



# Alzheimer's Disease

Abhinav Rajpal MD, MPH

# Age of Onset

- Typical – after 65 years of age – most cases
- Early-onset – before the age of 65 – approximately 5%
- Inherited Alzheimer's disease < 1%

# Patient Presentation

- Memory impairment – most common
  - Early Alzheimer's disease
    - Changes in learning / forming new memories – remembering names of new people, forgetting material that was just read, losing or misplacing valuable objects.
    - Changes in executive functions – capacity to plan ahead, follow multiple step directions, decreased organization and ability to multitask.

# Patient Presentation

- Moderate stage Alzheimer's disease
  - Attention / calculations – difficulty managing money, working with numbers, difficulty recalling phone numbers / addresses.
  - Language – difficulty coming up with right words / names (can also be seen in early)
  - Difficulty with visuospatial – buttoning shirts, putting together furniture, making bed.
  - Judgement – difficulty choosing the right clothing for the season
  - Behavioral disturbances – agitation, aggression, wandering, hallucinations.

# Patient Presentation

- Severe stage
  - Difficulty with orientation – unaware of their surroundings, current year or their name.
  - Motor symptoms – difficulty walking, sitting, eating

# Diagnosis

- National Institute of Aging and Alzheimer's Association (NIA-AA) criteria for probable Alzheimer's Disease
  - Presence of dementia plus:
    - Interference with ability to function at work or at usual activities
    - Not explained by delirium or major psychiatric disorder
    - Cognitive impairment established by history taking from the patient AND a knowledgeable informant

# Diagnosis

- Cognitive impairment involving at least 2 of the following
  - Decreased ability to remember new information
  - Impaired reasoning and handling of complex tasks, poor judgement
  - Impaired visuospatial abilities
  - Impaired language function
  - Changes in personality, behavior, or comportment

# Diagnosis

- Other core clinical criteria
  - Insidious onset
  - Clear-cut history
  - Amnesia



# Tools

- Tools such as Montreal Cognitive Assessment (MoCA), Mini-mental status exam can be helpful as guides, however, the diagnosis remains clinical.

# Treatment

Patients with Alzheimer's disease have decreased cerebral content of acetylcholine (Ach)

- Cholinesterase inhibitors – donepezil, rivastigmine, and galantamine are used.
  - Used for mild, moderate, and severe dementia.
- Help increase Ach in synaptic cleft – modest symptomatic relief.
- Memantine – NMDA receptor antagonist
  - Used for moderate and severe dementia.

# References

- 1. Alzheimer's Association. (2023, October). *Stages of Alzheimer's*. Retrieved from [www.alz.org: https://www.alz.org/alzheimers-dementia/stages](https://www.alz.org/alzheimers-dementia/stages)
- 2. Johns Hopkins Medicine. (2023, October). *Stages of Alzheimer's Disease*. Retrieved from [hopkinsmedicine.org: https://www.hopkinsmedicine.org/health/conditions-and-diseases/alzheimers-disease/stages-of-alzheimer-disease](https://www.hopkinsmedicine.org/health/conditions-and-diseases/alzheimers-disease/stages-of-alzheimer-disease)
- 3. Press, D., & Buss, S. S. (2021, September 30). Treatment of Alzheimer disease. (S. T. DeKosky, & K. E. Schmader, Eds.) Retrieved October 2023, from UpToDate: [https://www.uptodate.com/contents/treatment-of-alzheimer-disease?search=treatment%20of%20alzheimer%20disease&source=search\\_result&selectedTitle=1~150&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/treatment-of-alzheimer-disease?search=treatment%20of%20alzheimer%20disease&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1)
- 4. Wolk, D. A., & Dickerson, B. C. (2021, October 8). *Clinical features and diagnosis of Alzheimer disease*. (S. T. DeKosky, Editor) Retrieved October 2023, from UpToDate: [https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-alzheimer-disease?search=clinical%20featureess%20and%20diagnosis%20of%20alzheimer%20&source=search\\_result&selectedTitle=1~150&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-alzheimer-disease?search=clinical%20featureess%20and%20diagnosis%20of%20alzheimer%20&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1)



# Alzheimer's Dementia Updates

Natalie Kayani, M.D.

Summa Geriatric Medicine

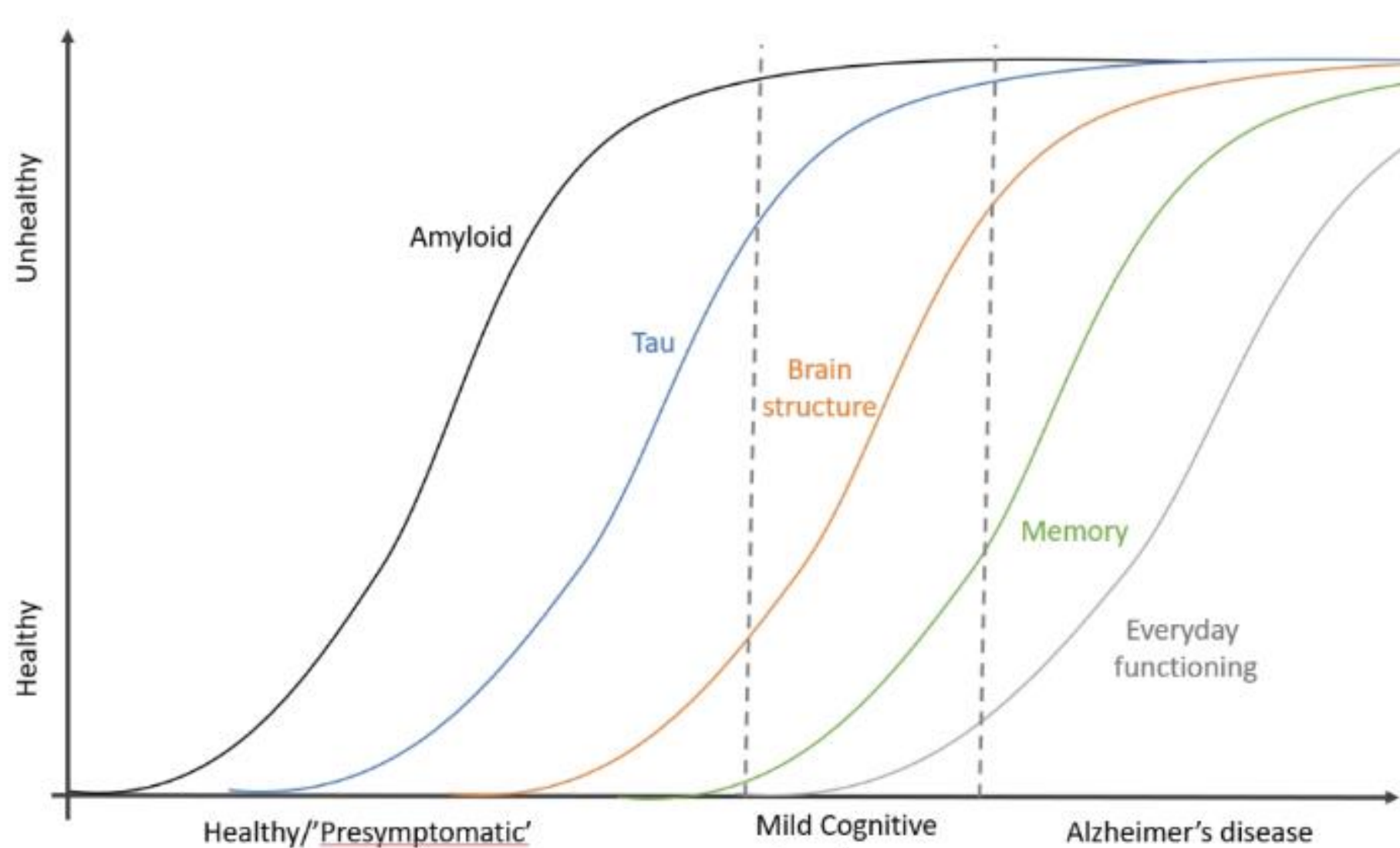
10.13.2023



# Agenda

1. Direct to consumer blood tests
2. Newest medications
3. Updated criteria controversy

# Theoretical progression of Alzheimers

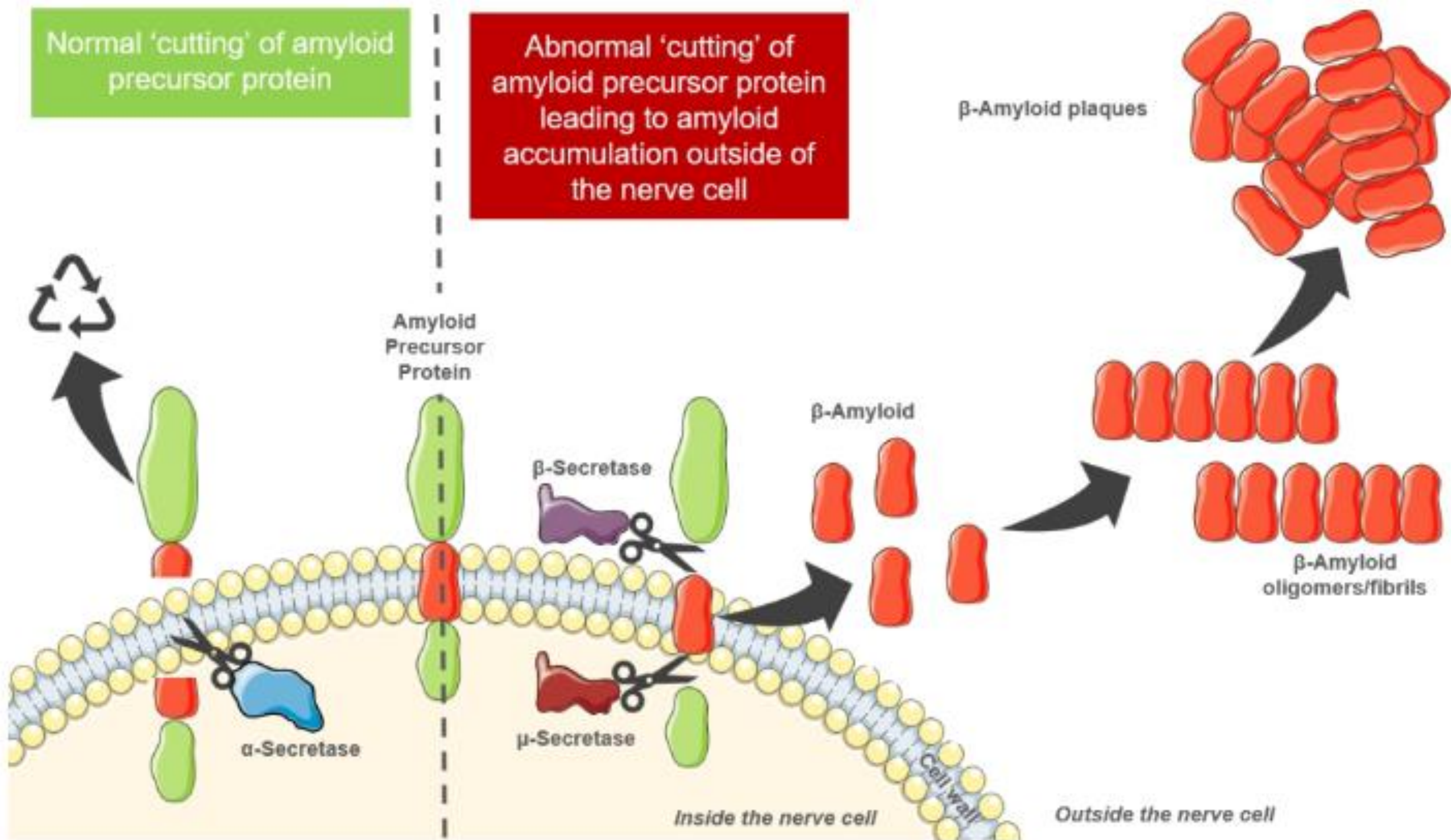




# Direct to consumer blood tests for Alzheimer's Dementia

Normal 'cutting' of amyloid precursor protein

Abnormal 'cutting' of amyloid precursor protein leading to amyloid accumulation outside of the nerve cell





# Alzheimer's Blood Test

- Measures the ratio amyloid-beta 42/amyloid-beta 40
  - Lower ratio= higher likelihood of amyloid plaques
  - Several companies have developed this test
  - None are FDA approved



## Alzheimer's blood test

- Quest Labs marketing direct to consumer test
  - AD-Detect Test \$399
  - No published data on how it was validated
  - Not FDA approved
  - poster at 2022 AAIC- sensitivity 0.89/ specificity 0.71
  - Only 43% of positive results would be true positives

## AD-Detect Test for Alzheimer's Disease Risk

Exclusively available at Quest. This screening test provides an amyloid ratio, which is a risk factor of Alzheimer's disease. This ratio is based on two biomarkers that have been reported as helping to detect early signs associated with the risk of developing Alzheimer's disease. This can potentially help you and your doctor design interventions and a management plan that is most beneficial to you. [Read more](#)

**Sample type:** Blood

**Preparation:** You do not need to do anything special to prepare for the sample collection. [More details](#)

**Test type:** In Person

[Find Patient Service Centers](#)

**\$299.00** ~~\$399.00~~

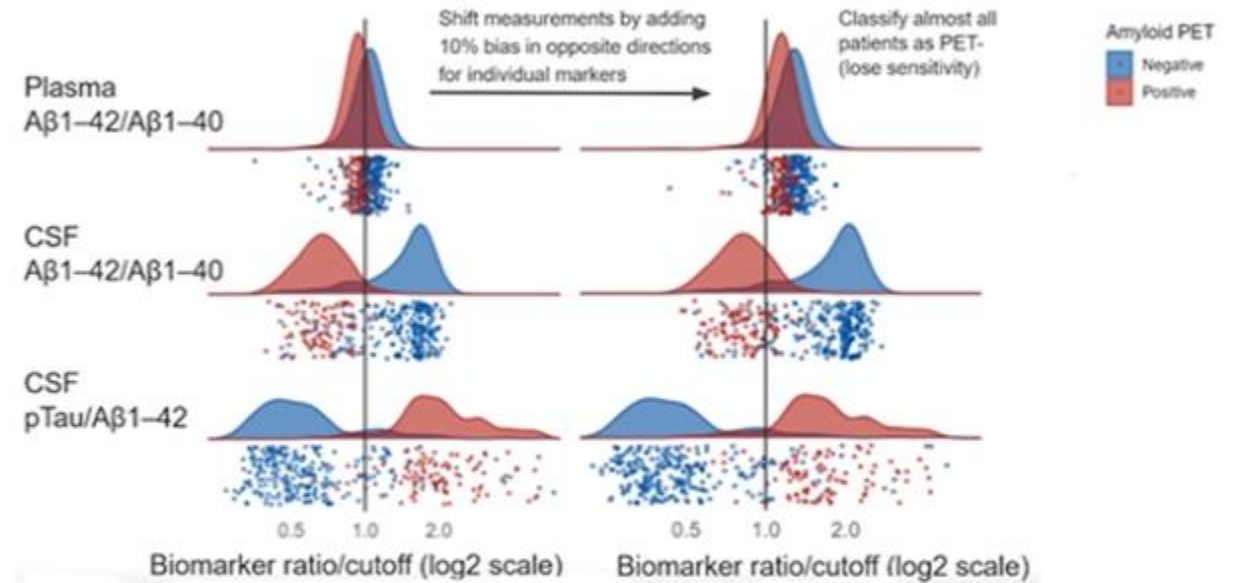
+ \$13.00 Physician Service Fee

**Add to Cart**

# Alzheimer's blood test

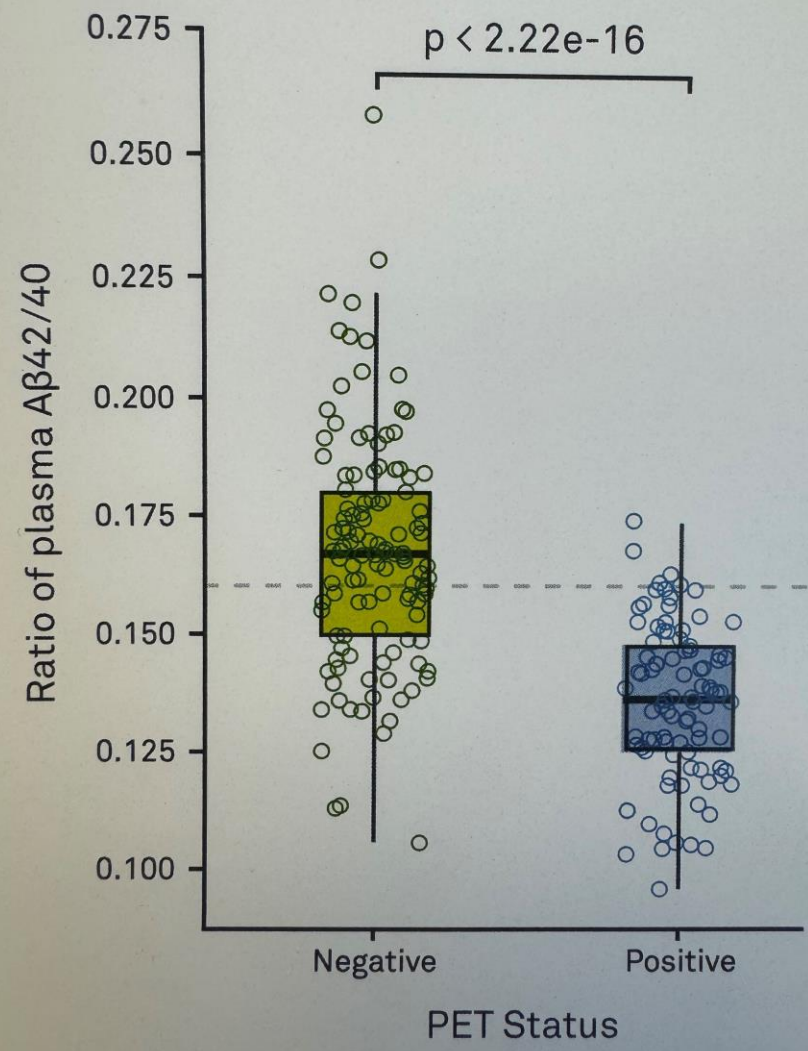
- A beta 42/A beta 40- in plasma vs. CSF

- considerable overlap between the “positives” and “negatives”
- slight batch-to-batch changes in reagents that might creep in over time can skew the results



**Darned Drift.** With plasma  $A\beta 42/40$  measurement, any slight variation due to assay bias or sample handling could misclassify people whose result lies near the cutoff (top line). For CSF  $A\beta 42/40$  and p-tau ratios, variability has less dramatic effects because the fold change between positivity and negativity is larger. (Amyloid PET positive: blue; negative: red). [Courtesy of Christina Rabe.]

# QUEST AD-Detect Amyloid Beta 42/40 vs amyloid-PET status<sup>1,2</sup>



## Alzheimer's blood test- conclusion

Not ready for prime time

# New medications

# Medication options

- Cholinesterase inhibitors
  - Donepezil (Aricept)
  - Rivastigmine (Exelon)
  - Galantamine (Razadyne)
- NMDA receptor antagonist
  - Memantine (Namenda)
- Anti- amyloid monoclonal antibodies
  - Solanezumab- trials around 2013- did not improve clinical outcomes
  - Aducanumab (Aduhelm)- studies terminated due to failure to show benefit 2019- resurrected 2021
  - Lecanemab (Leqembi)- FDA approved 2023
  - Donanemab (also targets tau)- close to approval

# Lecanemab (Leqembi)

- Requires a diagnosis of MCI or early Alzheimers
  - Amyloid evidence- PET scan or CSF
  - Baseline MRI
  - ApoE4 genetic testing (homozygous 50% increase bleeding risk)
  - IV infusion every 2 weeks (each 1 hour)
  - Repeat MRI's prior to 5<sup>th</sup>, 7<sup>th</sup> & 14<sup>th</sup> infusions
  - Only exclusion on package insert- hypersensitivity to drug
- Study excluded following patients:
  - Any neurologic condition that could contribute to cognitive impairment
  - Any psychiatric diagnosis (including depression)
  - Contraindications to MRI
  - Significant pathologic changes on MRI
  - Any immunological disease that requires treatment
  - Bleeding disorder not under adequate control
  - Elevated TSH, low B12 or any other clinically significant abnormalities in exam, vitals or labs
  - Subjects with malignant neoplasms within 3 years
  - Suicidal ideation
  - Planned surgery needing general anesthesia
  - Severe visual or hearing impairment



## Lecanemab (Leqembi) trial outcomes

- 1795 people with MCI or early AD
- Plus amyloid on PET scan or CSF testing
- 10 mg lecanemab IV Q2 wks vs placebo
- Outcomes at 18 months
- Reduced cognitive decline by 27%
- Absolute difference of 0.45 points (1.66 points for placebo vs 1.21 for lecanemab) on Clinical Dementia Rating-Sum of Boxes (18 point scale) – see next slide
- Adverse event- ARIA (amyloid-related imaging abnormalities)
- Hemorrhage or edema
- Asymptomatic ARIA in 21% of lecanemab patients
- Symptomatic ARIA in 3%

**Table 3. Sum of Boxes Staging Category**

CDR Sum of Boxes Range	Staging Category
0	Normal
0.5-4.0	Questionable cognitive impairment
0.5-2.5	Questionable impairment
3.0-4.0	Very mild dementia
4.5-9.0	Mild dementia
9.5-15.5	Moderate dementia
16.0-18.0	Severe dementia

## FDA approved

- Accelerated Approval pathway

- FDA may approve drugs for serious conditions
- where there is an unmet medical need
- drug is shown to have an effect on a surrogate endpoint
- reasonably likely to predict a clinical benefit to patients

## Anti-amyloid therapies

The jury is still out

## 2023 Revision of NIA-AA Criteria for the diagnosis of Alzheimer's

# Controversy

# Revised clinical criteria for Alzheimer's

- 2018 National Institute on Aging-Alzheimer's Association (NIA-AA)- original criteria
  - Separated criteria for research framework vs clinical care
  - 2023 guidelines will expand the research framework to also cover clinical care
- American Geriatrics Society (AGS) feels guidelines are premature

# American Geriatrics Society response

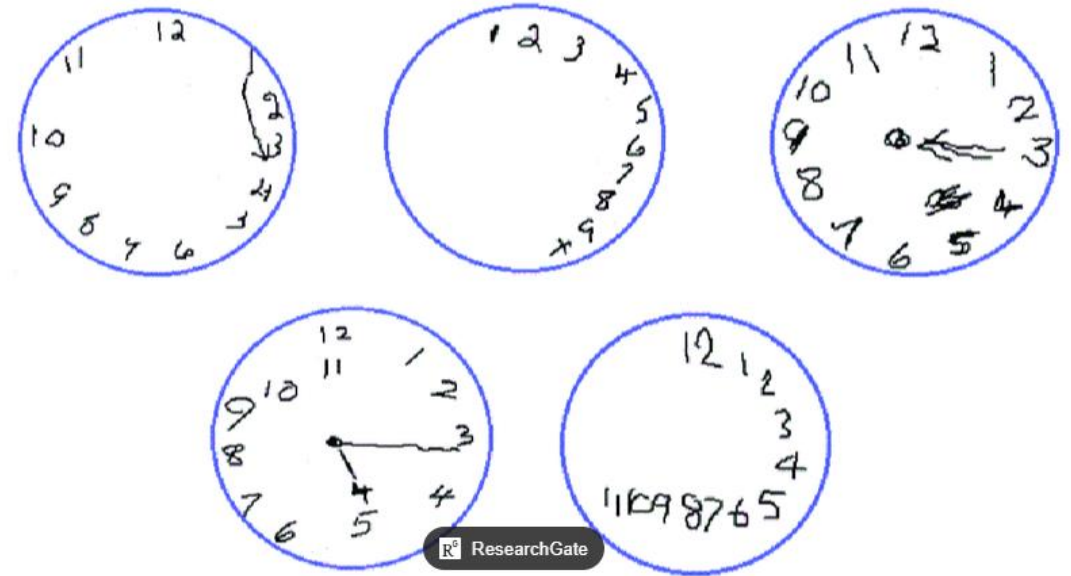
- No evidence that biomarker positivity in cognitively normal person should lead to clinical intervention
- No evidence that removing amyloid helps a cognitively normal person who is biomarker positive
- Concerns about heavy influence from industry on the committee writing the guidelines
- Disregard of important distinctions across fields of clinical practice
- NIA not involved in the update
- Concern about the use of a biomarker diagnosis- will assign an Alzheimer's diagnosis to biomarker positive individuals with normal cognition

Next draft of the criteria set to be posted “late September” or “early October”



# Screening

- Start screening early
  - Routine yearly assessments regardless of cognitive complaints
- Important to identify patient's early
  - To prevent negative consequences (by increasing supervision/ put in safeguards)
  - To plan for future
- Refer to Summa Senior Health Center if concerns

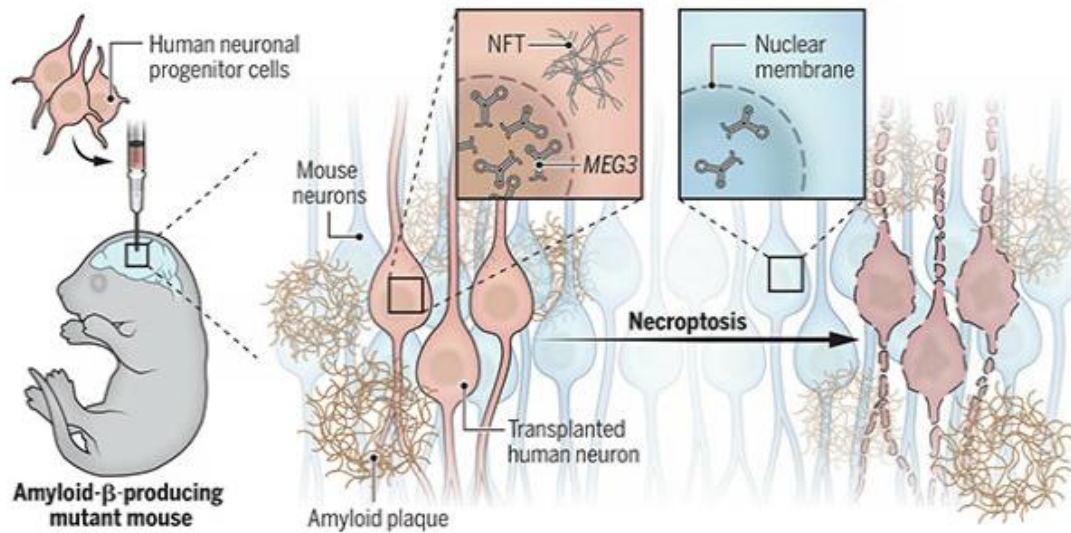


# Thank you!

# Potential Alzheimer's treatment targets

- Anti-amyloid
  - Monoclonal antibodies
    - May prevent beta-amyloid from clumping into plaques
    - May also removed plaques already formed
  - Production blockers
    - Block the activity of the beta and gamma secretase
- Anti-tau
  - Tau aggregation inhibitors
  - Tau vaccines
- Anti-inflammation
  - Sargramostim (Leukine)
- Insulin resistance research
  - Nasal insulin was NOT effective

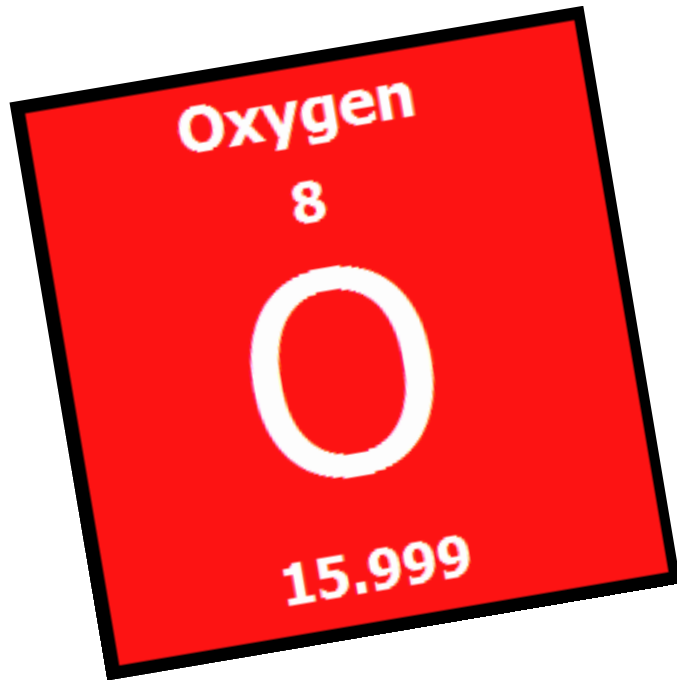
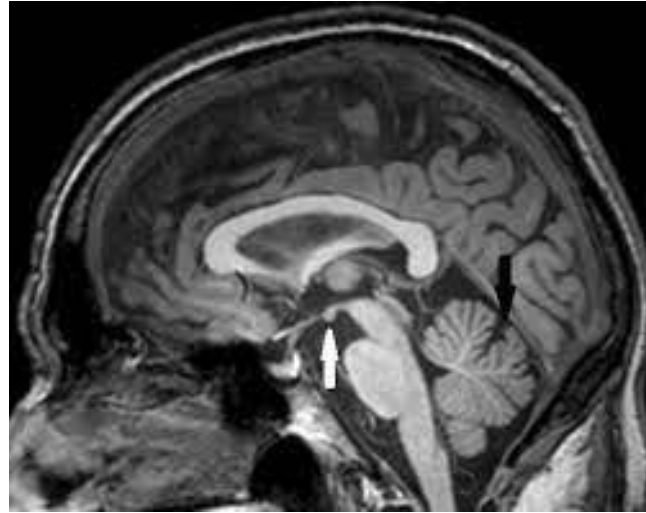
## Ongoing research



**Death by Amyloid.** Human neural progenitor cells transplanted into a mouse model of amyloidosis ultimately develop tau pathology and succumb to necroptosis, while their murine neighbors survive. [Courtesy of Sirkis and Yokoyama, *Science Perspectives*, 2023.]

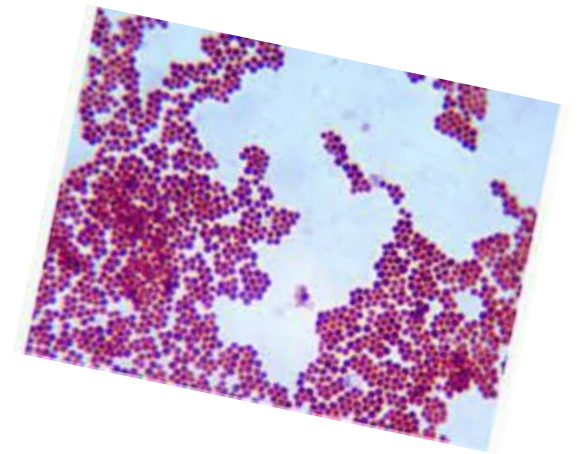
- **When Faced with Amyloidosis, Human Transplants Die by Necroptosis; Science 9/15/23**
- **Astrocyte Receptor Suppresses Neurotoxic Lipids, Preserves Neurons; Nature Metabolism 9/7/23**
- **Sit Less, Move More to Induce Irisin and Stave Off Dementia; JAMA 9/12/23**
- **CSF Proteomic Panel Better Predicts Decline Than Do Classic AD Biomarkers; Science Translational Medicine 9/6/23**

# Thank you



# Chief Complaint: Altered

Randall McComb, MD, MSc  
SUMMA Emergency Medicine PGY-2



## Objectives

Definition of  
encephalopathy

Where do these  
patients come  
from

Differential

Work up in the  
ED

Resources  
Available





# Encephalopathy

- Any disease process that causes a change in mental state or functioning of a patient<sup>1</sup>
  - Acidosis
  - Endocrine, Electrolytes
  - Infections
  - Oh... drugs
  - Uremia
  - Trauma
  - Ischemia
  - Pressures
  - Seizures



## Patient Population

- 67 yo F w/ PMH of currently diagnosed UTI on Keflex....
- Dementia, Alzheimer's, autism spectrum patients, Trached and peds
- Demographics anecdotally: LTACs nursing homes



<https://www.healthline.com/health/tracheostomy>



<https://www.harpethpediatrics.com/>



- AEIOU TIPS
- Favorite topic to teach medical students
- Interpreter → Manager

# The workup: Acidosis

## COPD

- COPD: BMP CBC VBG CXR  
Respiratory Panel duonebs  
steroids +/- Abx +/- BiPAP



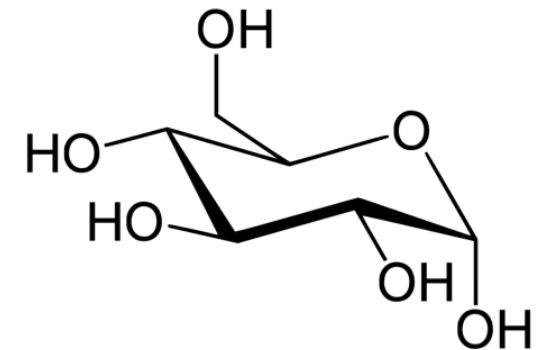
<https://medicalxpress.com/news/2012-11-patient-centric-solution-chronic-respiratory-insufficiency.html>

## DKA

- DKA: BMP CBC VBG BHB UA +,  
CXR 2L LR Insulin gtt



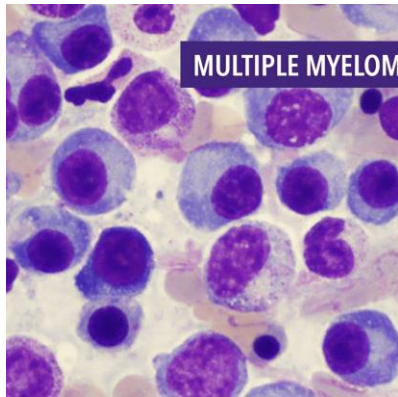
<https://www.teepublic.com/poster-and-art/2729753-glucose-c6h12o6>



# The Workup: Electrolytes and Endocrine

## HYPO-HYPER EVERYTHING

- CMP- all things electrolyte
- Urine Na, Urine Osm, Plasma Osm, NPO
- Replacing electrolytes
- Hypercalcemia- fluids, calcitonin, bisphosphonates



• <https://news.cancerconnect.com/multiple-myeloma/supportive-care-for-multiple-myeloma>

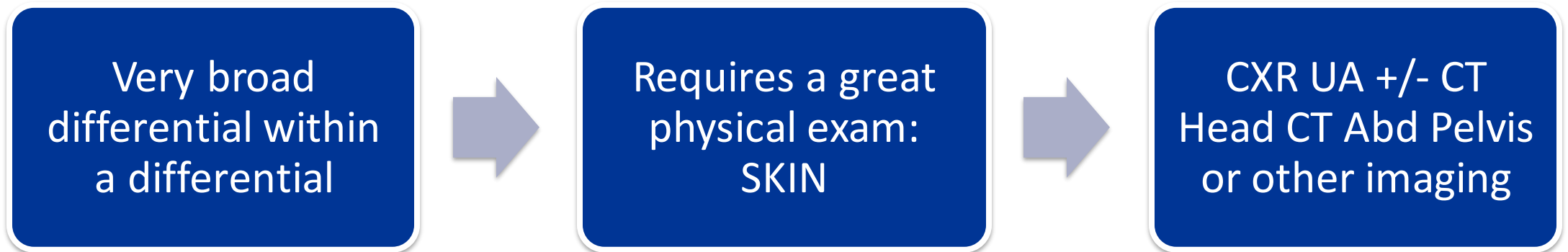
## THYROID AND LIVER

- TSH and Free t4
  - PTU, Propranolol, Steroids
- Ammonia- hepatic encephalopathy




<https://www.theliverinstitute.com/news-blog/2022/may/the-most-common-liver-diseases/>

## The Workup: Infection



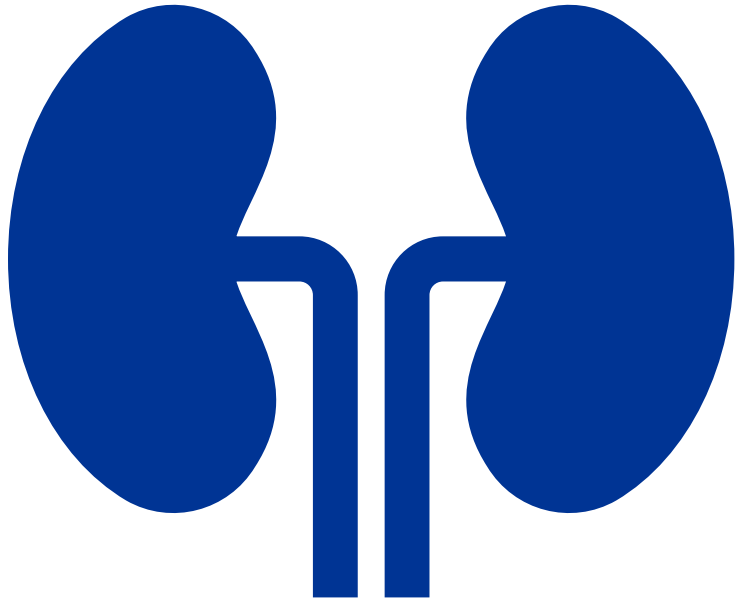




# THE WORKUP: OPIATES AND OTHER DRUGS

- DOES NARCAN EVER HURT...
- BEDSIDE NURSING SAYS IT DOES
- DIFFERENTIAL INCLUDES OTHER THINGS BESIDES FENTANYL
- WORKUP
  - UDS
  - TYLENOL AND ASA LEVEL
  - SERUM OSM
  - URINE OSM
- AMS ISNT JUST DEPRESSED MENTAL STATE... THEY CAN BE PSYCHOTIC
  - HALDOL 5MG AND MIDAZOLAM 2MG IM
  - KETAMINE IM

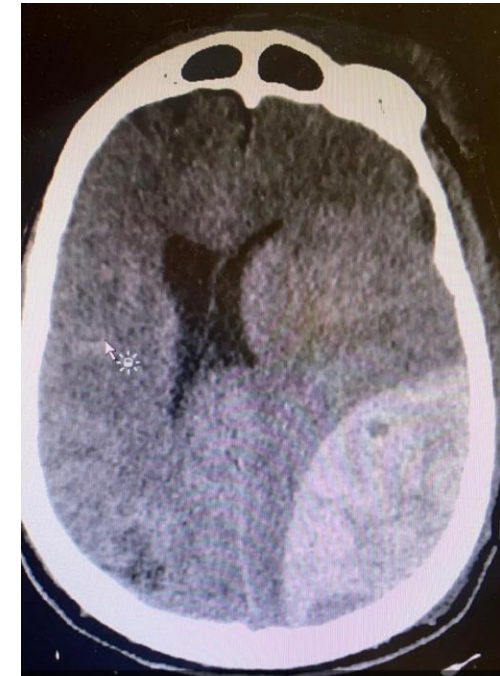
# The Workup: Uremia



- Urea is a waste product and also helps concentrate solutes in the nephron
- High levels of urea can cause encephalopathy
- The problem is only in a select population would our department be okay with just stopping at a BMP
- The workup: Thorough physical exam, vitals, BMP CBC CT H and other lab work depending on context
- Treatment: Dialysis, RRT

# Trauma

- This patient population comes in as a fall on thinner most often
- Workup: CT head + CT max + other imaging
- Fall on thinner w/ brain bleed consider reversal agents
  - 4 factor PCC, FFP, Vit K
  - Protamine sulfate
  - DDVAP
  - Andexa





# Ischemia

- Strokes can cause AMS
  - The first point on the NIHSS is level of consciousness
- ACS causing decreased perfusion to brain = AMS
- Orders: CT H CTA head and neck CT perfusion ECHO BP control ekg

# Pressures

- Hypertensive Encephalopathy
  - Any form of HTN with end organ damage
  - Blood pressure control
- Hypotension or Shock
  - Sepsis and all the problems that come with that can produce AMS



- The differential is broad...
- Often these are unwitnessed and now we are seeing the post-ictal
- Orders: poc glu up front, Midazolam or Lorazepam
- Orders really depend on the history, first time seizure in adult = Head CT
- Reproductive age? Hcg
- Tox workup, CMP, CBC, infectious workup
- Review home meds! Sz lowering threshold meds?

# Seizures



# Summary of Workup

- Point of care glu now
- Concern for stroke, trauma, ACS?
- Blood work
- Tox
- Imaging

## Resources...

- Chart Review on Epic
- Need some collateral history
- We rely on nursing staff
- Consultants
- MAT Program



## Works Cited

- 1. <https://www.healthdirect.gov.au/encephalopathy>



