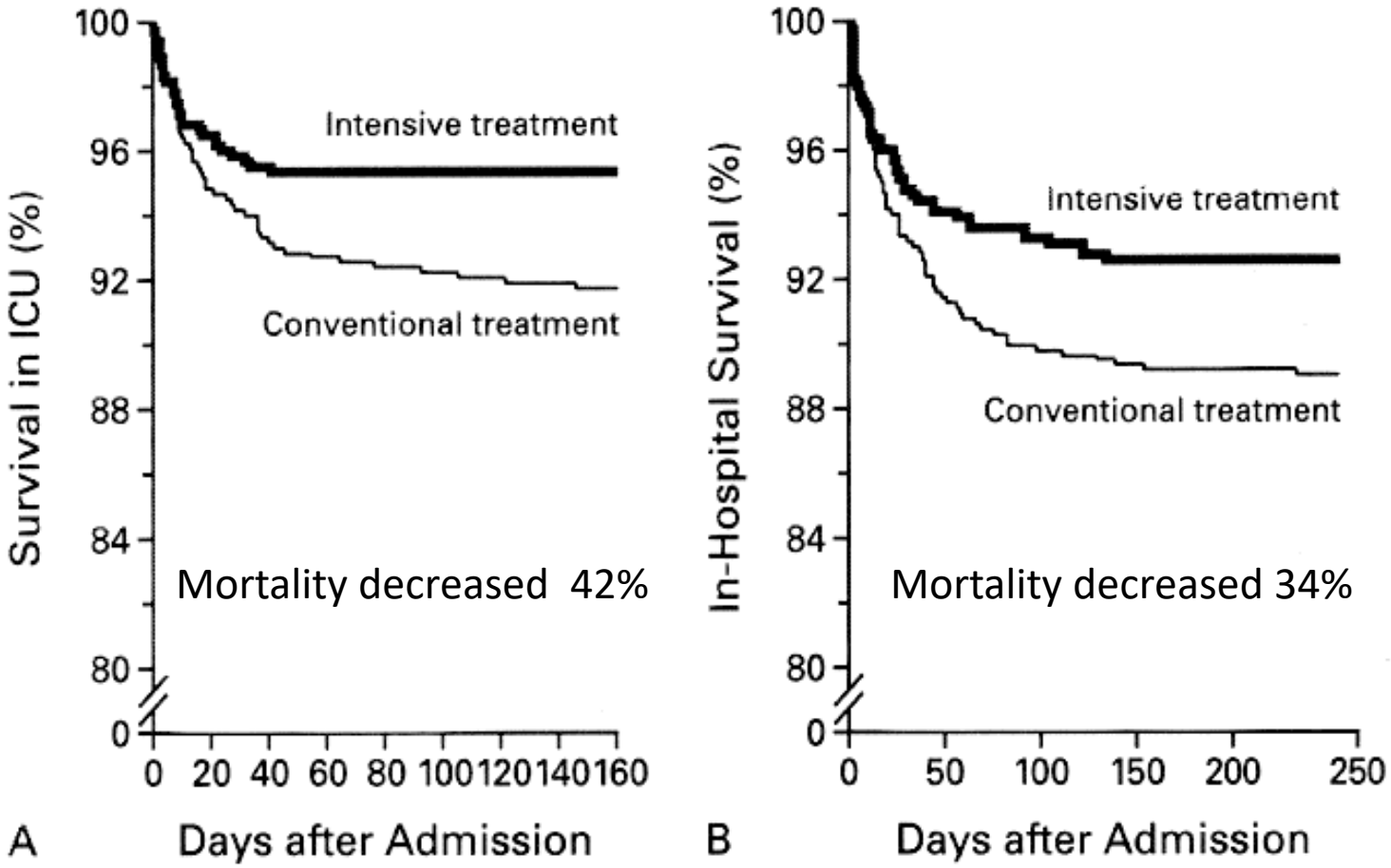


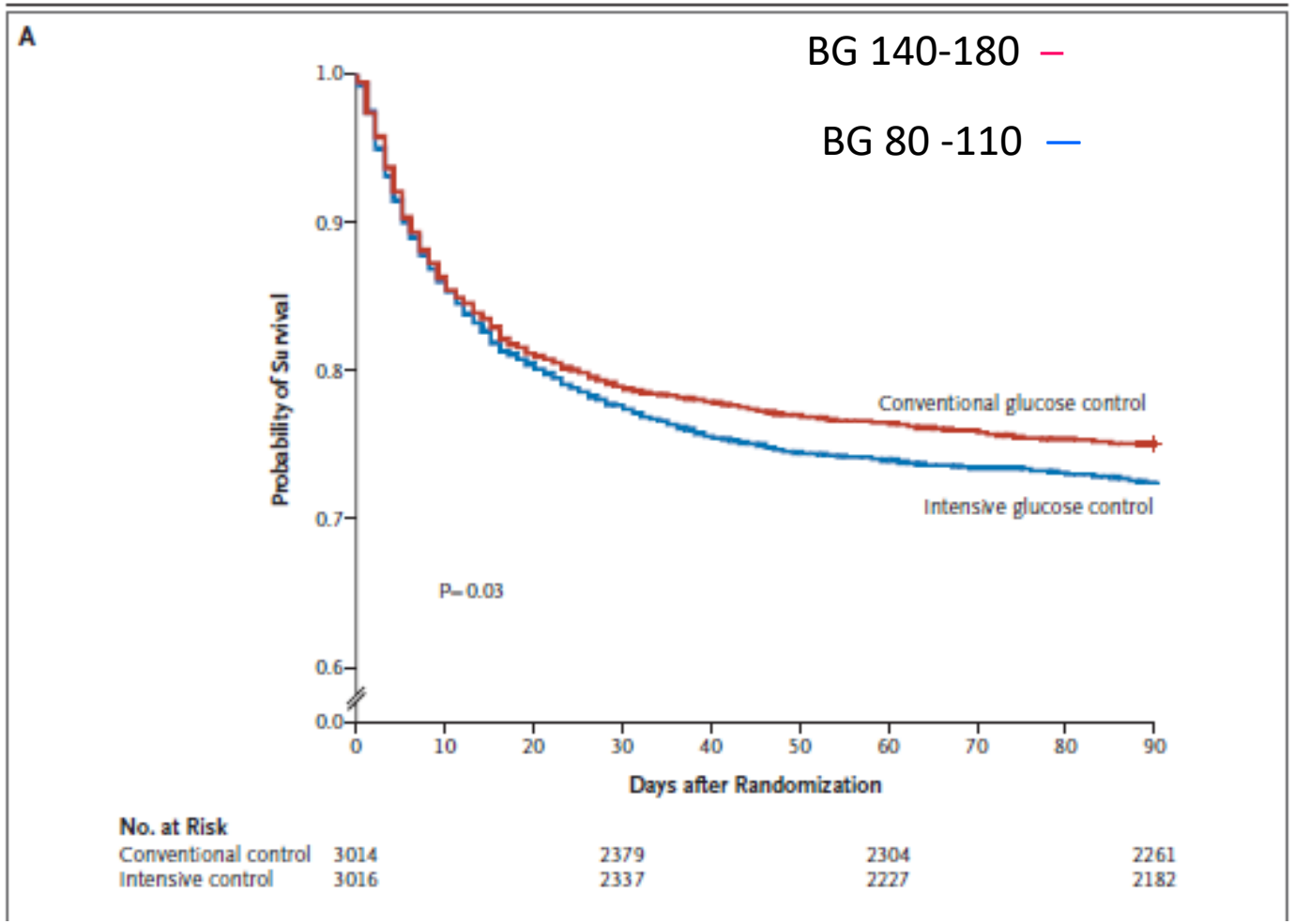
Kosiborod et al Circulation 117:1018-1027, 2008

Insulin Infusion to Maintain Euglycemia (80-110mg/dl) Reduces SICU Mortality



Van den Berghe et al, NEJM 345:1359,2001

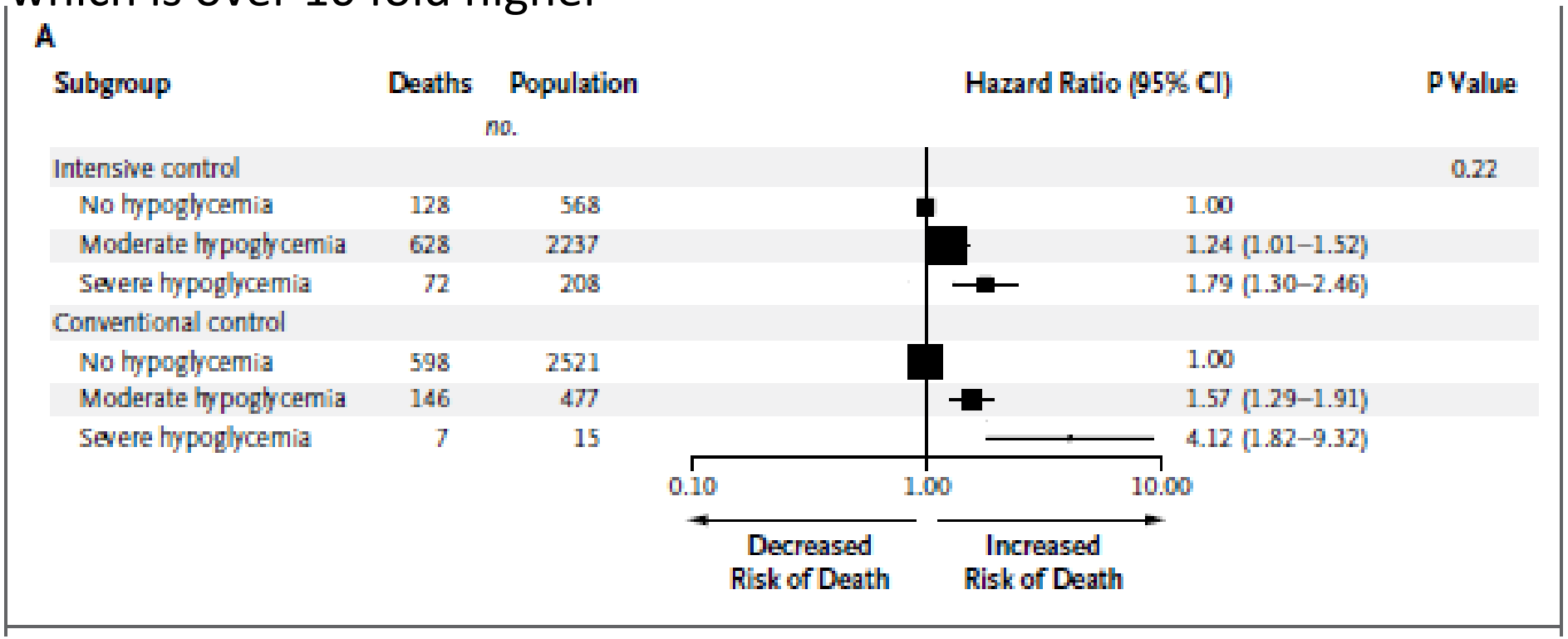
NICE-SUGAR Data: International study of SICU and MICU Patients



NEJM 360:1283, 2009

Mortality and hypoglycemia in NICE-SUGAR

Hypoglycemia occurred in 6.8% in intensive vs 0.5% in conventional which is over 10 fold higher



NEJM 367:1108, 2012

AACE/ADA recommended target glucose levels in the ICU

- IV insulin infusion is the preferred therapy for glucose management
- Starting threshold of no higher than 180 mg/dL for iv insulin infusion
- Once IV insulin is started, the glucose levels should be maintained between 140 and 180 mg/dL
- Lower glucose targets (110-140 mg/dL) may be appropriate in selected patients (cardiac surgery)
- Targets <110 mg/dL or >180 mg/dL are not recommended

Not recommended <110	Acceptable 110-140	Recommended 140-180	Not recommended >180

Moghissi ES, et al; AACE/ADA Inpatient Glycemic Control Consensus Panel. Endocr Pract. 2009;15(4).

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Measuring Glucose in the ICU: How to Do It?

- Plasma glucose measured on a lab analyzer is the gold standard
- Due to turn-around time and required blood volume this isn't practical if rapid results and multiple tests are needed for management
- POC testing offers
  - Convenience as done at the bedside
  - Low required blood volume
  - Immediate actionable results
- But is it accurate?

POC testing and Accuracy

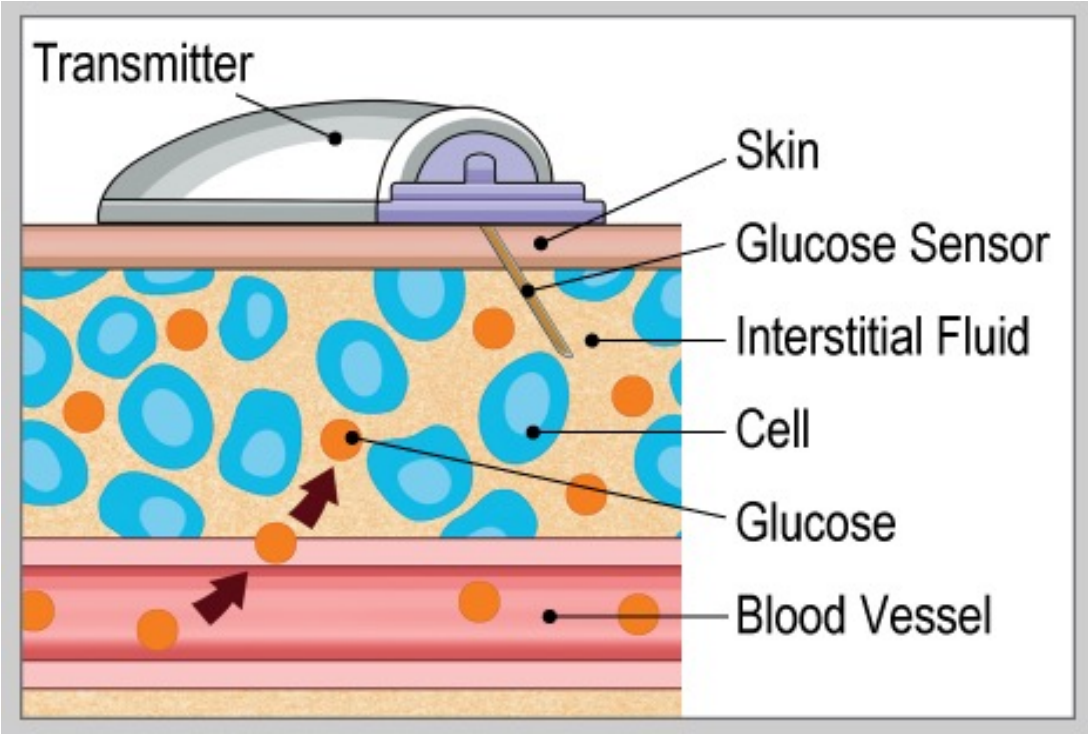
- Required accuracy for Hospital: 95% of values within 12% of reference
  - This standard allows for some hypoglycemia to be undetected by POC
  - Median absolute relative difference(MARD) of POC to reference is 9%
- Sources of variability
  - Arterial vs venous vs capillary source
  - Hematocrit <20% or >55% will result in overestimation or underestimation
  - Medications
    - Acetaminophen
    - Ascorbic acid
  - Poor peripheral perfusion(even Reynaud's)
  - Very low O2 saturation gives falsely higher glucose

J Diabetes Sci Technol. 2018 Nov; 12(6): 1095–1100.

What About Continuous Glucose Monitoring?

- Allows for glucose measurements without obtaining blood sample
- Sensor calculates glucose every 5 minutes and transmits to receiver
- Intravascular catheter may be more accurate than interstitial
- Thrombus can form on intravascular catheter

Cutaneous CGM



J Diab Sci and Tech 2020 14:822-832

CGM Trials in the ICU

- Accuracy data does not yet meet FDA requirements
  - MARD for interstitial catheter in the ICU is 14%-20% and intravascular is 6.5%
- Outcomes comparable to POC testing but not better
- Additional training of nursing staff is needed to implement use
- Select patient groups may benefit (no pressors, no acidosis, good perfusion)
- 74% fewer fingersticks
- Endocrine Society Clinical Guideline 2022 suggests using CGM in non-critical hospitalized patients so use is expanding

J Diabetes Sci Technol. 2019 Jul; 13(4): 682–690

J Diabetes Sci Tech 2020 14:822-832

JCEM 2022 107:2101-2128

Time to Think

- A 60 year old male with a history of metformin controlled type 2 diabetes(A1C 6.8) undergoes a 3 vessel CABG. On transfer to the ICU POC glucose from arterial line is 192 mg/dl.
- You suggest:
  - Repeat in 1 hour
  - Start sliding scale regular insulin sc q 6 hours
  - Start metformin through NG tube
  - Start iv insulin drip

IV Insulin Infusion Protocol: Advantages

- Useful for covering basal requirements
- Maintains glucose in a pre-specified range
- Able to be easily adjusted as patient needs change
- Most protocols are equivalent in results as long as nursing is adequately trained
- Low risk of hypoglycemia with higher goals

IV Insulin Infusion Protocol: Disadvantages

- Technically difficult requiring intensive nursing and hourly glucose values
- Does not address prandial (intermittent feeding)needs of the patient

- Must be transitioned to another form of insulin delivery for long term glucose management
  - Subcutaneous regimens should contain use of basal(long-acting) and bolus(rapid acting) insulins
  - Subcutaneous regimen should have sufficient overlap with iv insulin to prevent rebound hyperglycemia

Example of a “paper” nurse driven protocol

Table 2: ADJUSTMENT FACTOR (MULTIPLICATION) FACTORS					
CURRENT Blood Glucose	CHANGE IN Blood Glucose since the prior reading				
	DEcreased more than 30	DEcreased 11-30	No change +/- 10	INcreased 11-30	INcreased more than 30
70-110	X 0.25	X 0.50	X 0.75	Continue Current Rate	X 1.5
111-150	X 0.50	X 0.75	Continue Current Rate	X 1. 25	X 1. 5
151-180	X 0.75	Continue Current Rate	X 1. 25	X 1.5	X 2.0
181-210	Continue Current Rate		X 1.5		X 2.0
Above 210	Continue Current Rate	X 1.5		X 2.0	

COVID-19 and Glycemia: New Challenges

- Patients with diabetes/ hyperglycemia have worse prognosis after contracting COVID-19
- Frequent glucose monitoring increases exposure of nursing staff and uses more PPE
- Patients are often treated with
  - Steroids raising glucose
  - Continuous enteral feedings raising glucose
- High levels of inflammation in COVID-19 lead to insulin resistance

Journal of Diabetes Science and Technology 2020, Vol. 14(4) 813–821

Diabetes Care 2020;43:e81–e82

Considerations for management in COVID-19

- Use CGM with remote monitoring and iv insulin with insulin outside the room
  - FDA approved emergency use of CGM in ICU in COVID-19 patients in April 2020
  - Significant reduction in need to enter patient room
- Reduce fingersticks to q 6 hours and manage with sc insulin
  - Doesn’t require special training or expensive equipment
  - Insulin absorption may be unpredictable in patients on pressors

SAGE Open Med. 2020; 8: 2050312120974174

Suggested References

- **Thyroid function in critically ill patients**
  - Prof Eric Fliers, MD, Prof Antonio C Bianco, MD, Lies Langouche, PhD, and Prof Anita Boelen, Phd
    Lancet Diabetes Endocrinol 2015 Oct 3(10) 816-825
- **Glucose management in critically ill adults and children**
  - *Dieter Mesotten*, Jean-Charles Preiser, Mikhail Kosiborod*
    Lancet Diabetes Endocrinol 2015; 3: 723–33
- **New insights into the controversy of adrenal function during critical illness**
  - *Eva Boonen, Stefan R Bornstein, Greet Van den Berghe*
    Lancet Diabetes Endocrinol 2015 3:805-815

- **Diabetes Technology in the Inpatient Setting for Management of Hyperglycemia**
  - Georgia Davis, R Galindo, A Migday, G Umpierrez
    Endocrine and Metabolic Clinics of North America 49:79-93, 2020
- **Critical illness and adrenal insufficiency**
  - G Van den Berghe
    JCEndocrinol Metab. 2022 Jun 16;107(7):2057-2064
- **Update on Non-Thyroidal Illness Syndrome**
  E Fliers and A Boelen
  J of Clinical Invest 2021; 44(8): 1597–1607.

Board Review Question

73 yr old male with a large MI complicated by CHF has been in the ICU for a week, intermittently requiring vasopressor infusion. He was started on continuous enteral tube feedings in the past 48 hours. He again becomes acutely hypotensive with BP 85/60, P 120, O2 sat 90% on 2 l nasal cannula and T of 99 F.

Labs drawn at this time include:

Na 138 meq/L K 4.2 meq/L Cl 100 meq/L CO2 20 meq/L BUN 70 mg/dl Creatinine 2.2 mg/dl

Glu 210 mg/dl

WBC 15,000 /micro liter D-Dimer 1104 ng/ml(nl to 250)

Random cortisol 21 mcg/dl

Thyroid tests done prior day because of weight loss:

TSH 2.0 mU/L (nl .5-5)

Free T4 1.0 ng/dL (nl .8-1.7)

Total T3 60 ng/dL (nl 80-200)

Board Review Question

- Which of the following would you initiate?
  1. Start liothyronine(T3) at 10 mcg bid per ng tube
  2. Order ACTH stim test to evaluate for adrenal insufficiency
  3. Initiate iv insulin drip
  4. Start hydrocortisone 200 mg iv/24 hours

Board Review Question

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Board Review Question

- Which of the following would you initiate?
  1. Start liothyronine(T3) at 10 mcg bid per ng tube
     1. Thyroid function tests are most consistent with NTIS. Replacement of T3 is not recommended in this setting.
  2. Order ACTH stim test to evaluate for adrenal insufficiency
     1. Baseline cortisol level essentially rules out adrenal insufficiency so further testing is not indicated
  3. ***Initiate iv insulin drip***
     1. ***This is recommended given elevated glucose in critically ill patient even if there is no history of diabetes***
  4. Start hydrocortisone 200 mg iv/24 hours
     1. Initial management of hypotension in this setting would be vasopressor therapy and search for causes.

End of Presentation