Menopause Management in 2020: *everything you need to know!*

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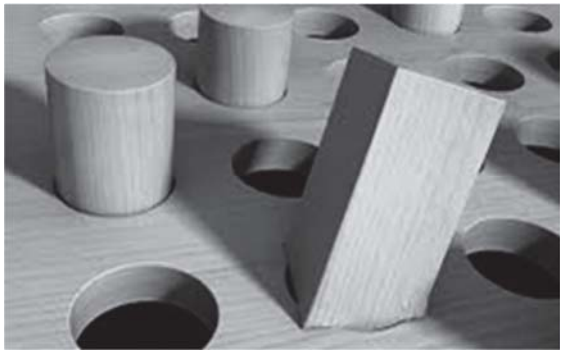
Disclosures:

- I have no commercial interest in any of the products I will discuss today
- I will discuss both on- and off-label uses of drugs
- My perspective is solely that of a clinician and educator

Learning Objective:

- After this talk, you will know important guidelines regarding hormone therapy use in various clinical settings

NOT…



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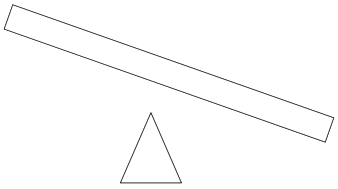
BUT…

Balancing Benefits and Risks

The WHI was ***not*** designed to address the **benefits** of hormones for symptomatic women

The WHI is the ***best*** medical evidence we have to date concerning the **risks** of hormone therapy



Individualizing:

- Risks differ for different women depending on
  - Dose
  - Duration
  - Route of administration
  - Timing of initiation
  - Progestin or not?
- Periodic reevaluation

The Seven Dwarves of Menopause

Which are caused by menopause?
Which can be relieved by hormones?

- Sweaty
- Sleepless
- Bone-dry
- Grumpy
- Anxious
- Dopey
- Sexless

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Benefits of Hormone Therapy for symptoms

Unequivocal

- Hot flashes and night sweats
- Vaginal dryness

Probably Beneficial

- Poor sleep
- Adverse mood

Conflicting/ Inadequate Data

- Sexual function
- Urinary incontinence
- Joint pains
- 'Brain fog'
- Changes in body composition
- Skin dryness/wrinkling

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It's not just symptoms, it's long term health too!

Essential to know:

Menopause: The Journal of The North American Menopause Society
Vol. 24, No. 7, pp. 728-753
DOI: 10.1097/GME.0000000000000921

POSITION STATEMENT

The 2017 hormone therapy position statement of The North American Menopause Society

Abstract

The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) updates the 2012 Hormone Therapy Position Statement of The North American Menopause Society and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2012 Position Statement, evaluate new literature, assess the evidence, and reach

How We're Going to Think About This Today:

CASES

then POSITION STATEMENT

Patient #1

- 45 yo woman
- Periods are heavier and more unpredictable, skips a period now and then
- 10 hot flashes per day
- 3 night sweats per night

- Using dong quai and evening primrose oil

Cycle Control in Perimenopause

- HT not usually effective for perimenopausal irregular bleeding because these women need **CYCLE CONTROL**
- HT dosages are about ¼ the strength of the lowest dose oral contraceptive (not enough to control irregular bleeding)

Is it weird that she's hot flashing so much at such a young age?

Natural History of Hot Flashes

Transition Stage	% affected*	Age
Premenopause	20-45%	<45
Pre- to-Early Perimenopause	25-55%	45-47
Early-to-Late Perimenopause	50-80%	47-49
Late Peri-to-Postmenopause	35-75%	49-55
Late Postmenopause (>5yr)	16-44%	56+

References:
Barnabei V et al. Obstet Gynecol 2002; 100:1209-18
Gold EB, et al, Am J Pub Health 2006; 96:1226-35
Politi MC, et al. J Gen Intern Med 2008;23:1507–13.

Patient #1 how to manage?

- Consider endometrial sampling
- Stop the dong quai and evening primrose oil
- Low dose monophasic OCP
- When to stop?

Patient #2

- 54 yo woman
- LMP 2 years ago
- 10 hot flashes per day
- 3 night sweats per night
- Waking more than she used to

Patient #2 How to manage?

- She is fully menopausal and incredibly symptomatic
- Start E + P
- Vivelle 0.5 mg/day biweekly patch
- prometrium 100 (200) mg at night
  - Could also consider LNS IUD
- Give her sleep hygiene recs
- See her back in 6-8 weeks

Vasomotor Symptoms

NAMS Position Statement

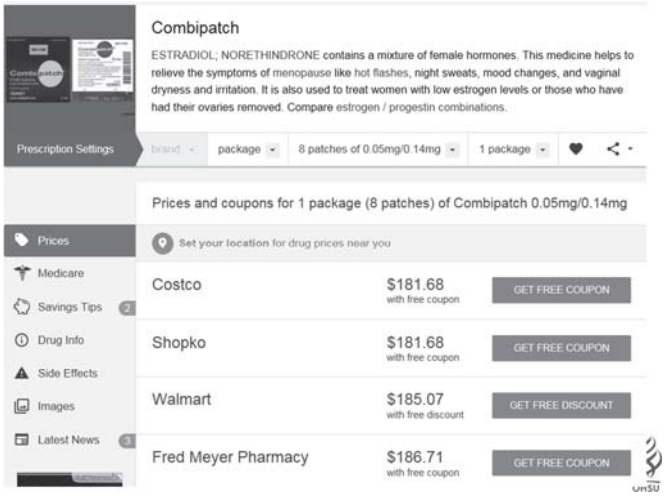
- HT is the gold standard for relief of vasomotor symptoms
  - ET
  - E+PT
  - PT
- Use the **lowest dose that gives relief** and periodically reevaluate
- SSRIs/SNRIs best alternative; gabapentin third-line

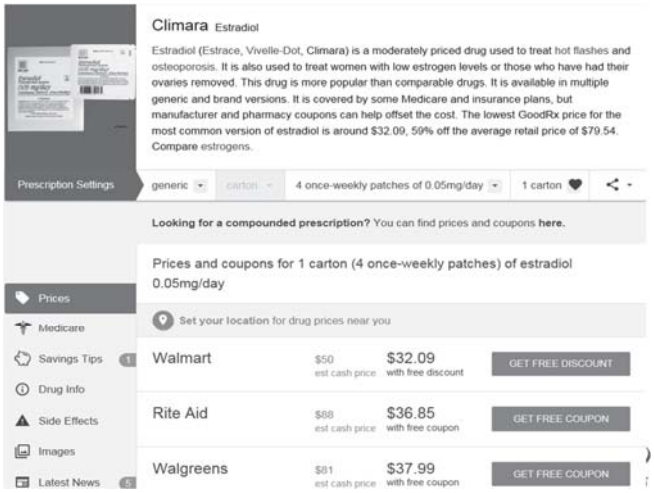
Type, dose, regimen, duration

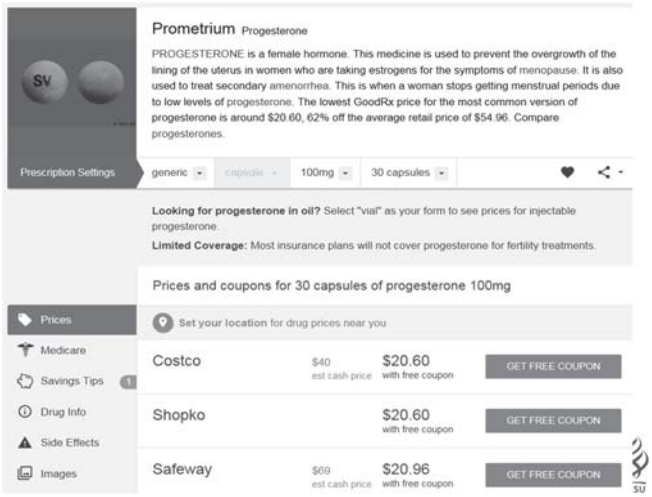
- Women with a uterus need P
  - Prometrium 100 mg q hs (200)
  - Mirena or Skyla IUD
- Transdermal may decrease some risks
  - No RCT data, observational only
- Decisions about continuation must be individualized

Oral vs. transdermal estrogen therapy and thromboembolic complications

Study Publication	Oral Estrogen	Transdermal Estrogen
	Odds Ratios (95% Confidence Intervals)	
Scarabin, et al. Lancet, 2003, 362(9382): p. 428-32.	3.5 (1.8-6.8)	0.9 (0.5-1.6)
Canonico, et al. Circulation, 2007,115: 840-845	4.2 (1.5-11.6)	0.9 (0.4-2.1)







Practice Pearl : dosing gabapentin for vasomotor symptoms

	Morning	Afternoon	Evening
First 7 days			100 mg
Next 7 days	100 mg		100 mg
Next 7 days	100 mg	100 mg	100 mg
Next 7 days	100 mg	100 mg	200 mg
Next 7 days	200 mg	100 mg	200 mg
etc	Etc up to 300 mg	Etc up to 300 mg	Etc up to 300 mg

What about herbs/botanicals?

- Soy and maca a little more effective than placebo
- Not more effective than placebo:
  - Red clover
  - Dong quai
  - Women's botanical formulas
  - Evening primrose oil
  - Black cohosh

Patient #3 how to evaluate?

- 35 year old woman
- No period for 10 months

Patient #3 how to manage?

- 35 year old woman
- No period for 10 months
- HCG neg
- TSH, PRL normal
- FSH 59, Estradiol 12
- Neg P withdrawal bleed

Early menopause/POI

- Benefits outweigh risks
  - Bone
  - Heart
  - Cognition
  - VVA/GSM
  - Sexual function
  - Mood
- HT recommended at least until age of menopause
- Younger women may require higher doses

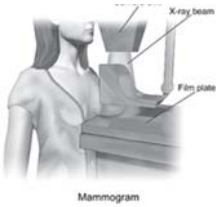
Patient #4 how to manage?

- 40 year old woman
- BRCA+
- Planning RRBSO

Family history of breast cancer

- HT doesn't alter risk for breast cancer in women with a family history
- This risk should be assessed when counseling women
- BRCA+ women who have undergone RRSO should be given HT until at least the age of menopause

Breast cancer



Mammogram

- HT's effect on risk of breast cancer is complex and conflicting
- May depend on
  - Type of HT, dose, duration of use
  - Regimen, route of administration
  - Individual characteristics

Breast cancer and WHI

- Increased risk of invasive breast cancer after 3-5 years of CEE + MPA
- No increased risk of breast cancer seen with 7 years of CEE alone
- Allows more flexibility in use of HT in women without a uterus
- Risk is greater from **sedentary lifestyle, obesity, or alcohol intake** than from estrogen

Survivors of endometrial cancer

- YES if early stage
  - Especially if younger than age 51
- Non-hormonal therapies recommended for more advanced stages
- Low dose vaginal ET works for GSM/VVA

Survivors of breast cancer

Survivors of breast cancer

- NO!
- Selected cases with compelling reasons may be discussed with medical oncologist
- After nonhormonal options have failed
- Local ET for GSM/VVA is OK
  - Try nonhormonal options first
- NOT if on aromatase inhibitors without consultation

Duration

- Risk/benefit balance (vasomotor sx, bone loss)
- Absolute risks that increase with age
  - CHD
  - Stroke
  - VTE
  - PE
  - Breast cancer
- No recommendation to automatically stop at age 65

Patient #5

- 59 yo African American woman
- Has been struggling with hot flashes for years
- T2DM
- On a statin and a BP med

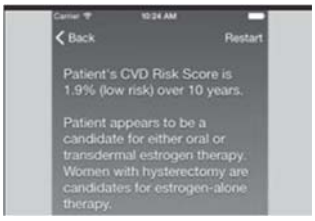
NAMS MenoPro App incorporates the ASCVD risk calculator

The app asks you

- Age?
- Less than 10 years past the onset of menopause?
- Hysterectomy?
- Ethnicity?
- Smoker?
- Treatment for HTN?
- Systolic BP?
- Diabetes?
- On cholesterol-lowering medication?
- Total cholesterol level?
- HDL?

Then you wait…

Results Page



- Gives the patient's CVD Risk Score over 10 years
- Gives you a list of every appropriate treatment option and dosages

Patient #5

- "The CVD Risk Score is 13.9% (high risk) over 10 years"
- "Patients with CVD risk scores above 10% should avoid initiation of systemic hormone therapy but may be candidates for non-hormonal therapy"

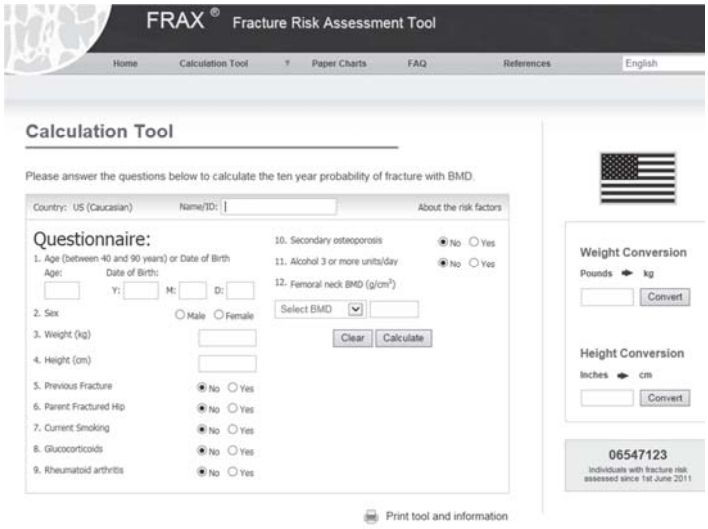
Patient #6

- 56 yo woman
- BMI 19.6
- Smoker
- Mother had a hip fracture

BMD testing recommendations

- All women age 65 and older
- Postmenopausal women younger than age 65 if FRAX score for 10-year risk of major fracture is ≥9% (average fracture risk for healthy women)
- Postmenopausal women with medical causes of bone loss
- Postmenopausal women with history of fragility fracture

Pfister AK *Ann Intern Med* 2011;155:275-6



Osteoporosis risk assessment

- Identify postmenopausal women at risk for fracture using FRAX
- Reduce modifiable risk factors through dietary and lifestyle changes
- If indicated, prescribe pharmacologic therapy or refer for this treatment

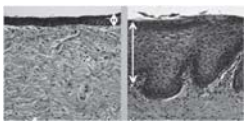
HT and Fracture Prevention

- WHI showed that HT reduced risk of fractures even in low risk women
- Average T scores of women in WHI
  - hip -0.94
  - spine -1.3
- Vertebral and radiologically-detected not included in global index

Patient #6

- 10 year risk of osteoporotic fracture = 11%
- 10 year risk of hip fracture = 1.2%
- Can consider HT because she is higher than average risk for healthy women

FDA-approved indications for HT



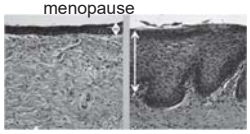
FDA-approved indications for HT

Vasomotor symptoms

Surgically or medically menopausal women

Treatment of women at high risk for osteoporosis

Genitourinary syndrome of menopause



US Preventative Services Task Force 2017

Final Recommendation Statement

Hormone Therapy in Postmenopausal Women: Primary Prevention of Chronic Conditions

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Postmenopausal women	The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal women.	D
Postmenopausal women who have had a hysterectomy	The USPSTF recommends against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal women who have had a hysterectomy.	D

Grade D = evidence of no net benefit or harms outweigh benefits

Patient #7

- 59 year old woman
  - No hot flashes
  - Increasing dyspareunia

Genitourinary Syndrome of Menopause

- **SYMPTOMS**
  - Vulvar/vaginal dryness
  - Decreased lubrication with sex
  - Discomfort or pain with sex
  - Bleeding after sex
  - Decreased arousal, orgasm, desire
  - Irritation, burning, or itching of vulva or vagina
  - Painful urination
  - Urinary frequency/urgency
- **SIGNS**
  - Decreased moisture
  - Decreased elasticity
  - Labia minora get thinner
  - Pale vaginal tissue
  - Loss of vaginal folds
  - Tissue fragility/splitting

Prevalence of Genitourinary Syndrome of Menopause

About 50% of all postmenopausal US women have GSM*

Only 6%-7% treated

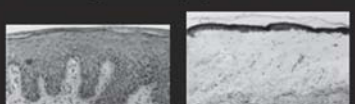
Many women are unaware that symptoms progress without treatment and that safe and effective treatments are available

Simon JA, et al. *Menopause*. 2013;20:1043
MacBride MB, et al. *Mayo Clin Proc*. 2010;85:87
Prairie BA, et al. *J Womens Health*. 2014;23:513
Nappi RE, et al. *Climacteric*. 2012;15:36
Courtesy of NAMS *(modified)*

* Understanding of GSM, including prevalence and impact on sex, limited by current assessment tools

Vulvovaginal Atrophy Strongly Associated with Female Sexual Dysfunction

- Menopause Epidemiology Study cross-sectional, population-based study
- 1,480 sexually active postmenopausal US women, aged 40-65 years
- Prevalence of vulvovaginal atrophy: 57%
- Women with FSD were 3.8 (CI 3.9-4.9) times more likely to have vulvovaginal atrophy than women without FSD

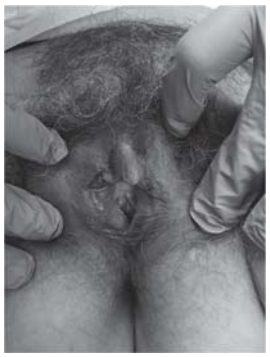


Premenopause Postmenopause

Levine K, et al *Menopause* 2008; 15:661

Diagnosis of GSM

- Look for it in peri or post menopausal women
- Thin thin thin
- Dry dry dry
- Ask about symptoms



NAMS guidelines for GSM

- Start with OTC lubricants and moisturizers
- Lubricants with sexual activity
  - Coconut oil
  - Silicone
- Moisturizers for weekly maintenance
- If no improvement after 3 months, move to estrogen

Vaginal Moisturizers

FDA-approved estradiol treatments

- Topical vaginal cream (Estrace)
  - 1 gm on fingertip nightly x 2 weeks then 2x week
- Vagifem tablets or Estring inserted in the vagina
- Estrogen softgel approved June 2018 ("more elegant delivery system")

Safety of local E therapy

- Reassuring when serum levels are measured
  Serum levels: E cream > E tablet > E ring
  All within menopause levels
- Reassuring when endometrial stripes are ck'd
- We now have 7-year follow up
- Breast cancer survivors need to know what is safe!

VAGIFEM® 10mcg
estradiol vaginal inserts

SCARY PACKAGE LABELLING!

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VAGIFEM® safely and effectively. See full prescribing information for VAGIFEM®.

Vagifem® (estradiol vaginal inserts)

Initial U.S. Approval: 1999

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

See full prescribing information for complete boxed warning

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)**
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)**

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) (5.2)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)**

RECENT MAJOR CHANGES
- Warnings and Precautions, Malignant Neoplasms (5.3) 11/2017

INDICATIONS AND USAGE
- Vagifem® is an estrogen (estradiol) indicated for the treatment of atrophic vaginitis due to menopause (1.1).

DOSAGE AND ADMINISTRATION
Vagifem® should be administered intravaginally:
- 1 insert daily for 2 weeks, followed by 1 insert twice weekly (for example, Tuesday and Friday) (2.1)

DOSAGE FORMS AND STRENGTHS
- Vagifem® 10 mcg insert. One vaginal insert contains 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol (3)
- Vagifem® 25 mcg insert. One vaginal insert contains 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg of estradiol (3)

CONTRAINDICATIONS
- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.3)
- Known or suspected estrogen-dependent neoplasia (4, 5.3)
- Active DVT, PE, or history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.2)
- Known anaphylactic reaction or angioedema to Vagifem®
- Known liver impairment or disease (4, 5.11)
- Known protein C, protein S, or antithrombin deficient, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS
- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- The Vagifem® applicator may cause vaginal abrasion (5.17)
- Monitor thyroid function in women on thyroid replacement therapy (5.12, 5.19)

ADVERSE REACTIONS
In prospective, randomized, placebo-controlled, double-blind studies the most common adverse reactions (incidence ≥5 percent) were upper respiratory tract infection, headache, abdominal pain, back pain, genital pruritus, moniliasis, vulvovaginal mycotic infection and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-888-824-4336 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS
- Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

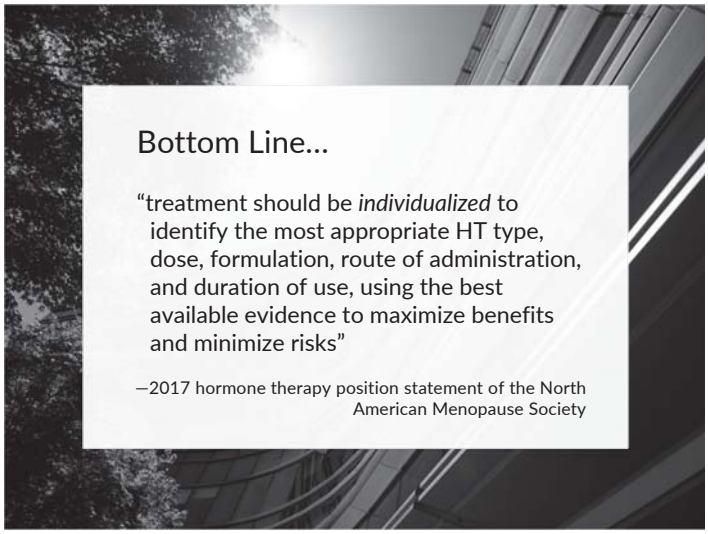
USE IN SPECIFIC POPULATIONS
- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2017

Choices of local therapy

- User abuse less likely with vaginal tablets or vaginal ring – temptation to use lots of cream
  - Med oncs are happier with tablet or ring than cream
  - OK if you take time to explain to your patient!



Bottom Line…

"treatment should be *individualized* to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks"

—2017 hormone therapy position statement of the North American Menopause Society

Menopausal Zest

- In a Gallup survey of 752 women, in the majority of women these areas were better or stable:
  - role at work
  - family life
  - partner/sexual relationship
  - friendships
  - self-fulfillment
  - and physical health.

Utian WH Menopause 1999;6:122-8

Thank You

The Challenges of Vaginitis

Amy L Stenson MD, MPH
Associate Professor Obstetrics and Gynecology
Residency Program Director
Program in Vulvar Health, Oregon Health & Science University

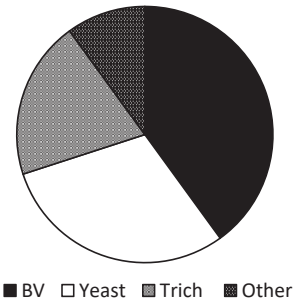
- No disclosures

Objectives

- Review common vaginitis
  - Pathogenesis
  - Diagnosis
  - Treatment
- Discuss difficult/unusual cases
  - Recurrent Yeast and BV
  - Resistant Trichomoniasis
  - Non-infectious vaginitis
- Understand when to refer to gyn/vulvar

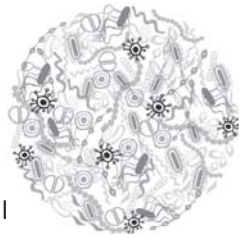
Vaginitis Basics

- Caused by infection, inflammation or changes in the normal vaginal flora
- Most common causes
  - Yeast (17-39%)
  - BV (22-50%)
  - Trich (4-35%)
  - Other (7-10%)



- Symptoms include: vaginal discharge, odor, pruritus, irritation or discomfort

Vaginal Health and the Microbiome



- Estrogen promotes mature epithelial cell
- Glycogen in epithelial cells supports lactobacilli
- Lactobacilli produce lactic acid and lower pH
  - Normal vaginal pH is <4.5
- Acidic environment is protective
- Normal flora is heterogeneous, but in balance
  - Commonly includes *Gardrenella, E. Coli, GBS, Mycoplasma, Candida, but dominated by lactobacilli*

Prepuberty and Menopausal Women

- lack of estrogen inhibits normal growth of the vaginal bacterial ecosystem;
- microscopy typically shows a paucity of epithelial cells and background bacteria
- Rare to see BV or yeast in these patients, so consider alternate diagnosis

Case 1

- 36yo G0 single woman with Mirena IUD who presents with concerns of vulvovaginal itch and burn

Office Evaluation: History

Quality: onset, frequency, duration, location, severity, consistency, color, & odor

Exposure to contact irritants: soaps, spermicide, bathing products or intra-vaginal products

Vulvar Hair Hygiene: shave, laser, wax

Hormonal status : Relation to Menstrual cycle? Estrogen depleted? (postpartum, menopausal, birth control)

Sexuality: partners, barrier BCMs, lubes, toys, other

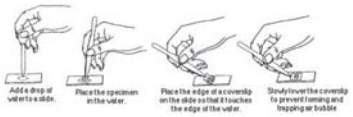
Treatments: OTC, CAM or prescribed medications

Tools for Evaluation

- **Physical Exam**
  - Visual inspection of vulva , perineum, anus & vagina (speculum)
- **Microscopy**
  - pH immediately
  - Saline/KOH prep
  - Whiff test: amine odor with application of KOH
- **Vaginal Culture**: vaginal side walls or fornix, not cervix
  - Fungal culture helpful
  - General bacterial culture generally not helpful
- **Rapid tests:** when indicated or unable to do microscopy
  - BV, GC/CT,
- **Vulvar Biopsy**
  - Only when notable skin changes
  - Random biopsy not helpful and can be traumatic for the patient

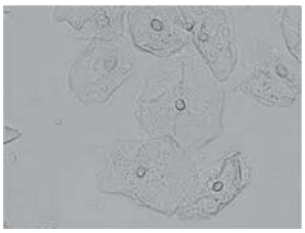
Wet Prep

1. Check Vaginal pH
   - prior to using lidocaine, gel etc ideally
   - Using pH paper graded from 3-5.5
   - Ask about bleeding, sex and intravaginal products (affect pH)
2. Collect specimen
   - From vaginal side walls
   - Consider recollecting, I usually collect twice
3. Place specimen in saline on 2 slides (or in carrier container)
   - Check to ensure that it appears cellular, if not recollect and add more cells
4. On second slide add KOH
5. Place cover slips



What can we see in a Saline Prep?

- Epithelial Cells
  - mature squamous cells
- WBCs
- RBCs
- Parabasal Cells
  - immature squamous
- Trichomonas
- Clue Cells
- Hyphae/spores
- Debris



	pH	WBC	Para-basals	Features	Discharge
Normal	3.5-4.5	Few or none	no	Mature epithelial cells lactobacilli	Creamy white

	pH	WBC	Para-basals	Features	Discharge
Normal	3.5-4.5	Few or none	no	NI lactobacilli	Creamy, mucousy, white
Yeast	3.5-4.5	no	no	Hyphae Spores (400x)	White, Curdy
BV	>4.5	no	no	Clue Cell	Yellow, grey w/ odor
Trich	>5.0	yes	maybe	Motile trich	Greenish yellow, frothy
DIV	>5.0	yes	yes	Mixed bactertia, reduced lacto	Yellow, profuse
GSM	>5.0	maybe	yes	Scant cells, few bacteria	Scant, dry

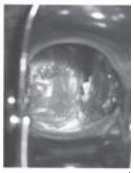
Vaginal Culture

- Appropriate for recurrent, difficult vaginitis
- Culture for **recurrent yeast**
  - Request sensitivity and speciation
- Culture for **resistant trichomonads**
- Not helpful for recurrent or resistant BV
  - Unsure role of other coliforms, therefore not recommended to obtain bacterial culture of vagina in most cases

Vulvovaginal candidiasis

Vulvovaginal Candidiasis (VVC)

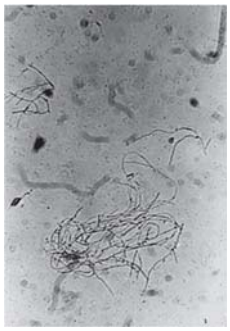
- 13 million cases annually in the USA
- Second most common cause of vaginitis
- Primary symptoms
  - Itching
  - Thick, curdy, white discharge
- 29-49% of women w/ at least 1 lifetime episode
- 5% of women develop recurrent infection



Foxman, 2013, CDC 2010 STD Treatment Guidelines

Diagnosis

- Microscopy, convenient and specific
  - Only 50-70% sensitive
- Culture
  - resistant/recurrent infection
- PCR (39-99% sensitive)
  - BD AFFIRM (candida y/n)
  - BD MAX (subtype)



Vulvovaginal Candidiasis (VVC)

- **<u>Uncomplicated</u>**
- Sporadic, infrequent
- Mild-moderate
- Likely *C. albicans*
- Non-immunocompromised

- **<u>Complicated</u>**
- Recurrent (>3/year)
- Severe (clinical exam)
- Non-albicans
- Diabetes, immunocompromise

2015 CDC STD Treatment Guideline

Treatment of uncomplicated yeast

- Topical (vaginal) OTC azole preparation x 3-7d
- Oral fluconazole 150mg as single dose
- Very Effective >90%

- Topical tx recommended in pregnancy, as oral fluconazole was associated with increased miscarriage rate.

Quiz Question 1

Candida albicans is the most common cause of recurrent vulvovaginal yeast infections. Several **uncommon** species of yeast can also cause recurrent infection. Which species of fungus is the most common in THIS category?

a. Candida parapsilosis
b. Candida glabrata
c. Saccharomyces cerevisiae
d. Tinea

Acute Infection: non-*albicans*?

- ~5-10% women with recurrent VVC have non-*albicans* species
  - *C. glabrata* ***
  - *C. parapsilosis*
  - *C. krusei*
  - *Saccharomyces cerevisiae*

Spinillo, A, 1995. **85**(6): p. 993-8
Sobel, Am J Obstet Gynecol, 2001

How to treat non-*albicans*?

- Fluconazole? >50% non-response if *Candida glabrata*
- Itraconazole 200mg QD or 100mg BID x 3-7d
- Boric acid 600mg capsules intra-vaginally QHS-BID x 14ds
  - 92 women failed conventional treatment with -azoles had 98% mycologic cure with boric acid
  - Case series of resistant VVC , 81% pt responded to 600mg QDx14d boric acid compared to <50% -azole
- Flucytosine 5% cream intravaginally 5g QHS x 14d

Nyirjesy, Am J Obstet Gynecol, 1995
Guaschino, Am J Obstet Gynecol, 2001
Van Slyke, Am J Obstet Gynecol, 1981
Sobel, Am J Obstet Gynecol, 2003
Sobel JD, Clin Infect Dis 1997
Jovanovic, J Reprod Med, 1991

Recurrent VVC Diagnosis

- Defined as 4 or more episodes/year
- Begin with office evaluation
  - Data supports women poor at self-diagnosis
- Microscopy, KOH increases sensitivity
- Consider rapid point of care test (AFFIRM®)
- Vaginal culture, most will be *C. albicans*
  - Consider ID & sensitivities for difficult case

Ferris, Obstet Gynecol 2002;99:419; Ferris, J Fam Pract. 1996;42(6):595. Sobel, AJOG 1985; 152:924
Allen-Davis, Obstet Gynecol 2002;99:18; CDC 2010 STD Treatment Guidelines

Can a Woman Accurately Diagnose Herself?

Ferris, Obstet Gynecol, Vol 99 (3), 2002.

Final Diagnosis	N	%
Normal	13	13.7
VVC	***32***	***33.7***
Trichomonas	2	2.1
BV	18	18.9
Other*	10	10.5
VVC+BV	18	**18.9**
BV+Trich	1	1.1
VVC+Trich	1	**1.1**

Recurrent VVC: Risk Factors

- Antibiotic use
- Estrogen excess (pregnancy, vaginal estrogen)
- Immune suppression (SLE, HIV, oral steroids)
- Vulvar dermatoses (LS, LP, psoriasis)
  - Likely due to steroid use
- Diabetes mellitus

2010 CDC STD Treatment Guideline
Sobel, JD. Candida vaginitis. Infect Dis Clin Pract 1994; 3:334.

Complicated/Recurrent Infection

- Topical OTC azole preparation x 14days
- Oral fluconazole 150mg x 2, 3d apart
- Oral fluconazole 150mg q 3-5days x 14days
- Topical 5-Flucytosine 5g intra-vag QHSx14days

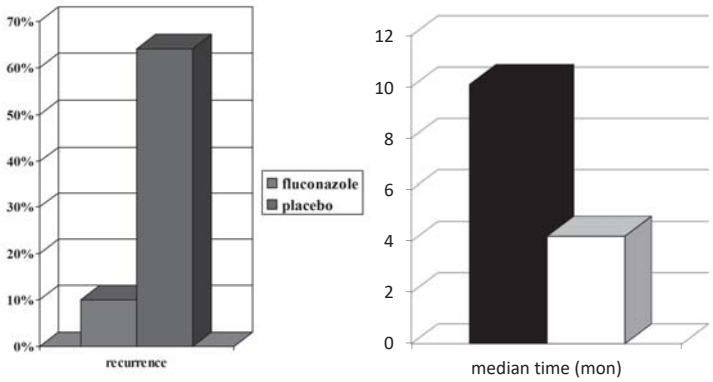
Sobel, Am J Obstet Gynecol, 2001
Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America, Clin Infect Dis. 2009 Mar 1;48(5):503-35
Rodgers, C.A. and A.J. Beardall, Int J STD AIDS, 1999.

Preventing Recurrence: Suppression

- Begin prophylaxis:
  - **Fluconazole 150mg Q week x 6 mon
  - Clotrimazole 500mg vag supp weekly x 6 mon
  - Boric acid 600mg intravag 2x/week x 6 mon
- Weekly oral fluconazole is very effective and safe
- Recurrence after suppression up to 30%
- Safety profile of long term use of boric acid not proven

Sobel, 1992 2015 CDC STD Treatment Guideline

VVC: Why Suppression?



Sobel, NEJM 2004; 351:876

What Predicts Recurrence?

Patel et al, AJOG 2004; 190:644

- Prospective cohort: 65 with RVVC despite maintenance, classic risks controlled, logistic regression for behaviors associated with recurrence
- **RISK:** panty-liners, pantyhose, cranberry juice, consumption of acidophilus products (oral & vaginal), hx of BV, <40yo
- **NO RISK:** OCPs, oral sex, vaginal sex

Preventing Recurrence?

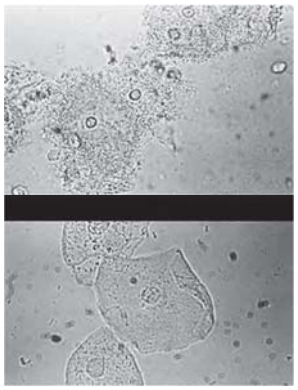
- Control Classic risk factors:
  - uncontrolled DM
  - Immuno-suppression
  - HIV+
  - antibiotic use
- Data does not support
  - use of probiotics
  - treatment of male partner

Fong 1992, William 2001, Priotta 2004, Witt, 2009

Summary: Recurrent VVC

- Defined as 4 infections/year
- Office evaluation/culture to confirm dx & species
- Treat acute infection aggressively (*Candida albicans)*
  - Fluconazole 150mg x 3 doses, Days 1, 4 and 7
  - Intra-vaginal –azole QHS x 14d
- Suppression x 6 months
  - Fluconazole 150mg weekly
  - Intra-vaginal –azole weekly
- 30% will recur after 6 months suppression
- Long term safety established with oral Fluconazole
- Look at behaviors for risk factors

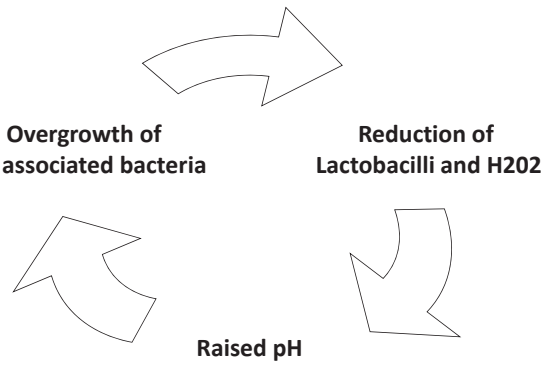
Bacterial Vaginosis



Quiz Question 2

True or False: Most bacterial vaginosis is asymptomatic.

BV: Etiology



Wilson, STI 2004;80: 8-11; Ling BMC Genomics 2010; 11: 488.

BV: Risk Factors & Associations

- Sexual activity (hetero and lesbian)
- AA ethnicity
- Multiple sex partners
- Douching
- Smoking
- STIs (CDC recommends STI testing)

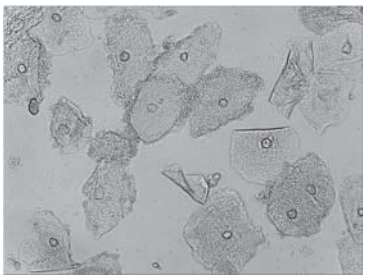
2015 CDC STD Treatment Guidelines

BV: Diagnosis

Amsel criteria: 3 of 4 findings

(1) Homogeneous, thin grayish-white vaginal discharge
(2) clue cells > 20%
(3) positive whiff test
(4) vaginal pH >4.5

A positive test for gardrenella on BD affirm, is not diagnostic for BV.



Gardnerella vaginalis, *Prevotella* species, *Porphyromonas* species, *Bacteroides* species, *Peptostreptococcus* species, *Mycoplasma hominis*, and *Ureaplasma urealyticum*, as well as *Mobiluncus*, *Megasphaera*, *Sneathia*, and *Clostridiales* species *Fusobacterium* species and *Atopobium vaginae* are also common

Other Tests

- Gram Stain with Nugent scoring
- Non-amplified nucleic-acid test
  - BD affirm (identifies Gardnerella only)
- Chromogenic test of sialidase enzyme activity
  - OSOM BV Blue
- PCR and DNA probe technology
  - BD Max (ratio of lactobacilli and BV assoc bacteria)
- Over diagnosis of BV is common!

BV: Treatment

Recommended Treatment Regimens

1. Metronidazole 500mg PO BID x7d
   - most effective treatment with **90% clinical cure**
2. Metronidazole Gel 0.75% 5g vaginal once daily x 5d
   - **as effective** as oral metronidazole
3. Clindamycin 2% cream 5g intravaginally daily x 7d

Alternatives

- Tinidazole 2g PO daily x 2 d
- Tinidazole 1g PO daily x 5d
- Clindamycin 300mg oral bid x 7d
- Clindamycin ovules 100mg intravaginally daily x 3d

CDC 2015

BV: Recurrence

- 30% women recur within 3 month
- 58% recur within 12 months
- Chronic defined as 3 episodes/year

Wilson, 2004 Bradshaw, 2006, Powell 2014

Recurrent BV:

Step 1: Treat the Acute Infection

- Treat longer, 10-14d
- Change agent

Step 2: Consider Suppression

- Twice weekly MetroGel (or Clindamycin)

Baylson, Obstet Gynecol 2004; 104:931-2
2010 CDC STD Treatment Guidelines

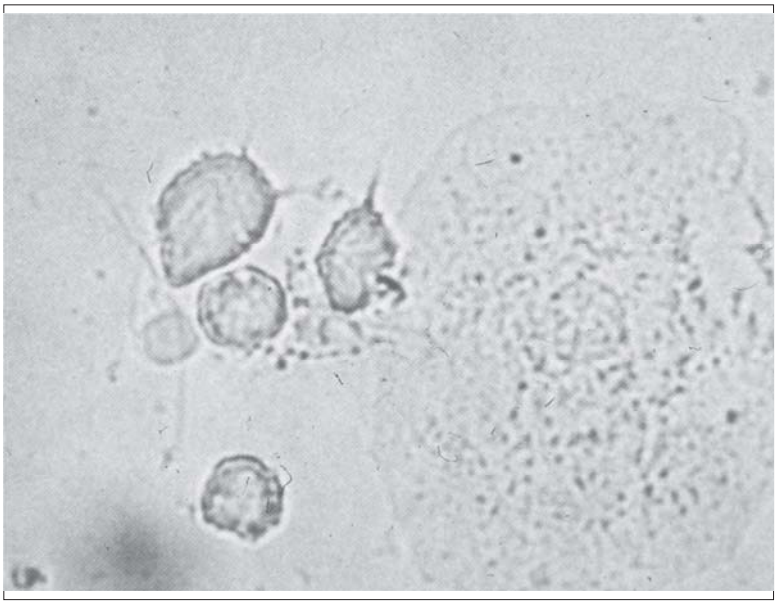
Probiotics or Alternative Treatments?

Data lacking therefore unclear benefit

- Evidence does not support replacing lactobacilli oral or vaginally
- Difficult to obtain specific species (*L. crispatus* and *L jensenii*) that adhere to vaginal walls and produces H202 used to maintain ecosystem
- Douching with H202 may exert a short term disinfection but does nothing to restore balance and can actually kill *Lactobacillus*
- Role of boric acid is unclear, may have some benefit in supporting vagina but not primary treatment

Recurrent BV: Helpful Hints

- Treat longer 10-14d for acute infection
- Consider suppression with MetroGel
- Condom first 4 weeks after treatment
- Clean sex toys
- Careful hygiene, no douching
- Suppress periods

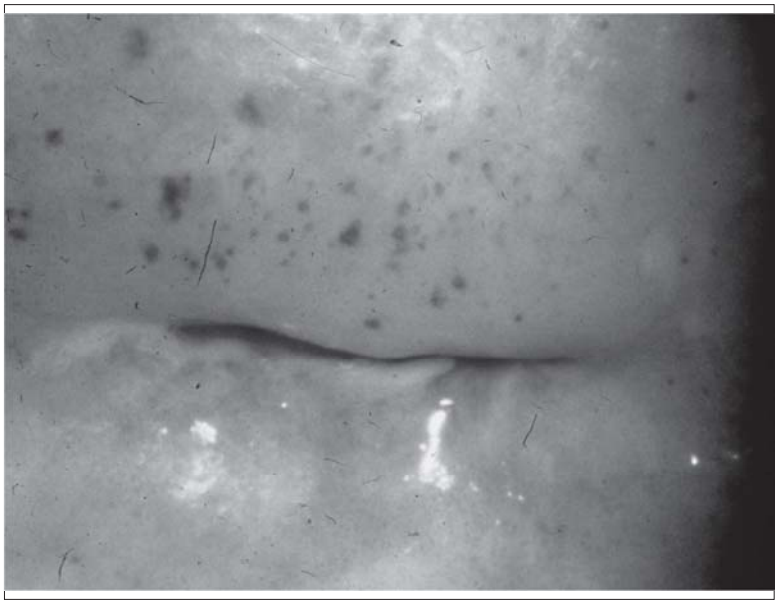


Trichomonas vaginalis: Fast facts

- Prevalence **3.1%**
- Virtually always sexually transmitted, assoc w/ other STIs
- Asymptomatic carriage for prolonged periods of time possible. . . . ? Not always able to establish vector
- If female diagnosed, most male partners +
- Risk Factors
  - Black race
  - Number of sex partners
  - Low SE status
  - douching

Symptoms

- Symptoms range from none to severe
- <10% have classic frothy discharge, suspect if pH>5.0 and WBC on wet mount



Diagnosis

- Basic microscopy
  - Elevated pH, WBCs on wet mount, trichomonads
  - Low sensitivity (50-60%), not first line
- Gold Standard
  - NAAT
  - antigen-detection
  - PCR test
  - Culture (alternative)

Perks & Pitfalls of Making the Diagnosis

	Wet mount	Diamond's Medium	AFFRIM Culture Kit	OSOM Trich Rapid Test	Pap Smear
Sensitivity Specificity	60-70%	>95%	>95% >95%	>88% 98%	50%
Pitfall	High false negative Dry slide	Obtain culture, Takes 7d	Not office based, sent to lab	Purchase kit	unreliable
What is it?	Slides + microscope	Culture medium	Swab inoculated into tube	Swab + dipstick + reagent	Slides, ? Liquid base
Perk	Available most offices	Accurate	<2 hrs Yeast&BV	In office kit, <10 min	Increase suspicion
Logistics	Office + lab	Office swab then incubate in micro lab	Becton Dickenson, San Jose, CA	GenZyme 1-800-330-3591, Office	Office + lab

Quiz Question 3

True or False: Trichomoniasis can be equally and effectively treated with either oral or vaginal medicines.

Treatment of Trichomoniasis

Recommended Regimens:

1. **Metronidazole 2 g** orally as single dose
2. **Tinidazole 2 g** orally as single dose

Alternative Regimen

Metronidazole 500 mg orally twice a day for 7 days

CDC 2015 STD Treatment Guidelines

Treatment of Trichomoniasis

- **90-95% cured**
  - with Metronidazole or Tinidazole
- MUST treat partner
  - Concurrent partner ~75% positive trich by PCR
- NO VAGINAL preparations
- No ETOH for 1-3d after use of medication
- Refrain from sex for 7d AFTER completed

- **Re-infection & Noncompliance are COMMON**
- Compliance enhanced with single 1 DAY Tx

Resistant Trichomoniasis

- If resistant then try. . . .
  - 1. Tinidazole 2g x 5d
    - Some Metro-resistant trich (2-5%) respond to high dose Tinidazole
  - 2. Metronidazole 500mg BID x 7d
- Most will respond to higher and longer doses
- If not, consider culture for resistant strain (1-2%)
- In patients with suspected resistance to Metronidazole, CDC recommends in vitro culture and drug susceptibility testing (CDC, # 404-718-4141)

Schwebke , Antimicrob Agents Chemother. 2006 Dec;50(12)
2015 CDC STD Treatment Guideline

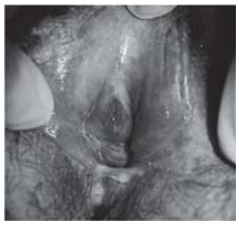
Recurrent Vaginitis: think outside the box!

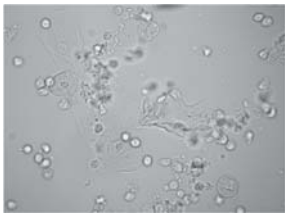
- Chemical, allergic or hypersensitivity reaction
- Foreign body, retained tampon
- Mucopurulent cervicitis (GC/CT)
- Vulvar Skin diseases
  - Erosive Lichen planus
  - Lichen sclerosus
- Vulvodynia
- Genitourinary Syndrome of Menopause (Atrophy)
- Desquamative inflammatory vaginitis (DIV)

Sobel, NEJM 1997 Vol 337

Desquamative Inflammatory Vaginitis

- Symptoms
  - Burning
  - Pain with sex
- Exam
  - Profuse purulent discharge
  - Erythema, petichiae
  - Elevated vaginal pH >4.5
- Microscopy
  - WBCs, parabasal cells
- Treatment
  - 6 week course of intravaginal clindamycin 2% or hydrocortisone 10%





Genitourinary Syndrome of Menopause

- Symptoms
  - Dryness, irritation, itching
  - Burning, Pain with sex
- Exam
  - Erythema, lack of rugae
  - Elevated vaginal pH >4.5
- Microscopy
  - Lack of cellularity,
  - Parabasal cells
- Treatment
  - Topical or systemic estrogen
  - Vaginal moisturizers
  - Topical Lidocaine

Sexual Pain in Women

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Residency Program Director
Program in Vulvar Health, Oregon Health & Science University

Karen Adams, MD
Professor Obstetrics and Gynecology
Vice Chair of Education
Menopause and Sexual Medicine Program, Oregon Health & Science University

- No disclosures

Objectives

- Review epidemiology of sexual pain in women
- Discuss how to approach patients with sexual pain
- Discuss the most common causes
  - Vestibulodynia (localized, provoked vulvodynia)
  - Pelvic floor myalgia
  - Vulvovaginal atrophy (genitourinary syndrome of menopause – GSM)
  - Other

Epidemiology

- Incidence of painful intercourse 8-22%
  - Variation by culture, age, definition and study design
- Prevalance of vestibulodynia 8-15%
- Risk Factors
  - History of sexual abuse
  - Anxiety and depression
  - Hx of PID
  - Menopausal status (or other hypoestrogenic states)
  - Black race

Ask

- Many women are reluctant to discuss sexuality and pain
- Normalize discussion of sexuality in context of health
- Environment of openness, comfort, trust and confidentiality
- Ensure you have enough time
  - Consider scheduling a follow up visit to discuss separately

Trauma informed care

- 1 in 5 women have been raped in their lifetime
- Survivors have high rates of dyspareunia & sexual dysfunction
- ACOG recommends screening all women for a history of abuse, particularly women who report a history of pelvic pain or sexual dysfunction

Department of Justice, March 2013, ACOG Committee Opinion April 2014

Trauma informed care

- Women with a history of sexual pain and/or abuse may have a history of painful, traumatic pelvic exams, anxiety is likely to be high

Overwhelmed by emotion	62%
Unwanted or intrusive thoughts	44%
Abusive memory triggered during	45%
Body memories triggered during	43%
Felt detached from body	55%

Robohm, Women Health1996 24(3):59-75

Ask about difficulty or pain with exams in the past

"Is there anything about this visit/exam that might be especially difficult for you?"

Avoid the word relax, use neutral terms
Offer a mirror or for patient to place speculum themselves
Small Pederson or pediatric speculum
Encourage interaction, questions and information exchange
Offer lidocaine for patients with vestibular pain




Case 1

- 28yo G0 on OCPs who presents with dyspareunia. She complains of a raw and burning sensation with penetration. She has never been able to use tampons and sometimes feels uncomfortable wearing tight clothing.

Differential diagnosis for sexual pain

- Anatomic
  - Mullerian anomalies
  - Pelvic floor myalgia (vaginismus)
  - Endometriosis
- Infectious
  - Cadidiasis
  - STDs (GC/CT/HSV)
  - PID
  - UTI
- Hormonal
  - Genitourinary Syndrome of Menopause
  - Lactational hypoestrogenism
  - Hormonal suppression
- Psychosocial and Relationship
- Trauma
  - Perineal injury
  - Surgery
  - Radiation
- Inflammatory
  - Lichen sclerosus or planus
  - Inflammatory vaginitis
- Neurologic
  - Multiple sclerosis
  - Fibromyalgia
  - Peripheral neuropathy
  - Vestibulodynia

History

- Quality: onset, frequency, provoked or unprovoked, location, severity, circumstances, description of pain
- Exposure to contact irritants: soaps, spermicide, lubricants, bathing products or intra-vaginal products
- Vulvar Hair Hygiene: shave, laser, wax
- Hormonal status : Estrogen replete vs depleted (postpartum, menopause, anti-estrogen breast cancer treatment)
- Skin changes: associated symptoms of itching, ulceration, fissures or skin breakdown
- OTC or other treatments tried

Tools for Evaluation

- Physical Exam
  - Visual inspection of vulva , perineum, anus & vagina (speculum)
  - Qtip test
  - Evaluation of pelvic floor muscles
- Microscopy: swab side walls/fornix not cervix
  - pH immediately
  - NaCl and KOH: fresh prep or suspend in saline
- Vaginal Culture: vaginal side walls or fornix, not cervix
  - Fungal culture helpful for identification and speciation of yeast
  - General bacterial culture not helpful
  - AFFRIM® for common vaginitis (>90% sensitive)
- Vulvar Biopsy:
  - Reserved only for SKIN CHANGES, Random biopsy not helpful

Differential diagnosis for sexual pain

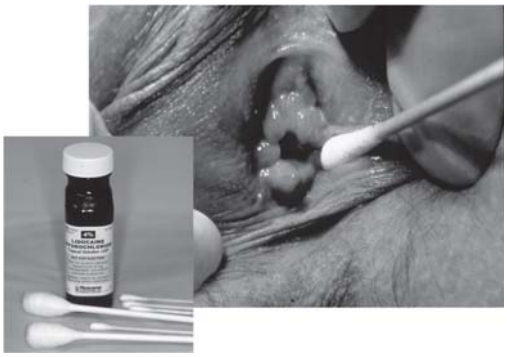
- Anatomic
  - Mullerian anomalies
  - Pelvic floor myalgia (vaginismus)
  - Endometriosis
- Infectious
  - Cadidiasis
  - STDs (GC/CT/HSV)
  - PID
  - UTI
- Hormonal
  - Genitourinary Syndrome of Menopause
  - Lactational hypoestrogenism
  - Hormonal suppression
- Psychosocial and Relationship
- Trauma
  - Perineal injury
  - Surgery
  - Radiation
- Inflammatory
  - Lichen sclerosus or planus
  - Inflammatory vaginitis
- Neurologic
  - Multiple sclerosis
  - Fibromyalgia
  - Peripheral neuropathy
  - Vestibulodynia

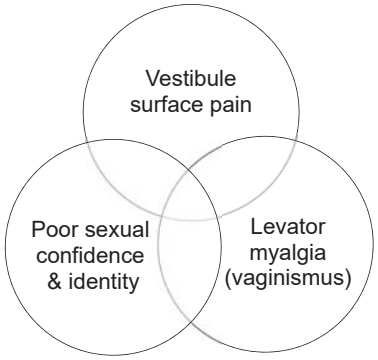
Vestibulodynia

- Localized provoked vulvodynia or vestibulitis
  - Pain that is provoked by touching the vulvar vestibule
  - Primary: present from first touch
    - (tampon, speculum or sex)
  - Secondary: develops later in life
- Diagnosis
  - History: pain with vestibular touch
    - sex, tampons, tight clothing
  - Exam: positive q-tip test
  - Diagnosis of exclusion

Qtip Test

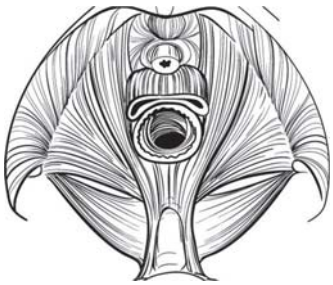
- Gently roll moist Qtip
  - no pressing or poking
- Vestibule clock-face
  - 12, 2, 4, 6, 8, 10 o'clock
  - Record pain level
    - (0-10)
    - Mild, mod, severe
- 3 minute application of 4% liquid lidocaine
- Re-test and record pain scale





Pelvic Floor Myalgia - Vaginismus

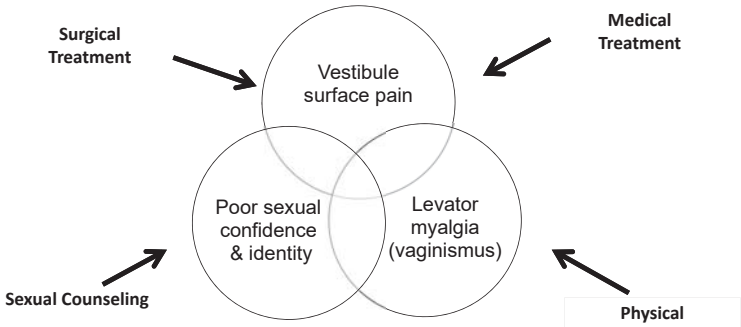
- Tight painful pelvic floor muscles
- Muscle spasms/bands
- Hyer or hypotonicity
- Poor control of muscles
- Inability to contract/relax
- Can be palpated on exam
  - Levator ani
  - Obturators



Psychosexual confidence and identity

- Often have significant distress around issues of sexuality
- May have impact on overall psychological wellbeing
- Anxiety, depression, fear, catastrophizing and hypervigilance are common
- Relationships can be strained or complicated as a result
- Important to assess
  - Desire
  - Arousal
  - Orgasm
  - Sexual frequency
  - Sexual practices
  - Relationship/s

The Oregon Approach: Management of Vestibulodynia



Treatment of Vestibulodynia

- Hygiene & Vulvar Care Measures
- Alternative Therapy (CAM, diet)
- Medical Therapy
- Physical Therapy
- Psychosexual Care
- Surgical Management

Promotion of Vulvar Health

- Reduce contact with potential irritants
  - soaps, creams, douches, vaginal wipes, pads
  - scented products, dyes, or chemicals
  - tight, synthetic, uncomfortable clothing
- Encourage all cotton (pads, underwear)
- Reduce vulvar hair removal
- Encourage bland emollients and lubricants
  - Vaseline, plain Crisco, Aquaphor,
  - coconut oil, Pjur, Slippery Stuff

Symptomatic Relief

- Lidocaine applied topically
  - 4% solution (soak on cotton ball and apply for 3-5 min)
  - 2 % gel (may last longer)
- Cool compresses or moistened tea bags
  - Applied for 10-15 minutes
  - gel packs, frozen peas, crushed ice
- Sitz baths
  - Epsom salts
  - Colloidal oatmeal

Complementary and Alternative Therapy

- Acupuncture
  - Pilot studies showed benefit in vulvar pain, dyspareunia and sexual function, though data is limited
  - Minimal risk
  - May be preferred by patients
- Dietary Modification
  - no evidence to support efficacy of any specific diet
  - Low Oxalate, high Calcium Diet (not effective)
  - Patients often want to try something and this is a safe, reasonable thing to try

Medical treatment of vestibulodynia

- Topical therapy – no strong evidence to support efficacy
  - 5% lidocaine cream (2 RCTs showed no benefit)
  - Gabapentin 2-6%
  - Amitriptyline 2%/ Baclofen 2%
  - Estrogen 0.01% +/- Testosterone 0.05%
  - Capsaicin 0.025-0.05% (from hot chili peppers)
- Oral Neuromodulators – no strong evidence to support efficacy
  - Tricyclic Antidepressants (RCT demonstrated no benefit)
  - Gabapentin or pregabalin
  - SNRIs
- Other Options - no strong evidence to support efficacy
  - Botulinum toxin type A injections
  - Nerve blocks (pudendal neuralgia – generally treats a different condition

Topical Treatments for Vestibulodynia

Name	Dosing	Efficacy
Lidocaine 5%	Applied daily	No clear benefit over placebo in 2 RCTs; both groups improved [27, 28] Descriptive study showed improved pain/frequency of sex [36]
Gabapentin 2-6%	Applied daily	No RCTs. Descriptive study showed improvement in pain and increased frequency of intercourse[37]
Amitriptyline 2%/ Baclofen 2%	Applied daily	No RCTs. Descriptive study reported improved pain [38]
Estrogen 0.01% +/- Testosterone 0.05%	Applied daily	No RCTs. Case series demonstrated significant decrease in pain [29]
Capsaicin 0.025-0.05%	Applied daily for 20 min and removed	No RCTs. Observational studies demonstrated decreased pain. [39, 40]

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Oral Therapy for Vestibulodynia

Name	Dosing	Titration
Tricylic Antidepressants **Amitriptyline (Elavil)** **Nortriptyline** **Desipramine**	10-100mg/day (average 50-75mg/day)	Start at 10-25mg and titrate up by 10-25mg every 7 days to max dose. Pain benefit usually 50-150mg
Duloxetine (Cymbalta)	20-60mg/day	Start at 20 mg and titrate up every 7 days to max dose. Pain benefit usually >/=60mg
Gabapentin (Neurontin)	100-3600mg/day in 3 divided doses	Start at 100mg and titrate up by 100mg/day every 5-7 days if well-tolerated. Pain benefit 900-2700mg
Pregabalin (Lyrica)	150-300mg/day in 2-3 divided doses	Start at 150mg and titrate up by to 300mg after one week if well tolerated.

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General principles – oral neuromodulators

- Titrate up to therapeutic range, titrate down to get off
  - No abrupt changes
- Managing side effects are important
  - Warn the patient what to expect
  - Side Effects: dry mouth, constipation, dizziness, fatigue, clouded thought, arrhythmias, seizures with abrupt discontinuation, headaches, nausea, fatigue, ataxia, tremor, decreased libido, anxiety
- Careful with concomitant use of ETOH and sedatives
- Unclear safety in pregnancy
- Most take 3-6 weeks for therapeutic benefit

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Physical Therapy and Biofeedback

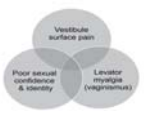
- Treats pelvic floor myalgia, levator muscle spasm, hypertonicity and poor contraction/relaxation phase.
- Biofeedback with dilator therapy increases patient awareness (home program), accommodation (of increasingly larger stretch) and control over muscles
- Good evidence that PT improves pain and decreases dyspareunia, independent of skin treatment
- Evidence that supports the PT in combination of surgery improves outcome
- Role for dilators in transitional intercourse

Managing Psychosexual Distress

- Profound psychological, physical and emotional impact of vulvar pain on women's mental health
- Unique impact on intimacy and relationships
- Therapy options
  - Individual counseling,
  - Cognitive behavioral therapy
  - Mindfulness,
  - Couples Counseling,
  - Sex Therapy
  - Group Therapy

Surgical Treatment of Vestibulodynia

- Vestibulectomy – Surgical technique that removes the painful superficial vestibular skin
- Highly effective treatment in reported series
  - 60-100% improvement (average is ~85%)
- No RCTs evaluating effectiveness or techniques
- Works best in combination (PT and psychosexual)
- Optimization of post op healing is important
- Complication rate is low



Authors	Year	Pt number	% cure/improve	F/U (mo)
Woodruff/Friedrich	1985	44	95%	NS
Friedrich	1987	38 (2nd surg for 13)	60%	NS
Marinoff	1991	73	97%	12-36
Foster	1995	93	88%	>48
Kehoe	1996	37	89%	3-34
Bornstein	1997	79	100%	12
Marinoff	1997	107	82%	3-48
Westrom	1998	42	90%	6
Kehoe	1999	54	89%	2-42
McCormack	1999	42	83%	12-120
Bergeron, Khalife	2001	38	68%	13-120
Schneider	2001	54	83%	6
Gaunt	2003	42	83%	6-24
Lavy (superficial)	2005	59	87%	6-120
Traas	2006	126	89%	13-57
Goetsch (superficial)	2009	155	94%	6-240
Tommolo	2012	39	89%	11-114
Swanson	2014	115	84%	NS
Brokenshire	2014	23	93%	36
Kliethermes	2016	20	100%	0-34

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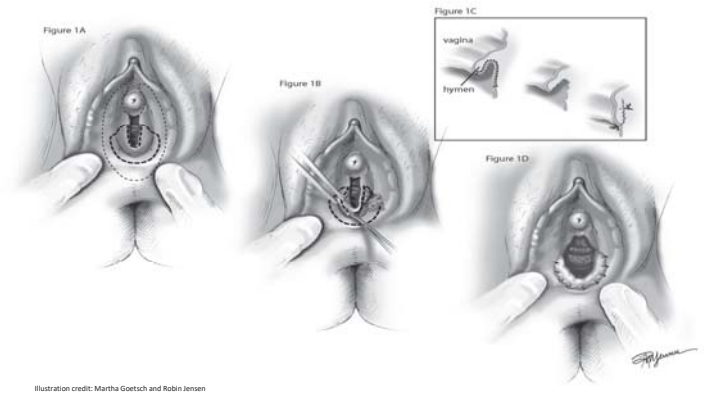
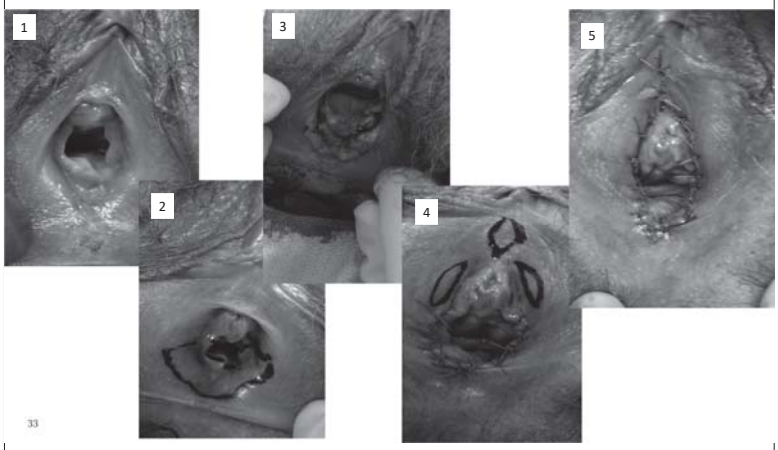


32 Illustration credit: Martha Goetsch and Robin Jensen



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Post-Operative Management

- **Initially:**
  - Pain management, rest and ice (first 72 hours)
  - limited activity, off work, minimal stretch (2 weeks)
- **2wks Post-op office visit:**
  - reassurance, sutures intact, liberalize activity, return to work
- **6 wks Post-op office visit:**
  - reassurance, sutures dissolved, Qtip test
- **8 weeks and ongoing**
  - PT for scar remodeling, vaginal accommodation and pelvic floor muscle teaching
  - Psychosexual Distress

- **Resumption of Sexual Intercourse**
  - Discuss transitional penetration
  - Data tells us most no earlier than 4 month postop
  - Voyeur to own pain (managing the psychosexual distress)

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Issues Around Surgical Treatment

- Ambivalence and opposition to surgery
  - Vulvodynia is vague and confusing
  - A procedure for something confusing seems risky
  - Continues to be thought of as a "last resort"
- Some disagreement on the best way to approach
  - Woodruff procedure
  - Simplified Goetsch procedure
  - Univ of Rochester procedure (middle ground)

- **Multiple studies show surgery BEST option for resolution of vestibular skin pain in vestibulodynia**

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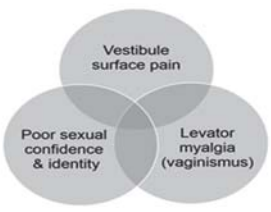
Our experience and research suggest that combining surgery with physical therapy and counseling result in the best outcomes.



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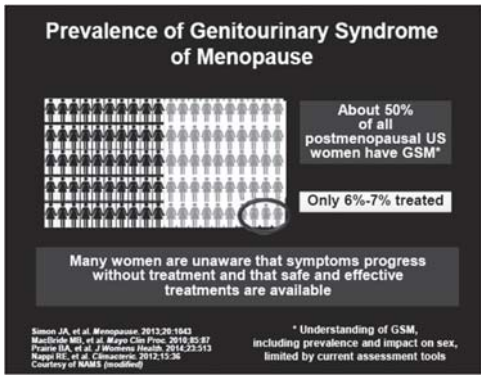
Menopause Patient #7

- 59 year old woman
  - No hot flashes
  - Increasing dyspareunia

Genitourinary Syndrome of Menopause

- **SYMPTOMS**
  - Vulvar/vaginal dryness
  - Decreased lubrication with sex
  - Discomfort or pain with sex
  - Bleeding after sex
  - Decreased arousal, orgasm, desire
  - Irritation, burning, or itching of vulva or vagina
  - Painful urination
  - Urinary frequency/urgency
- **SIGNS**
  - Decreased moisture
  - Decreased elasticity
  - Labia minora get thinner
  - Pale vaginal tissue
  - Loss of vaginal folds
  - Tissue fragility/splitting



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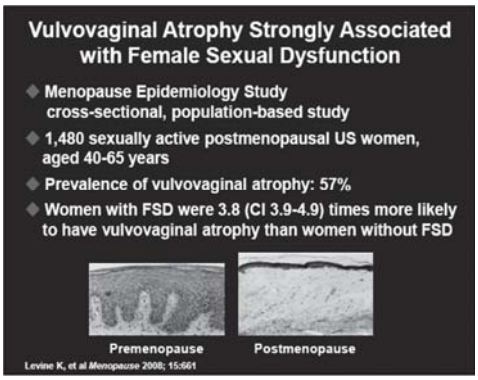

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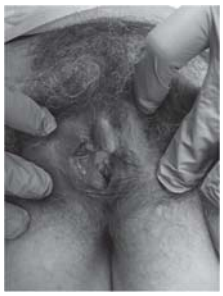
Diagnosis of GSM

- Look for it in peri or post menopausal women
- Thin thin thin
- Dry dry dry
- Ask about symptoms



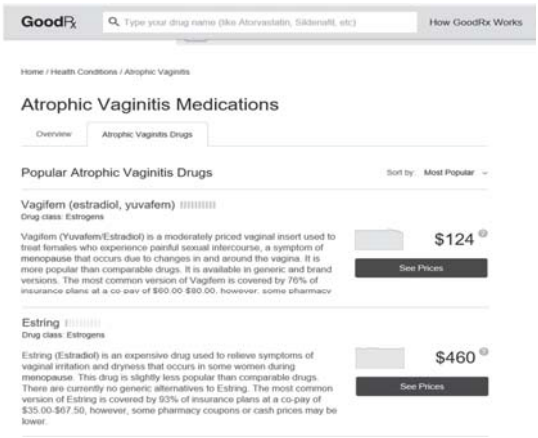
NAMS guidelines for GSM

- Start with OTC lubricants and moisturizers
- If no improvement after 3 months, move to estrogen

Vaginal Moisturizers

FDA-approved estradiol treatments

- Topical vaginal cream (Estrace)
  - 1 gm on fingertip nightly x 2 weeks then 2x week
- Vagifem tablets or Estring inserted in the vagina
- Estrogen softgel approved June 2018 ("more elegant delivery system")



Safety of local E therapy

- Reassuring when serum levels are measured
  Serum levels: E cream > E tablet > E ring
  All within menopause levels
- Reassuring when endometrial stripes are ck'd
- We now have 7-year follow up
- Breast cancer survivors need to know what is safe!

Choices of local therapy

- User abuse less likely with vaginal tablets or vaginal ring – temptation to use lots of cream
  - Med oncs are happier with tablet or ring than cream
  - OK if you take time to explain to your patient!

Menopausal Zest

- In a Gallup survey of 752 women, in the majority of women these areas were better or stable:
  - role at work
  - family life
  - partner/sexual relationship
  - friendships
  - self-fulfillment
  - and physical health.

Utian WH Menopause 1999;6:122-8

Differential diagnosis

- Anatomic
  - Mullerian anomalies
  - Pelvic floor myalgia (vaginismus)
  - Endometriosis
- Infectious
  - Cadidiasis
  - STDs (GC/CT/HSV)
  - PID
  - UTI
- Hormonal
  - Genitourinary Syndrome of Menopause
  - Lactational hypoestrogenism
  - Hormonal suppression
- Trauma
  - Perineal injury
  - Surgery
- Inflammatory
  - Lichen sclerosus or planus
  - Inflammatory vaginitis
- Neurologic
  - Multiple sclerosis
  - Fibromyalgia
  - Peripheral neuropathy
  - Vestibulodynia
- Psychosocial and Relationship

Endometriosis and adenomyosis

- Normally present with cyclic pain starting a week before menses and through first few days of menses
- Can become chronic, consistent pain. Can lead to anatomical changes that lead to sexual pain
- Often have pain with deep penetration/thrust

Treatment

Hormonal suppression

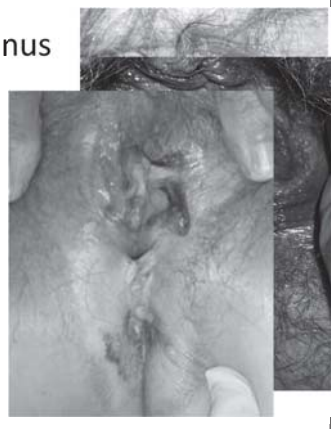
- OCPs, implants, GnRH

Surgical excision

- lesions and adhesions

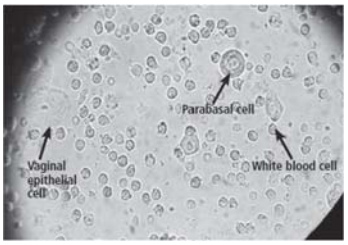
Lichen sclerosus and planus

- Inflammatory (autoimmune) disorders of the vulva and vagina (planus)
- Can lead to skin thinning, fissures, ulcers, increased sensitivity and significant scarring of the vulva
- Treatment is generally with ongoing topical steroid ointment
- Surgical correction can be indicated for patients with narrowed introitus and complaint of sexual pain



Desquamative Inflammatory Vaginitis

- Symptoms
  - Burning
  - Pain with sex
- Exam
  - Profuse purulent discharge
  - Erythema, petichiae
  - Elevated vaginal pH >4.5
- Microscopy
  - WBCs, parabasal cells
- Treatment
  - 6 week course of intravaginal clindamycin 2% or hydrocortisone 10%



Summary

- Sexual pain is common
  - affects 10-20% of women and has a significant impact on quality of life
- ASK patients about sexual function and pain routinely
- Trauma informed care/exam
  - hx of abuse or sexual pain
- Effective Treatment of sexual pain improves quality of life
  - Estrogen
  - Moisturizers and lubricants
  - Pelvic floor physical therapy
  - Counseling, CBT, mindfulness
  - Couples and Sex therapy
  - Lidocaine for temporary relief
  - Surgical vestibulectomy

Thank You!

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Practice Pearls for Comprehensive Pain Management

Kimberly Mauer, MD

Slides not provided

Post-Menopausal Osteoporosis for the Primary Care Provider

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Associate Professor, OHSU
Endocrinology; Bone and Mineral Unit
February 13th, 2020

63 year old post-menopausal woman

- Fractured left shoulder (proximal humerus) at age 61 while walking her dog. Her first fracture
- Menopause age 51, No history of estrogen replacement therapy
- Bone Density T-score
  - Lumbar spine: - 2.8
  - Total hip: -2.4
  - Femoral neck of hip: -1.8
- No history of steroid therapy, kidney stones, cancer

PMH / MEDS

- GERD
- Hypertension
- Insomnia
- Surgical History
  - Shoulder fracture repair
  - C-section
- Omeprazole 40 mg BID
- Amlodipine 5 mg daily
- Trazodone 50 mg bedtime
- Calcium with Vitamin D daily
- Multivitamin daily
- B Complex daily

SH / FH / ROS

- Wine nightly, no tobacco/drugs
- Lives with husband and dog
- Active lifestyle
- Yogurt every morning
- Father had curved spine
  - No hip fracture
- Mother died age 58 (breast cancer)
- ROS
  +back pain
  + bloating

Physical Exam

- BP 116/70 P 78 R 12 Pain 0 Weight 124 lbs Height 61.5 inches
- Gen: appears well
- EENT: no goiter, stable dentition
- CV: Reg
- Lungs CTA
- Abd: Soft, + BS
- MS: no spine pain to palpation, no kyphosis
- Skin: no bruising
- Psych: intelligent and conversational

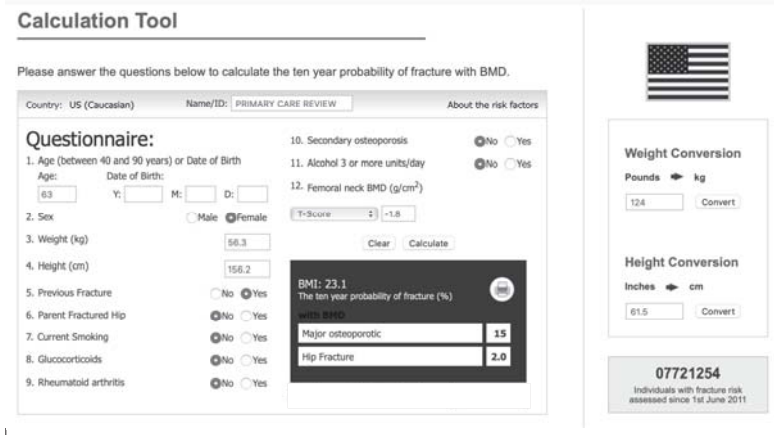
Bone Specific History / Exam Details

- Age of menopause
  - FRAX risk assessment (early is less than 45 yo)
- History of kidney stones
  - Hypercalciuria
- Daily dairy consumption
  - Calcium intake
- Parental history of HIP FRACTURE specifically
  - FRAX risk assessment
- Spine assessment on exam
  - Imaging workup
- Dental assessment on exam
  - Drug safety

Diagnosis of Osteoporosis

- 1) Clinical Judgment: Fragility fractures, general frailty
- 2) Bone density
  - T-score less than -2.5 at spine, total hip, or femoral neck of hip
- 3) Fracture Risk Assessment Tool (FRAX) – Free calculator
  - 20.0 % or greater 10 year risk of any osteoporotic fracture

  OR
  - 3.0 % or greater 10 year risk of hip fracture



Diagnosis of Osteoporosis - YES

- 1) Clinical Judgment: Fragility fractures, general frailty
- 2) Bone density
  - T-score less than -2.5 at spine, total hip, or femoral neck of hip
- 3) Fracture Risk Assessment Tool (FRAX)
  - 20.0 % or greater 10 year risk of any osteoporotic fracture

  OR
  - 3.0 % or greater 10 year risk of hip fracture

Clinical Pearl

- FRAX most useful in patients with osteopenia on bone density
  - T-score of -1.0 to -2.4 at spine, total hip, or femoral neck of hip
- Identifies patients with osteoporosis based on fracture risk
  - Parental history of hip fracture important data point
- Provides assurance that fracture risk is not elevated
  - Avoids over treatment

Osteoporosis Workup

- Highly Recommended
  - Complete Metabolic Panel (corrected calcium for low albumin)
    - Corrected Calcium = 0.8 * (4 – Albumin) + Measured Calcium
  - Phosphorus
    - Rare disorders of low phosphorus, osteomalacia
  - Vitamin D (25 – OH)
  - PTH (parathyroid level)
  - TSH
- General recommendation
  - Magnesium
  - CBC
  - Spine x-ray (abnormal exam finding)
  - 24 hour urine calcium (kidney stones = hypercalciuria?)
- Not Recommended
  - Bone turnover markers (NTX, CTX)
  - SPEP
  - Vitamin D (1,25 – OH)

Osteoporosis Treatment - Calcium

- A vital component of care!
- Total daily MINIMUM = 800 mg from all sources combined
  - Dairy plus supplements
  - Maximum intake = 2000 mg
- Assume 250 mg of calcium for every serving of dairy
  - Soy, almond, and coconut milk must say FORTIFIED on the package
- Leafy green vegetables are a potential source of calcium
  - Collard Greens: 250 mg / cup
  - Turnip greens: 200 mg /cup
  - Kale / Bok Choy: 150 mg / cup
  - Spinach contains oxalate which will impede absorption of calcium
  - All other greens contain < 150 mg / cup (broccoli, okra, swiss chard, peas)

Osteoporosis Treatment - Calcium

- Supplement to a level of 800 mg daily if required with tablets/caplets/chews/liquid/powder
- Will not cause a heart attack
- Calcium carbonate – most common form
  - 1 serving = 1 tablet will provide 500-600 mg calcium
  - Take with food
- Calcium Citrate – enhanced absorption over calcium carbonate
  - 1 serving = 2 tablets will provide 500 mg calcium
- Jarrows Bone Up™, Osteoblend™ are acceptable
  - Large serving size (3-6 tablets) to provide 500-800 mg calcium

Clinical Pearl

- Our patient on proton pump inhibitor therapy
- Reduces absorption of calcium carbonate
  - H2 blockers (ranitidine, famotidine) not a concern
- Confirm her supplement and switch to Calcium Citrate based regimen
  - Citracal™ is my personal favorite
- Other conditions to consider calcium citrate
  - Post gastric bypass
  - Crohns or Inflammatory bowel disease
  - Gluten intolerance

Osteoporosis Treatment – Vitamin D

- Goal Vitamin D (25 – OH) level
  - Optimal: 30 – 80 ng/ml (no difference between 34 and 68 ng/ml)
  - 20 ng/ml is absolute minimum
- 4000 IU (international units) daily from all supplement sources is safe and effective
- Add on 50,000 IU prescription dose weekly for 8 weeks to boost very low baseline levels (< 15 ng/ml)
- Check level after 6-8 weeks of repletion
- 6000 – 8000 IU daily are needed for some patients
  - No toxicity until over 100 ng/ml

Clinical Pearl

- Vitamin D3 (cholecalciferol) is the standard vitamin D supplement
  - Human/animal form
- Vitamin D2 (ergocalciferol) is plant based form
  - Same mechanism of action as D3 but shorter half-life
    - Vegan preferred
  - Prescription 50,000 IU capsule is Vitamin D2 – short term use
- Some labs report out Vitamin D3 (25-OH) and Vitamin D2 (25-OH) values
  - This is absurd, the total value (D3 (25-OH) + D2 (25-OH)) is what matters

Osteoporosis Treatment - Exercise

- Best weight bearing exercise program:

- Oregon State University Better Bones and Balance Program
  - $15.00 workout DVD

  - https://extension.oregonstate.edu/bbb/better-bones-balancer-store#dvd

Our Patient

- Ca 8.8 mg/dl Phos 2.8 mg/dl Cr 0.6 mg/dl
- Vitamin D (25 – OH) : 24 ng/ml
- PTH 82 pg/ml
- TSH Normal

- Stop calcium carbonate
- Start calcium citrate 500 mg daily (2 tablets daily)
- Start Vitamin D3 2000 unit capsule daily
- Maintain MVI and Yogurt intake
- Provide DVD order form

- CALCIUM, VITAMIN D, WEIGHT BEARING EXERCISE ARE THE FOUNDATIONS OF BONE HEALTH
  - Ensure that all three elements are addressed in your patient prior to medical therapy

Osteoporosis Treatment – Medications Bisphosphonates

- Bisphosphonates enter bone matrix and inhibits osteoclast cells (bone eating cells)
  - Known as ANTI-RESORPTIVES
- 1) Alendronate 70 mg tablet by mouth once weekly
  - Generic for Fosamax™
  - No role for Actonel™ (risedronate) nor Boniva™ (ibandronate)
- Empty stomach, water only, no lying down for 30 minutes
- Reduces spine, hip, and other fractures (humerus, radius, rib etc..)
- A first line agent

Osteoporosis Treatment – Medications Bisphosphonates

- 2) Reclast™ (zoledronic acid) 5 mg infusion
- Once yearly
- 100% adherence, no gastrointestinal side effects
  - inexpensive
- Excellent fracture prevention
- Post infusion reaction 1 – 5 days post therapy
  - Flu like symptoms
  - Acetaminophen, hydration, rest

Our patient

- Use of high dose proton pump inhibitor (> 40 mg daily)
  - Concern for ulcers, Barrett's esophagus, esophageal strictures
- Would avoid oral bisphosphonate (alendronate)
- Recommend IV zoledronic acid

Clinical Pearl

- Mild GERD not contraindication to oral alendronate
  - Safe to try for 4-8 weeks to assess GI side effects
- Caution patients on post infusion reaction to zoledronic acid infusion
- Ensure normal calcium levels and calcium intake
- Ensure normal vitamin D (25 – OH) level and vitamin D intake
- Minimum GFR for bisphosphonates: 40 ml/min
  - Calculate via Cockcroft-Gault equation
    - Accounts for weight, gender, age, and creatinine (MDRD does not account for weight)
    - Women less than 100 lbs will have low GFR despite normal creatinine

Osteoporosis Treatment – Medications Prolia™ (denosumab)

- Inhibits osteoclast signaling (only agent with this mechanism of action)
  - Classified as an anti-resorptive, like bisphosphonates
- 60 mg subcutaneous injection every 6 months
  - Must be in health care setting, not for patient self injection
- Superb spine, hip, and other fracture prevention
  - Similar to Reclast™ (zoledronic acid)
- Alternative for those with adverse reaction to bisphosphonates
  - Myalgias, infusion reaction
- Minimum GFR is 30 ml/min (excellent choice for CKD)
- Expensive, requires insurance pre-authorization
- Ensure adequate calcium and vitamin D intake

Osteonecrosis of the Jaw - ONJ (bisphosphonates and denosumab)

- Very rare: 1 in 10,000 patient-years
  - Fear of this adverse event not sufficient to avoid osteoporosis therapy
- Precautions
  - Poor dentition (you will know it when you see it)
  - History of radiation therapy to jaw/mouth
  - No regular dental care (unless full dentures)
  - Planned dental extraction or root canal
- Dental clearance not required
- No lab tests nor imaging available to predict, monitor for ONJ

Surveillance / Monitoring of Therapy

- Bone density after 1 year of therapy
  - Same or improved values
    - No declines over 5 %
- Routine labs not required

Duration of Therapy

- Alendronate: Not to exceed 5 years of continuous therapy
- Zoledronic acid: Not to exceed 3 years of continuous therapy
- Prolonged bisphosphonate exposure increases risk of atypical mid-femur shaft fractures
  - 1/1000 risk after 8 years of therapy
- Can restart therapy after 2 year drug holiday
- Denosumab: Safety data up to 10 years (20 injections) continuously
  - Therapy cessation associated with accelerated bone loss

2nd Line Therapeutic Options

- Evista™ (raloxifene) : Selective estrogen receptor modulator (SERM)
- 60 mg tablet daily
  - No regard to food or medications
- Prevents spine fractures
  - No hip fracture prevention data
- Reduces risk of breast cancer
  - Our patient with family history of breast cancer
- Risk of blood clots similar to estrogen
  - No uterine bleeding (progesterone not needed)

2nd Line Therapeutic Options

- Estrogen replacement (HRT)
- Prevents fractures
  - Breast and clot related side effects
- Should be used in conjunction with relief of menopausal symptoms
  - Should not be used solely for bone health
- Can be used in combination with any osteoporosis agent
  - Except raloxifene
- Rapid declines in bone mass occur after cessation

Specialized Anabolic Agents

- Forteo™ (teriparatide) and Tymlos™ (abaloparatide)
- Parathyroid hormone analogs
  - Stimulate osteoblasts (bone forming cells)
- Extremely effective with trabecular bone (spine bone mass)
  - Symptomatic compression fractures
  - T-score less than -3.0 at spine
- 2 year limit of use (black box warning regarding osteosarcoma)
  - Pagets disease of bone, radiation therapy, unexplained elevation of alk phos levels
- Daily subcutaneous injection
- Very expensive, requires insurance pre-authorization
- Must be followed by an anti-resorptive agent to maintain gains

New and Future Agents

- Evenity™ (romosozumab) – sclerostin inhibitor
  - Sclerostin inhibits bone formation
  - 210 mg subcutaneous injection every 30 days
- Inhibiting an inhibitor results in powerful anabolic agent
- Black box warning of increased risk of heart attack or stroke
  - Limited to 1 year of therapy
- Unclear where it currently fits in treatment paradigm
  - Alternative to teriparatide or abaloparatide
    - No osteosarcoma risk

Summary

- Calcium, Vitamin D, and weight bearing exercise are the foundations of bone health
  - Must be present for medical therapy to succeed
- Use calcium supplements to *supplement* to 800 mg of calcium daily
- Calculate FRAX score for patients with osteopenia
- Alendronate PO, zoledronic acid IV, and denosumab SQ are the primary osteoporosis agents
- Bisphosphonates (alendronate/zoledronic) have duration limits
- ONJ is a rare adverse effect
- Anabolic agents require attention to black box warning

Updated Dietary Recommendations for Pregnant Women, Infants and Toddlers (B-24)

Diane Stadler, PhD, RDN, LD

Slides not provided

Perioperative Medicine:
Pearls, Myths, and Complexities of Care

51st Primary Care Review

February 13th, 2020

Avital O'Glasser, MD, FACP, FHM

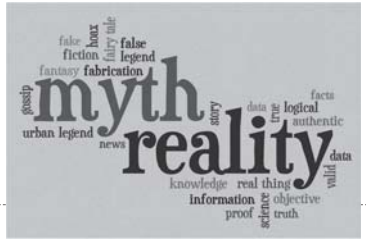
Introduction:

- No relevant financial disclosures

Introduction:

- Objectives
  - Discuss foundations of preoperative risk assessment for primary care clinicians
  - Identify common pitfalls and areas of confusion in perioperative medicine
  - Examine the nuances and "grey zones" of the guidelines
  - Empower the audience to find perioperative medicine an engaging type of patient-centered care and an exciting opportunity for multidisciplinary involvement

- Myth #1:
  - *"Can you CLEAR this patient for surgery?*
  - *"This patient needs an H&P within 30 days"*



Quantify and qualify the known co-morbid conditions, and perform a detailed investigation for the as yet undiagnosed risk factors.

- 2007 ACC/AHA perioperative guidelines:

"The preoperative consultation may represent the first careful cardiovascular evaluation for the patient in years or, in some instances, ever."

https://twitter.com/DavidWienerMD/status/1110590381262102530

"It is not like aviation when we have a clear runway. Our runways are rarely clear... more often I would say they are 'navigable'."
--Dr. Katie Schenning (OHSU Anesthesiologist)

"Cleared for Take Off?"

- Surgeon = pilot
- Anesthesiologist = co-pilot
- Medicine = ground crew

Who grounds the plane?

- analogy credit: Dr. Kurt Pfeifer, Dr. Sunil Sahai, Dr. Frank Michota

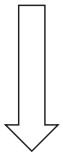
https://twitter.com/TWorrest/status/1113169078598766592

Knowledge is ~~Power~~ Empowering

This patient
This surgery
This surgeon
This indication
This time
This venue

Peri-Operative Assessment:

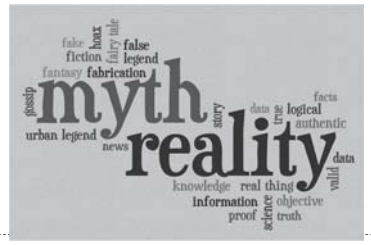
Can you CLEAR my patient for surgery?

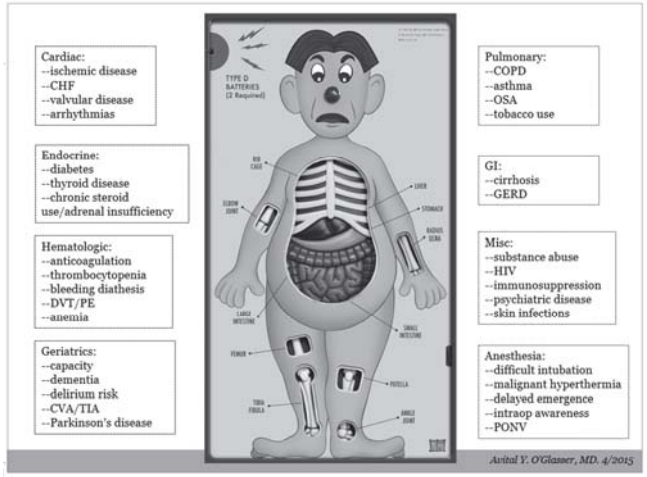


???

Peri-operative risk assessment & reduction:
Is this patient STABLE AND/OR OPTIMIZED for the specific surgery?

- Myth #2:
  - *"This patient has CARDIAC clearance, so we're good to go to the OR"*





Peri-Operative Pulmonary Risk:

- Postoperative Pulmonary Complications (PPCs) versus cardiac complications:
  - More common
    - **PPCs ~6.8% based on systematic review**
  - More costly:
    - Respiratory = $52,460 → mean LOS 19 days
    - Cardiac = $18,310 → 4d
    - Thromboembolic = $7,789 → 20d
    - Infectious = $1,398 → 9d

Dimick, JB, Chen, SL, et al. J Am Coll Surg 2004; 199:531

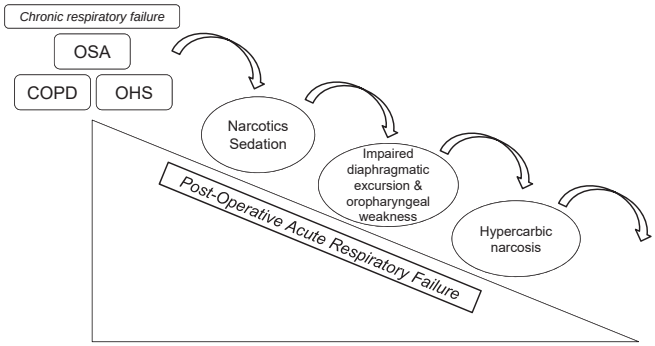
Post-Op Pulmonary Complications:

- OSA:

	Kaw, et al 2012 meta-analysis	Hai, et al 2014 meta-analysis
Post-op respiratory failure	OR 2.43	OR 2.42
Post-op ICU transfer	OR 2.07	OR 2.46
Cardiac events	OR 2.81	OR 1.63

- OHS:
  - Postop respiratory failure OR 10.9
  - Postop heart failure OR 5.4
- Pulmonary HTN:
  - Morbidity and Mortality OR13
  - Post-operative heart failure OR11.9

The Slippery Slope:

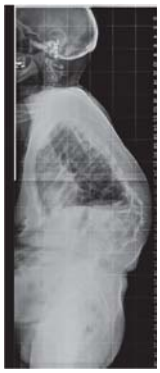


- Myth #3:
  - *"I can still forget most of what I learned about surgeries from 3rd year of med school"*

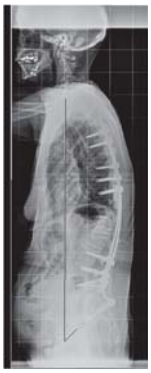
This patient
This surgery
This surgeon
This indication
This time
This venue

"The Marvelous Mrs. Maisel", Season 2, Episode 10

Surgery-specific details and risk:

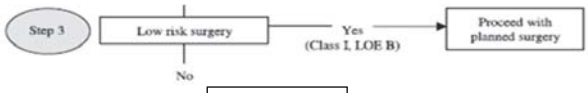


x 8-12 hours

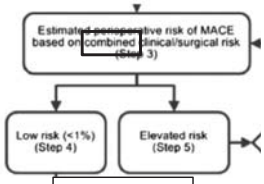


Long intraop time
Fluid shifts
Blood loss
Transfusion needs
Hemodynamic instability
Prone positioning

Combined Patient/Procedure Risk:



2007



2014

Combined Patient/Procedure Risk:

Estimate risk of perioperative myocardial infarction or cardiac arrest.

Age 70

Creatinine ≥1.5 mg/dL / 133 µmol/L

ASA Class ASA 3

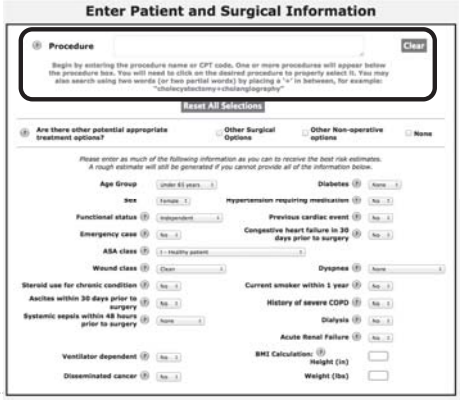
ASA 1 = Normal healthy patient
ASA 2 = Patients with mild systemic disease
ASA 3 = Patients with severe systemic disease
ASA 4 = Patients with severe systemic disease that is a constant threat to life
ASA 5 = Moribund patients who are not expected to survive without the operation

Preoperative Function Partially Dependent

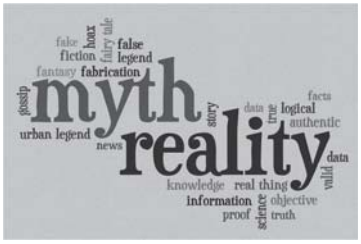
Procedure Hernia (ventral, inguinal, femoral)

Submit

Combined Patient/Procedure Risk:



- Myth #4:
  - *It's not an elective surgery, so a pre-op assessment isn't necessary or won't add value"*



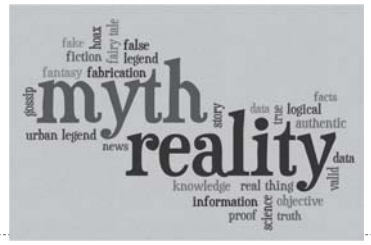
This Indication:

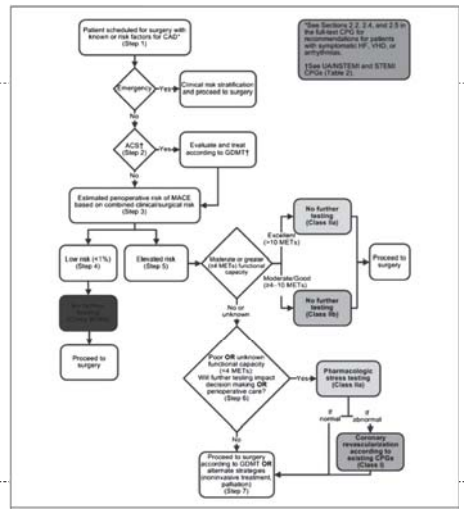
- Source of confusion = aka "Definitions"
  - Emergency
    - life [illegible]
    - me for no or very limi[illegible]
    - Typi[illegible] 6 hours
  - Urge[illegible]
    - here may be time for [illegible]
    - 6-2[illegible]
  - Time-sensitive.
    - "a delay of > 1 to 6 weeks to allow for an evaluation and significant change in management will negatively affect outcome"
    - ***What temporizing measures MIGHT be available??*
  - Elective
    - "could be delayed for up to 1 year"

Primary care based pre-op clinical evaluation assessment

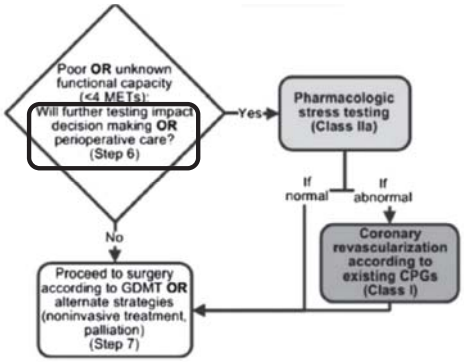
Primary care based pre-op clinical evaluation" assessment

- Myth #5:
  - *"I'm going to have to decide about stress testing on EVERY patient!"*



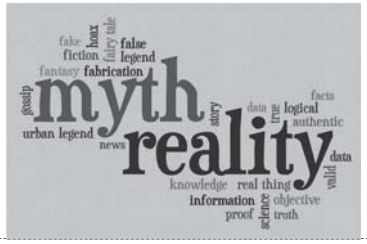


The DREADED Step 6!!

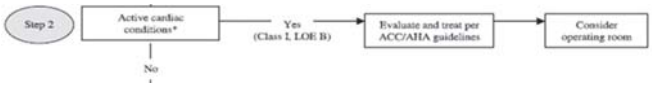


- Myth #6:
  - *"My patient doesn't need a stress test, so they're cleared for surgery!"*

- Myth #6—REPHRASED:
  - *"My patient doesn't need a stress test, so they can just go have their surgery done"*



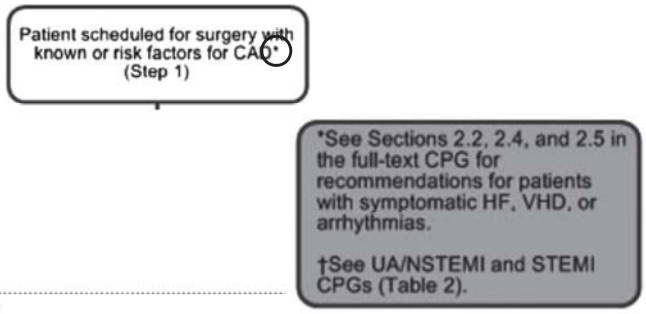
Cardiac Risk Assessment:



Active Cardiac Conditions:
1. Unstable coronary syndromes
   1. Unstable/severe (CCS class III/IV) angina
   2. Recent MI
2. Decompensated heart failure
3. Significant arrhythmias
4. Severe valvular disease

Cardiac Risk Assessment:

- But what about other "active" or other previously diagnosed cardiac conditions?



Heart Failure:

- For all the emphasis on CAD in risk prediction models (and pre-op consult Qs), patients with CHF have a significantly higher risk of post-op death and complications

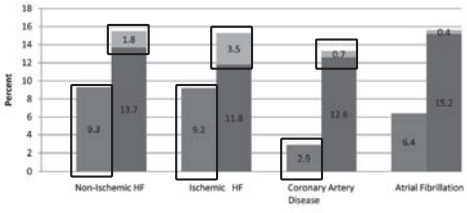


Figure 3. Unadjusted 30-day perioperative mortality (blue), rehospitalization (red), and cardiac rehospitalization (green). HF indicates heart failure.

Van Diepen, Bakal, McAlister. Circulation 2011.

JAMA | Original Investigation

Association of Left Ventricular Ejection Fraction and Symptoms With Mortality After Elective Noncardiac Surgery Among Patients With Heart Failure

Benjamin J. Lerman, BS; Rita A. Popat, PhD; Themistocles L. Assimes, MD, PhD; Paul A. Heidenreich, MD, MS; Sherry M. Wren, MD

- Heart failure associated with increased risk 90 day mortality:
  - aOR 1.67 [95%CI 1.57-1.76]
- Symptomatic patients with heart failure
  - aOR 2.37 [95%CI, 2.14-2.63]
- Asymptomatic patients with heart failure
  - aOR, 1.53 [95%CI, 1.44-1.63]
- Stratified by degree of LV dysfunction

https://jamanetwork.com/journals/jama/article-abstract/2724189

Heart Failure:

CLASS IIa

1. It is reasonable for patients with dyspnea of unknown origin to undergo preoperative evaluation of left ventricular (LV) function. *(Level of Evidence: C)*
2. It is reasonable for patients with heart failure (HF) with worsening dyspnea or other change in clinical status to undergo preoperative evaluation of LV function. *(Level of Evidence: C)*

CLASS IIb

1. Reassessment of LV function in clinically stable patients with previously documented LV dysfunction may be considered if there has been no assessment within a year. *(Level of Evidence: C)*

Valvular Heart Disease:

- 2014 ACC/AHA:
  - CLASS I: clinically suspected MODERATE or SEVERE valvular STENOSIS or REGURGITATION, undergo ECHO:
    - No prior ECHO within 1 year
    - Significant change clinical status or exam since last evaluation
    - Proceed with valve repair for symptomatic/severe disease before ELECTIVE noncardiac surgery when standard indications met

- Myth #7:
  - *"My patient doesn't need a stress OR an ECHO, but I still need to do EKG, CXR, CMP, CBC, INR, aPTT, UA, T&S…"*

Pre-Op Testing:

- Labs:
  - Large source of low value care
  - We over test!!
  - False positives → patient anxiety, additional testing
  - Limited ability to predict post-op adverse outcomes or change management
  - $$$
    - potential savings $154.3 million from pre-op INR/aPTTs/Platelet
    - Another study: save $82million annually with aPTT/INRs
  - Clinical indications
    - Baseline pre-test probability of abnormalities
    - Nature of surgery (fluid shifts, blood loss)

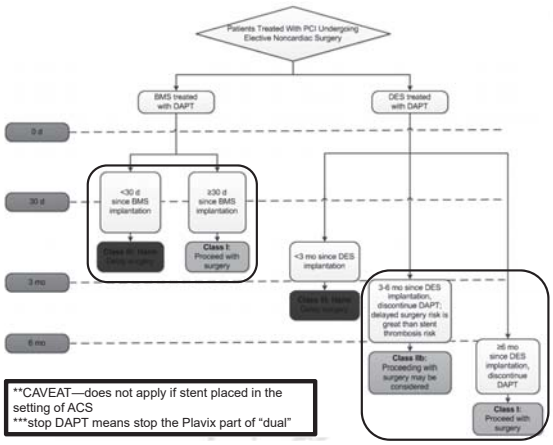
Pre-Op Testing:

- EKG:
  - No clear age cutoff
  - Order based on risk of underlying disease
- CXR
  - Not recommended for non-cardiothoracic surgery!

- Myth #8:
  - *"My patient doesn't need a stress OR an ECHO, so they can just go have their surgery done"*

This patient
This surgery
This surgeon
This indication
This time
This venue

2016 ACC/AHA DAPT Guidelines:

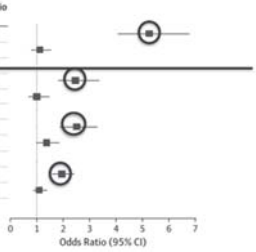


**CAVEAT—does not apply if stent placed in the setting of ACS
***stop DAPT means stop the Plavix part of "dual"

Surgery versus MI:

Figure 2. Adjusted Odds of Major Adverse Cardiac Events by Stent Indication and Time From Percutaneous Coronary Intervention (PCI)

Time From PCI	Stent Indication	Adjusted Odds Ratio (95% CI)
<3 mo	MI	5.25 (4.08-6.75)
	Unstable angina	1.11 (0.80-1.53)
	Non-ACS	[Reference]
3-6 mo	MI	2.45 (1.80-3.35)
	Unstable angina	0.99 (0.68-1.45)
	Non-ACS	[Reference]
6-12 mo	MI	2.50 (1.90-3.28)
	Unstable angina	1.36 (1.00-1.85)
	Non-ACS	[Reference]
12-24 mo	MI	1.95 (1.58-2.40)
	Unstable angina	1.08 (0.86-1.37)
	Non-ACS	[Reference]



- Non-cardiac surgery with stent in setting of ACS → increased risk of MACE → consider delay in surgery for 6 mons REGARDLESS of stent type

Holcomb et al. JAMA Surg. 2016 May 1;151(5):462-9.

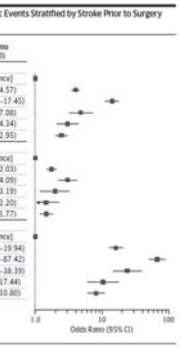
European Guidelines:

A multidisciplinary expert team should be considered for pre-operative evaluation of patients with an indication for DAPT before elective surgery.	IIa	C
In patients with recent MI or other high ischaemic risk features[c] requiring DAPT, elective surgery may be postponed for up to 6 months.[17,214,215,234]	IIb	C

Stroke:

Figure 1. Adjusted Odds Ratios of 30-Day Major Adverse Cardiac Events Stratified by Stroke Prior to Surgery and Time Elapsed Between Stroke and Surgery

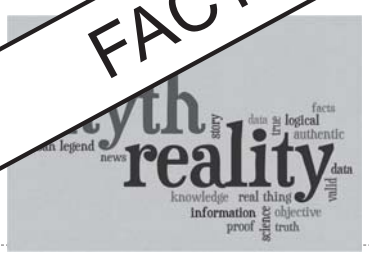
Source	Crude Events, No.	Sample Size, No.	Odds Ratio (95% CI)
30-d MACE			
No prior stroke	1923	474 046	1 [Reference]
Prior stroke anytime	389	7137	4.03 (3.55-4.57)
Stroke <3 mo prior	153	862	14.23 (11.61-17.45)
Stroke 3 to <6 mo prior	34	469	4.85 (3.32-7.08)
Stroke 6 to <12 mo prior	37	898	3.04 (2.13-4.34)
Stroke ≥12 mo prior	165	4908	2.47 (2.07-2.95)
30-d all-cause mortality			
No prior stroke	2914	474 046	1 [Reference]
Prior stroke anytime	254	7137	1.75 (1.53-2.03)
Stroke <3 mo prior	66	862	3.07 (2.30-4.09)
Stroke 3 to <6 mo prior	21	469	1.97 (1.22-3.19)
Stroke 6 to <12 mo prior	29	898	1.45 (0.95-2.20)
Stroke ≥12 mo prior	138	4908	1.46 (1.21-1.77)
30-d ischemic stroke			
No prior stroke	368	474 046	1 [Reference]
Prior stroke anytime	210	7137	16.24 (13.23-19.94)
Stroke <3 mo prior	103	862	67.60 (52.27-87.42)
Stroke 3 to <6 mo prior	21	469	24.02 (15.03-38.39)
Stroke 6 to <12 mo prior	16	898	10.39 (6.18-17.44)
Stroke ≥12 mo prior	70	4908	8.17 (6.19-10.80)



https://jamanetwork.com/journals/jama/fullarticle/1887763

- Myth #9:
  - *"Age is just a numbe*

FACT



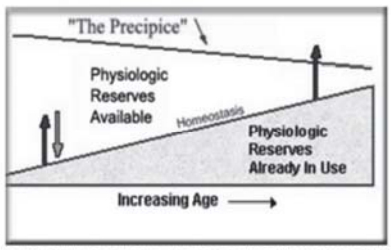
Peri-operative Geriatric Syndromes:

SURGERY IS PHYSIOLOGICALLY STRESSFUL

Significant disruption of homeostasis

Significant drain on already limited physiologic reserves

Frailty = predictor of post-op morbidity and mortality



Richard W. Besdine, DinTu WuAging of the Human Nervous System: What do We Know?,Geriatrics, Vol 91,May 2006

Preop Frailty Screening

Original Investigation

March 2017

Association of a Frailty Screening Initiative With Postoperative Survival at 30, 180, and 365 Days

Daniel E. Hall, MD, MDiv, MHSc[1,2]; Shipra Arya, MD, SM[3,4]; Kendra K. Schmid, PhD[5]; et al

> Author Affiliations

JAMA Surg. 2017;152(3):233-240. doi:10.1001/jamasurg.2016.4219

Editorial Comment

Key Points

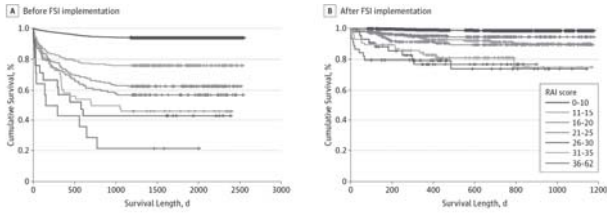
Question Can surgical outcomes of frail patients be improved by facility-wide frailty screening and subsequent administrative review of perioperative surgical decision making?

Findings After implementing a quality improvement project called the Frailty Screening Initiative in a prospective cohort of 9153 patients who underwent surgery, postoperative mortality decreased significantly at 30, 180, and 365 days. Multivariate models revealed a 3-fold survival benefit after controlling for age, frailty, and predicted mortality.

Meaning Frailty screening of preoperative patients is feasible and may be an effective tool for improving surgical outcomes for an aging and increasingly frail US population.

Pre-Operative Frailty:

- Overall 30-day mortality decreased, 1.6% → 0.7% (p<0.001)
  - Improvement was greatest among frail patients, 12.2% → 3.8%
  - Mortality rates also decreased for "robust" patients, 1.2% → 0.3%
  - Larger magnitude of improvement for frail pts at 180 days (23.9 to 7.7%) & 365 days (34.5 to 11.7%)



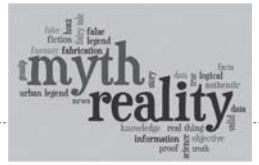
Hall et al. Association of a Frailty Screening Initiative with Postoperative Survival at 30, 180, and 365 JAMA Surgery, March 2017.

Recent OHSU Pre-Op Clinic Initiatives:

- Patients ≥ 65 presenting prior to elective, inpatient surgery
  - Preoperative Cognitive Screening: Mini-Cog
  - Preoperative Frailty Screening: Edmonton Frailty

Domain	Item
Cognition	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten after eleven'
General Health Status	In the past year, how many times have you been admitted to a hospital?
	In general, how would you describe your health?
Functional Independence	With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications)
Social Support	When you need help, can you count on someone who is willing and able to meet your needs?
Medication Use	Do you use five or more different prescription medications on a regular basis?
	At times, do you forget to take your prescription medications?
Nutrition	Have you recently lost weight such that your clothing has become looser?
Mood	Do you often feel sad or depressed?
Continence	Do you have a problem with losing control of urine when you don't want to?
Functional Performance	I would like you to sit in this chair with your back and arms resting. Then, when I say 'GO', please stand up and walk at a safe and comfortable pace to the mark on the floor (approximately 3 m away), return to the chair and sit down'

- Myths #10, 11, 12, & 13:
  - *"Even once I state risk, especially if 'high', I can't lower it"*
  - *"I can't talk a surgeon out of surgery"*
  - *"I can't talk a patient out of surgery"*
  - *"surgeons and patients will hate me if I postpone or cancel surgery"*



- Myth #14:
  - *"This surgery is still going to happen no matter what I put in my assessment…"*

In accord with ORS.41675 related to QA, Teaching & Supervision of Medical Staff Physicians

Risk Prediction Models

Taking About & Modifying Risk:

- PREDICTING peri-operative complications:
  - Modifications to the surgical plan
    - *Open surgery? Minimally invasive?*
  - Modifications to the anesthetic plan
    - *General? Local/Regional?*
  - Patient counseling/education, risk-benefit/informed consent
  - Modifications to post-operative care
    - *PROACTIVE versus REACTIVE* management and monitoring strategies
    - Location of care, ex day-patient versus inpatient, ward versus ICU
      - Step up OR step down
  - Predict LOS and discharge needs/location
  - Time to optimize even slightly?

Why talk about RISK?

- What if my patient says:
  - "But I just need to fix this!"
  - "I don't care if I die on the table."

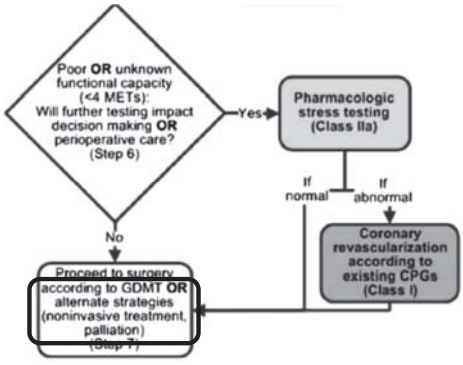
Is "mortality" really the best way to phrase discussions about surgical risk versus benefit?

- Is there a fate worse than death?
- Failure to rescue from complications?
- Quality versus quantify of days?
- "I'm not afraid of dying" → what ARE you afraid of?

Goals of Care:

- Don't ask your patient "what's the matter"…Ask them "what matters?"
  - Eric Schneidewind, President of the AARP
  - *(thanks to Dr. Monty Mythen, 14th Perioperative Medicine Summit Presentation, 2/2019)*

The DREADED Step 6!!



"And I Think That We Can Fix It"

Mental Models Used in High-risk Surgical Decision Making

Jacqueline M. Kruser, MD, Kristen E. Pecanac, MS, RN,† Karen J. Brasel, MD, MPH,‡ Zara Cooper, MD, MSc,§ Nicole M. Steffens, MPH,¶ Martin F. McKneally, MD, PhD,‖** and Margaret L. Schwarze, MD, MPP¶††*

- "Whether patients can transition between understanding *how* their disease is fixed with surgery to a subsequent deliberation about *whether* they should have surgery is unclear and may have broader implications for surgical decision making. "

Annals of Surgery: April 2015 - Volume 261 - Issue 4 - p 678–684

Aspects of Being a "Good Surgeon":

- "Knowing when to operate, knowing how much to operate, and knowing when not to operate"
  - Dr. Martin Schreiber on Dr. Vinay Prasad's "Plenary Session"

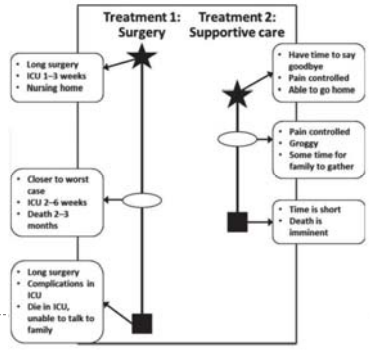
54:01 -22:17

ilitary Surgical Advances with Dr. M

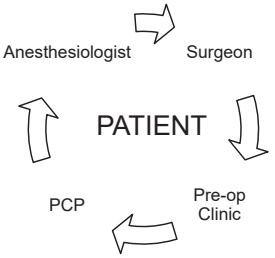
Plenary Session — January 15, 20

"Best Case/Worst Case":

Kruser JM, et al. "Best Case/Worst Case": Qualitative Evaluation of a Novel Communication Tool for Difficult in-the-Moment Surgical Decisions. J AM Geriatr Soc. 2015 Sept; 63(9):1805-11.



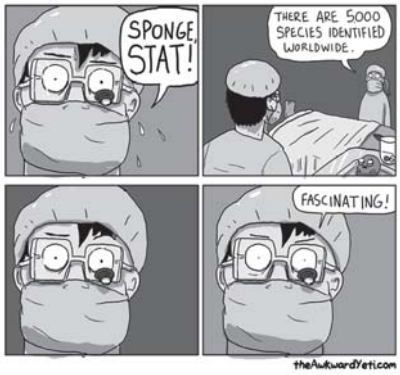
- *"Who can pull together this information...and say 'here's the reality about the risk of surgery…once these evaluations are completed?"*



This patient
This surgery
This surgeon
This indication
This time
This venue

Conclusions:

- Perioperative myths abound, but the literature guides our patient-centered best practice
- Ask the who/what/when/where/why for patient-centered preoperative evaluations
- Pre-op assessment is about far more than "stress"/"don't stress"
- Pre-op assessments are not just passive, data-gathering encounters


SPONGE, STAT!
THERE ARE 5000 SPECIES IDENTIFIED WORLDWIDE.
FASCINATING!
theAwkwardYeti.com

Questions?

MISSED OPPORTUNITIES FOR HIV SCREENING AND DIAGNOSIS

Principal Investigator: Kristine Simpson

Co-Investigators: Cara Varley, Marcel Curlin

OHSU IRB: 17850

Background

Why screen for HIV?

1.2 million people in the United States have HIV
- *Only 45% of people in the US have been tested*
- *1 in 7 people with HIV are unaware of their infection*
- *Nearly 40% of new HIV infections are transmitted by people who are unaware of their status*

Early detection is key
- *People who are aware of their infection are less likely to transmit to others*
- *Initiating therapy early leads decreased complications for the patient*
- *When in treatment and virally suppressed, the risk of transmission to others is eliminated*
- *IF testing is negative and the patient has risk factors for HIV, we have an opportunity to offer pre-exposure prophylaxis (PrEP)*

https://www.cdc.gov/hiv/basics/testing.html
https://www.cdc.gov/hiv/statistics/overview/ataglance.html

Background

Who to screen for HIV?

- Universal Screening: screen everyone, regardless of patient or provider perception of risk
- The CDC (2006) and USPSTF (2013) recommend universal screening for all adults and adolescents (ages 13-64, 15-65 respectively).
- Opt-out screening is recommended
  - *Example: "Kelly, I see here that we don't have an HIV test on record for you. We test all patients at least once in their lifetime as part of general health screening. I'll test you today for HIV unless you tell me not to."*
- Some groups have CDC recommendation to have *at least annual* HIV screening

https://www.cdc.gov/hiv/basics/testing.html
https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/hiv-testing-us-508.pdf
https://www.cdc.gov/hiv/statistics/overview/ataglance.html
https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/COMMUNICABLEDISEASE/DISEASESURVEILLANCEDATA/HIVDATA/Pages/HIV_Cluster.aspx

Background

Who to screen at least annually for HIV?

- Men who have sex with men
- Sexual partner who has HIV
- More than one sex partner since last HIV test
- Injection drug use with shared needles, syringes, or other drug injection equipment
- Transactional sex
- Diagnosed or treated for another sexually transmitted disease
- Diagnosed with or treated for hepatitis or tuberculosis (TB)
- Anyone with a recent Shigella diagnosis

https://www.cdc.gov/hiv/basics/testing.html
https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/COMMUNICABLEDISEASE/DISEASESURVEILLANCEDATA/HIVDATA/Pages/HIV_Cluster.aspx

Background: HIV in Oregon

- 7,557 Oregon residents are living with an HIV diagnosis
  - *1,230 residents were unaware they were infected*
  - *Nearly 1/3rd of patients are diagnosed at a late stage of HIV*
- There were 230 new cases of HIV in 2018
  - *43% in Multnomah county*
  - *Increase in people who inject drugs (PWID)*
- Communities of color are disproportionally impacted
  - *Incidence in Blacks and African Americans is 5x higher than Caucasians*
  - *Hispanics 1.7x higher*

https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/COMMUNICABLEDISEASE/DISEASESURVEILLANCEDATA/HIVDATA/Pages/HIV_Cluster.aspx
https://apps.state.or.us/Forms/Served/le9998.pdf
https://www.endhivoregon.org/#partners-1

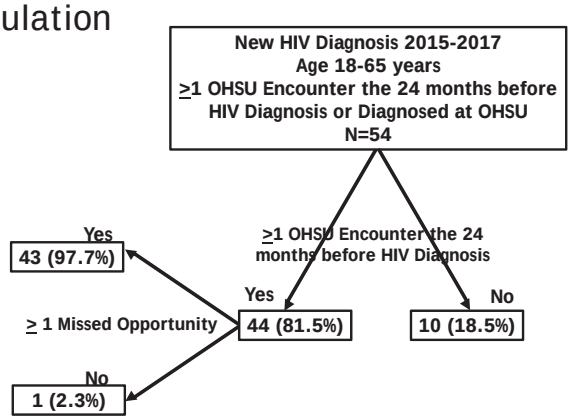
Study Aims

- **Aim 1:** Identify patients who had at least one missed opportunity for HIV screening
  - Missed Opportunity: An OHSU encounter where HIV screening could have been performed and was not
- **Aim 2:** Identify factors associated with early vs. late HIV diagnosis in those with at least one missed opportunity
  - *Late HIV Diagnosis: Diagnosed with AIDS or progressed to AIDS within one year of HIV diagnosis*
- **Aim 3:** Describe STI and hepatitis testing in our study population

Study Design

- **Population**
  - Retrospective cohort of Oregon residents newly diagnosed with HIV between November 1, 2015 and November 30, 2017
  - Had at least one documented physical encounter with a provider at OHSU at the time of HIV diagnosis or in the 24 months preceding diagnosis
  - Adults ages 18-65 at time of diagnosis
- **Chart Review** – 24 months before HIV diagnosis
  - Setting of encounters and specialty of providers
  - Identification of risk-increasing patient characteristics
  - Identification of risk-increasing laboratory findings

Population



Variable	Frequency	Percent
Age		
18-30 Years	16	29.6
30-40 Years	22	40.7
40-50 Years	9	16.7
> 50 Years	7	12.9
Male Gender	46	85.2
Caucasian	40	74.1
Transmission Category		
Adult with undetermined infection mode	5	9.3
Heterosexual contact with IDU	4	7.4
IDU only	5	9.3
MSM only	31	57.4
MSM/IDU	9	16.7
HCV at HIV diagnosis	9	16.7
STI at HIV diagnosis	2	3.7

Results:

Aim 1: Identify patients who had at least one missed opportunity for HIV screening

- 43 (79.6%) patients had at least one missed opportunity
- 11 (20.4%) were tested at their initial OHSU encounter
- Missed Opportunities
  - *Cumulative total of 201 encounters with missed opportunities*
    - 132 [65.6%] outpatient office visit
    - 51 [25.4%] emergency department
    - 18 [9.0%] hospital admission
  - *Median 2.5 encounters/person (range 1-26)*

Results:

Aim 2: Identify factors associated with early vs. late HIV diagnosis in those with at least one missed opportunity

	Late Diagnosis		P value	OR (95% CI)
	Yes N = 10 (23.3%)	No N= 33 (76.7%)		
Mode of Transmission: IDU	8 (80.0%)	6 (18.2%)	< 0.01	18.0 (3.0-107.2)
≥1 Clinic Visit 24 Months Prior to Diagnosis Median (range)	4 (40.0%) 0 (0-20)	27(81.8%) 1 (0-23)	0.02	0.1 (0.03-0.7)
≥1 Admission 24 Months Prior to Diagnosis Median (range)	5 (50.0%) 0.5 (0-3)	6 (18.8%) 0 (0-2)	0.09	4.5 (0.9-20.6)
Age > 40 years at Diagnosis	5 (50.0%)	10 (30.3%)	0.25	2.3 (0.5-9.8)

KS [

Slide 11

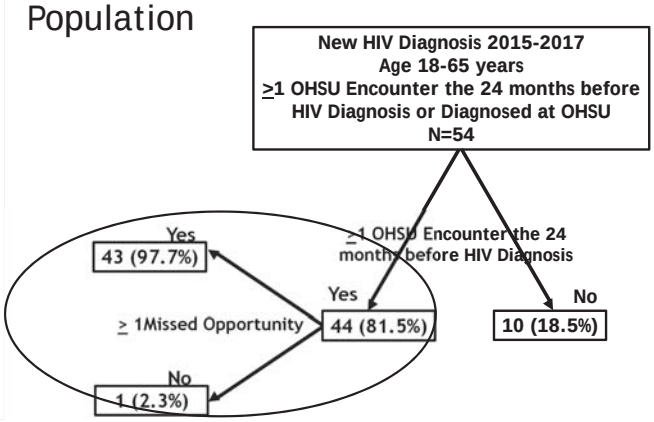
KS [2]27 OK, so IDU and clinic visits are the take aways. How can we expand on this just a bit more. The range of 0-23 is so large we lose some meaning. What if we considered bins for number of OVs? 0-2, 3-5, 6-10, >10,. This is important to the PCP because it reminds them of how many opportunities there actually are. Dig into this a little and see what numbers separate out.
Kristine Simpson, 1/24/2020

Results:

Aim 2: Identify factors associated with early vs. late HIV diagnosis in those with at least one missed opportunity

	Late Diagnosis	
	Yes N = 10 (23.3%)	No N= 33 (76.7%)
≥1 Clinic Visit 24 Months Prior to Diagnosis	4 (40.0%)	27(81.8%)
0 Visits	6 (60%)	7 (21.2%)
1-2 Visits	0	16 (48.4%)
3-6 Visits	2 (20%)	7 (21.2%)
7-10 Visits	0	1 (3%)
> 10 Visits	2 (20%)	2 (6.1%)
≥1 Admission 24 Months Prior to Diagnosis Median (range)	5 (50.0%)	6 (18.8%)
0 Admissions	5 (50%)	27 (21.2%)
1-2 Admissions	2 (20%)	5 (81.8%)
3-6 Admissions	3 (30%)	7 (15.2%)

Population



Results:

Aim 3: Describe sexual history documentation, STI and HCV testing in our study population

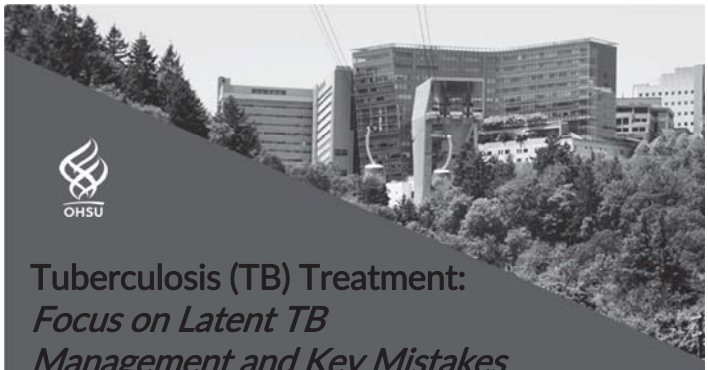
- **Testing**
  - *2/44 (2.6%) HIV*
  - *3/44 (6.8%) syphilis*
  - *6/44 (13.6%) chlamydia and gonorrhea*
  - *3/41 (7.3%) HCV*
- **Sexual History**
  - *14/44 (31.8%) had something documented for sexual history.*
    - *Partner gender – 13 (92%)*
    - *Number of partners – 3 (21%)*
    - *History of STIs – 2 (14%)*
    - *HIV Positive Sexual Partner – 3 (21%)*
    - *Condom Use Frequency – 5 (36%)*
    - *Transactional Sex – 1 (7%)*
  - *PrEP Discussed – 3 (21.%)*

Summary

- Every patient should be screened for HIV
- Anyone with risk factors should be screened at least annually
- Sexual history and STI screening were not performed on ~70% of our cohort
- 90% of our cohort had a risk factor for HIV identified by our Public Health colleagues
- Approximately 80% of patients newly diagnosed with HIV had at least one missed opportunity for HIV screening
- Most of these missed opportunities are in the outpatient setting
- People who inject drugs are more likely to have a late diagnosis

Thanks!

- Oregon Health Authority
  - *Tim Menza*
  - *Denise Skrypkar*
- Oregon Health & Science University
  - *Kristine Simpson*
  - *Marcel Curlin*



Tuberculosis (TB) Treatment: *Focus on Latent TB Management and Key Mistakes to Avoid with Active TB*

February 13, 2020

Luke Strnad, MD @lstrnad5
Assistant Professor of Medicine & Epidemiology
OHSU Division of Infectious Diseases & OHSU/PSU School of Public Health

Disclosures

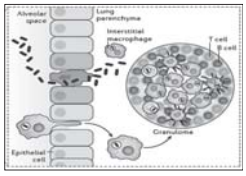
- Luke Strnad:
  - No financial disclosures
  - Sentinel Hotel

Session Objectives

- Briefly summarize the appropriate diagnostic evaluation and test interpretation for latent TB.
- Highlight who to prioritize for latent TB testing and treatment.
- Outline in more detail the different latent TB treatment regimens and how to choose and monitor them in a primary care setting.
- Understand some common pitfalls in the recognition of active TB in those you think have latent TB.

Tuberculosis (TB) pathophysiology

- In 90%, *infection* remains controlled as "latent TB" (LTBI)
- Spread of limited by immune system
  - Organisms hang out for years (life?)



- 10% develop *disease* at some point
  - Weakening of the immune system increases risk of progression from infection or "latency" to "disease"
  - Most commonly in the lung, but can be anywhere…

Pai et al. Nat Rev Dis Primers. 2016;2:16076

TB immune-based testing (PPD/IGRA) is imperfectly sensitive

***VS* QFT-GIT**

- **PPD/TST** slightly lower sensitivity and much less specific
- **T-SPOT** similar sensitivity and specificity
- **QFT-plus** slightly higher sensitivity (85-90%) and specificity

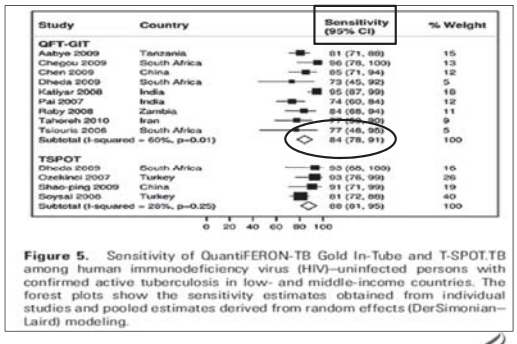


Figure 5. Sensitivity of QuantiFERON-TB Gold In-Tube and T-SPOT.TB among human immunodeficiency virus (HIV)–uninfected persons with confirmed active tuberculosis in low- and middle-income countries. The forest plots show the sensitivity estimates obtained from individual studies and pooled estimates derived from random effects (DerSimonian–Laird) modeling.

Metcalf, et al. JID. 2011. 204:S1120–29
Horne D et al. IJTLD 2018. 22 (6), 617-621

LTBI Testing: imperfect science

- With imperfect sensitivity and specificity, positive and negative predictive value **depends on prevalence…**

A Game of Theory

	Disease+	Disease-		10% Prevalence	
Test+	90	90		Total	1000
Test-	10	810		Disease	100
Total	100	900		Not Disease	900
			50% of positive tests real		
Sensitivity	0.9				
Specificity	0.9				
			31% of negative test are false		
	Disease+	Disease-		80% Prevalence	
Test+	720	20		Total	1000
Test-	80	180		Disease	800
Total	800	200		Not Disease	200
Sensitivity	0.9				
Specificity	0.9				

"CDC discourages use of diagnostic tests for LTBI among individuals and populations at low risk for infection with *M. tuberculosis*." – CDC 2013

So now their LTBI testing is positive
What next??

- CXR!! Sx screen alone suboptimal sens
- Sputum for AFB smear/cx if the CXR is abnormal ***or*** the person is symptomatic
- HIV screen
- A1C?
- LFTs?
  - Meds, liver Dz, HIV, pregnant/post-partum

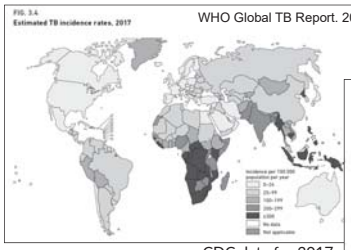
Screening tool	Pooled sensitivity % (95% confidence interval)	Pooled specificity % (95% confidence interval
Chest radiography		
Any abnormality compatible with TB (active or inactive)	98 (95–100)	75 (72–79)
Abnormalities suggestive of active TB	87 (79–95)	89 (87–92)
After positive screening for symptoms[a]	90 (81–96)	56 (54–58)
Symptom screening		
Prolonged cough (lasting >2–3 weeks)	35 (24–46)	95 (93–97)
Any cough	57 (40–74)	80 (69–90)
Any TB symptom (settings with low prevalence of HIV)	70 (58–82)	61 (35–87)
Any TB symptom (settings with high prevalence of HIV)	84 (76–93)	74 (53–95)
Any TB symptom (settings with low prevalence or high prevalence of HIV)	77 (68–86)	68 (50–85)

[a] Results from only one study, data for any abnormality on chest radiography.

WHO. Systematic screening for active tuberculosis 2013

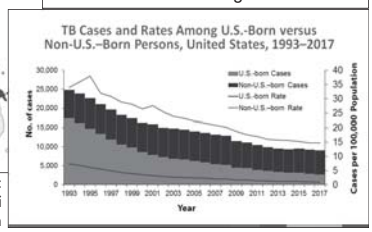
LTBI Testing Prioritization
From an area of TB endimicity is a risk

- Want to prioritize testing the following:
  - Those likely to be exposed (latently infected)
  - Those most likely to progress to active disease



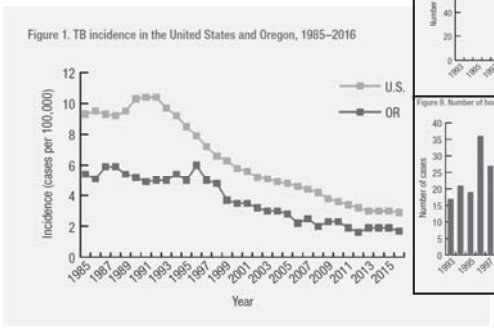
WHO Global TB Report. 2018

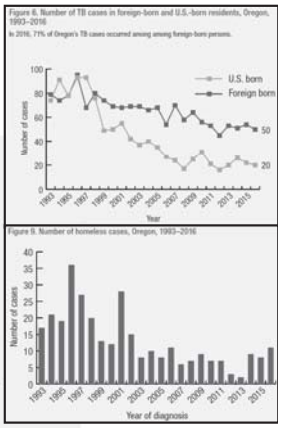
Moral:
Prioritize those born/raised in endemic countries for LTBI testing and treatment.



CDC data for 2017:
https://www.cdc.gov/tb/statistics/reports/2017/default.htm

Oregon tuberculosis epidemiology

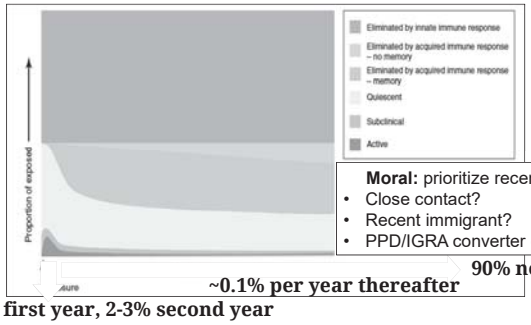




https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/COMMUNICABLEDISEASE/TUBERCULOSIS/Documents/data/or2016data.pdf

More recent infection is a risk

- In general: 5-10% lifetime risk of Active TB



Moral: prioritize recent infections
- Close contact?
- Recent immigrant?
- PPD/IGRA converter (neg → pos)

90% no disease

~0.1% per year thereafter

5% first year, 2-3% second year

Figure: Esmial and Barry. Drug Discovery 2012
Slide adapted from: Lisa Chen, Curry Center, personal communication, 2015

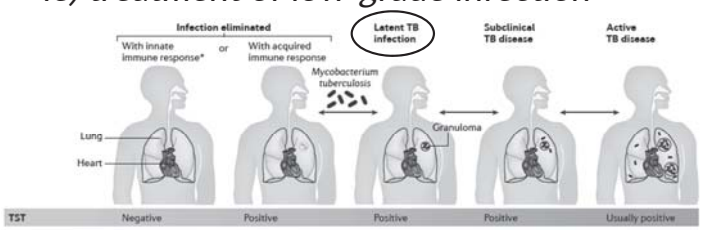
Weakened immune system is a risk

The risk of progression is 7-10% each year!!

Risk Factor for active TB disease	Relative Risk (95% CI)
Advanced untreated HIV	9.9 (8.7-11)
Close Contacts	**6.1 (5.5-6.8)**
CXR c/w prior healed TB	**5.2 (3.4-8.0)**
Prednisone ≥15mg/day	2.8 (1.7-4.6)
Chronic Renal Failure	2.4 (2.1-2.8)
TNF alpha inhibitor	2.0 (1.1-3.5)
Poorly controlled diabetes	1.7 (1.5-2.2)
Weight <10% below normal	1.6 (1.1-2.2)
Smoking	1.5 (1.1-2.2)
Kids are the double whammy: Risk may double if <4 years old, 40% risk if < 12mo	

Horsburgh and Rubin, NEJM. 2011;364(15):1441-8
LTBI guide for primary care providers. CDC. 2013

Latent TB Treatment
ie) treatment of low-grade infection



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Pai et al. Nat Rev Dis Primers. 2016 Oct 27;2:16076

What does low-grade infection mean for treatment?

- Fewer organisms
  - Shorter time to eradication
  - Less risk of resistance developing

LTBI treatment regimens

INH = isoniazid (300mg Qd)
RIF = rifampin (600mg Qd)
RFP = rifapentine (900mg Qwk) + INH (900mg Qwk)

Drugs	Duration	Interval	Minimum doses
Isoniazid	9 months	Daily	270
Isoniazid	6 months	Daily	180
Isoniazid and Rifapentine	3 months	Once weekly*	12
Rifampin	4 months	Daily	120

* Non-directly observed therapy allowable in selected patients

- Efficacy relatively equal for INH 9 mo, RIF 4 mo, and INH/RFP 3 mo

Becoming preferred regimens

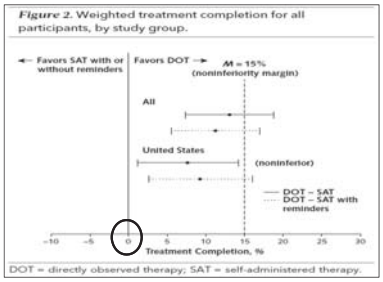
Likelihood of Completion:
9 months INH: 45-60% completed
6 months INH: 55-57% completed
4 months RIF: 69-78% completed
3 months INH + RFP: 75% completed

www.cdc.gov
Schechter et al. AJRCCM. 2006;173:922-6

Jasmer Ann Intern Med 2002;137:640-7
Menzies. AJRCCM 2004;170:445-9

Self-administered (SAT) weekly INH/RFP may or may not be the equivalent of DOT but you can do it if you choose patients correctly

CDC release: MMWR June 29, 2018 / 67(25);723–726 → **SAT okay**



Non-inferiority: **15% margin**
N = 1002
DOT: **87.2%** completion
SAT: **74.0%** completion

Belknap et al. Ann Intern Med. 2017;167:689-697

LTBI treatment: *so how do I decide?*

- **Hepatotoxicity:**
  - INH 9mo > INH + RFP 3mo > RIF 4mo
  - Esp with INH risk linearly increases with age
- **Drug-drug interactions:**
  - Rifamycins have a lot (the most) drug-drug interactions
  - *CYP450* → metabolize (lower level of) other drugs
  - Esp worry: anticoagulation, neuro meds, cardiac meds
- **Host characteristics**

Interaction check!!!

Stagg et al. Ann Intern Med. 2014;161(6):419-28

LTBI treatment monitoring
You don't need all those LFTs!!

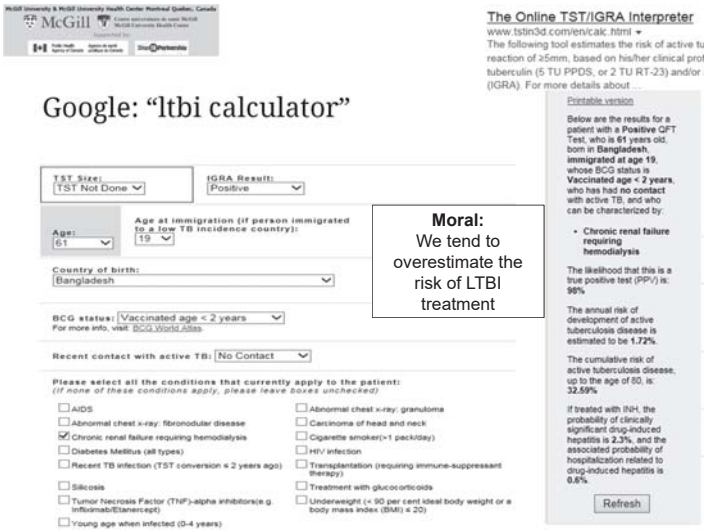
- Baseline LFTs are ***not*** indicated for all at start of LTBI treatment (tx)
- Baseline LFTs are indicated at the start of LTBI tx **if:**
  - Liver disorders/history of liver disease/risks for chronic liver disease
  - Regular alcohol use
  - HIV infection
  - Pregnancy or within 3 months of delivery
  - On an individual bases for patients on other hepatotoxic medications
- After baseline, routine retesting is recommended for: **1)** persons who had abnormal initial results; **2)** other persons at risk for hepatic disease
- If LFTs abnormalities during tx, hold tx **if:**
  - LFTs > 3x upper limit of normal with symptoms
  - LFTs > 5x upper limit of normal but asymptomatic

CDC Division of TB Elimination. Page last reviewed: March 11, 2019. Page accessed Feb 3, 2020. https://www.cdc.gov/tb/publications/ltbi/treatment.htm#patientMonitoringEducation

LTBI treatment:
common side effects

https://www.cdc.gov/tb/education/provider_edmaterials.htm

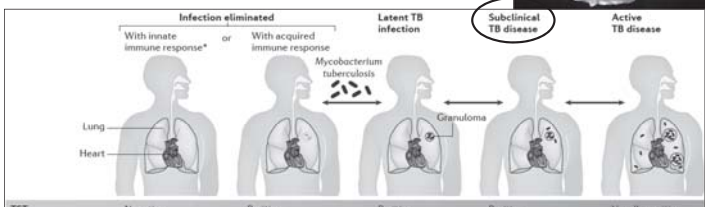
- **Isoniazid:**
  - Mild neurologic symptoms
  - Peripheral neuropathy (mitigated by pyridoxine – B6)
  - Rash
  - Hepatitis (transaminitic)
- **Rifampin:**
  - Gastrointestinal upset (nausea/vomiting > diarrhea/constipation)
  - Orange/bronze urine (not dangerous and will go away on completion!!)
  - LFT abnormalities (cholestatic > transaminitic)
  - Drug-drug interactions
  - Metabolizes contraceptive medications!!
- **Rifapentine:**
  - Rifampin SE plus:
    - Feeling a little "off" on the one day/week of dosing (could also be high dose INH)
    - Anaphylaxis



Moral: We tend to overestimate the risk of LTBI treatment

Picking the out active TB cases

How do you know it's not active disease?!?



TST	Negative	Positive	Positive	Positive	Usually positive
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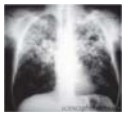
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Pai et al. Nat Rev Dis Primers. 2016 Oct 27;2:16076

Infection = bacilli in your body / ***Disease*** = bacilli are making you sick



Tuberculosis clinical presentation:

Sites of disease presentation

- Most case (75%) are in lungs (pulmonary)
  - Lung cavity or infiltrate
- 10-15% extrapulmonary
  - Lymph nodes, pleura
  - Bone, brain, kidneys, gut
- 5% disseminated
  - Everywhere

Table 24.1: Percentage of anatomic location of extra-pulmonary tuberculosis

Study	Peto 2009	Sandgren 2013	Zhang 2011**	Rodriguez 2011	Gunal 2011	Prakasha 2013	Jamtsho 2013
Location	USA	EU*	Denmark	Spain	Turkey	India	Bhutan
Total Patients	47,293	108,345	1,644	705	103	528	469
Lymphatic	40.4%	30.5%	49.1%	30.6%	9.7%	24.8%	41.6%
Pleural	**19.8%**	**36.7%**	**13.6%**	**41.1%**	**10.7%**	**28.0%**	**30.5%**
Bone or Joint	11.3%	9.0%	13.0%	5.8%	10.7%	12.3%	3.0%
Genitourinary	6.5%	6.9%	9.2%	7.0%	27.2%	4.4%	3.0%
CNS	5.4%	3.4%	2.6%	4.1%	19.4%	12.5%	1.5%
Peritoneal or Gastrointestinal	4.9%	2.6%	5.6%	4.5%	9.7%	9.7%	9.8%
Other	11.8%	10.9%	6.9%	6.8%	12.6%	8.3%	10.7%

* EU = European Union
** 52% of patients of Somali or Asian origin

Strnad et al. Ch 24 – Effusions from Infections:

Moral: Positive LTBI testing in a risk host without pulmonary symptoms and with normal CXR does not guarantee they don't have active disease

Strnad et al. Ch 24 – Effusions from Infections: Tuberculosis. Textbook of Pleural Disease 3E. ed Richard Light and YC Gary Lee

Testing for tuberculosis disease:

AFB smears are fast but imperfect

Table 1 | **Technologies reviewed by the WHO for the diagnosis of active TB disease and the detection of drug resistance**

Test	Assay principle	Use	Sensitivity (%) *	Specificity (%)	TAT*	Target setting‡	Year endorsed
Microscopy							
Conventional sputum smear microscopy	Direct visualization of mycobacteria using light microscopy	Active TB disease diagnosis	32–94	50–99	Same day	Peripheral and reference laboratories	Included in the WHO guidelines for many years
LED fluorescence smear microscopy§	Direct visualization of mycobacteria using fluorescence microscopy	Active TB disease diagnosis	52–97	94–100	Same day	Peripheral and reference laboratories	2011
Culture-based techniques							
Liquid culture with DST	Mycobacterial culture on liquid media	• Active TB disease diagnosis • Drug resistance	• 89 (among smear-positive and culture-positive) • 73 (among smear-negative and culture-positive)	>99	10–21 days	Reference laboratory	2007

Moral: assume smears are 50/50

*Microscopy sensitivity lower in HIV/other immunocompromise

Pai et al. Nat Rev Dis Primers. 2016 Oct 27;2:16076

Testing for tuberculosis:

PCR helps but is less good than other bacteria

Table 1 | **Technologies reviewed by the WHO for the diagnosis of active TB disease and the detection of drug resistance**

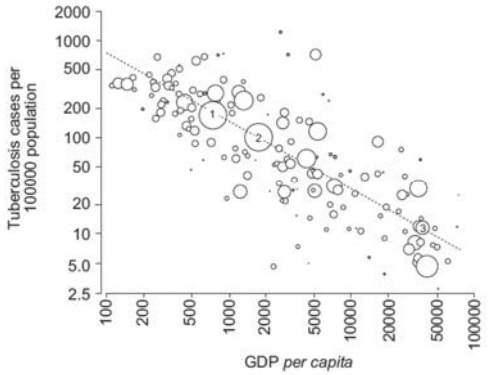
Test	Assay principle	Use	Sensitivity (%)	Specificity (%)	TAT*	Target setting‡	Year endorsed
Molecular techniques (nucleic acid amplification tests)							
Xpert MTB/RIF¶#	NAAT (qPCR)	• Active TB disease diagnosis • Drug resistance (rifampicin)	• 98 (smear-positive and culture-positive) • 67 (smear-negative and culture-positive) • 95 (rifampicin resistance)	• 99 (smear-negative and culture-negative) 98 (rifampicin resistance)	Same day	District or sub-district laboratory	2010
First-line LPA (GenoType MTBDRplus¶ and NIPRO#)	NAAT (LPA)	• Active TB disease diagnosis • Drug resistance (isoniazid and rifampicin)	• 98 (rifampicin resistance) • 84 (isoniazid resistance)	• 99 (rifampicin resistance) • >99 (isoniazid resistance)	1–2 days	Reference laboratory	2008

Moral: PCR is better than smear, but a panacea to waiting for cultures

Why is sensitivity lower in the smear negative cases?

Pai et al. Nat Rev Dis Primers. 2016 Oct 27;2:16076

TB Geography is Linked to **Poverty**



2004-2005 WHO data

Doubling GDP → 38.5% decrease TB incidence

Janssens, J.P. and Rieder H.L. Eur Resp J 2008. 32(5):1415-1416

Does Poverty and Inequality Really Confer a Causative Physiology?

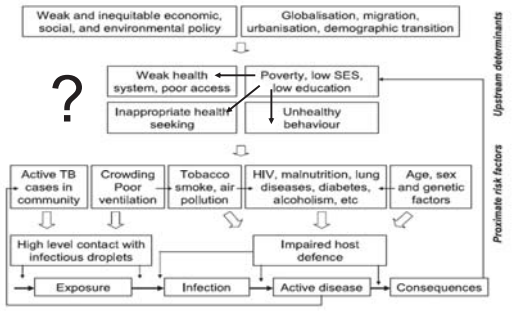


Fig. 4. Framework for proximate risk factors and upstream determinants of TB.

LÖnnroth et al. Social Science & Medicine. 2009. 68:2240–2246

The end
Questions?

Some resources:

- CDC guide for primary care providers (2013): https://www.cdc.gov/tb/publications/ltbi/pdf/targetedltbi.pdf
- McGill LTBI risk calculator: http://www.tstin3d.com/en/calc.html
- California State LTBI info packet: https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%
- TB educational products from the Curry Center (the western regions TB education center, based in Oakland): http://www.currytbcenter.ucsf.edu/products
- Oregon Health Authority TB program: http://www.oregon.gov/oha/PH/DISEASESCONDITIONS/COMMUNICABLEDISEASE/TUBERCULOSIS/Pages/index.aspx
  - TB controller: **Heidi Behm**

Extra slides

LTBI modeled epidemiology

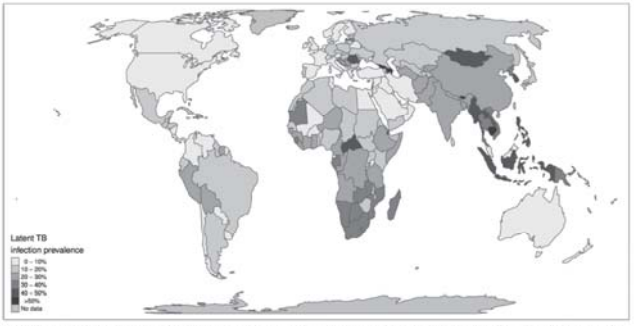


Fig 2. Global map of prevalence of latent TB infection. Median estimated population prevalence of latent *Mycobacterium tuberculosis* infection by country, 2014.

Houben and Dodd. PLoS Med. 2016 Oct 25;13(10):e1002152

What is the moral: the pre-test probability for TB exposure matters!!

California Tuberculosis Risk Assessment Adults

LTBI testing is recommended if any of the 3 boxes below are checked.

☐ **Birth, travel, or residence** in a country with an elevated TB rate for at least 1 month
- Includes any country other than the United States, Canada, Australia, New Zealand, or a country in western or northern Europe
- If resources require prioritization within this group, prioritize patients with at least one medical risk for progression (see the California Adult Tuberculosis Risk Assessment User Guide for this list)
- Interferon Gamma Release Assay is preferred over Tuberculin Skin Test for foreign-born persons ≥2 years old

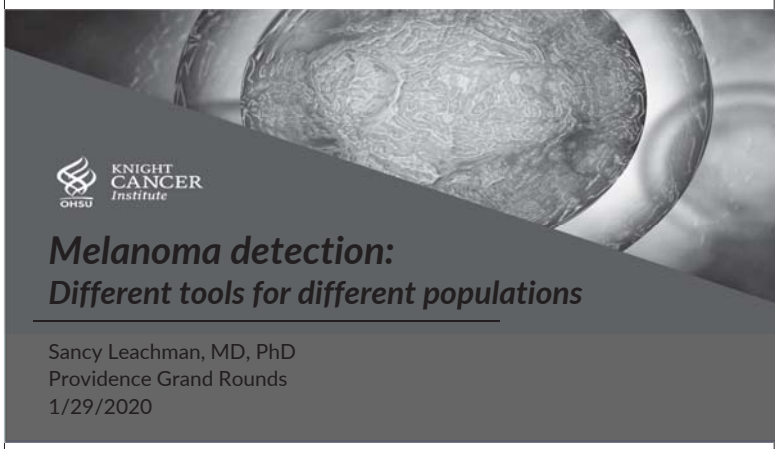
☐ **Immunosuppression**, current or planned
HIV infection, organ transplant recipient, treated with TNF-alpha antagonist (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone ≥15 mg/day for ≥1 month) or other immunosuppressive medication

☐ **Close contact** to someone with infectious TB disease during lifetime

Treat for LTBI if LTBI test result is positive and active TB disease is ruled out.

- **Moral:** decision to test should be decision to treat
  - Do so wisely

https://www.cdph.ca.gov/Programs/CID/DCDC. Updated Dec 2017. Accessed March 2018.



KNIGHT CANCER Institute

Melanoma detection:
Different tools for different populations

Sancy Leachman, MD, PhD
Providence Grand Rounds
1/29/2020

KNIGHT CANCER Institute

No Relevant Conflicts of Interest
MoleMapper (iPhone App) free & open source
Non-topic related COI:

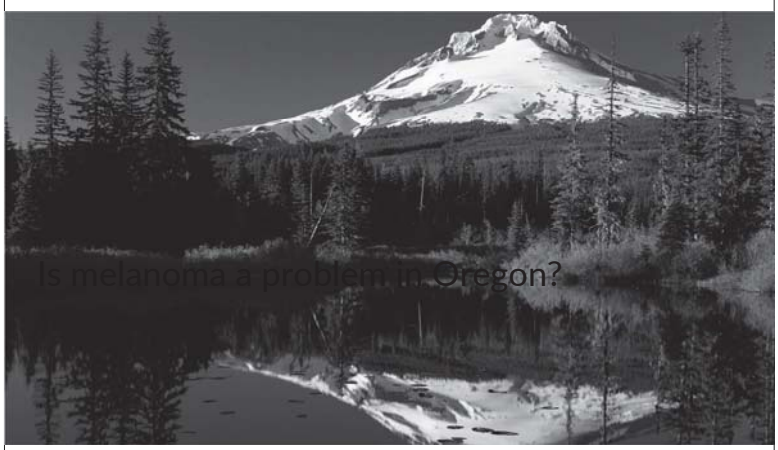
- Myriad Genetic Laboratories (early access)
- Castle BioSciences (early access)
- Palvella Therapeutics (advisory board)
- DermDetect (Business Associate Agreement)
- Merck (advisory board)
- Orlucent (advisory board

Today's Objectives

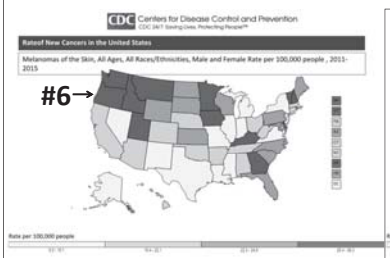
- **WoM:** Discuss melanoma epidemiology and the need for early detection
- **USPSTF:** Discuss the USPSTF screening recommendations for high-risk or symptomatic individuals
- **CME:** Preview the online/in-person CME course for medical providers on visual diagnosis, screening and biopsy
- **Materials:** Describe where to find un-branded patient education materials and education or volunteer opportunities on our website

Objective #1

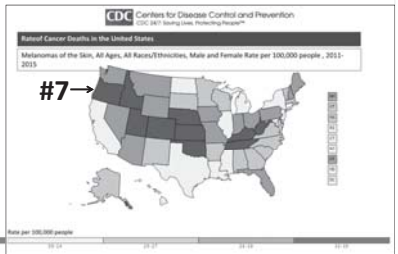
Discuss melanoma epidemiology and the need for early detection



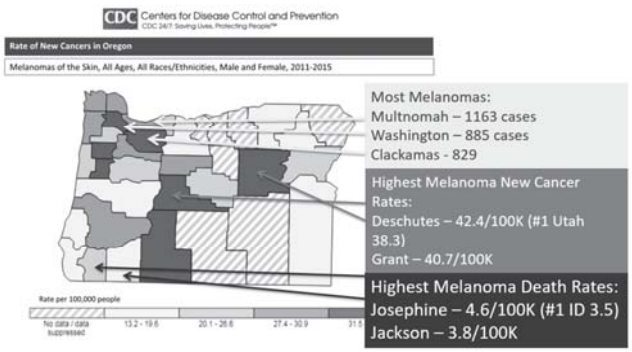
Melanoma Rates in Oregon are Above Average

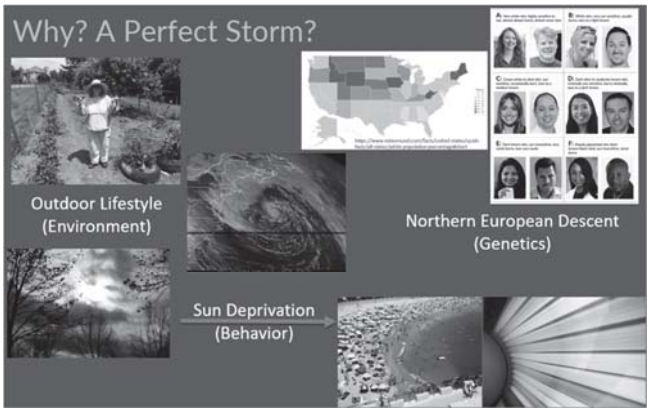


New melanomas in the U.S.



Melanoma deaths in the U.S.





What can we do?

EUROCARE Study: Suggests Early Detection Works in Melanoma

– 16,113 cutaneous melanomas, 17 countries
– 45 cancer registries (3.5 million cancers)

"Survival rates improved between 1978 and 1989 probably attributable to the detection of increasing proportions of better prognosis, thinner tumours."

"In the younger age groups, this may be related to public awareness campaigns."

Smith JA, Whatley PM, Redburn JC. Eur J Cancer. 1998 Dec;34(14 Spec No):2197-203.
Improving survival of melanoma patients in Europe since 1978. EUROCARE Working Group. South & West Cancer Intelligence Unit, Highcroft, Winchester, U.K.

Patient Knowledge & Skin Awareness Reduces Delay in Diagnosis

- 255 cases, newly diagnosed melanomas
- From population-based case control (1987-89)
- Personal interviews
- Skin awareness and delay: Adjusted OR 0.30 (0.12-0.71)
- Knowledge & Delay: OR 0.43-0.81

"Awareness of skin changes was associated with a reduced Breslow depth for stage I melanomas."

"Individuals who are aware of skin changes and abnormalities appear to be less likely to delay seeking medical attention for melanoma."

"Knowledge of melanoma signs and symptoms may also contribute to a decreased delay in melanoma diagnosis."

Oliveria SA, Christos PJ, Halpern AC, Fine JA, Barnhill RL, Berwick M. J Clin Epidemiol. 1999 Nov;52(11):1111-6.
Patient knowledge, awareness, and delay in seeking medical attention for malignant melanoma.

Self-Skin Examination, Provider Examination, and Attitude Matters in Melanoma Early Detection

- Cross-sectional, questionnaire-based, multicenter study of 685 SSMs and NMs
- Assessed SSEs, PSEs and perceptions in prior year
- <2 mm "thin" melanoma in 81% of SSMs and 27% of NMs.
- SSE performers had thinner SSM (OR = 2.61; 1.14-5.40) but not thinner NM (OR = 2.39; 0.84-6.80).
- SSE signs were markers of thicker SSM and NM
- Interest in skin cancer was associated with thinner NM.

"Our findings underscore the importance of complementary practices by patients and physicians for the early detection of melanoma, including regular whole-body PSE, SSE, and increased patient awareness."

Dessinioti C, Geller AC, Stergiopoulou A, Swetter SM, Baltas E, Mayer JE, Johnson TM, Talaganis J, Trakatelli M, Tsoutsos D, Tsourouflis G, Stratigos AJ. JAMA Dermatol. 2018 May 1;154(5):544-553. doi: 10.1001/jamadermatol.2018.0288.

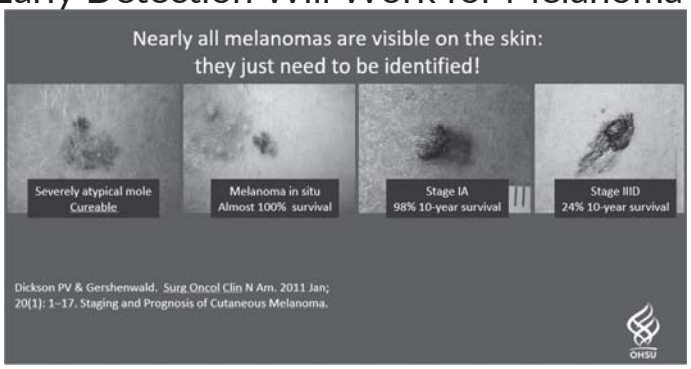
Is melanoma a problem for your patients?

Mindi, Fighting Stage IV

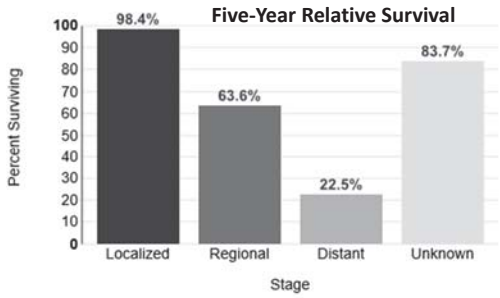
Jennifer, Survivor

Kim, Passed Away Due to Melanoma

Early Detection Will Work for Melanoma



Early Detection Works for Melanoma



SEER 18 2008-2014, All Races, Both Sexes by SEER Summary Stage 2000

Why Early Detection for Melanoma?

- Saves lives
- Reduces morbidity (including disfigurement)
- Reduces side effects from aggressive therapies
- Reduces cost (probably)

Objective #2

Discuss the USPSTF screening recommendations for high-risk or symptomatic individuals

USPSTF Statement on Skin Cancer Screening

Published Statement for Screening ***Asymptomatic*** Adults 2016:
"Current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults."

BUT IT ALSO STATES….

*"This recommendation applies to asymptomatic adults who **do not have a history of premalignant or malignant skin lesions**. Patients who present with a **suspicious skin lesion** or who are already **under surveillance because of a high risk** of skin cancer, such as those with a familial syndrome (e.g., familial atypical mole and melanoma syndrome), are outside the scope of this recommendation statement."*

How High Risk Is High Enough?

Comparison of Risk Factors Receiving USPSTF "A" or "B" with Melanoma Risk Factors

USPSTF Approved Screening (RR)
- Lipid panel in obesity and morbid obesity (1.9)
- Ultrasound for AAA in male ever-smoker (3.1)
- CT for Lung Cancer:
  - Current female smoker (7.8)
  - 30-40 pack-year female (12.9)
  - Current male smoker (23.6)
  - 30-40 pack-year female (24.6)

Similar Melanoma RR
- Fitzpatrick type II + III vs IV (1.8)
- History of sunburn (2.0)
- 2 atypical nevi (2.1)
- High density freckling (2.1)
- 40-60 common nevi (2.2)
- Red hair vs dark (3.6)
- History of AK, BCC or SCC (4.3)
- Indoor tanning ever-use 30-39yo F (4.3)
- 100-120 common nevi (6.9)
- Personal history melanoma (8.2-13.4)
- CDKN2A carrier (14-28)

Johnson MM, Leachman SA, et al. (MPWG); Melanoma Manag. 2017 Mar;4(1):13-37.

Table 1. Proposed Skin Cancer Screening Guidelines

Adults aged 35-75 years with one or more of the following risk factors should be screened at least annually with a TBSE:

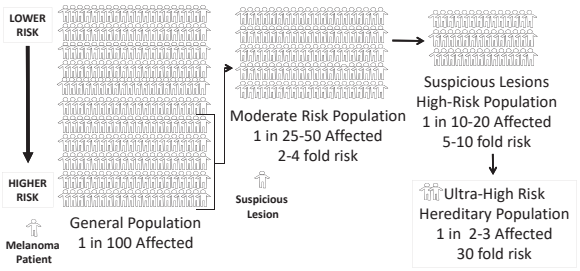
Personal history	Personal history of melanoma, AK, or KC *CDKN2A* (or other high-penetrance gene*) mutation carrier Immunocompromise*
Family history	Melanoma in 1 or more family members Family history suggestive of a hereditary predisposition to melanoma
Physical features	Light skin (Fitzpatrick I-III*) Blonde or red hair >40 total nevi ≥2 atypical nevi* Many freckles Severely sun-damaged skin
UVR overexposure	History of blistering or peeling sunburns History of indoor tanning

Table 1: TBSE: Total body skin exam; includes evaluation of entire skin surface (scalp, face, ears, neck, chest, abdomen, back, buttocks, genitals, upper and lower extremities, hands, feet), eyes (iris and sclera), oral mucosa, hair, and nails. **AK**: actinic keratosis. **KC**: keratinocyte carcinoma. ***CDKN2A***: cyclin-dependent kinase inhibitor 2A. *High penetrance genes: CDKN2A, CDK4, MITF, BAP1, p14 ARF, TERT, POT1, ACD, TERF2IP, BRCA2, PTEN [77-79]. *Immunocompromise includes patients with suppressed immune systems due to a disease (e.g., HIV/AIDS) or medication (e.g., anti-rejection medications for organ transplants, chemotherapies, or immunosuppresants for autoimmune disorders). *Fitzpatrick skin types [80]. *Atypical nevi clinical criteria is based on International Agency for Research on Cancer (IARC) [31]. Consideration should be given to individuals that have a combination of risk factors, potentially elevating them to a higher risk category.

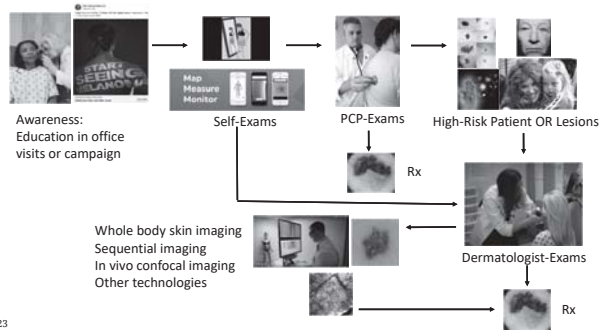
When Should Patients be Referred to Dermatology?

- Dependent on PCP's comfort level
  - –Always OK to refer
- Consider referral for high risk patients with challenging skin exams
  - –Hundreds of nevi
  - –Multiple clinically atypical nevi
  - –Severely photodamaged skin (covered in lentigines)
  - –Strong family history of melanoma or family members who carry melanoma mutations
  - –Personal history of recent melanoma (5 years)

Risk Stratified Screening



Putting It All Together



Objective #3

Preview the online CME course for medical providers on visual diagnosis, screening and biopsy

Melanoma Early Detection Toolkit

1. CME Training (Online or In-Person)
2. Patient education materials and tools (Order Form)
3. Melanoma Risk Evaluation Tool (in progress)

www.startseeingmelanoma.com → "For Medical Professionals"

Objective 1: Risk Assessment Guidelines

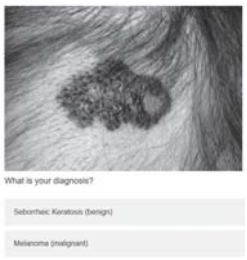
- Online for general public and office use

Patients age 21-75 – Administer Risk-Assessment Survey for New Patients			
	Some Risk (0-3)	Moderate Risk (4-8)	High Risk (9-12)
Melanoma risk factors:	• **Blue or green eyes vs. dark** • **Indoor tanning use vs. never** • **Fitzpatrick skin type 1, 2, or 3 vs 4** • **History of sunburn vs. no** • **High density freckles vs. low** • **16-60 nevi**	• **Family history of melanoma in one or more first-degree relative** • **Red hair vs. dark** • **Total common nevi 61-80 vs <15** • **History of AK vs no** • **Indoor tanning in women aged 30-39**	• **Indoor tanning in women aged <30 vs never used** • **Total common nevi 80 or more** • **Personal history of melanoma** • **Transplant recipient**
Recommendations			
Education	• Warning signs and self- exams	• Warning signs and self-exams • Provider Skin Exam	• Warning signs and self-exams • Provider Skin Exam • NCCN Guidelines
Self-exams	**Monthly**	**Monthly**	**Monthly**
Medical Provider Exam	See a doctor if you have any concerns, consider a full-body skin check every other year by a medical provider	See any medical provider for a full-body skin check every year or if you identified a suspicious lesion	Full body skin check at least annually by a dermatologist (as recommended)

Melanoma Early Detection Online Training (Preview)
www.waronmelanoma.org

Objectives:

- Identify high-risk patients
- Apply screening recommendations
- Diagnose melanoma and non-melanoma skin cancer with increased accuracy
- Educate patients using provided resources



OHSU School of Medicine designates this enduring material for a maximum of 3.0 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Credits:

(We drew from all leading education for Primary Care, as well as listening to Oregon providers)

This training was developed with input, assets and content from the following contributors:

- National Primary Care Training in Schleswig-Holstein, Germany
- INFORMED Curriculum; Martin Weinstock, M.D., Brown University
- Laura Ferris, M.D., Ph.D., University of Pittsburgh Medical Center
- Karen Edison, M.D., and Emily Hoffman-Smith, M.D., University of Missouri
- OHSU Team: Sancy Leachman, MD, PhD, Elizabeth Berry, MD, Mariah Johnson, MD, Oliver Wisco MD, Kim Sanders, PA
- Visual Perception Training; Steve Xu, M.D., MS.c., Northwestern Medicine Feinberg School of Medicine
  - Visual Perception Training was developed by Rebecca Xu, Andrew Choi MD, June Robinson MD, and Shuai Xu MD. It is copyrighted by Northwestern University and available with written permission from the developers.

Key Information for PCPs:

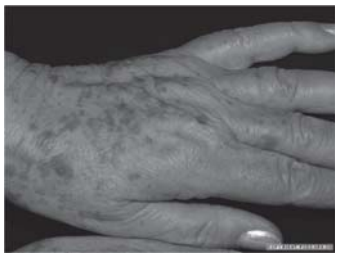
- Be aware of malignant features
- Educate patients about suspicious lesions
- Encourage patients to return to clinic if they are worried
  - Industry standard for 'acceptable' wait time for suspicious lesions: 4-6 weeks
- Listen to patients if they report change in appearance
- Assess patient risk factors and discuss screening recommendations

Evaluating the Individual

Who should be screened?

Case #1

Ms. Smith is a 55 year old woman who has heard an educational advertisement that suggested anything abnormal on her skin should be evaluated by her provider. **She has several spots on her hands that she feels are suspicious and would like to know if any of them look worrisome to you**.



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Case #1: Doorway Risk Assessment

You evaluate her hands and reassure her that the solar lentigines are benign. However, you also notice that she has:

- Fair complexion (very light skin, red hair, green eyes)
- Numerous freckles
- Many visible moles on her face, neck, and arms
- Sun-damaged skin

Case #1: Clinical History

You ask her a few questions to complete the risk assessment

Populations at risk for developing melanoma
Adults aged 35-75 years with one or more of the following risk factors should be screened at least annually with a total body skin examination:

• Personal history:
  ○ History of melanoma, actinic keratosis/es, basal cell carcinoma, or squamous cell carcinoma
  ○ CDKN2A (or other high-penetrance gene*) mutation carrier
  ○ Immunocompromise
  ○ History of blistering sunburns
  ○ History of indoor tanning bed use
• Family history:
  ○ Melanoma in one or more family members
  ○ Family history suggestive of a hereditary predisposition to melanoma
• Physical features:
  ○ Fair skin (Fitzpatrick I-III)**
  ○ Blonde or red hair
  ○ >40 total nevi
  ○ ≥2 atypical nevi†
  ○ Many freckles
  ○ Severely sun-damaged skin

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Case #1: Clinical History

- She admits to using a tanning bed several times a month for about 5 years when she was in her 20s and having a few blistering sunburns as a child
- No personal history of skin cancer
- No family history of melanoma
- She has never had a skin exam before and is otherwise healthy

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Case #1: Management

After reassuring her that the lesions on her hands are benign, what would you do next?

A) Perform an opportunistic exam (face, neck, arms, etc.)
B) Recommend a skin cancer screening exam during the current visit or with you at another time
C) Recommend that she ask a dermatologist about regular screenings
D) Recommend that she track her moles at home and let you know if she sees something new or changing

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How to perform a total body skin examination

✓ Rapid total body skin examination:
- 5 minutes or less
- Start with the scalp/face, then work your way down
- Do it in the same order every time

Thorough skin examination +/- dermoscopy:
- Necessary for patients with numerous nevi
- Consider referral to derm

✓ Opportunistic exam:
- Exam areas of skin that are readily available without having the patient change into a gown

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Skin Exam Video

Case #1: Exam Findings

During Ms. Smith's full body skin exam it is noted that she has:

- 3 actinic keratoses on her face
- Suspicious nevus on her back
- Several benign-appearing nevi

Case #1: Documentation

Assessment/plan:

- **Neoplasm of unspecified behavior (D49.2)**
  - Biopsy (11102-11107)
- **Actinic keratosis(es) L57.0**
  - Destruction of premalignant lesions (17000)
- **Sun damaged skin (code L57.8), including solar lentigines (L81.4)**
- **Multiple pigmented nevi (D22.7)**
- **History of tanning bed use (Z91.89)**
- **Skin cancer risk assessment:**
  - Discussed with patient increased risk factors for skin cancer (red hair, fair skin, dense freckling, sun-damaged skin, history of indoor tanning bed use).
  - Recommend annual routine skin cancer screening.

Quick Reference Guide Online in the Toolkit

Skin Cancer Screening Reference Guide

Screening Recommendations

Populations at risk for developing melanoma

Adults aged 35–75 years should be screened at least annually with a total body skin examination when presenting with one or more of the following risk factors:

- Personal history of skin cancer, pre-cancerous lesions, or predisposing genetic mutation;
- Family history suggestive of a predisposition toward melanoma; or
- Physical features suggestive of susceptibility for skin cancer.

See over for a table that provides more details on risk factors.

Intake Form

Dermoscopy risk assessment

- Fair complexion
- Blonde, red, or light brown hair
- Blue, green, or hazel eyes
- Light skin colors (Fitzpatrick I–III, Fitzpatrick 1988)
- Numerous freckles
- Many visible moles
- Evidence of sun-damaged skin

Key Clinical History Questions

- Do you have a history of skin cancer?
- Have you ever had a mole biopsied?
- Do you have a history of immunosuppression?
- Do you have a history of severe UV exposure?
- How many sunburns did you have as a child?
- How many blistering sunburns have you had in your lifetime?
- Have you ever used a tanning bed or solarium?
- Do you have a family history of skin cancer?

Diagnosis Codes

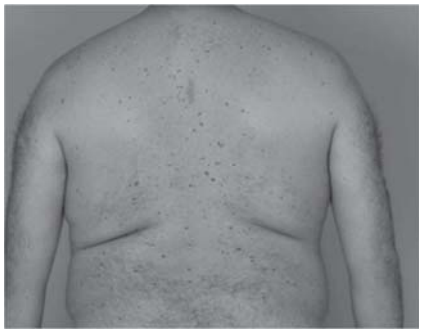
Atypical nevus (need to specify site) – D22.X
Family history of melanoma – Z80.8
Family history of skin cancer – Z80.8
Freckles – L81.2
History of atypical nevus – Z87.898
History of sun-damaged skin – Z87.2
Multiple pigmented nevi of the trunk and extremities – D22.7
Personal history of melanoma – Z85.820
Personal history of skin cancer – Z85.828
Personal risk factors not otherwise specified – Z91.89
Screening for skin cancer – Z12.83
Skin tanning due to UV light – L56.8
Sun-damaged skin – L57.8
Tanning bed use – Z91.89

Sample EPIC SmartPhrase (dot phrase) for Risk Factor Assessment

- Fitzpatrick skin type I–III: (YES/NO/43)
- Blond or red hair: (YES/NO/43)
- >40 total nevi (YES/NO/43)
- >2 atypical nevi: (YES/NO/43)
- Many freckles: (YES/NO/43)
- Severely sun-damaged skin: (YES/NO/43)
- History of blistering or peeling sunburns: (YES/NO/43)
- History of indoor tanning: (YES/NO/43)
- Personal history of melanoma, actinic keratoses, or nonmelanoma skin cancer: (YES/NO/43)
- Personal history of CDKN2A (or other high-penetrance gene) mutation carrier: (YES/NO/43)
- Personal history of immunocompromise: (YES/NO/43)
- Family history of melanoma in one or more first degree family members: (YES/NO/43)
- Family history suggestive of a hereditary predisposition to melanoma: (YES/NO/43)

Case #2

Mr. Jones is a 55 year old male patient who presents for follow-up of COPD, HTN, CHF, DM2. While auscultating his lungs, you realize he has multiple moles on his back.



Case #2: Management

Along with addressing his chronic comorbidities, how would you manage this patient?

A) Perform an opportunistic screening of his back
B) Perform a total body skin examination
C) Recommend a skin cancer screening exam at his next visit
D) Recommend that he ask a dermatologist about regular screenings

Case #2: Management

You perform an opportunistic screening of his back and all nevi are benign appearing. Mr. Jones returns to clinic in 2 months for a total body skin examination.

On his second visit, you identify many (>50) nevi, several of which are slightly atypical. However, the atypical nevi all resemble each other. There is no single lesion that stands out as an "ugly duckling."

You suggest he perform monthly self skin exams and use MoleMapper to follow the slightly atypical lesions on his body. You ask him to return to see you in 3 months to compare the photographs and ensure the lesions are stable.

If lesions are stable at that visit, he can start an annual screening regimen.

Self-Exams: Empowering Patients

- Performance of a monthly Total Self-Skin Exam (TSSE) is **associated with thinner melanomas and reduced mortality**
- Roughly 75% of melanomas are first detected **by the patient**, not the provider
- Patients should conduct a TSSE once a month to look for **new, changing, or non-healing lesions**

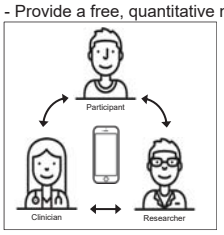
Self Exams and Partner Exams

- Use mirrors (ideally full-length and hand mirror) to examine skin from head to toe
- If available, a partner can assist in monitoring difficult-to-see areas
- Take serial photos

3 Goals for Mole Mapper App

For "The People" - Provide a free, quantitative mole-tracking tool

For Providers & Patients: Facilitate productive patient visits

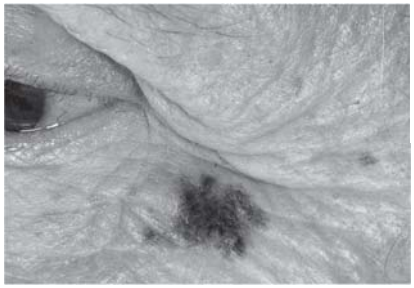


For Researchers: Conduct a large-scale, Crowdsourced research study

Evaluating the Lesion

What should be biopsied?

What is your diagnosis?

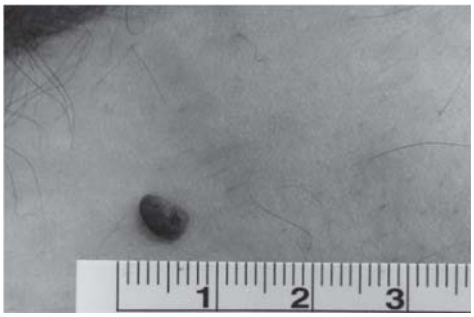


Reference: Visual Perception Training, Northwestern

What is your diagnosis?

Reference: Visual Perception Training, Northwestern

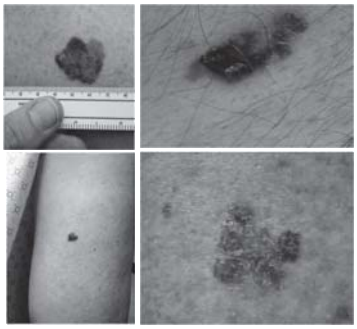
What is your diagnosis?



Reference: Visual Perception Training, Northwestern

Superficial spreading melanoma

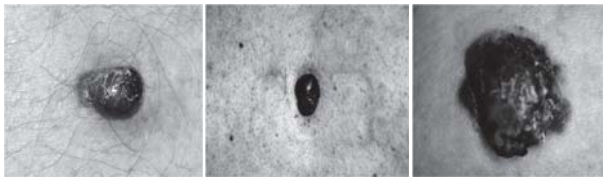
- Most common (70%)
- Intermittently sun-exposed skin
  - Backs of men
  - Legs of women
- Variable pigmented macule with irregular borders
- Thinner Breslow depth



Reference: Missouri ECHO

Nodular melanoma

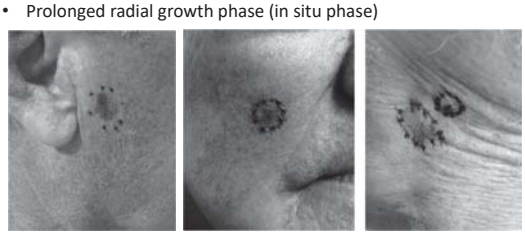
- Second most common (15-30%)
- Darkly pigmented papules or nodules, may be pink/amelanotic, may have even symmetric borders
- Early vertical growth phase → deeper Breslow depth



Reference: Missouri ECHO

Lentigo maligna

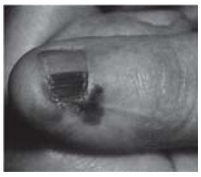
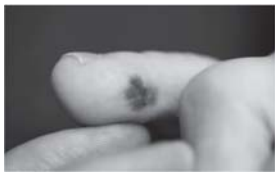
- Third most common (10-15%), incidence rising
- Chronically sun-damaged skin
- Slowly enlarging irregularly pigmented macule
- Prolonged radial growth phase (in situ phase)



Reference: Missouri ECHO

Acral lentiginous and subungual melanoma

- Less than 5%, most common subtype in dark-skinned individuals
- Palmar, plantar, subungual surfaces
- Irregularly pigmented macules or patches
- Thickening band of pigment within the nail plate or nail fold


Reference: Missouri ECHO

Comparison

Nevus

- Symmetric
- Round to oval
- Uniform Color
- Small
- Non-changing

Melanoma

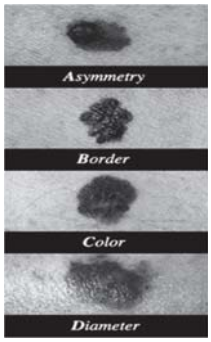
- Asymmetric
- Irregular border
- Irregular or multicolored
- Large
- Evolving / changing

Keys to Early Diagnosis of Melanoma

- Maintain a HIGH index of clinical suspicion
- Maintain a LOW threshold for biopsy
- Utilize good biopsy technique insuring adequate specimen

ABCDE's of Melanoma

- Not all of these criteria need to be met
- Some melanomas only have one "strike" against them!
- A= Asymmetry
- B= Border
- C= Color
- D= Diameter > 6mm
- E= Evolution
- most important criteria!

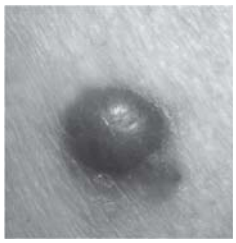


E= Evolution

- "My mole is changing"
- "My mole is growing"
- "My mole is itching"
- "This is a new mole"

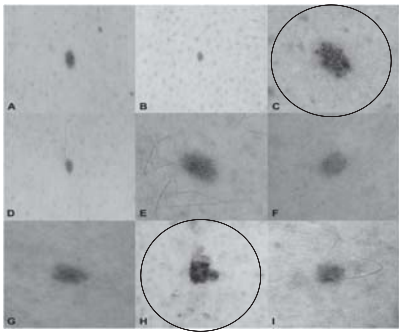
Difficult melanomas- the "EFGs"

- **E**levation
- **F**irm
- Continuous **G**rowth for greater than one month
- Helps in diagnosing spitzoid, amelanotic, desmoplastic melanomas, etc which typically lack characteristic features of melanoma



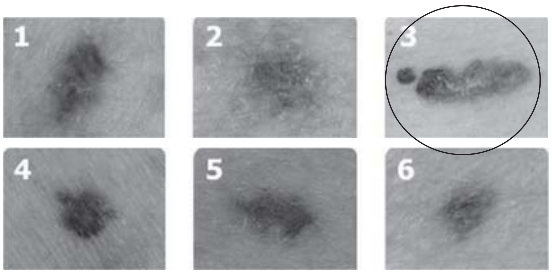
Chamberlain AJ, et al. J Am Acad Dermatol. 2003;48(5):694

The Ugly Duckling Sign



Ilyas, et al. JAAD 2017;77(6):1088-1095

The Ugly Duckling Sign



Reference: Informed

Biopsy Tutorial

Triggers for Biopsy

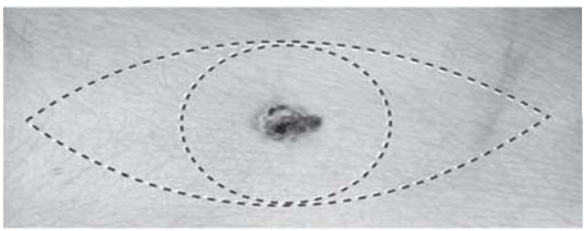
- **ABCDEs , EFGs, "ugly duckling" sign**
- **Rapidly growing** (weeks to months)
- **Tender** to palpation
- **Bleeding** without manipulation
- I**mmunosuppressed** patient
- **If the patient is concerned**! *Especially* if they have a history of skin cancer
- At minimum, photograph, measure, and follow-up in 3-6 months, educate the patient to contact you sooner if there are changes

Biopsies

- Incisional biopsy = removal of a <u>portion</u> of the lesion
  - Non-melanoma skin cancers
  - Only need enough to make the diagnosis
  - Can use shave or punch technique
- Excisional biopsy = removal of <u>entire</u> lesion
  - PIGMENTED LESIONS
  - Must remove the whole lesion for staging purposes
  - Can use deep shave/ saucerization, punch, or elliptical excision technique

Biopsy Technique

The single best treatment for melanoma is complete excision prior to metastasis.



Biopsy Key Points

- For pigmented lesions, remove the ENTIRE lesion (excisional biopsy)
  - Punch biopsy
  - Deep shave/ saucerization biopsy
  - Elliptical excision with scalpel
- Lesions <8mm in diameter = PUNCH BIOPSY
- Lesions >8mm in diameter = SAUCERIZATION or ELLIPTICAL EXCISION

Biopsy Key Points

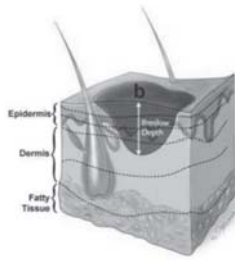
- If an excisional biopsy is impractical due to very large size or location (face), may perform partial biopsy as a last resort
  - For thin melanomas on the face, consider:
    - Broad thin shave biopsy
    - Multiple small shave biopsies ("scouting biopsies")
  - For multicolored lesions, each color in the lesion should be sampled

Biopsy Results

- If a melanoma is detected, the standard of care is to arrange treatment within 4 weeks of diagnosis
- Refer melanomas with <0.8mm Breslow depth to dermatology
- Refer melanomas with ≥0.8mm Breslow depth to surgical oncology and dermatology

Biopsying Pigmented Lesions

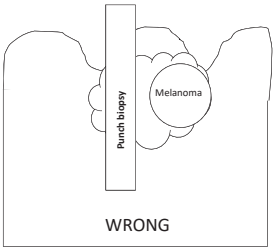
*The most important prognostic indicator in melanoma is the Breslow depth



Reference: Missouri ECHO

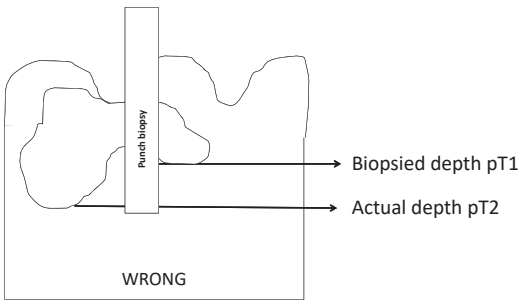
Biopsying Pigmented Lesions

Partial biopsy can lead to diagnostic inaccuracy or misdiagnosis



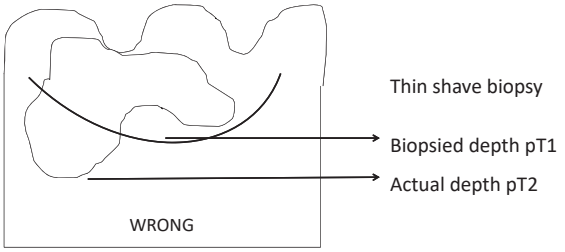
Reference: Missouri ECHO

Biopsying Pigmented Lesions



Reference: Missouri ECHO

Biopsying Pigmented Lesions



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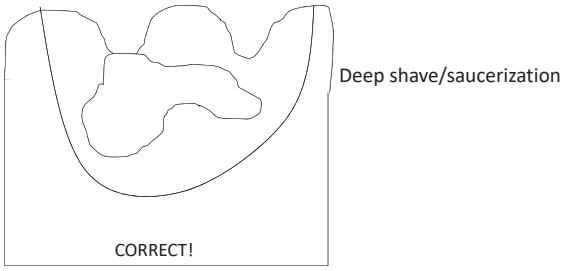
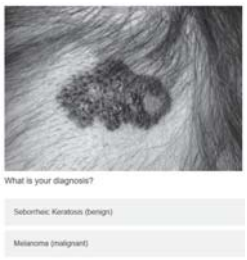


Reference: Missouri ECHO

Melanoma Early Detection Online Training (Preview) www.waronmelanoma.org

Take the training for more visual identification practice and biopsy demonstration videos

OHSU School of Medicine designates this enduring material for a maximum of 3.0 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.



Objective #5

Describe where to find un-branded patient education materials and education or volunteer opportunities on our website

Toolkit Part III: Patient Education

- Mole Mapper App
- Self-Exams Download
- Early Detection Download
- Sun Safety Download
- Biopsy and Diagnosis Handout
- Online Learning on the website
- Waronmelanoma.org

Thank you!

leachmas@ohsu.edu
www.WarOnMelanoma.org
www.StartSeeingMelanoma.com
503-494-6024 (Katie)

The 60 Second Neuro Exam

Upper Extremity	**C5**	**C6**	**C7**	**C8**	**T1**
DTR	Bic (Musc.)	BR (Radial)	Tri (Radial)	-	-
Strength	**Sh Abd** (Axillary)	Wr Ext/**Elb Flx** (Radial/Musc)	Wr Flx/**Elb Ext** (MedUln/Rad)	**Fing Flx** (MedUln)	**Fing Abd** (Ulnar)
Sensation	Lat. Sh. (Axillary)	Thumb (Med/Rad)	Middle (Med/Rad)	Little (Ulnar)	Med. Arm (MBC)
Lower Extremity	**L2**	**L3**	**L4**	**L5**	**S1**
DTR	-	-	Patellar (Femoral)	-	Achilles (Tibial)
Strength	Hip Flx (Femoral)	Knee Ext (Femoral)	Ankle DF (Peroneal)	Gr. Toe Ext (Peroneal)	Ankle PF (Tibial)
Sensation	-	-	Med. Mall. (Saphenous)	1st DWS (Deep Per.)	Lat. Heel (Sural)

Chronic Kidney Disease for the Non-Specialist

Tonja Dirkx, MD

Slides not provided

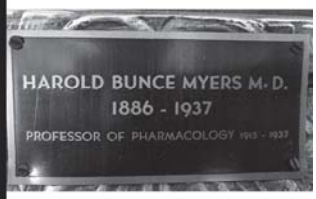
Familial Hypercholesterolemia: Another Rare Disease?

P. Barton Duell, M.D.
Professor of Medicine
Director, LDL Apheresis Unit
Director, Lipid-Atherosclerosis Laboratory
Knight Cardiovascular Institute
Oregon Health and Science University
Portland, OR

Conflict of Interest Disclosure

Disclosure

Institutional Grants and/or Consultant: Akcea, Astra Zeneca, Esperion, Regeneron, RegenxBio, Retrophin



Chair, Dept. of Pharmacology and Asst. Dean 1915-1937

OHSU

Artist: Sydney Bell 1937

Harold Bunce Meyers, M.D.

Born on July 31, 1886 in Oberlin, Ohio

Talented athlete: Held the western record for the half-mile in college

Invited to compete in the Olympics as a runner, but declined

Developed angina in his 40s

Age 48 (1934), had a presumed “coronary thrombosis” attack

Age 50 (1936), unable to walk more than a few feet without resting; collapsed in front of his class

March 17, 1937 died from myocardial infarction at 50 yo

What was his likely diagnosis?

What is Familial Hypercholesterolemia (FH)?

It is not simple hypercholesterolemia that runs in families

FH refers to autosomal dominant hypercholesterolemia that is associated with

LDL-C > 190 mg/dl (often > 220 mg/dl)

Severely increased risk of CHD

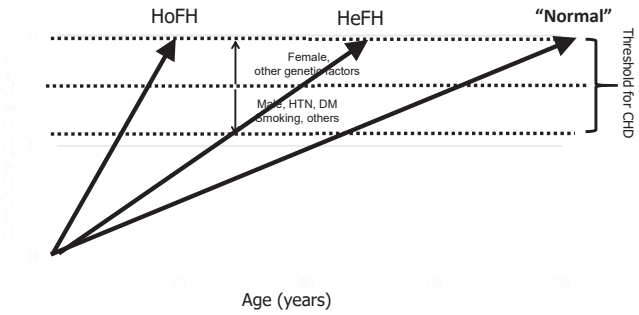
Characteristic clinical findings and family history:

- early corneal arcus, tendon xanthomas, early CAD

Does it Matter if We Diagnose FH?

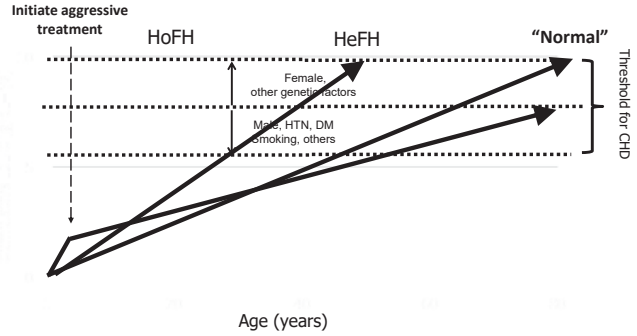
- Hypercholesterolemia can be treated regardless of the diagnosis
- **CHD Risk is increased 10-20 fold in FH!**
- Diagnosis of FH helps provider and the patient recognize the importance of lifelong treatment
- Diagnosis is important for Cascade Screening (testing direct relatives of all affected patients)
- Recognition of extreme CHD risk encourages lower threshold for cardiac screening
- > 90% of patients with FH are undiagnosed!

Cumulative Exposure to LDL-C Determines Age At Which CHD Threshold is Reached



FH=familial hypercholesterolemial; HoFH = homozygous FH;
Adapted from Horton JD, et al. J Lipid Res. 2009;50:S172-S177.

Cumulative Exposure to LDL-C Determines Age At Which CHD Threshold is Reached



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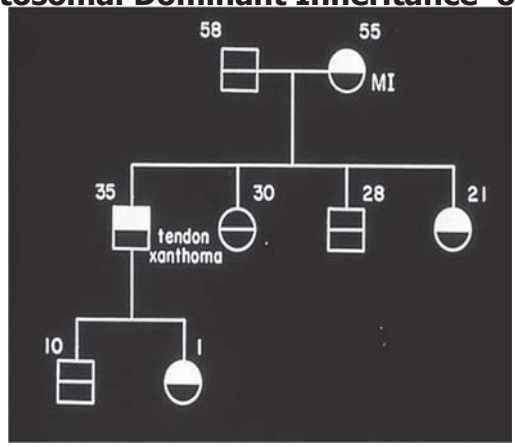
Adapted from Horton JD, et al. J Lipid Res. 2009;50:S172-S177.

Autosomal Dominant Inheritance of FH



Genetic Basis of Familial Hypercholesterolemia

Most cases are due to mutations in LDL-R (85-95%)

Small proportion are due to mutations in apo B (5-15%) (Familial defective apo B)

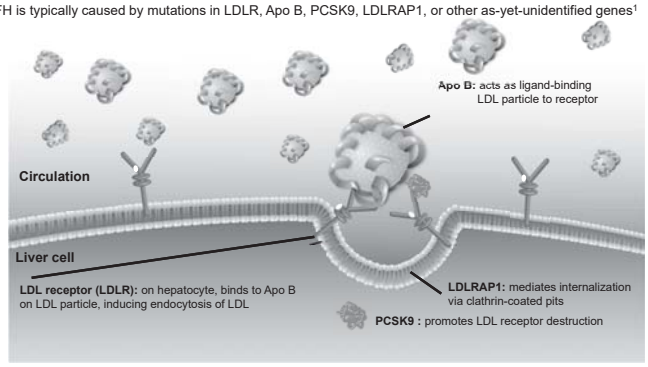
Infrequently due to mutations in PCSK9 (< 1%)

Rarely due to homozygosity for recessive mutations in LDLR-AP1 (Autosomal recessive FH)

Many cases (25-35%) have an unknown genetic cause

Mutations in FH Impair Hepatic LDL Particle Clearance

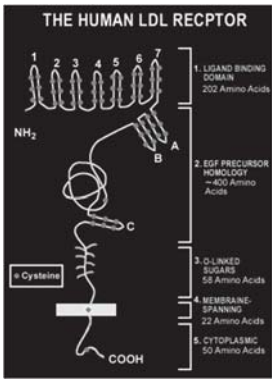
FH is typically caused by mutations in LDLR, Apo B, PCSK9, LDLRAP1, or other as-yet-unidentified genes[1]



LDLRAP1 = low-density lipoprotein receptor adaptor protein 1.
Image reproduced from: Department of Life Sciences and Institute and Institute of Genome Sciences Web site. http://www.dls.ym.edu.tw/ol_biology2/ultranel/Endocytosis.html. Published June 11, 2001. Accessed January 19, 2012.

1. Raal F, Santos R. Homozygous familial hypercholesterolemia: Current perspectives on diagnosis and treatment. Atherosclerosis 2012;223:262-68.

> 1600 Mutations in the LDL-R Cause Familial Hypercholesterolemia



Case

38 yo man

<u>Family history</u>:
Dad had MI at age 45
Brother had MI at age 39

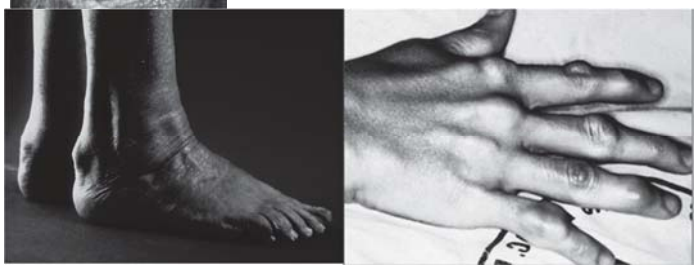
He is otherwise well and takes no medications

Case

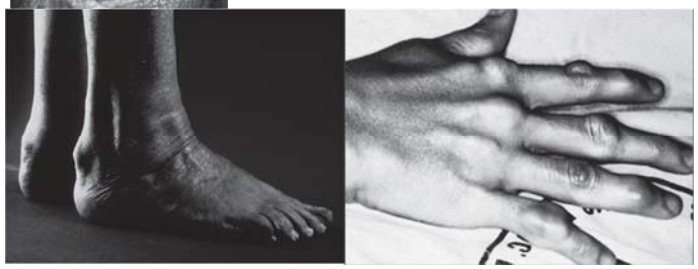
<u>Lipid Profile Results</u>:

Total cholesterol	**416 mg/dl**
(Normal < 180-200 mg/dL)	
LDL cholesterol	**354 mg/dl**
(Normal < 100-130 mg/dL)	
HDL cholesterol	**45 mg/dl**
(Normal > 40 men, >50 women)	
Triglycerides	**82 mg/dl**
(Normal < 150 mg/dL)	

Case



Case



Early corneal arcus; tendon xanthomas
Diagnosis: Heterozygous Familial Hypercholesterolemia

Relevant Clinical Features of the Case?

- Family history of early onset CAD
- Early corneal arcus
- Tendon xanthomas
- Severe hypercholesterolemia

Relevant Clinical Features of the Case?

- Family history of early onset CAD
- Early corneal arcus
- Tendon xanthomas
- Severe hypercholesterolemia

- Would you do any further testing?

Relevant Clinical Features of the Case?

- Family history of early onset CAD
- Early corneal arcus
- Tendon xanthomas
- Severe hypercholesterolemia

- Would you do any further testing?

- CT coronary artery calcium score imaging can be very useful

FAMILIAL HYPERCHOLESTEROLEMIA

	Potential Receptor Number*	LDL Cholesterol	Estimated Prevalence
"Normal"	100%	120 mg/dl	
Heterozygote	50%	240-450	1:200-250
Homozygote	0% (null)	450-1200	1:250,000

** Defect also can be in apo B or PCSK9*

Familial defective apo B100 is usually due to a single mutation (R3500Q) in the gene encoding apo B

Average Age of Onset of CAD in Untreated Familial Hypercholesterolemia

	Symptomatic CAD
Homozygous	< 10-15 years old
Heterozygous	
Male	40-50 years old
Female	50-65 years old

Stormie Jones

Born May 30, 1977

Age 6 yo: Diagnosed with FH

- Total chol 1200 mg/dl
- LDL-C 1130 mg/dl
- Progressive xanthomas
- No LDL-R on fibroblasts

Age 6 yr 6 mo: Angina --> 2v CABG

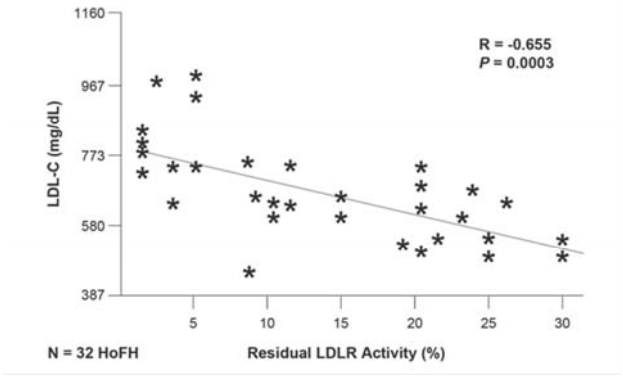
Age 6 yr 8 mo: Second CABG

Age 6 yr 9 mo: Ischemic cardiomyopathy with heart failure

Age 6 yr 9 mo: Combined heart liver transplant --> total chol 250 mg/dl

Age 12 yr 6 mo (Nov 1990): Died from rejection of her second transplant

Plasma LDL-C Concentration is Inversely Related to Residual LDL-R Activity



ATVB 1999;19:408-418 Atherosclerosis 2012;223:262-268

Making the Diagnosis of FH

- **Clinical diagnosis of FH is based on[1]**
  - **Personal and Family History of hypercholesterolemia, xanthomas, and early CAD**
  - **Genetic screening may be used but a negative test does not exclude FH**
- **Three groups have developed clinical diagnostic validated criteria for HeFH**
  - **US Med Ped Program[3]**
  - **Simon Broome Register group in United Kingdom[4]**
  - **Dutch Lipid Clinic Network[5]**
- **Criteria for HoFH are less well defined**

1. Goldberg AC et al J Clin Lipid 2011; 5 Num3(Supp. 1), June 2011.
2. www.nhlbi.nih.gov/guidelines/cvd_ped/index accessed Jan 23, 2012.
3. Williams R. et al. Am J Cardiol 1993;72:171-176
4. BMJ 303, 893-896, 1991.
5. Yuan et al. CMAJ 2006

Criteria for Total Cholesterol and LDL-C for the Diagnosis of Probable HeFH in the US Population (MED-PED Criteria)*

Ages	First-Degree Relative	Second-Degree Relative	Third-Degree Relative	General Population
<18 years	220 (155)	230 (165)	240 (170)	270 (200)
20-29 years	240 (170)	250 (180)	260 (185)	290 (220)
30-39 years	270 (190)	280 (200)	290 (210)	340 (240)
≥40 years	290 (205)	300 (215)	310 (225)	360 (260)

*Total cholesterol levels in mg/dL (LDL-C levels in parentheses) expected to diagnose HeFH with 98% specificity. First-degree relatives are parents, offspring, brothers, and sisters; second-degree relatives are aunts, uncles, grandparents, nieces, and nephews; third-degree relatives are first cousins and siblings of grandparents.

Adapted from Robinson JG. *J Manag Care Pharm.* 2013;19(2):139-149.

Simon Broome Register Diagnostic Criteria for HeFH

Definite FH is defined as:

- Total-C >6.7 mmol/L (260 mg/dL) or LDL cholesterol above 4.0 mmol/L (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/L (290 mg/dL) or LDL cholesterol above 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pretreatment or highest on treatment).

PLUS

- Tendon xanthomas in a patient, or in first- degree relative (parent, sibling, child), or in a second- degree relative (grandparent, uncle, aunt).

OR

- DNA-based evidence of an LDL-receptor mutation, familial defective Apo B-100.

Possible FH is defined as:

- Total-C >6.7 mmol/L (260 mg/dL) or LDL cholesterol above 4.0 mmol/L (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/L (290 mg/dL) or LDL cholesterol above 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pretreatment or highest on treatment).

And at least 1 of the following:

- Family history of myocardial infarction below 50 years of age in second- degree relative or below 60 years of age in a first- degree relative.
- Family history of raised cholesterol in a first- degree relative, or >7.5 mmol/L (290 mg/dL) in a second-degree relative.

Marks D et al. *Atherosclerosis.* 2003;168(1):1-14.

WHO Criteria for Diagnosis of HeFH (Dutch Lipid Network Clinical Criteria)

Family History			
a. First-degree relative with known premature (men <55 yrs, women <60 yrs) coronary and vascular disease			1
b. First-degree relative with known LDL-cholesterol >95th percentile for age and sex			
and/or			
a. Frist degree relative with tendon xanthomata and/or arcus cornealis			2
b. Children below 18 yrs with LDL cholesterol >95th percentile for age and sex			
Clinical history			
a. Patient has premature (men <55 yrs, women <60 yrs) coronary artery disease			2
b. Patient has premature (men <55 yrs, women <60 yrs) cerebral or peripheral vascular disease			1
Physical examination			
a. Tendon xanthomata			6
b. Arcus cornealis below the age of 45 yrs			4
Laboratory analysis			
	mmol/L	mg/dL	
a. LDL cholesterol	>8.5	>330	8
b. LDL cholesterol	6.5-8.4	250-329	5
c. LDL cholesterol	5.0-6.4	190-249	3
d. LDL cholesterol	4.0-4.9	155-189	1
(HDL cholesterol and triglycerides are normal)			
DNA analysis			
a. Functional mutation low-density lipoprotein receptor gene present			8
Diagnosis of HeFH is:			
Certain When		>8 points	
Probable When		6-8 points	
Possible When		3-5 points	

World Health Organization. http://whqlibdoc.who.int/hq/1999/WHO_HGN_FH_CONS_99.2.pdf. Accessed June 17, 2013.

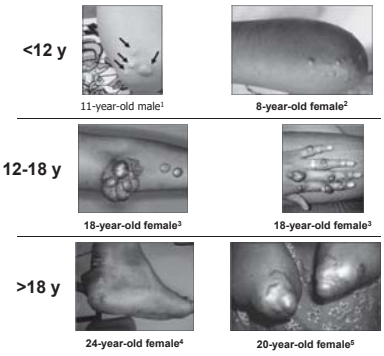
Simplified Diagnosis of Familial Hypercholesterolemia

Heterozygous FH (HeFH):
LDL-C > 160 mg/dL (4 mmol/L) for children
LDL-C >190 mg/dL (5 mmol/L) for adults
with one first degree relative similarly affected
or with positive genetic testing for an LDL-C raising gene defect
(LDL receptor, apolipoprotein-B (apo B) or PCSK9)

Homozygous FH (HoFH):
LDL-C > 400 mg/dL (10 mmol/L) and
one or both parents having clinically diagnosed FH,
positive genetic testing for an LDL-C raising gene defect or
autosomal recessive FH
HoFH highly likely if: LDL-C > 560 mg/dL (14 mmol/L) or
LDL-C > 400 mg/dL (10 mmol/L) with aortic valve disease or
xanthomata at less than 20 years of age, homozygous FH.

Gidding SS et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. Circulation. 2015;132:2167-2192

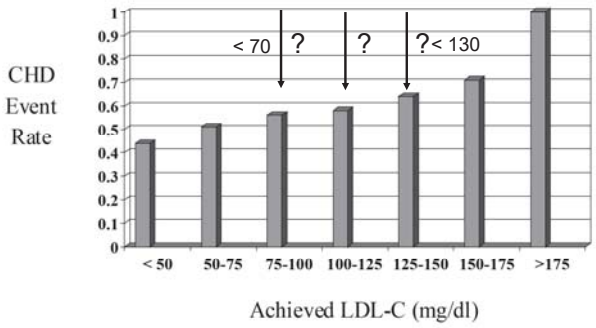
Planar, Tuberous, and Extensor Tendon Xanthomas in Homozygous FH



1. Ohshiro T, et al. J Atheroscler Thromb. 2009;16(5):698-701.
2. Poovazhagi V, et al. Familial hypercholesterolemia in siblings with Diabetes Mellitus.http://www.pediatriconcall.com/fordoctor/ViewersChoice/diabetes.asp Published February 2011. Accessed January 20, 2012.
3. Riche DM, East HE. Pharmacotherapy. 2009;29(12):1496.
4. East He, et al. Familial hypercholesterolemia in African Americans. Poster.
5. Basavarai A, et al. J Assoc Physicians India. 2006;54:330-332.

TREATMENT GOALS and Options

Risk of CHD Events vs Achieved LDL-C



Boekholdt SM, et al. JACC 2014;10:1016

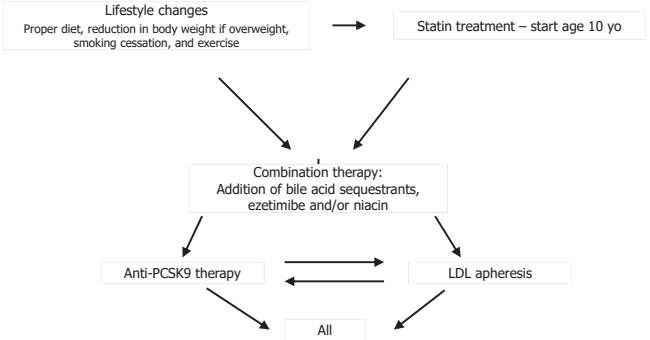
CURRENT TREATMENT OPTIONS

Familial Hypercholesterolemia

Efficacy of Drugs in Treatment of Hypercholesterolemia

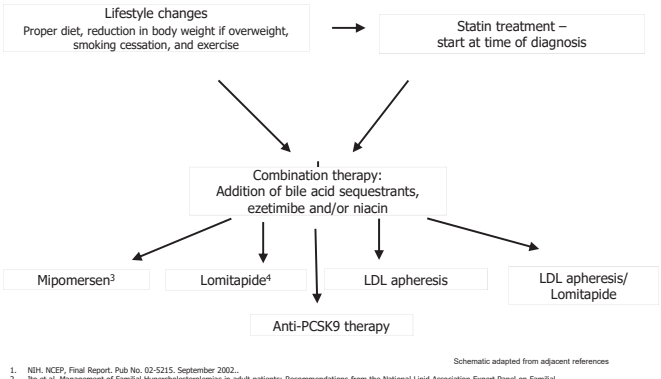
DRUG	% LDL-C Lowering
"Statins"`	18-60%
Niacin	15-30%
Bile-Acid Sequestrants	15-18%
Fibrates (gemfibrozil, fenofibrate)	10-15%
Ezetimibe	16-20%
Dietary intervention (typical response)	10-20%
Plant sterols/stanols	8-10%
Anti-PCSK9 mAbs (alirocumab/evolocumab)	50-60%

Treatment Algorithm for Heterozygous FH



1. NIH. NCEP, Final Report. Pub No. 02-5215. September 2002..
2. Ito et al. Management of Familial Hypercholesterolemias in adult patients: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia Journal of Clinical Lipidology (2011) 5, S38–S45
3. Raal FJ et al. Lancet. 2010;375:998-1996
4. Cuchel M, et al. Lancet. 2013;381:40-46

Treatment Algorithm for HoFH



Schematic adapted from adjacent references

1. NIH. NCEP, Final Report. Pub No. 02-5215. September 2002..
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4. Cuchel M, et al. Lancet. 2013;381:40-46

Current Lipid Lowering Therapies for HoFH

Class	Primary Mechanism of Action (Effects on Lipoprotein Metabolism[1])	% Reduction in LDL-C HoFH
Statins	Inhibition of HMG-CoA Reductase (↑ LDLC clearance via LDL receptors)	Up to 28%[2]
Bile Acid Sequestrants	↓ Bile acid re-absorption (↑ LDLC clearance via LDL receptors)	<10%
Cholesterol Absorption Inhibitor	↓ Intestinal Cholesterol absorption via NPC1L1 (↑ LDLC clearance via LDL receptors)	<10%
Stanol esters	↓ Intestinal Cholesterol absorption (↑ LDLC clearance via LDL receptors)	<10%
Nicotinic acid	Inhibits lipolysis in adopocytes (↓ VLDL/LDL synthesis; ↓ HDLC clearance)	<10%
LDL/Lipoprotein apheresis	Removal of ApoB containing particles via dextran sulfate or polyacrylate column (↓ VLDL, IDL, LDL, RLP)	20-40%[3] (up to 83% acutely[4])
ApoB Synthesis Inhibitor (mipomersen)	Inhibits ApoB containing particles (↓ VLDL, IDL, LDL, TC, Non HDL-C, ApoB, Lp(a))	25%[2]
MTP Inhibitor (lomitapide)	Inhibits Microsomal Triglyceride Transport Protein (MTP) (↓ VLDL, IDL, LDL, TC, Non HDL-C, ApoB)	40%[5]
Evolocumab	Monoclonal antibody binds PCSK9	30%

Table adapted from Rader DJ, et al. J Clin Invest. 2003;111(12):1796-1803.

1. Stone, NJ and Blum, CB. (2005) Management of Lipids in Clinical Practice. 5th Ed.
2. Raal FJ et al. Lancet. 2010;375:998-1996
3. Ito MK, et al. J Clin Lipidol. 2011;5(3 Suppl):S38-S45.
4. Gordon BR, et al. Am J of Card. 1998;81(4):407-411.
5. Cuchel M, et al. Lancet. 2013;381:40-46

LDL/Lipoprotein Apheresis:
For Refractory LDL-C Elevation

*Lowers LDL-C (73%- 83%) over 2-3 hours
*Also lowers Lp(a), VLDL and VLDL remnants
*Improves endothelial dysfunction; lowers CRP
*Improves myocardial perfusion
*Reduces cardiovascular events

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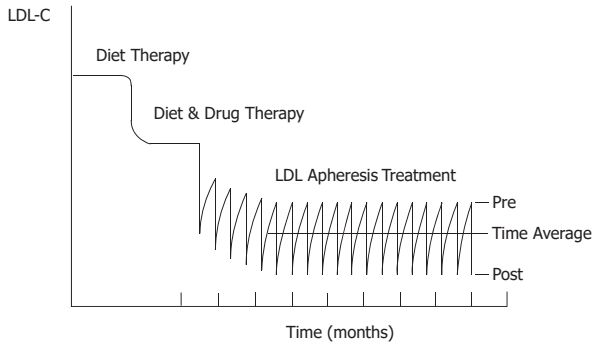
*Improves endothelial dysfunction; lowers CRP
*Improves myocardial perfusion
*Reduces cardiovascular events

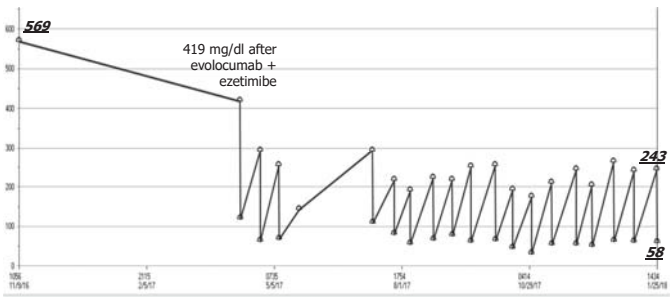
FDA approved for patients with FH and:
(1) CAD and LDL-C > 100 mg/dl or
(2) without CAD and LDL-C > 300 mg/dl after maximum drug and lifestyle therapy

LDL Apheresis



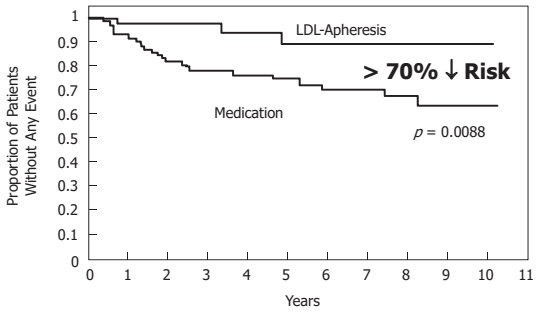
LDL Apheresis in Homozygous FH Treated with Ezetimibe and Evolocumab

Baseline LDL-C 642 mg/dl ---> 569 mg/dl after ezetimibe



Time-averaged LDL-C = 193 mg/dl
(58 + 0.73 x delta LDL-C)

LDL APHERESIS REDUCES CARDIOVASCULAR EVENTS COMPARED TO DRUG THERAPY ALONE



KAPLAN-MEIER CURVES SHOWING PROPORTION OF PATIENTS WITHOUT CORONARY EVENTS

Data From the FH Foundation Cascade FH Registry

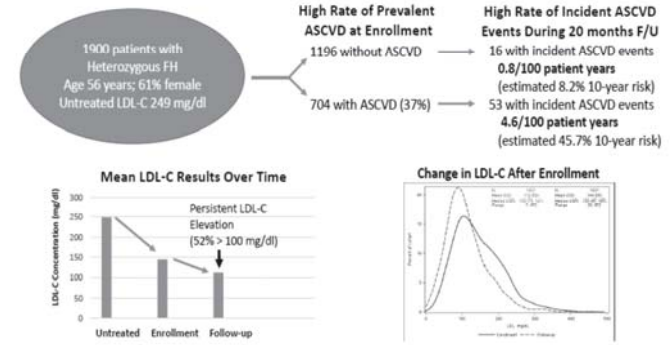
Includes more than 5000 patients with FH treated at lipid specialty clinics in the US

Among 1900 with HeFH and longitudinal follow-up:
- 37% had known ASCVD at enrollment
- Enrollment LDL-C 152 mg/d without CAD, 134 mg/dl with CAD
- 63 undergoing lipoprotein apheresis
- At F/U: more than 50% had LDL-C > 100 mg/dl despite multidrug LDL-C lowering therapy

2.2% annualized prospective ASCVD event rate

Duell PB et al. Atherosclerosis 2019;289:85-93

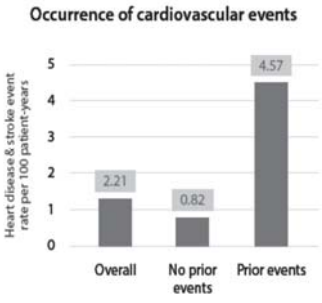
CASCADE FH REGISTRY
Longitudinal Follow-Up Analysis



Duell PB et al. Atherosclerosis 2019;289:85-93

Cascade FH Patient Registry: Longitudinal Follow-up Over 2 years

2/3 were taking > 2 lipid lowering medications



Duell PB et al. Atherosclerosis 2019;289:85-93

Case 2

38 yo woman

Complains of progressive fatigue
Gradual weight gain over the last 6 months

Total cholesterol 318 mg/dl
LDL-C 250 mg/dl
HDL-C 50 mg/dl
Triglycerides 90 mg/dl

Is this FH?

Case 3

38 yo woman

Complains of progressive fatigue
Gradual weight gain over the last 6 months

Total cholesterol 318 mg/dl
LDL-C 250 mg/dl
HDL-C 50 mg/dl
Triglycerides 90 mg/dl

Is this FH? → TSH 110 µU/ml

Case 4

38 yo woman

Eats a bacon cheeseburger and fries twice daily
BMI 35 kg/m^2

Total cholesterol 408 mg/dl
LDL-C 340 mg/dl
HDL-C 50 mg/dl
Triglycerides 90 mg/dl

Is this FH?

Case 5

38 yo woman

Total cholesterol 1480 mg/dl
LDL-C 1411 mg/dl
HDL-C 40 mg/dl
Triglycerides 145 mg/dl

Is this FH?

Case 5

38 yo woman

Total cholesterol 1480 mg/dl
LDL-C 1411 mg/dl
HDL-C 40 mg/dl
Triglycerides 145 mg/dl

Is this FH?
Apo B 100 mg/dl

Case 5

38 yo woman

Total cholesterol 1480 mg/dl
LDL-C 1411 mg/dl
HDL-C 40 mg/dl
Triglycerides 145 mg/dl

Is this FH?
Apo B 100 mg/dl
ALT 230
Alkaline phosphatase 350
Bilirubin 12

Summary

FH is a highly atherogenic disorder

Risk of CHD is increased 10-20 fold

Prevalence is higher than previously recognized ~ 1:250

Phenotype is highly variable

Early aggressive LDL-lowering treatment is needed - age 10 yo

Under diagnosis is a problem - > 90%

Patients with FH can potentially live a full life

It is fabulous to have 7 (8) classes of drugs (+ apheresis)

Homozygous Familial Hypercholesterolemia: Pre- and Post-1990 Advances in Lipid Lowering Therapy

Table 1. Cardiovascular Morbidity and Mortality Characteristics of Patients With Homozygous Familial Hypercholesterolemia Pre-1990 and Post-1990

	Pre-1990 (n=36)	Post-1990 (n=113)
Females/males, n	24/12	58/55
Age at death, y, mean±SD		
All causes	18.4±10.1 (n=27)	32.9±15.5 (n=36)*
Cardiovascular cause	17.7±10.1 (n=22)	31.7±13.3 (n=28)†
Age at first nonfatal MACE, y, mean±SD	12.8±5.9 (n=6)	28.3±10.8 (n=44)‡
Nonfatal cardiovascular events, No. of patients	6 (14 Events)	44 (90 Events)
Myocardial infarction	5 (7 MIs)	10 (11 MIs)
Coronary procedures (CABG, AVR, PTCA, stent)	5 (7 Procedures)	43 (69 Procedures)
Other vascular procedures (carotid surgery, aortoiliac bypass surgery)	None	5 (8 Procedures)
Cerebrovascular events (TIA, stroke)	None	2 (2 Events)

MACE indicates major adverse cardiac event; MIs, myocardial infarctions; CABG, coronary artery bypass surgery; AVR, aortic valve replacement; PTCA, percutaneous coronary angioplasty; and TIA, transient ischemic attack.
*P< 0.0001.
†P<0.001.
‡P<0.01.

Table 2. Lipid Concentrations of Patients With Homozygous Familial Hypercholesterolemia According to Receipt of Modern Lipid-Lowering Therapy (Statin With or Without Ezetimibe) and Percentage Change on Therapy

	Untreated	Taking Modern Lipid-Lowering Therapy	Change, %
Total cholesterol, mmol/L	17.3±3.8	13.1±3.3*	−24.3
Triglycerides, mmol/L	1.28±0.81	1.18±0.63	−7.8
HDL-C, mmol/L	0.89±0.33	0.91±0.25	2.2
LDL-C, mmol/L	15.9±3.9	11.7±3.4*	−26.4
LDL/HDL ratio	21.4±10.9	13.5±5.9*	−36.9

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
Results are expressed as mean±SD.
*P<0.0001.

Raal FJ, et al. Circulation. 2011;124(20):2202-2207.

The Accessible Clinic:
More than Doors and Walls

Presented by:
Ian Jaquiss, Interim ADA Coordinator, Oregon Health & Science University

WHO I AM.

Why I'm here.

I might look familiar . .

.

My first job was as a model.

Ground Rules

1. Vegas training (safe room)
2. I'm funny
3. Your input is wanted and needed*

* *Your questions/comments will enrich this training. Please speak even if it feels awkward*

Session Objectives

- After today
  - Will know how to create a more welcoming place for people with disabilities
  - Know better language related to disability
  - Know why language and attitude towards people with disabilities is so important

Your

First

Encounter

With A

Person with

A Disability

Close Your Eyes…

Brief Timeline of Disability History

Discard ⇨ Patronize ⇨ Recognize as People

*ADA created in 1990, enacted in 1991.

ADA: promise vs. delivery

[redacted]

Health Indicator	Disability	No disability	Source
Adults who engage in no leisure time physical activity	54.2%	32.2%	NHIS
Children and adolescents considered obese (age 2-17)	21.1%	15.2%	NHANES
Adults who are obese	44.6%	34.2%	NHANES
Adults who smoke	28.2%	18.0%	NHIS

NHIS = National Health Interview Survey 2008
NHANES = National Health and Nutrition Examination Survey 1999-2010
NHIS = National Health Interview Survey 2010

Disabilities – *roughly one in five people*

The problem with this logo.

Disabilities – *roughly one in five people*

When Arriving at a Medical Clinic:

What do you expect:

- Parking
- Path
- Entrance
- Easy access to services

- Not everyone expects that
- Some groups of people know they will not get any of that.

Accessible Medical Facilities

The ADA requires accessible:

- Doors
- Pathways
- Space to enter and turn around, lobbies and rooms
- Lifts
- Examination Tables
- Medical Equipment (scales, x-rays, machines, etc.)

<u>The ADA does *not* require employees at those facilities:</u>

- To be sensitive to the concerns of patients with disabilities
- To know how to talk about those concerns

Terminology: do all of these terms mean the same thing?

Physically challenged

Person with a disability

The disabled

Differently-abled

Handicapable!

Handicapped

Crippled

Another way to think about disability

Disabilities have added to every life:

1. Curb Cuts
2. Automatic Doors
3. Wider bathroom stalls

You Are Welcome.

Recap

- People with Disabilities, in general, are less healthy than people with disabilities.
- Know when to tell someone with a disability they are an inspiration.
- Tell kids its okay to look and it is okay to ask.

Thank You

Contact me

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