TESTING IN THE ELDERLY

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INTRODUCTION

- ✓Laboratory data can play a significant role in care of older adults
- ✓Even more so in patients with dementia or altered mental status, where ability to obtain history may be limited.

INTRODUCTION

- Evaluation of lab data in elderly is complicated by :
  - Lack of elderly in sampled to determine "reference ranges",
  - Misconceptions of meaning lab reference ranges,
  - Normal physiologic changes influence tests results,
  - Difficulty distinguishing normal changes from pathologic changes,
  - Presence of chronic conditions
  - Use of medications

INTRODUCTION

- Even in younger, clinicians struggle to determine whether a lab test indicates patient is "normal."
- Interpreting abnormal result depending on factors:
  - ✓ Sex
  - ✓ Age
  - ✓ Ethnicity
  - ✓ Intended purpose of test:
    - screen for general health,
    - diagnose particular disease,
    - manage disease,
    - follow up on a past result,
    - determine risk for developing a disease in future

REFERENCE INTERVAL

- Starting from 1960s to 1970s,lab shifted from reporting "normal values" to "reference intervals".
- Due to term "normal" is hard to define clinically.
- In 1970s,international societies began to codify criteria for creating "reference intervals" which in widespread use today.

REFERENCE INTERVAL

- Reference intervals determined by assembling reference population, who are all given test.
- Reference populations:"healthy"subjects,to avoid any confounding effects of ill-health on results.
- People with no chronic diseases, no medications
- Chronic disease, however, is prevalent with aging.

REFERENCE INTERVAL

- In 2008,92% US elderly had one or more chronic diseases
- In 2010,87% US elderly using one or more medications.
- sampling methods exclude majority of olders from determination of reference ranges.
- A study found only 7% of olders free from chronic disease and eligible for reference population.

REFERENCE INTERVAL

- "Healthy" senior reference subjects without disease or medication are so rare, unrepresentative of seniors as a whole.

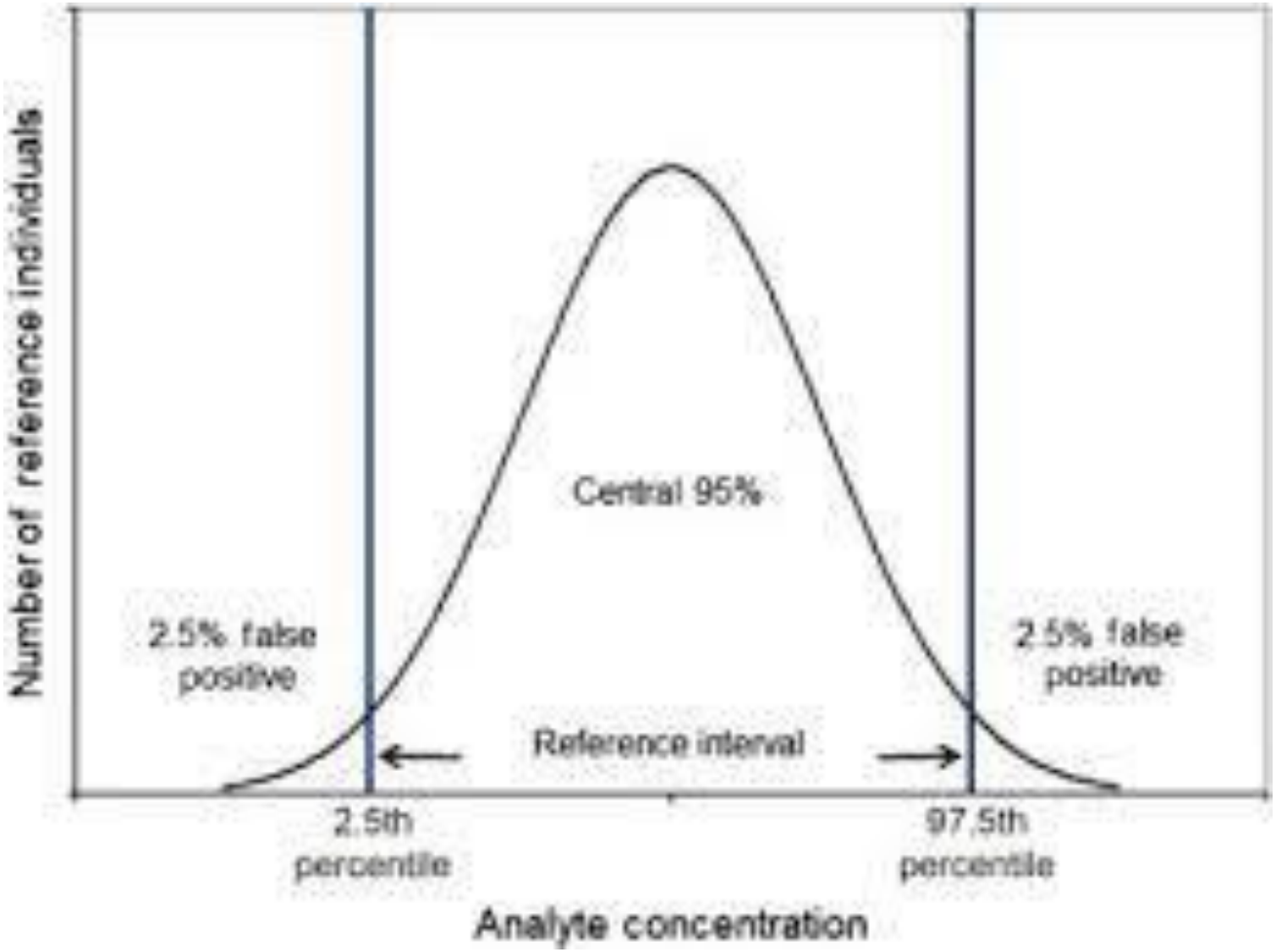
- In practice , most adult reference populations consist of subjects less than 60.

REFERENCE INTERVAL

- Once assemble reference population, range of values of test in sampled population enumerated.

- Reference interval is determined from range of values in which 95% of population falls

- designating bottom 2.5% and upper 2.5% of values as outside reference range.


Number of reference individuals
Central 95%
2.5% false positive
2.5% false positive
Reference interval
2.5th percentile
97.5th percentile
Analyte concentration

REFERENCE INTERVAL

- 5% of all results from "healthy" fall outside of reported reference range , considered abnormal.

- In practice, useful for screening purposes, particularly if a value falls far outside reference range.

- However, values near upper or lower limit hard to interpret as may truly be normal results.

REFERENCE INTERVAL

- This approach is problematic for parameters change with age.
- There is risk for false negatives: missed diagnoses,
- Risk for false positive: inappropriate interventions.
- Surks et al; 2007, TSH rise with age with normal T4.
- 97.5th percentile for TSH rises from 3.56 mIU/L in 20–29 to **7.49 in ≥80.**
- 70% of traditionally considered subclinical hypothyroidism were within a normal range using age specific reference ranges.

REFERENCE INTERVAL

- Goal for treatment hypothyr with levothyroxine is normalization of elevated TSH.

- Elderly have improved longevity with higher TSH and increased harms with higher doses of levothyroxine,

- American Thyroid Association guideline counseled target TSH in olders should raised from 0.4–4.0 mIU/L to **4–6 mIU/L**.

- While TSH may rise, free T4 and T3 remain stable with aging.

CLINICAL DECISION LIMIT

- An alternative approach is test patients with and w/o disease to determine a threshold level for a test

- beyond which probability of specific disease is high enough to do clinical actions.

- These threshold levels is "clinical decision limits."

CLINICAL DECISION LIMIT: D-DIMER

- example is D-dimer for diagnosis VTE.
- Protein fragments by degradation of fibrin in clots
- Rise with: deep vein thrombosis
  - Pulmonary embolism
  - Inflammatory conditions,
  - Malignancy,
  - Liver disease,
  - Trauma
  - And aging

D-DIMER

- Elevated D-dimer are sensitive indicator of VTE but have poor specificity.
- Studies shown using a lower cutoff increases sensitivity at expense of poorer specificity.
- Raising cutoff improves specificity but lowers sensitivity.

D-DIMER

- Because VTE is fatal,clinical decision limit for D-dimer which maximizes sensitivity, and poor specificity, is optimal, minimizing chance of missed diagnoses.

- D-dimer used to“rule out”VTE: when negative and pretest probability of VTE is low.

- Positive tests, require further confirmatory tests, because of poor specificity.

D-DIMER

- Inflammation is common with advancing age,
- Rising prevalence D-dimer ↑ among olders W/O VTE.
- As age rises,D-dimer becomes less useful to R/O VTE.
- In a study, using standard clinical decision limit for D-dimer, excluded P/E in 58% of people ≤40,
- 26% of people 60–69,
- 17% of people 70–79,
- only 5% of people aged ≥80

D-DIMER

- Clinical decision limit for D-dimer for VTE in olders should be adjusted upward, from standard 500 µg/L to

❖**Multiplying age by 10 in aged ≥50**

- Use of age-adjusted D-dimer decision limit increased proportion of people **≥** 75, safely R/O pulmonary embolism.

ESR

- Aging influences other inflammatory markers.
- Women have higher ESR levels than men.

Formula for Age- Related Normals

- Men:

  ESR(mm/hr)= (age in years)/2

- Females

  ESR (mm/hr)= (age in years + 10)/2

CRP

- C-reactive protein levels increase with aging
- Higher in olders with rheumatoid arthritis
- Impacting judgments regarding success of anti-inflammatory treatment.

FERRITIN

- Ferritin levels increase in healthy subjects with increasing age .

- As a result, cutoff ferritin for iron deficiency increased from 25 to **50 ng/mL** in elderly.

THE GLOMERULAR FILTRATION RATE

- GFR ↓, by 1 mL/min per year after age 40;
- No evidence of decline with age in1/3.
- ↓GFR leads to increased serum creatinine.
- ↓Creatinine are proportional to muscle mass .
- Remain stable as renal function declines in olders,
- Unreliable indicator of renal function in elderly.

GFR

- Equations developed to estimate GFR.
- Many laboratories report estimated GFR: "eGFR".
- Most used equation is 4-variable "Modification of Diet in Renal Disease" (MDRD).
- MDRD uses age, race, gender, and creatinine.
- Derived in population with no subjects ≥70
- Not contain variable for weight

GFR

- Some using newer CKD-EPI,“super equation”
- Uses age,race,gender,and cr,not include weight .
- Cockcroft-Gault equation,uses age,weight,gender, and cr,
- more accurate predictor of renal function in olders than MDRD and CKD-EPI.

GFR

- MDRD and CKD-EPI estimate higher in olders than Cockcroft-Gault,
- Leading to increased risk drugs overdosing.
- Cockcroft-Gault uses weight,not reporting eGFR by labs
- Requires direct calculation by practitioner.

ELECTROLYTES

- ↓ GFR is accompanied by ↓ renal tubular function.
- ↓ Ability to compensate for sudden changes in water or electrolyte intake,
- Increased prevalence of ↕ Na in elderly.
- In a non-stress state, no change in baseline Na, K, ch, or cal with aging.

PHOSPHORUS

- Phosphorus decreasing steadily with age,

Age group	women	men
20s	3.7 mg/dL	3.8mg/dL
≥ 84	3.4mg/dL	3.0mg/dL

PHOSPHORUS

- No associated decrease in serum calcium.
- This may related to decline in tubular phosphate reabsorption with aging.
- Lower limit of normal for phosphorus in olders should be **2.2 mg/dL** rather than 2.5

LIVER FUNCTION TEST

- Aging in liver: ↓ hepatic blood flow & liver volume .
- Levels of liver tests as AST & ALP not change with age.
- Slight decline in albumin with age.

✓0.015 g/dL per year in men

✓0.012 g/dL per year in women.

- Most olders remained within reference range.
- Using threshold of 3.5 g/dL, only 2.4% of men and 1.5% of women had hypoalbuminemia

LFT

- Level of ALT decline with age,peak in 40–50
- Declining by 20% over 10 y of f/u,
- From a mean of 20 to 16 IU/L.
- ⬇ALT led to decreased sensitivity of 3 commonly tests for diagnosis nonalcoholic fatty liver dis ,that rely on rise ALT.
- Age-specific reference ranges for ALT might need to be defined.

LFT

- Bilirubin increased slightly with age from mean 0.48 mg/dL at baseline in 66 to 0.68 after average 13 y f/u.

- Absolute bilirubin levels stayed within typical reference range .

GLUCOSE LEVELS

- Increase in central adiposity
- Decreased lean muscle mass

- Insulin resistance
- Impairments in pancreatic beta cell function

- Decreased insulin secretion
- Glucose tend to increase with age

GLUCOSE LEVELS

- FBS increases on average by 1–2 mg/dL per decade.

- 2-hour oral glucose tolerance test rise by 6 mg/dL per decade from 3th to 8th decade .

GLUCOSE LEVELS

- Increasing prevalence of impaired fasting glucose, impaired glucose tolerance, and diabetes mellitus with aging .

prevalence of DM in 2012 in USA	
20–44 y	2.5%
45–64 y	12.5%
65–79 y	21%

GLUCOSE LEVELS

- Mortality increase with rising glucose in elderly.
- Studies among middle-aged individuals: DM risk starts to rise in high-normal range FBS(90–99),
- Challenging concept of "normality" in glucose testing,
- Suggesting rather than discrete threshold, a continuum of risk for DM.

HBA1C LEVELS

- Glycemic targets for treatment DM expressed by HbA1c.
- Formed by glycation: nonenzymatic attachment of glucose to Hb in RBCs.
- Reflect average blood glucose RBC lifespan(120 d)
- Diseases alter rate of production/destruction of RBC,impact HbA1c
- Less representative of actual glucose levels.
- More common in elderly

FALSE ELEVATION HBA1C

Severe CKD

- Erythropoietin ↓
- RBC lifespan ↑
- Glycation of RBCs ↑

Anemia

- Iron & vit B12 deficiency
- Erythropoiesis ↓

HEMOGLOBIN

- Average Hb levels decrease slightly with aging.

mean Hb level in Caucasian men	
50–59	15.2g/dL
60–69	14.9g/dL
70–79	14.7g/dL

HEMOGLOBIN

- Anemia is also more common in elderly.
- Majority had mild anemia, with only 2.8% of women and 1.6% of men with Hb<11 g/dl
- Only 0.9% women and 0.5% men Hb<10.
- Prevalence anemia rises with increasing age, to 20% of adults≥85
- Anemia associated with increased risk for functional decline and mortality.

HEMOGLOBIN

- Many dis lower Hb common in elderly, nutritional deficiencies, CKD, cancer,chronic inflammatory.
- No cause of anemia in 1/3 of cases .
- Whether benign form anemia and whether is due to "aging" rather than disease .
- Aging associate senescence hematopoietic stem cells as well as declining bone marrow cellularity.

HEMOGLOBIN

- Since 1968, anemia defined by WHO criteria:
- Hb <13 g/dL in men and <12 mg/dL in women.
- Validity of WHO criteria questioned in elderly.
- Developed from studies of nutritional def during pregnancy in women in developing countries.
- No elderly included in WHO criteria studies.
- They also didn't include African descent, with increased prevalence of hemoglobinopathies

HEMOGLOBIN

- No clear consensus for alternate criteria.
- One study of US adults ≥65:cutoff anemia should slightly higher than WHO in Caucasian men & women (<13.4 and 12.4 g/dL)
- Lower in African-American men & women (<12.3 and 11.3 g/dL)
- Another study proposed cutoffs should lower in frail elderly.

HEMOGLOBIN

- There is concern if a component of decline in Hb seen with aging is physiologic rather than pathologic, current diagnostic criteria may lead to overdiagnosis of anemia in elderly and unnecessary testing.

PLATELET

- In Western populations,reference interval for platelet accepted as 150 to 400 or 450× 10^3 µL.

- platelet counts decline with age.

- There is also significant variation in platelet counts with gender and ethnic background

PLATELET

- **females** had higher platelet counts than males
- **African- Americans** had higher platelet than Caucasians.

in all, decline in platelet with age		
Age group	Caucasian males	Caucasian women
17–19	260	300
60–69	242	264
≥70	232	254

PLATELET

- On average, platelet counts declined 10 × 10^3 by age 60–69 from young adulthood
- 20 × 10^3 in those ≥70.

Age group	Males	Women
15–64	141–362	156–405
>64	122–350	140–379

PLATELET

- Mechanism is not clear.
- One theory is:there may be a survival advantage with lower platelet
- Alternatively, due to reduction in hematopoietic function with age.

- While changes are small, have real impacts on diagnosis thrombocytopenia & thrombocytosis.

IMMUNE SYSTEM

- WBC count &diff not change with aging, however function declined.
- Part of overall decline in humoral &cell-mediated immune function called "immune senescence" .

-  Immune response delay diagnosis.

- Olders may have bacteremia w/o rise in WBCs.

IMMUNE SYSTEM

- less likely to mount fever in response infection.

- Nonspecific symptoms: altered mental status, weakness, falls, urinary incontinence, malaise first signs of serious infection in olders.

- However, noninfectious problems also cause similar symptoms.

IMMUNE SYSTEM

- When in doubt, clinicians rely on culture to determine if olders with nonspecific symptoms have infection;

- However B/C and U/C false-positive results.

- As many as half of positive B/C are due contaminants, can lead inappropriate antibiotic, prolonged hospital length of stay.

ASYMPTOMATIC BACTERIURIA

- Older women and men frequently have positive U/C w/o symptoms or signs of infection.
- Rarely seen in youngers and increasingly common at older ages.
- In up to 20% of community-dwelling women≥80
- 5–10% of men≥80
- 15 _50% of nursing home residents

ASYMPTOMATIC BACTERIURIA

- Pyuria (WBCs on U/A) universally seen with asymptomatic bacteriuria.

- Presence,magnitude of pyuria or colony count,on U/C can't distinguish true infection from asymptomatic bacteriuria .

- no benefits of treatment of asymptomatic bacteriuria.

ASYMPTOMATIC BACTERIURIA

- Nevertheless, olders with nonspecific symptoms of illness with positive U/C often treated for UTI ,
- Exposing needlessly to potential for antibiotic-associated adverse drug effects
- Potential harms from premature closure of search for true underlying diagnosis.
- Experts recommend U/C + should not treated in olders w/o specific signs of UTI :dysuria, frequency, urgency, suprapubic discomfort, or costovertebral angle tenderness.

LAB TESTS DO NOT CHANGE WITH AGE

- Free T4 and T3
- Sodium
- Chloride
- Potassium
- Bicarbonate
- Calcium
- Aspartate aminotransferase
- Alkaline phosphatase
- WBC count

Test	Change with aging	Clinical implication
TSH	The 97.5th percentile for TSH rises from 3.56 mIU/L in 20–29-year-olds to 7.49 mIU/L in those over the age of 80 [8]	The American Thyroid Association has stated that it may be appropriate for the target TSH in older adults treated for hypothryoidism to be raised from the prior standard of 0.4–4.0 mIU/L to 4–6 mIU/L [9]
Phosphorus	Decreases from a mean of 3.8 mg/dL in men in their 20s to 3.0 mg/dL in those 84 years of age and older. In women in the same study, phosphorus decreased from a mean of 3.7 mg/dL in their 20s to 3.4 in those 84 and older [30, 31]	It has been suggested that the lower limit of normal for phosphorus in older adults should be 2.2 mg/dL rather than 2.5 [31]
Erythrocyte sedimentation rate	Rises	The upper limit for normal ESR with age was estimated in one study as (age (in years) plus 10 if female) divided by 2 [17]
C-reactive protein	Rises	May impact diagnostic uses of this analyte as well as use in monitoring responses to therapeutics
D-dimer	Rises	An age-adjusted cut-off for D-dimer level (age × 10) has been clinically validated for use in adults above the age of 50 in diagnosis of pulmonary embolism [15]
Ferritin	Rises	Joosten proposed that the cutoff of ferritin levels for diagnosing iron deficiency should be increased from 25 to 50 ng/mL in the elderly [21]

Test	Change with aging	Clinical implication
Albumin	Slight decline	Unclear
Alanine aminotransferase	Declined by 20% over 10 years of follow-up in one longitudinal study, from a mean of 20 to 16 IU/L [34]	One study showed decreased sensitivity of tests for diagnosis of nonalcoholic fatty liver disease in the elderly [37]
Bilirubin	A slight increase shown in one longitudinal study [38] but two smaller cross-sectional studies did not show this [39, 40]	Unclear
Glucose	Fasting and postprandial levels rise	Increased prevalence of impaired fasting glucose, impaired glucose tolerance, and diabetes mellitus with aging [44]
Hemoglobin	Slight decline in mean hemoglobin with age	Anemia is more common in the elderly but the majority of older adults don't meet criteria for anemia. Alternate cutoffs for diagnosis of anemia in the elderly have been proposed but none have widespread acceptance
Platelets	Declines a small amount, on average in one study by 10×10^9/L by age 60–69 and 20×10^9/L in those older than 70 years [55]	Alternate reference ranges for age and gender have been proposed in Italy [56] but not in other populations
Urine culture	Increasing prevalence of asymptomatic bacteriuria present in up to 20% of community-dwelling women over age 80 and 5–10% of men over age 80 as well as between 15% and 50% of nursing home residents [62]	Increased risk of overdiagnosis of urinary tract infection in the elderly

سوال

- در یک فرد سامند که به علت هایپوتیروئیدی،داروی لووتیروکسین مصرف می کند، بهتر است سطح TSHدر چه محدوده ای نگه داشته شود؟
- بهترین فرمول برای محاسبه GFR در سالمندان کدام است؟
- دلایل افزایش کاذب HbA1c چه مواردی می باشد؟


THANK YOU