Clinical Pearls for College Health Providers

Summary of relevant research
2012-13

Objectives

- Define & summarize the process for determining relevance of research
- Share the recent evidence-based guidelines for preventive services that apply to college health
- Summarize the validity, results, and application of the top 12 research articles of the last year

The medical literature

Your Shuckers…

- Marcy Ferdschneider, DO
- Michelle Paavola, MD
- Cheryl Flynn, MD, MS, MA

None of us have disclosures to make

The process

- Reviewed journals & abstracting services from 8/2012-8/2013; USPSTF guidelines
- Selected original research relevant to college health
  - **Relevance** = common + patient-oriented outcome + change/re-affirm practice
- Consensus for top dozen
- Summarize validity, findings, and application to practice

U.S. Preventive Services
TASK FORCE

Rating	Recommendation	Review of Evidence
A	Yes, strongly	High certainty that net benefit is substantial
B	Yes	High certainty that net benefit is moderate or moderate certainty that net benefit is substantial
C	Not Routinely	Moderate certainty that net benefit is small; may be considerations that support use
D	No	At least moderate certainty of no benefit or harms > benefits
I	Unable to recommend	Evidence is lacking, poor quality, or conflicting

Screening for ETOH misuse: B

Alcohol misuse screening:

- screen those ≥18y/o
- offer brief behavioral interventions to those screen +

Cervical Cancer Screening: A

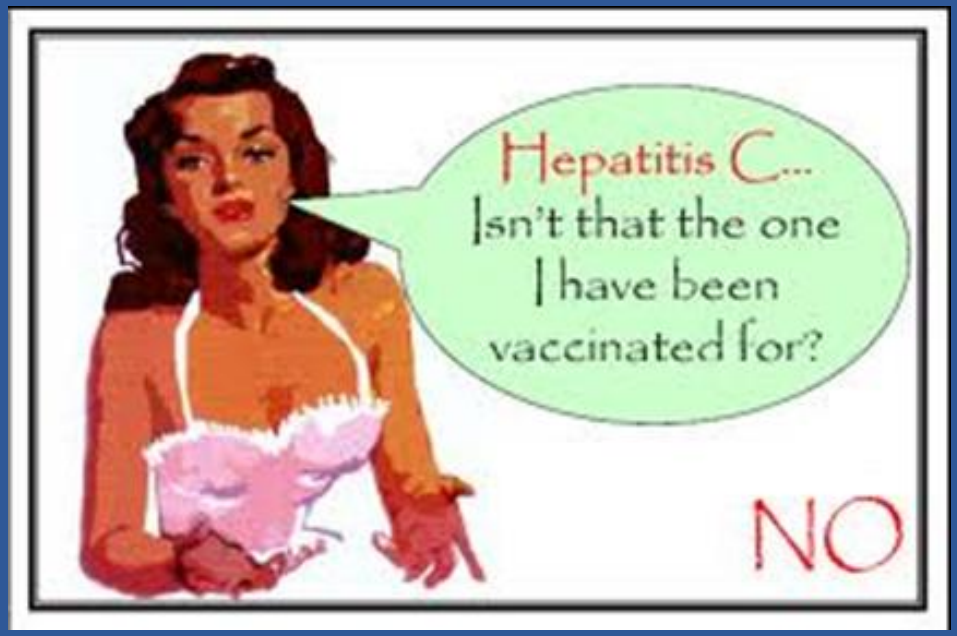
Cervical cancer screening:

- begin cervical CA screening at 21;
- pap Q3yrs;
- no screening HPV until age 30

Screening for Hep C: A

Hep C screening:

- *only* for those at risk (past/current IVDA, sex w/ IV drug user, blood transfusion before 1992)



Screening for HIV: A

HIV screening:

- screen those 15-65y/o
- interval not clear

Screening for Obesity: B

Obesity screening:

- calculate BMI for adults
- refer to intensive behavioral intervention for those w/ BMI ≥30

Now… onto the original research

Fasting Time and Lipid Levels

Arch Intern Med. 21012; 172(22):1707-1710

Background

- Lipid levels are used for both screening and and diagnostic purposes
- Current guidelines recommend measuring lipid levels in a fasting state
  - Fasting inconvenient
  - Some may not get testing done
- Recent studies suggest there is a minimal change to lipid levels in response to food

Question: Is there an association between fasting times and lipid levels

Methods

- Design:
  - Cross sectional examination of laboratory data, including:
    - Duration of fast
    - Lipid result—Total cholesterol, HDL, LDL, TGs
  - Performed over 6-month period
  - Excluded: missing hours from last meal and TGs >400
- Population:
  - Residents of Calgary, Alberta, Canada
- Outcome:
  - Lipid panel results at 9-12hr, and >8hr

Results

- Total of 209,180 lipid profiles

Table 2. Cholesterol Levels in Females by Fasting Time After Adjustment for the Effect of Age

Fasting Time, h	Sample Size[a]	Mean (95% CI), mg/dL			
		Total Cholesterol	HDL Cholesterol	Calculated LDL Cholesterol	Triglycerides
1	848	175.4 (171.5-179.2)[b,c]	57.8 (56.1-59.5)	92.2 (88.8-95.6)[b,c]	129.4 (121.3-137.6)[c]
2	415	175.0 (168.4-181.5)[c]	59.7 (56.8-62.6)	90.8 (85.1-96.6)[b,c]	130.3 (116.5-144.0)[c]
3	354	173.7 (167.6-179.8)	57.7 (55.0-60.3)	89.7 (84.4-95.0) [b]	134.4 (121.7-147.1)[c]
4	286	180.3 (173.3-187.3)	60.4 (57.3-63.5)	95.3 (89.1-101.4)[c]	124.4 (109.7-139.0)[c]
5	196	176.5 (168.4-184.6)	58.3 (54.7-61.9)	94.9 (87.8-102.1)[b]	122.5 (105.5-139.5)[c]
6	117	181.8 (173.0-190.6)	61.7 (57.8-65.6)	96.1 (88.3-104.0)	131.3 (112.9-149.8)
7	91	171.5 (163.0-180.0)	58.9 (55.2-62.7)	90.0 (82.6-97.5)	114.1 (96.3-131.9)
8	261	173.0 (165.5-180.4)	58.4 (55.1-61.7)	93.0 (86.4-99.5)	109.7 (94.1-125.3)
9	909	177.4 (171.7-183.1)	59.1 (56.6-61.6)	96.4 (91.3 101.4)	111.9 (99.9-123.8)
10	11 954	177.9 (175.4-180.3)	58.9 (57.8-60.0)	97.7 (95.5-99.8)	108.2 (103.1-113.3)
11	17 042	178.3 (175.8-180.9)	58.1 (57.0-59.3)	98.6 (96.3-100.8)	109.3 (104.0-114.7)
12	35 897	179.4 (177.6-181.3)	58.9 (58.0-59.7)	98.9 (97.3-100.5)	109.7 (105.8-113.6)
13	19 696	177.5 (175.3-179.7)	58.9 (57.9-59.8)	97.5 (95.5-99.4)[b]	107.3 (102.7-112.0)
14	12 789	182.2 (180.5-183.9)	59.9 (59.2-60.7)	100.5 (99.0-102.0)[b]	109.5 (106.0-113.1)
15	6131	181.4 (180.6-187.7)	59.9 (58.3-61.5)	102.4 (99.2-105.5)[b]	110.7 (103.2-118.2)
16	4062	183.8 (180.0-187.7)	59.5 (57.8-61.2)	101.9 (98.4-105.3)[b]	113.9 (105.9-121.9)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversion factors: To convert cholesterol and triglyceride values to millimoles per liter, multiply by 0.0259 and 0.0113, respectively.
[a] The total sample size for LDL cholesterol is smaller (110 192) because LDL cholesterol values were not reported if the triglyceride level was greater than 400 mg/dL.
[b] Statistically different ($P < .05$) from a 9- to 12-hour fasting time.
[c] Statistically different ($P < .05$) from a greater than 8-hour fasting time.

Results

- Variance of mean cholesterol subclass levels:
  - Total cholesterol: <2%
  - HDL: <2%
  - Calculated LDL: <10%
  - Triglycerides: <20%
- Statistically significant differences ($p<.05$) were present for a minority of fasting intervals when compared with either a 9- to 12-hour fasting time or greater than 8-hour fasting time

Conclusions/Limitations

- Fasting time showed little association with lipid subclass level

- Food choices pre-lab draw were not examined; only time between eating/phlebotomy
- Pharmacologic tx of subjects unknown
- Those who accept screening lipid panels may not be representative of general population
- Data did not include apolipoproteins
- gen. population

Bottom Line

- When ordering screening lipid panels, get the lipids at the same appointment
- No need to make people come back in the morning for blood work

Self Swab vs. Clinician swab for Gonorrhea/Chlamydia

BMJ 2012;345:e8107

Background

- Gonorrhea
  - 2nd most common STI in UK (where study takes place)
  - Often asymptomatic in females
  - Can cause PID and possibly lead to infertility
  - In UK, standard is to obtain a urethral and/or endocervical swab→necessitating a speculum exam
    - Many women find these embarrassing and uncomfortable
    - Requires clinic visit, use of exam room, vaginal speculum and a trained clinician
- Non-invasive samples eliminate some barriers to screening for GC/chlamydia
- Evidence suggests self-taken vaginal swabs have better sensitivity than first catch urine

Methods

- Design: Prospective study of diagnostic accuracy
  - Sxs suggestive of bacterial STI were identified (vaginal d/c, dysuria, intermenstrual or postcoital bleeding, deep dyspareunia and low abd pain)
  - Women were given written and verbal instructions and self swabs performed prior to clinician exam
  - Two different diagnostic tests were used
    1. Urethral and endocervical samples analyzed by culture
    2. Vulvovaginal and endocervical samples analyzed by Aptima Combo 2 (AP2) assay (nucleic acid amplification test)
  - Positive AC2 tests were further analyzed using Aptima GC assay (monospecific platform test with diff target than AC2)
- Population: Women, ≥16 y/o, STI clinic; willing to perform own vag swab
- Outcome: accuracy of various collection methods

Results

- 3859 women

Description	Value
Mean age	25
Self-reported ethnicity	White—80%,Black—9% Mixed—7%, Other—4%
Previous dx of STI	37%
Contact with partner with recent STI dx	7%
At least one symptom suggestive of bacterial STI	42%
Clinical dx of Cervicitis made	5%
Clinical dx of PID	4%
Infected with gonorrhea	2.5% (100 women)
Those with gonorrhea and co-infected with *C trachomatis*	55% (55 women)
Infected with *C trachomatis*, but not gonorrhea	9% (355 women)

Results

Description	Value
Overall Culture sensitivity	81%
Overall Clinician-taken endocervical NAAT	96%
Overall Self-taken vulvovaginal NAAT	99%
Sensitivities in women with ≥ 1 symptom	3.4 % were infected with gonorrhea Culture: 84% Clinician-taken endocervical: 100% Self-taken vulvovaginal: 100%
Sensitivities in women with no symptoms	1.8% were infected with gonorrhea Culture: 78% Clinician-taken endocervical: 90% Self-taken vulvovaginal: 98%

Conclusions/Limitations

- NAAT tested vulvovaginal swabs obtained by pts are:
  - Significantly more sensitive than endocervical gonorrhea cultures obtained by clinician
  - Equivalent to NAAT endocervical samples obtained by clinician
- Culture method missed 20% of gonorrhea cases

- Single center study
- Order of samples was not randomized or rotated→self-taken vulvovaginal swabs were collected first
- Negative AC2 tests were not repeated, so could have missed some false negative results (but each woman had 3 different samples analyzed for gonorrhea
- Not compared to urine NAAT GC/chlamydia
- Comparison of chlamydia accuracy not measured

Bottom Line

- Consider incorporating the use of self-taken vaginal swabs to test for gonorrhea and chlamydia.

Probiotics for Antibiotic-Associated Diarrhea

Aliment Pharmacol Ther 2012; 35: 1355-1369

Background

- Antibiotic-associated diarrhea (AAD) remains a common condition with a prevalence of 5-39%
- AAD can be a limiting factor to adherence to antibiotic regimens
- Probiotics have been linked to modulation of gut mucosal immunity, barrier function, metabolism,
- Earlier studies and meta analysis have suggested probiotic administration reduces the incidence of AAD
- Questions:
  1. Do probiotics reduce the incidence of AAD?
  2. How about during treatment for *H.Pylori?*
  3. Do the effects vary between children and adults?
  4. What probiotic species are more efficacious?

Methods

- Design:
  - Meta-analysis of randomized, double-blinded, placebo-controlled trials
- Population:
  - Patients treated with antibiotics and administered a probiotic for at least the duration of the antibiotic treatment
- Outcome:
  - Incidence of diarrhea, irrespective of *C.diff* or pseudomembranous colitis

Results

- Total of 34 studies with 4138 patients
- Mean age in the 10 pediatric trials→5
- Mean age in 24 adult trials→52
- Probiotics used alone or in combination:
  - Lactobacilli
  - Bifidobacteria
  - Enterococci
  - Streptococci
  - Yeast *S. boulardii*
- Duration of treatment varied between 3 days to several weeks

Results

Studies	RR	NNT
All studies	0.53	8
10 Pediatric studies	0.48	
24 Adult studies	0.53	
6 *H.pylori* treatment studies	0.37	5
Pooled studies excluding *H. pylori*	0.56	9

Conclusions/Limitations

- Probiotics are effective prevention for developing abx-associated diarrhea.
  - present across different probiotic species
  - observed equally in children and adults
  - appears to be independent of the concomitant antibiotic used and indication for antibiotic treatment

- Search strategy/Inclusion criteria may have missed some eligible trials
  - ie those with non-diarrhea 1^{o} outcomes but in which the incidence of diarrhea was measured
- Qualitative heterogeneity likely accounts for varied NNTs:
  - populations studied (adult vs. peds; inpt vs outpt)
  - Nature and modalities of intervention (probiotic strains, doses , antibiotics used and duration of treatment)
  - outcomes considered (definitions of diarrhea, its incidence and duration of follow up)

Bottom Line

- Giving probiotics when administering abx can decrease abx-associated diarrhea
- No clear recommendations re: type/dose can be made

Validation of Clinical Decision Rules for Sore Throat

	Score
Temperature ~>38°C	1
Absence of cough (as a cough is more likely to be associated with a viral infection)	1
Swollen tender anterior cervical lymph nodes	1
Tonsillar swelling or exudates	1
Age	
3–14 years	1
15–44 years	0
45 years or older	–1

Arch Intern Med. 2012; 172 (11): 947-852

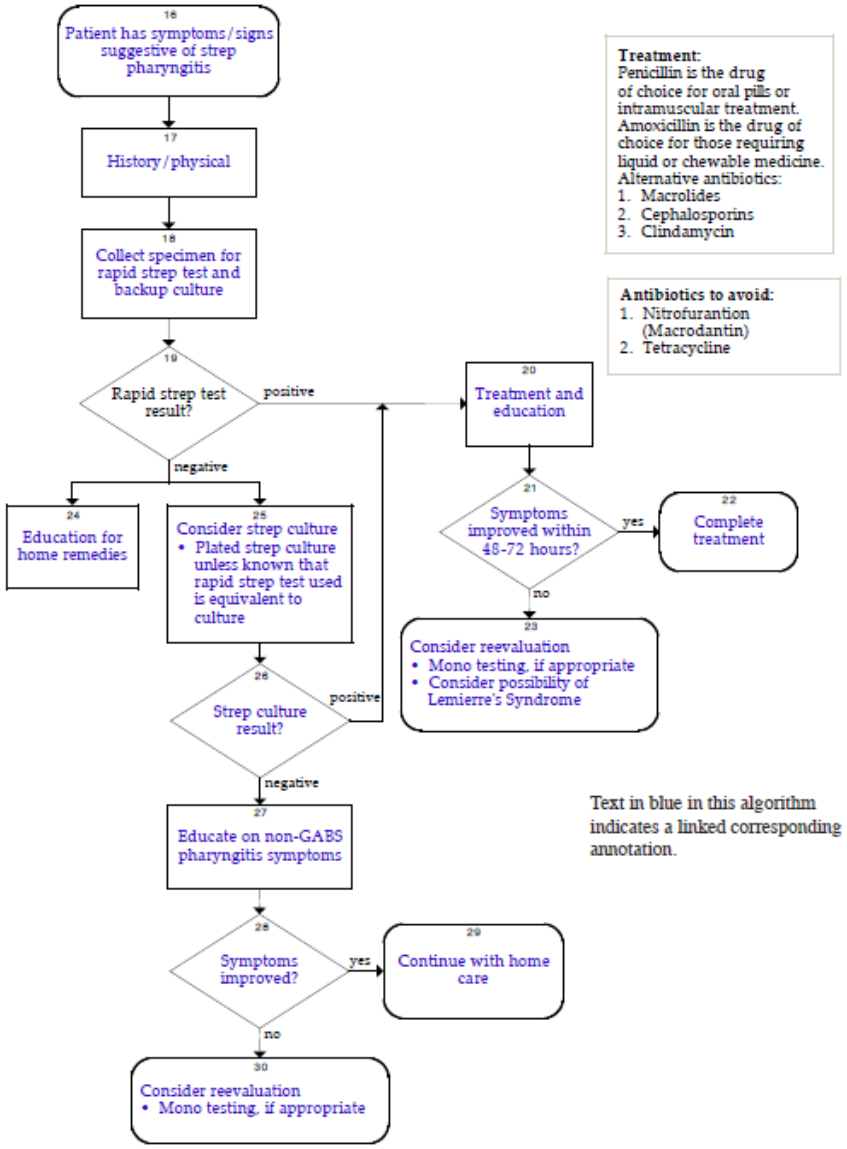
Background

- Sore throat is common presenting complaint in college health; often pts worry about strep as cause
- Evidence-based clinical scoring tools have supported selective testing &/or empiric tx for strep
  - Centor criteria and McIssac scores
  - Both derived on relatively small populations (centor: 286 ED pts; McIssac on 521 FP pts)
- This study was aimed at validating existing decision rules

Methods

- Design: National large-scale validation
  - Retrospective data collected from pts tested for GAS pharyngitis due to complaints of sore throat
  - Clinicians adhered to “Strep Pharyngitis Algorithm” from Institute for Clinical Systems Improvement
- Population:
  - Patients who went to Minute Clinic, a large, national, retail health chain
  - Included 206,870 encounters from 581 sites and 25 states.
    - 206, 870 patients ≥ 3 years old to validate McIsaac score
    - 142,081 patients ≥ 15 years old to validate Centor score
- Outcome: Proportions of patients testing positive for GAS pharyngitis according to the Centor and McIssac scores

Strep Pharyngitis Algorithm



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Results

Criteria	Tested positive for GAS
All patients ≥ 15 years old	23 %
≥ 15 years old with Centor score of 0	7%
≥ 15 years old with Centor score of 1	12%
≥ 15 years old with Centor score of 2	21%
≥ 15 years old with Centor score of 3	38%
≥ 15 years old with Centor score of 4	57%
All patients ≥ 3 years old (McIsaac score arm)	27%
≥ 3 years old with McIsaac score of 0	8%
≥ 3 years old with McIsaac score of 1	14%
≥ 3 years old with McIsaac score of 2	23%
≥ 3 years old with McIsaac score of 3	37%
≥ 3 years old with McIsaac score of 4	55%

Results

- In both groups, patients who tested positive for GAS pharyngitis were more likely to present with:
  - Tonsillar exudates
  - Swollen anterior cervical lymph node
  - Tonsillar swelling
  - History of fever in previous 24 hours
  - Absence of cough
  - Lack of rhinorrhea
  - Swollen posterior cervical lymph nodes
  - Exposure to GAS
  - Temp above 101F at time of presentation
- Odds of having GAS, in order of highest to lowest of Centor criteria:
  1. Presence of tonsillar exudates
  2. Swollen anterior cervical lymph nodes
  3. History of fever
  4. Absence of cough

Conclusions/Limitations

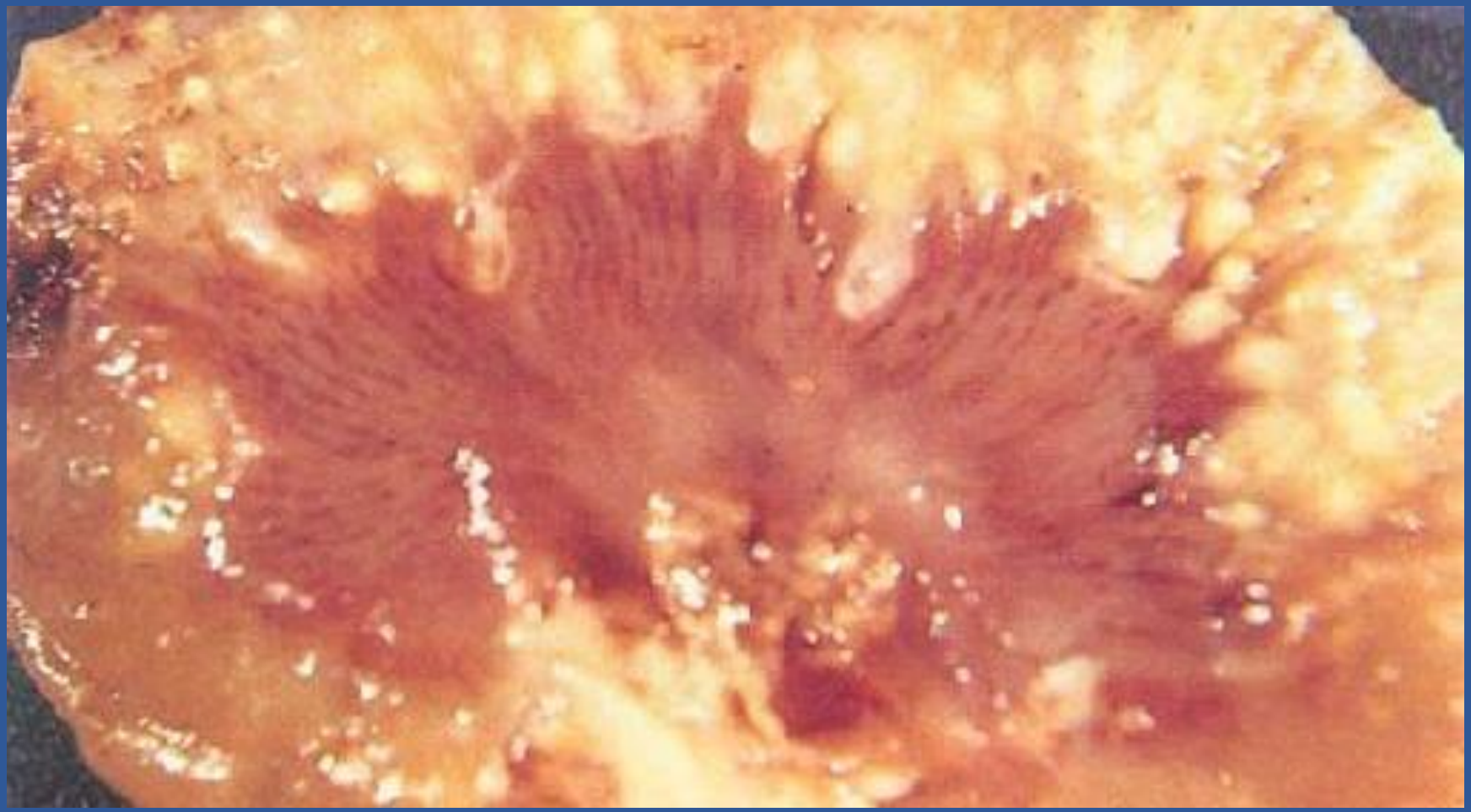
- Both Centor criteria and McIsaac scores are valid, useful tools for the diagnosis and treatment of patients with acute pharyngitis

- There may be some variability in clinical interpretation of Centor criteria
- Data are not available for calculating inter-observer or intra-observor reliability
- Most other bacterial causes of pharyngitis were unlikely to be detected by this data
- Asymptomatic strep carrier state not addressed, so symptomatic patients with positive DGAS test were assumed to be true positives and not carriers

Bottom Line

- Keep using Centor Criteria to guide assessment of patients with sore throat
  - Score 0-1: no test, no tx
  - Score 2-3: rapid strep testing; treat if positive result
  - Score 4: empiric abx Rx for strep reasonable
- In nonpediatric population Grp A strep culture not needed as “back-up” for those whose RST is negative

Pyelonephritis: Duration of Treatment



The Lancet 2012; 380:484-90

Background

- Common infection in adult women
- Antibiotic resistance of E. Coli is increasing
- Few controlled trials to assess the optimum duration of treatment
- Objective: is 7 days of cipro as effective as 14 days of cipro when treating pyelo?

Methods

- Design: Prospective, randomized, double-blind, non-inferiority trial with parallel groups
  - All patients received ciprofloxacin for 7 days, half received an additional 7 days (14 total) and the other half received an additional 7 days placebo
- Population: women aged 18 years and older with a presumptive diagnosis of Pyelonephritis from 21 Infectious Disease Centers in Sweden
  - Fever of at least 100.4, plus on of the following
  - Flank pain, CVA tenderness, dysuria, urgency or frequency
- Outcome: Compare short-term clinical and bacteriological efficacy and safety of 2 regimens. Assess long-term cumulative efficacy and the consequences of not treating asymptomatic bacteruria at short-term follow up

Results

Ciprofloxacin – 7 days

- n = 73
- 88% E. Coli
- Short-term efficacy
  - 71 cured (97%)
  - Clinical failure or recurrent UTI symptoms: 2 (3%)
- Cumulative efficacy
  - 68 cured (93%)
  - Clinical failure or recurrent UTI symptoms: 5 (7%)

Ciprofloxacin – 14 days

- n = 83
- 95% E. Coli
- Short-term efficacy
  - 80 cured (96%)
  - Clinical failure or recurrent UTI symptoms: 3 (4%)
- Cumulative efficacy
  - 78 cured (93%)
  - Clinical failure or recurrent UTI symptoms: 6 (7%)

Conclusions/Limitations

- Community-acquired acute pyelonephritis in women can be treated successfully and safely with oral ciprofloxacin for 7 days

- Results cannot be extrapolated to other classes of antibiotics
- Fluoroquinolones are recommended as first-line choice for empirical treatment of pyelo as long as the resistance rate does not exceed 10%

Bottom Line

- In women with acute pyelonephritis for who Ciprofloxacin will be the drug of choice, a 7 day course is not inferior to a 14 day course
  - Will reduce consumption of antibiotics
  - Reduction of certain side effects achieved by shorter course of treatment
  - Follow up cultures not necessary if clinical resolution of symptoms

Iron supplementation for fatigue with no anemia?

CMAJ 2012; 184 (11):1247-54

Background

- The prevalence of fatigue ranges from 14% to 27% among patients in Primary Care
- Women are three times more likely than men to mention fatigue
- Unexplained fatigue can be caused by iron deficiency
- Main objective: test the hypothesis that short-term oral iron therapy may improve fatigue, hemoglobin, iron stores and quality of life in menstruating nonanemic women whose ferritin levels are below 50 micrograms/L and to see if this effect is dependent on the initial levels of hemoglobin, ferritin or transferrin saturation

Methods

- Design: 12-week multi-center, double-blind, placebo-controlled, parallel group, pragmatic randomized trail with a 1:1 allocation ratio
- Population: 44 private practices in France recruited women presenting with fatigue who are:
  - Menstruating
  - Between 18-50 years old
  - Report considerable fatigue (>6 on a 1-10 Likert Scale), without obvious clinical causes
  - Not anemic (Hgb $\geq$12)
  - Have a low or borderline ferritin level (<50)
  - Not pregnant or breastfeeding
  - Not already taking iron supplementation
- Outcome: Improvement of fatigue as measured on the Current and Past Psychological Scale

Results

- Iron supplementation for 12 weeks decreased fatigue by almost 50% from baseline (19% in the placebo group)
- Iron supplementation did not have a significant effect on measured indicators of quality of life (outside of those related to fatigue)
- Iron supplementation improves hemoglobin, ferritin, hematocrit, mcv and soluble transferrin as early as six weeks after starting treatment

Conclusions/Limitations

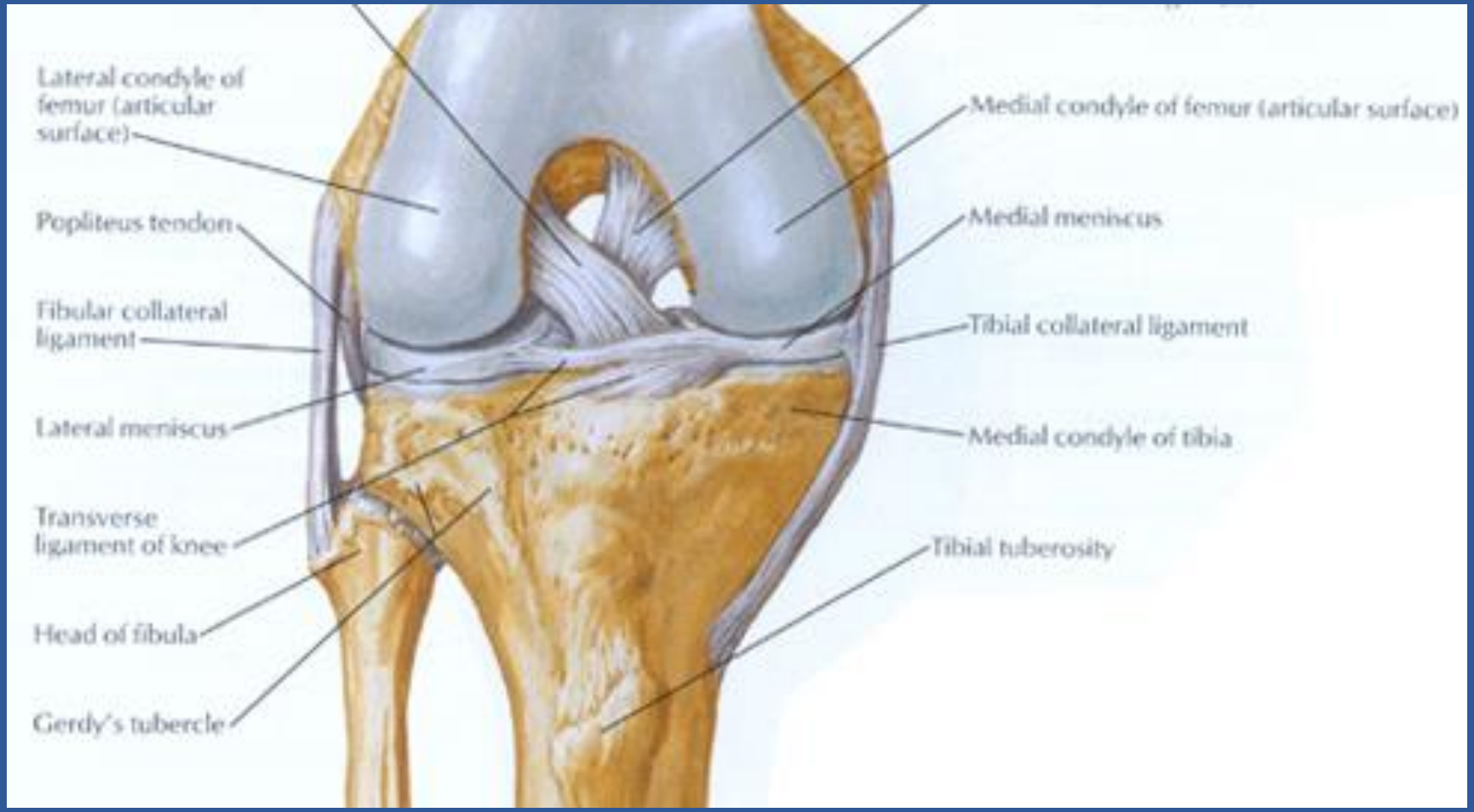
- Iron deficiency may be an under-recognized cause of fatigue in women of child-bearing age
- For women with unexplained fatigue, iron deficiency should be considered when ferritin values are below 50 micrograms/L, even when hgb values are above 12 g/L

- Blinding is challenging given the side effects of iron
- Fatigue is a subjective, patient-centered measure

Bottom Line

- Iron supplementation may be useful in patients presenting with fatigue and should be investigated by adding a serum ferritin level even with a presumably normal hemoglobin
- The addition of this test could save on the use of other resources and the attribution of symptoms to emotional or mental health issues

Treatment of acute ACL tear



BMJ 2013; 346:f232

Background

- Acute anterior cruciate ligament rupture is a common and serious knee injury in the young active population
- Many patients develop osteoarthritis of the knee irrespective of treatment
- Objective: Compare 2 treatment strategies – structured rehab plus early reconstruction or structured rehab with the option of later reconstruction if needed

Methods

- Design: Randomized, controlled trial (extended follow up of previous trial)
- Population: Active adults ages 18-35 with ACL tears no more than 4 weeks old to a previously uninjured knee
- Outcome: Change from baseline to five years on patient reported outcomes

Results

- No statistically significant differences in pain, symptoms, function in ADLs, function in sports and recreation, knee related quality of life, general physical or mental health status, current physical activity level, return to pre-injury activity level, radiographic osteoarthritis, or meniscus surgery

Conclusions/Limitations

- In young, active adults with an acute ACL tear, early reconstruction plus rehab does not provide better results than rehab with the option of surgery later

- Results do not apply to professional athletes or to less than moderately active people

Bottom Line

- Consider rehabilitation as a primary treatment option after an acute ACL tear

Amoxicillin for Acute LRI in Primary Care

Lancet Infect Dis 2013; 13:123-29

Background

- Lower-respiratory-tract infection is one of the most common acute illnesses managed in primary care
- Most patients receive antibiotics
- Objective: Evaluate benefit vs. risk

Methods

- Design: Parallel, randomized, placebo-control trial
- Population: Patients ≥ 18 years with acute cough (≤28 days) or presumptive dx of acute LRI from throughout Europe
- Outcome: Amoxicillin provides little benefit for acute lower-respiratory-tract infection in primary care and causes slight harms

Results

- 3 key outcomes
  - Duration of symptoms that were moderately bad or worse
    - Not statistically significant
  - Symptom severity
    - Not statistically significant
  - New or worsening symptoms
    - Better in the Amox group but high NNT (30)
- Increased side effects in Amox group and one case of anaphylaxis

Conclusions/Limitations

- Amoxicillin did not reduce the duration of symptoms rated “moderately bad” or worse or symptom severity compared with placebo

- Choice of antibiotic might have restricted efficacy
- Poor adherence could have diminished efficacy

Bottom Line

- Amoxicillin provides little symptomatic benefit for patients presenting in primary care with lower-respiratory-tract infections
- Any mild, short-term benefits should be balanced against the risks of side-effects and fostering resistance
- In other words… don’t do it

Acute bronchitis: cough duration?

Ann Fam Med 2013; 11:5-13

Background

- Acute cough illness/acute bronchitis very common; 2-3% of all outpatient visits
- Most caused by virus; abx not helpful
- Self-limited illness
  - ~50% still coughing at 2wk
  - No data re: pt expectation of cough duration though anecdotally shorter!
  - Mismatch expectation may lead to requests for abx
- Q: how long does the typical bronchitis last? How does this compare to patients' expectations?

Methods

Pt expectations

- Design: survey sharing case scenarios (Fever/no F; colored sputum/no sputum)
- Population: random digit dialing, >18 y/o
- Outcome: expected duration of cough; value of abx

Cough duration

- Design: meta-analysis of observational studies, or placebo arm of RCTs
  - Comprehensive search
  - Dual data extraction, validity assessment
  - Did not seek unpublished studies
- Population: adult pts with acute cough, no COPD, outpt only
- Outcomes: mean duration of cough in untreated arms

Results: pt expectations

- 493 respondents (43.6%)
- Median expected duration of cough 5-7 days
  - Scenarios with fever > no fever
  - Green sputum>yellow > dry cough
- Belief that abx were always helpful
  - Nonwhite race, some college education or less, past abx use for acute cough

Results: duration of cough

- 19 studies included, with total of 1230 pts
- US, Europe, with one study in Kenya

- Mean duration of cough 17.8 days
  - range 15.3-28.6
  - Mean duration of productive cough 13.9 days

Conclusions/limitations

- Significant mismatch between pt expectations and actual duration of cough in ACI
  - 7 days vs 18 days

- Though publication bias possible, unlikely
- Data confirms previous research about cough duration
- Survey data of GA residents only, though demographically diverse

Bottom line

- Typical cough lasts ~18 days in acute bronchitis; pts expect 7 days or less
- Provider education of patients warranted
  - may help decrease repeated phone calls, unnecessary abx

CV risk of azithromycin

NEJM 2012; 366: 1881-90; NEJM 2013; 368: 1704-12

Background

- Some macrolides demo risk of pro-arrhythmic effect (prolonged QT)
- >40million Rx for azithromycin in US
  - ~1/8 of of US population!
- 5/2012 observational study demo'd small but significant absolute increase in CV deaths during 5 days of azithromycin dosing, calling for warnings about its use
- Q: what is the risk of CV death in the general population from use of azithro?

Why some “hate” EBM…

- 5/2013 retrospective cohort study, using Danish national database drew seemingly contrary conclusions

- Review both studies (one from our search period, one from prior year) to compare/contrast and apply to our population in college health

Methods: Design

2012

- Retrospective cohort; 1992-2006
- Linked Medicaid database (enrollment, Rx, pt encounters) with statewide hospital-discharge database with death certifications
- Compared Azithro use to no abx, to Amox, and to cipro & levofloxacin

2013

- Retrospective cohort; 1997-2010
- Linked Rx-drug use with cause of death and potential confounders
- Compared Azithro use to no abx, and to PCN V
  - Post-hoc analysis also compared azithro to amox

Methods: Population

2012

- Tennessee Medicaid patients
- 30-74 y/o
- No h/o life-threatening nonCV illness, no h/o drug abuse, not in nursing home w/in 1 yr, nor hospitalized w/in 30 days
- Enrolled in medicaid for at least 1 yr, regularly uses medical care

2013

- Danish residents id'd via Danish Civil Registration System
- 18-64 y/o
- Not hospitalized nor any abx w/in 30 days of index date
- Lived in Denmark for at least 2 yr, and have filled at least 1 Rx within 1 yr of index date

Methods: *Control* Population

Index population rec'd azithromycin Rx

2012

- 4 control subjects matched on propensity score (based on 153 factors)but rec'd no Abx
- Additional control groups of eligible patients who took amoxicillin/augmentin, ciprofloxacin, and levofloxacin

- Statistically independent groups (ie no overlap of abx use in index time)

2013

- No use of abx, matched 1:1 on propensity scores

- All persons with use of oral penicillin V matched within quintile of propensity score
  - Separate sensitivity analysis where matched 1:1 also

- Those with other abx Rx during index period excluded

Methods: Outcomes

2012

- Primary end points
  - CV death
  - Death from any cause
- Secondary end point
  - Sudden cardiac deaths (independently validated computerized def)
- Evaluation periods:
  - Days 1-5
  - Days 6-10

2013

- Primary end point
  - CV death
- Secondary end point
  - nonCV death
- Evaluation periods:
  - Days 1-5
  - Days 6-10
  - “former use” = day 11-35

Methods: Analysis

2012

- Cumulative incidence (risk) of death→hazard ratio
- Adjusted w/ regression analysis for covariates
  - Propensity score
  - CV death risk
  - Indication for abx
- Estimated "additional risk per course of azithro Rx" vs amox

2013

- Poisson regression→rate ratio (= risk ratio)
- Adjusted for confounders
  - Propensity scores, and quintiles
  - Not consider abx indictation but post-hoc analysis of azithro vs amox also
- Estimated absolute difference in risk per 1 million Rx episodes

Results: 2012 cohort

Comparison Azithro (0.35M) vs:	CV death HR (95% CI)	All cause death HR (95% CI)
No abx (1.39M)	2.88 (1.79-4.63)	1.85 (1.25-2.75)
Amoxicillin (1.35M)	2.49 (1.38-4.50)	2.02 (1.24-3.30)
Ciprofloxacin (0.26M)	3.49 (1.32-9.26)	1.75 (0.91-3.37)
Levofloxacin (0.19M)	1.27 (0.66-2.47)	1.07 (0.61-1.85)

- Amoxicillin vs no abx with NO increase risk of CV death
- Estimated excess of 47 CV deaths per one million Rx of azithro vs amox

Results: 2013 cohort

Comparison Azithro (1.1M) vs:	CV death RR (95% CI)	NonCV death RR (95%CI)
No abx (7.1M)	2.85(1.13-7.24)	
Penicillin V (7.4M)	0.93(0.56-1.55)	0.82 (0.61-1.12)
Amox (post-hoc)	0.60(0.29-1.23)	

- Risk was higher in those with greater baseline risk
- Absolute risk azithro vs PCN similar; absolute risk azithro vs no abx not calculated

Conclusions

- 2012: azithromycin confers increased risk of CV death vs no abx and vs. amoxicillin
  - Thus risk attributed to azithro
  - Increase risk of death in those with higher baseline CV risk
- 2013: azithromycin confers a slight increased risk of CV death vs no abx, but did not increase risk vs PCN or amox
  - Thus risk attributed to baseline indication of abx
  - Increase risk of death in those with higher baseline CV risk
- Both studies found risk only associated with *current* use (not recent, not past) suggesting likely pro-arrhythmic effect

Limitations

- Both studies observational only
  - Possibility of confounding despite matching and regression analysis; cannot officially determine causality
- Populations in these 2 studies different
  - 2012 medicaid pop; 2013 general pop, younger
  - 2013 more generalizable to college population
- Amoxicillin vs PCN choice might be different in USA, so possibly accounting for differences in the two studies

Bottom Line

- Azithromycin carries a very small clinical risk of increased CV death during its use
- Weigh risks/benefits before prescribing
  - No benefit in outcomes for acute bronchitis vs incr risk of CV death!
  - Other abx options for other resp/GI infections

New treatment for head lice

NEJM 2012; 367:1687-93

Background

- Growing resistance to current 1st line treatment of lice
  - Permethrin & pyrethrins—up to 50%!
- 2nd line agents (lindane, malthion) w/ risks, inconveniences
  - Toxicity, odor, flammability
- Oral ivermectin found to be effective treatment for resistant lice
- Q: is topical ivermectin an effective treatment for lice?

Methods

- Design: 2 double-blinded RCTs, concealed allocation
  - 0.5% ivermectin lotion vs placebo applied to dry hair x 10min; no nit comb
  - Intention to treat analysis; last observation carried forward, as well as treatment failure sensitivity analysis
- Population: >6mo old; clinically id at least 3 nits for "index" patients
  - 8 separate sites across US
  - Household members with ≥1 louse
- Outcomes: louse free index pts at 1, 7, 14 days post tx
  - Total louse free pts on same schedule
  - Adverse effects: itching, excoriation, redness, eye irritation

Methods: Drug Co Sponsored

Results

- 289 index pt; 781 extended pop
- Baseline char. similar; mostly white; 40% hispanic; ~20% adolescents/adults
- Louse Free Index Patients:

Days post-tx	Ivermectin lotion	Placebo	Stat signif	Clin signif NNT
1	94.9%	31.3%	P<0.001	1.6
7	85.2%	20.8%	P<0.001	1.6
14	73.8%	17.6%	P<0.001	1.8

Results (2)

- Similar effectiveness for full population
  - Index pts plus household members with lice
- Intention to treat, LOCF, and treatment failure imputation—all confirming effectiveness

- Adverse effects fewer in treatment group
  - Though only statistically lower for itching

Conclusions/limitations

- 0.5% topical ivermectin is a safe, effective and simple option to treat head lice
- Similar or better outcomes to current alternative treatments
  - Oral ivermectin 92.4%; malathion 82.4%
- Persistence of “cure” rates suggest some possible activity against eggs/nymphs
  - Not found in oral ivermectin
- Though drug company sponsored, methods valid and results hold up to scrutiny

Bottom line

- Given costs and effectiveness, topical ivermectin lotion as choice for second line head lice treatment when permethrin fails
- Reasonable consideration for first line tx

- Sklice, $25 with coupon online!

Non-benzo hypnotics effectiveness in insomnia

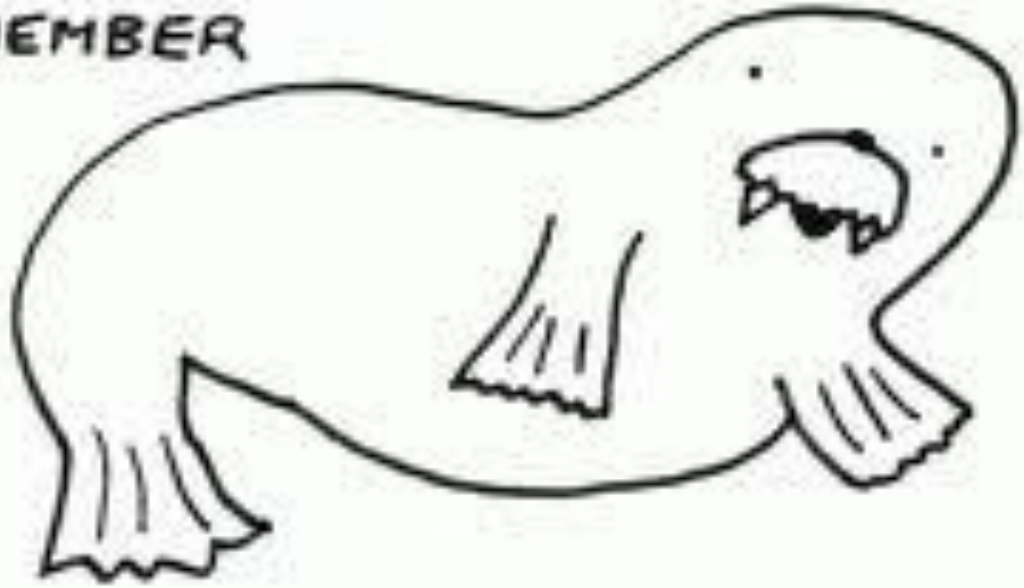
BMJ 2012; 345: e8343 doi

Background

- High rates of nonbenzo hypnotics (aka Z-drugs)
  - eszopiclone (lunesta), zaleplon (sonata), zolpidem (ambien)
  - >$285 million in US alone
- Prior meta-analyses demo benefit
  - Published vs nonpublished data suggest 1.5-2x overestimate of benefit
  - Seeming significant placebo benefit too

AMBIEN WALRUS

COME WITH ME ON
AN ADVENTURE
YOU'LL NEVER
REMEMBER



Clinical question & Methods

- *HOW* effective are Z-drugs in treating insomnia?
- What is the associated *placebo response* in adults?

- Meta-analysis of all data pre-FDA-approval
  - Published & unpublished
  - Double-blinded RCTs
  - Placebo vs Z-drug
  - Adults with primary insomnia

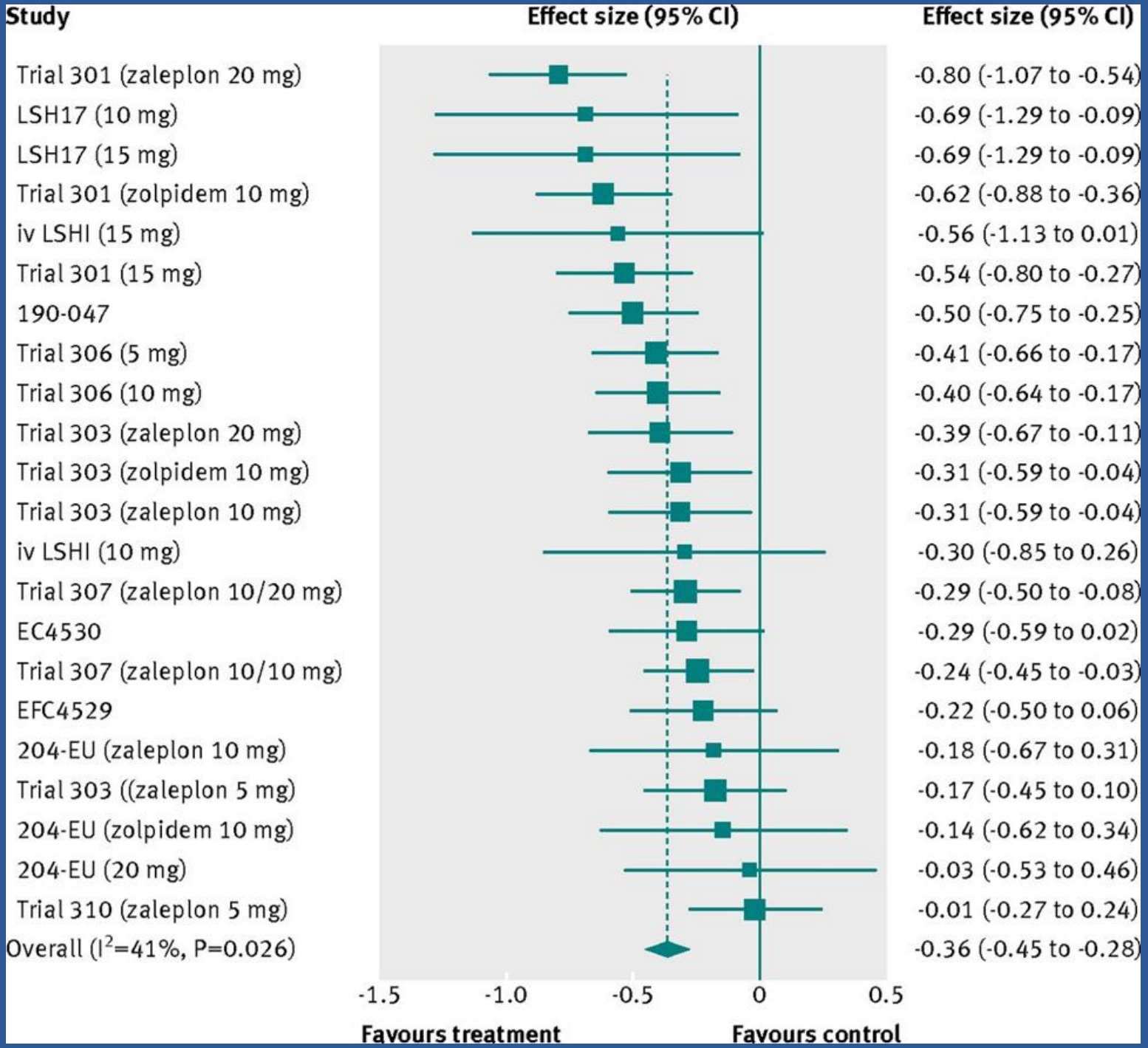
- No cross-over trials, no single night trials

Methods: data extraction

- Two separate investigators extracted results and quality scores
  - Blind to author, institution
  - High inter-rater reliability
- Primary outcome (2):
  - Polysomnographic and subjective sleep latency
  - Secondary outcomes (8)
- Analyses: random effects; effect size and quantitative

Results

- 13 trials; 65 drug/placebo combos (outcomes, dose, drug type); almost 4400 participants: 61% women; 61% ≤45y/o
- No publication bias; sensitivity analyses did not change results
- Consistent statistical benefit for primary outcomes
  - Inconsistent benefit for secondary outcomes

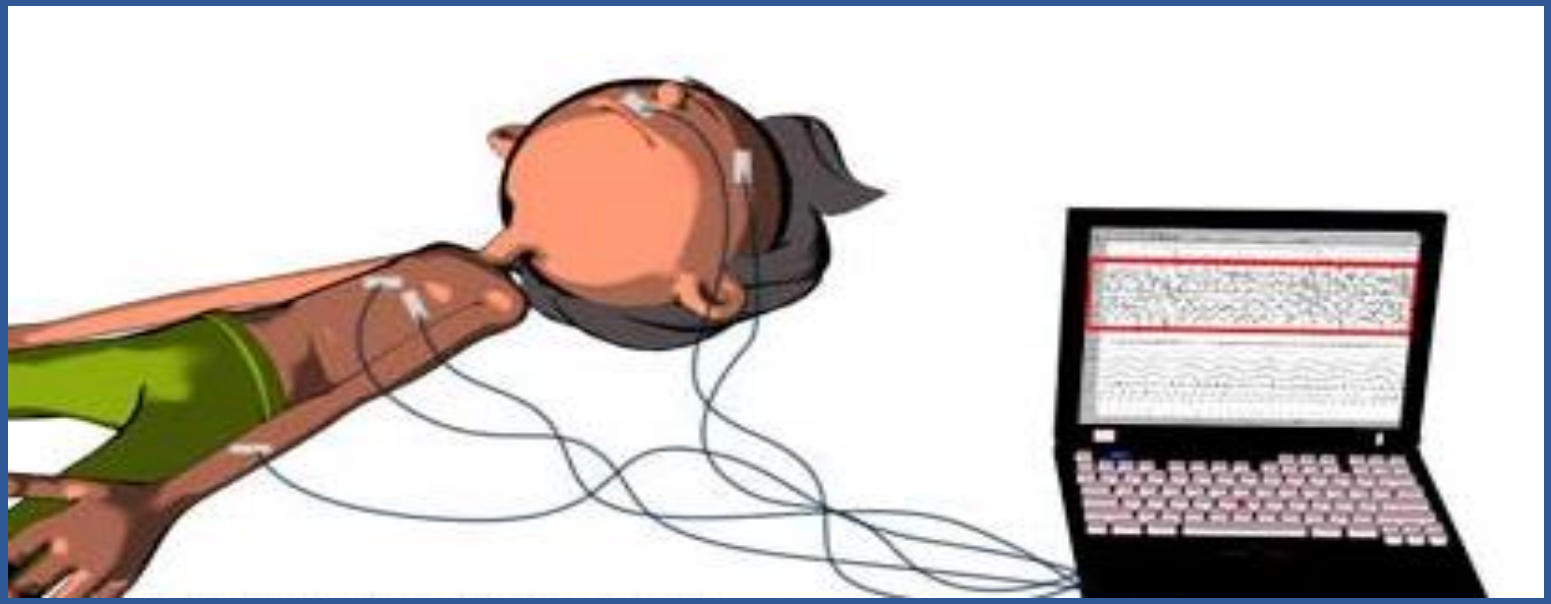

Study
Effect size (95% CI)
Effect size (95% CI)
Trial 301 (zaleplon 20 mg)
-0.80 (-1.07 to -0.54)
LSH17 (10 mg)
-0.69 (-1.29 to -0.09)
LSH17 (15 mg)
-0.69 (-1.29 to -0.09)
Trial 301 (zolpidem 10 mg)
-0.62 (-0.88 to -0.36)
iv LSHI (15 mg)
-0.56 (-1.13 to 0.01)
Trial 301 (15 mg)
-0.54 (-0.80 to -0.27)
190-047
-0.50 (-0.75 to -0.25)
Trial 306 (5 mg)
-0.41 (-0.66 to -0.17)
Trial 306 (10 mg)
-0.40 (-0.64 to -0.17)
Trial 303 (zaleplon 20 mg)
-0.39 (-0.67 to -0.11)
Trial 303 (zolpidem 10 mg)
-0.31 (-0.59 to -0.04)
Trial 303 (zaleplon 10 mg)
-0.31 (-0.59 to -0.04)
iv LSHI (10 mg)
-0.30 (-0.85 to 0.26)
Trial 307 (zaleplon 10/20 mg)
-0.29 (-0.50 to -0.08)
EC4530
-0.29 (-0.59 to 0.02)
Trial 307 (zaleplon 10/10 mg)
-0.24 (-0.45 to -0.03)
EFC4529
-0.22 (-0.50 to 0.06)
204-EU (zaleplon 10 mg)
-0.18 (-0.67 to 0.31)
Trial 303 ((zaleplon 5 mg)
-0.17 (-0.45 to 0.10)
204-EU (zolpidem 10 mg)
-0.14 (-0.62 to 0.34)
204-EU (20 mg)
-0.03 (-0.53 to 0.46)
Trial 310 (zaleplon 5 mg)
-0.01 (-0.27 to 0.24)
Overall (I^2=41%, P=0.026)
-0.36 (-0.45 to -0.28)
-1.5
-1.0
-0.5
0
0.5
Favours treatment
Favours control

Clinical significance of effect size

Cohen std	Effect Size	% results nonoverlapping
Large	0.80	47.4%
Medium	0.50	33.0%
	0.40	
	0.30	
Small	0.20	14.7%

Polysom ES 0.36
Subj ES 0.33

Sleep latency improvement



Subjective :
7 min faster

Polysomnographic:
22 min faster

Polysom: 42 min vs 20 min
Subj: 25 min vs 19 min

Conclusions/Limitations

- Z-drugs work to improve sleep latency in adults with primary insomnia
  - Small benefit clinically
  - Drug co sponsored data; no obligation to report to FDA, so possible overestimation of benefit
- Placebo works too!
  - Estim that 50% of benefit of Z-drugs attributable to placebo effect

Bottom line

- Benefit of Z-drugs for insomnia is of small clinical benefit
- Risks of adverse effects, tolerance and addiction exist

➢ 1st line treatment of insomnia = nonpharmaceutical interventions &/or OTC nonaddictive options

Questions, anyone?