25th ANNUAL DRUG THERAPY DECISION MAKING COURSE

April 11th and 12th, 2014
Fairmont Waterfront Hotel
Vancouver, B.C.

Friday Syllabus

Sponsored by

The THERAPEUTICS EDUCATION COLLABORATION
In Cooperation with the
DEPARTMENT OF FAMILY MEDICINE and
FACULTY OF PHARMACEUTICAL SCIENCES
UNIVERSITY OF BRITISH COLUMBIA

COURSE DIRECTORS
DRS. ROBERT RANGNO, JAMES MCCORMACK and MICHAEL ALLAN

The New Therapeutics: Ten Commandments

Thou shalt treat according to level of risk rather than level of risk factor.

Thou shalt exercise caution when adding drugs to existing polypharmacy.

Thou shalt consider benefits of drugs as proven only by hard endpoint studies.

Thou shalt not bow down to surrogate endpoints, for these are but graven images.

Thou shalt not worship Treatment Targets, for these are but the creations of Committees.

Thou shalt apply a pinch of salt to Relative Risk Reductions, regardless of P values, for the population of their provenance may bear little relationship to thy daily clientele.

Thou shalt honour the Numbers Needed to Treat, for therein rest the clues to patient-relevant information and to treatment costs.

Thou shalt not see detailmen, nor covet an Educational Symposium in a luxury setting.

Thou shalt share decisions on treatment options with the patient in the light of estimates of the individual's likely risks and benefits.

Honour the elderly patient, for although this is where the greatest levels of risk reside, so do the greatest hazards of many treatments.

Course Directors

Bob Rangno, Emeritus Prof., Medicine, Pharmacology, UBC & PHC
James McCormack, Prof., Pharmaceutical Sciences, UBC

Guest Faculty

G. Michael Allan, Assoc. Prof., Family Practice, University of Alberta
& Director, Evidence and CPD Program, Alberta College of Family Physicians
Steven Bellemare, Physician Risk Manager, CMPA, Ottawa, Ontario
Alan Cassels, Adj. Prof., Human and Social Development, University of Victoria, Victoria, BC.
Mike Kolber, Assoc. Prof., Family Medicine, University of Alberta
Tina Korownyk, Asst. Prof., Family Medicine, University of Alberta
Victor Montori, Prof., Medicine, Mayo Clinic, Rochester, Minnesota

Local Faculty

Hannah Briemberg, Clin. Assoc. Prof., Medicine, Neurology, VGH & UBC
Martin Dawes, Prof. and Head, Dept. of Family Practice, UBC
Ken Gin, Clin. Prof., Medicine, Cardiology, UBC & VGH
Andrew Krahn, Prof. and Head, Div. of Cardiology, UBC
Peter Loewen, Assoc. Prof., Pharm. Sciences, UBC & VCHA
Val Montessori, Clin. Assoc. Prof., Medicine, Infectious Diseases, UBC & PHC

PHC – Providence Health Care
UBC – University of British Columbia
VCHA – Vancouver Coastal Health Authority
VGH – Vancouver General Hospital

25th Annual

DRUG THERAPY DECISION MAKING COURSE

Friday, April 11, 2014

The Silver Anniversary Edition

07:00 Registration (Muffins & Coffee)

Chairs - Bob Rangno and James McCormack

"A SILVER LINING PLAYBOOK"

08:00	Welcome	Bob Rangno
08:10	Memories – 25 years to get here. Where's here?	Bob Rangno and James McCormack
08:30	Numbers – silver tongue/forked tongue	Mike Allan and James McCormack

"HI HO OR HI YO – IT'S YOUR CHOICE?"

08:50	"I have a plan. You go that way and I will go this way" – understanding the noncompliance we cause	Victor Montori
09:10	Questions	
09:20	Do we need to hide behind the mask of guidelines?	Steven Bellemare
09:40	"Which silver bullet will you use now, Kemosabe?" – making choices that reflect patient preference	Victor Montori
10:10	Questions	
10:20	Refreshment Break	

"THE PRAIRIE POSSE"

10:40	Menopause – a hunka, hunka burning love	Tina Korownyk
11:00	PSA testing – a shot in the dark?	Mike Allan
11:20	Questions	
11:30	Probiotics – less difficile than you think	Mike Kolber
11:50	Questions	
12:10	Lunch	

"LITTLE GIFTS THAT CAN CREATE BIG PROBLEMS"

13:00	STIs – keeping your gun in your holster	Val Montessori
13:20	Adult vaccines – a silver or trojan horse	Mike Kolber
13:40	Emporiatrics – when you go Hi-Yo Silver away	Val Montessori
14:00	Questions	
14:20	Refreshment Break	

"ROUND-UP"

14:40	Vitamin D – riding off into the sunshine	Mike Allan
15:00	Salt and Water – "Love and Marriage go together like a Horse and Carriage"	Peter Loewen
15:20	Pediatric myths and other bedtime stories	Tina Korownyk
15:40	Questions	
16:00	Adjourn	

Bob Rangno, Mike Allan, James McCormack

Welcome!!

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** Bob Rangno, Mike Allan, James McCormack
- **Relationships with commercial interests:**
  NONE

Objectives

1) Appreciate some of the strengths and limitations of the medical evidence and clinical practice guidelines when it comes to common conditions in primary care
2) Understand the responsibility of health professionals to incorporate patient values into the decision making process
3) To be able to incorporate the relevant evidence into shared-informed decision making for common conditions seen in primary care.

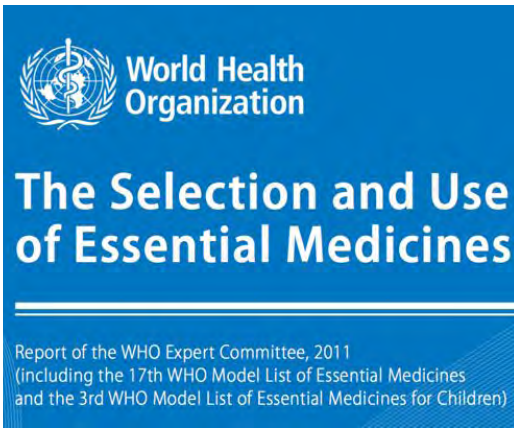
TOP DRUGS IN 1989

AMOXICILLIN
FUROSEMIDE
HYDROCHLOROTHIAZIDE
LEVOTHYROXINE
SALBUTAMOL
LORAZEPAM
TRIAZOLAM
OXAZEPAM
CAPTOPRIL
CIMETIDINE
RANITIDINE
ASA
DICLOFENAC
INSULIN
BECLOMETHASONE
DILTIAZEM
NITROGLYCERINE
DIGOXIN
TRIAMTERENE HCL
POTASSIUM CHLORIDE

Main Educational Goals

- to provide health care students, pharmacists, physicians, nurses, nurse practitioners, physician assistants, naturopathic doctors, other health professionals, and the public with current, evidence-based, practical and relevant information on rational drug therapy
- to encourage clinicians to engage in shared informed decision-making, critical thinking, and exercise some degree of healthy skepticism when it comes to the use of new and old medications

antibiotics
thiazides
many vaccines
ACE inhibitors
proton pump inhibitors
H2 receptor antagonists
contraceptives
corticosteroids
beta-agonists
anesthetics
narcotics
insulin
adrenalin
chemotherapy
warfarin



Bob Rangno, Mike Allan, James McCormack

Future Benefits and Harms aren't Known

Beta blockers - angina ➔ BP, migraine, glaucoma

Viagra - BP, angina ➔ pulmonary hypertension and you know what

Nitrates - angina ➔ rectal fissures and tendinopathies, Raynaud's

ACE inhibitors - BP ➔ heart failure, migraine

Antiepileptics - seizures ➔ migraine, neuropathic pain

Antidepressants - depression ➔ chronic pain

Drugs Removed from the Market

1950-70s

Thalidomide
Teratogenicity
LSD (psych cure-all)
Used recreationally
Diethylstilbestrol
Teratogenicity
Phenformin/Buformin
Lactic acidosis

1980s

Ticrynafen
Hepatitis
Zimelidine
Guillain-Barré syndrome
Phenacetin
Cancer/ kidney disease
Methaqualone
Addiction/overdose
Nomifensine (Merital)
Hemolytic anemia

1990s

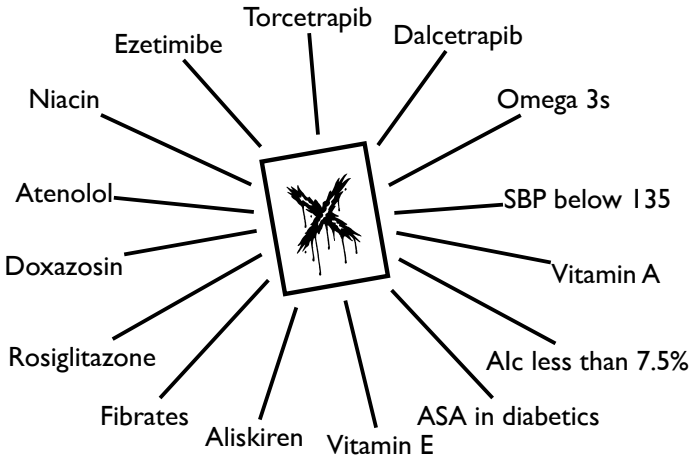
Triazolam
UK - psychiatric reactions
Terodiline (Micturin)
Prolonged QT interval
Temafloxacin
Allergic reactions/ hemolytic anemia
Flosequinan (Manoplax)
Increased hospitalization/ death
Alpidem (Ananxyl)
Hepatotoxicity
Chlormezanone (Trancopal)
Toxic epidermal necrolysis
Dexfenfluramine/fenfluramine
Heart valve disorder
Tolrestat (Alredase)
Hepatotoxicity
Terfenadine (Seldane)
Cardiac arrhythmias
Mibefradil (Posicor)
Dangerous interactions
Etretinate
Birth defects
Tolcapone (Tasmar)
Hepatotoxicity
Temazepam (Restoril)
Sweden and Norway - diversion, abuse, overdose
Astemizole (Hismanal)
Arrhythmias
Grepafloxacin (Raxar)
Prolonged QT interval

2000s

Troglitazone (Rezulin)
Hepatotoxicity
Alosetron (Lotronex)
Fatal complications of constipation
Reintroduced 2002 on a restricted basis
Cisapride (Propulsid)
Cardiac arrhythmias
Amineptine (Survector)
Hepatotoxicity
Dermatological
Abuse potential
Phenylpropanolamine (Dexatrim)
Stroke
Trovafloxacin (Trovan)
Liver failure
Cerivastatin (Baycol)
Rhabdomyolysis
Rapacuronium (Raplon)
Fatal bronchospasm
Rofecoxib (Vioxx)
Myocardial infarction
Co-proxamol (Distalgesic)
Overdose dangers
Hydromorphone ER (Palladone)
Overdose dangers
Thioridazine (Mellaril)
UK - cardiotoxicity
Pemoline (Cylert)
Hepatotoxicity

Ximelagatran (Exanta)
Hepatotoxicity
Pergolide (Permax)
US - heart valve damage
Tegaserod (Zelnorm)
Heart attack and stroke
Aprotinin (Trasylol)
Death
Inhaled insulin (Exubera)
Long-term safety and too high a cost
Lumiracoxib (Prexige)
Liver damage
Rimonabant (Accomplia)
Severe depression and suicide
Efalizumab (Raptiva)
Progressive multifocal leukoencephalopathy
Sibutramine (Reductil)
Cardiovascular risk
Gemtuzumab (Mylotarg)
US – no benefit and venoocclusive disease
Rosiglitazone (Avandia)
Europe - heart attacks and death

Therapies with NO BENEFIT and in some cases HARM



A unique "Mechanism of Action"

≠

Better Outcome

Beta-blockers - selective/nonselective
NSAIDs - COX-2
Sustained release
Enteric-coated

Synergy

2 little doses are better than one big dose

Blood pressure
Asthma
Pain control

2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations

TARGETS OF THERAPY

Risk level	Primary target: LDL-C	Class, level
High CAD, PVD, atherosclerosis Most patients with diabetes FRS ≥20% RRS ≥20%	<2 mmol/L or ≥50% ↓ LDL-C and <1.80 g/L	Class I, level A
Moderate FRS 10% to 19% LDL-C >3.5 mmol/L hs-CRP >2 mg/L in men >50 years and women Family history of premature CAD modulate risk	<3 mmol/L* or ≥50% ↓ LDL-C	Class IIa, level A
Low FRS <10%	≥50% ↓ LDL-C	Class IIa, level A

"Recommended target"
≤2 mmo/L/80mg/dL

TREATMENT TARGETS

Level A = recommendation based on evidence from **multiple randomized trials or meta-analyses**

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

"The Expert Panel was UNABLE TO FIND RCT EVIDENCE to support titrating cholesterol-lowering drug therapy to achieve target LDL–C or non-HDL-C levels, as recommended by ATP III"

Bob Rangno, Mike Allan, James McCormack

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Guideline	Population	Goal BP, mm Hg
2014 Hypertension guideline	General ≥60 y	<150/90
	General <60 y	<140/90
	Diabetes	<140/90
	CKD	<140/90

JAMA. doi:10.1001/jama.2013.284427 Published online December 18, 2013

Metformin - the "GOLD" standard

ARTICLES

Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) Lancet 1998;352:854-65

in newly diagnosed obese type 2 diabetics - over 10 years - metformin reduced MI/ death by ~ 7-8%

Reappraisal of Metformin Efficacy in the Treatment of Type 2 Diabetes: A Meta-Analysis of Randomised Controlled Trials PLoS Med 2012 9(4): e1001204. doi:10.1371/journal.pmed.1001204

"Although metformin is considered the gold standard, its benefit/risk ratio remains uncertain"

18 "NEGATIVE" STUDIES IN A ROW

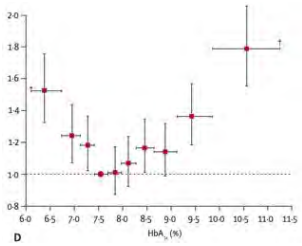
LIPIDS
AIM-HIGH, HPS2-THRIVE (niacin)
ACCORD (fibrates)
dalOUTCOMES (dalcetrapib)

BLOOD PRESSURE
ALTITUDE (aliskiren)
VALISH, AASK, ACCORD
(aggressive BP lowering)

DIABETES
ACCORD, ADVANCE, VADT
(aggressive A1c lowering)
ROADMAP (olmesartan)
ORIGIN (insulin)
SAVOR-TIMI 53 (saxagliptin), EXAMINE (alogliptin)

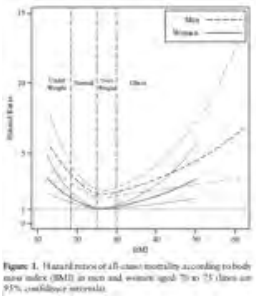
GENERAL
ACTIVE (irbesartan/afib)
CRESCENDO (rimonabant)
VISTA-16 (Varespladib)

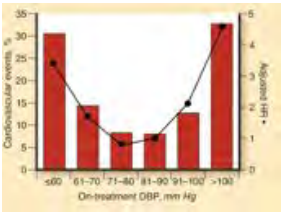
U curve or YOU curve



A1C[1]

BMI[3] over 65





Diastolic BP[2]

Similar data for 25-59 years of age
JAMA 2007;298:2028-37

1) Lancet 2010; 375: 481–89
2) Curr Hypertens Rep (2010) 12:290–295
3) J Am Geriatr Soc 2010; 58:234–241

ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

5145 overweight type 2 diabetics

intensive lifestyle intervention (calories and activity)

followed for 10 year - study stopped early - NO REDUCTION in cardiovascular disease

N Engl J Med 2013;369:145-54.
DOI: 10.1056/NEJMoa1212914

Guidelines and the Law

"As per the Canadian Medical Association Handbook on Clinical Practice Guidelines, guidelines should NOT be used as a legal resource in malpractice cases as "their more general nature renders them insensitive to the particular circumstances of the individual cases."

CJD Canadian Journal of Diabetes

CONTENTS: April 2013 • Volume 37 • Supplement 1

Bob Rangno, Mike Allan, James McCormack

Risk: Relative, Absolute & NNT

If you don't know where you start, it's hard to know where you finish

Zoster Vaccine reduces shingles up to 70%

Study	Placebo	Zoster Vac	Benefit	NNT (3 yrs)
Age 50-59 (3 yrs)	2%	0.6%	1.4%	71
Age ≥60 (3 yrs)	3.4%	1.7%	1.7%	59

"60 / 360 @ 60"

Bottom-Line: Over 3 years, one in 60-70 patients will avoid shingles due to the vaccine

- One in 350 for post-herpetic neuralgia

Tools for Practice
Nov 12, 2012

Heart Failure

In systolic heart failure, 3 drugs do Big things

- Aldosterone antagonists[1,2] ~25%
- β-blockers[3] ~29%
- ACE inhibitors[4,5] ~23%

Assuming mortality= 25%/yr (after 1st hospitalization),[6]
Number needed to Treat are

- Aldosterone antagonists = NNT 16
  - 25% of 25% = 6.25% ➜ 100/6.25 = 16
- β-blockers = NNT 14
  - 29% of 25% = 7.25% ➜ 100/7.25 = 14
- ACE inhibitors = NNT 18
  - 23% of 25% = 5.8% ➜ 100/5.8 = 18

1. NEJM. 1999; 341:709–17. 2. NEJM. 2011; 364:11–21. 3. Arch Intern Med. 2000; 160:621–7. 4. JAMA. 1995; 273(18):1450–6. 5. Lancet. 2000; 355:1575–81. 6. NEJM. 2006;355(3):260-9.

5 things we've learned

well maybe 9

1. Conflict of interest
2. Scepticism
3. Low dose
4. Genetic Mongrels - N=1
5. Old drugs
6. Outcomes vs surrogates
7. NNT/NNH
8. Re-evaluation
9. Patient values!!!!!!

Victor Montori

I have a plan. You go that way and I will go this way.

Understanding the noncompliance we cause

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Learning Objectives

- To enumerate two forms of adherence that require different approach to management.
- To identify the elements of the cumulative complexity model and how these relate to adherence.
- **To critically connect respect for capacity with the notion of clinical inertia in judging practice**

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

Faculty: VICTOR MONTORI

Relationships with commercial interests:
Grants/Research Support: NONE
Speakers Bureau/Honoraria: NONE
Consulting Fees: NONE
Other: NONE

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

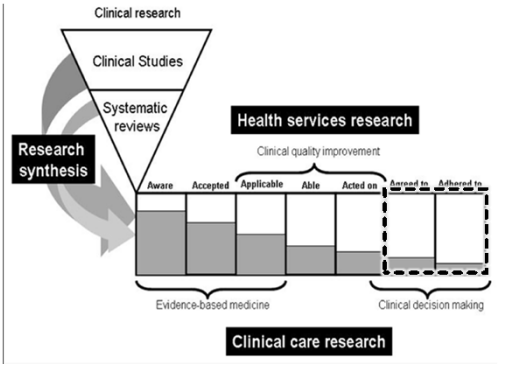
This program has not received financial or in-kind support from any organization.

Potential for conflict(s) of interest:
None

Disclosures

Relevant Financial Relationships
None

Off Label Usage
None



Glasziou and Haynes ACP JC 2005

Victor Montori

Key problem:
Do not follow advice

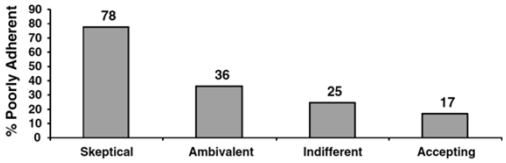
Wasted or misallocated healthcare resources:
US$ 290b (100b in avoidable hospitalizations)

Poor health despite cost and side effects

Complicated patient-clinician relationship

Cutler and Everett NEJM 2010 10.1056/NEJMp1002305

Beliefs and adherence in diabetes



Need	Low	High	Low	High
Concerns	High	High	Low	Low

Mann D et al. J Behav Med (2009) 32:278–284

Coercion thru threats of dire outcomes from poor control of the disorder are doubly unethical: it does not work and high anxiety patients withdraw from care when threatened.

Haynes et al. JAMA 2002

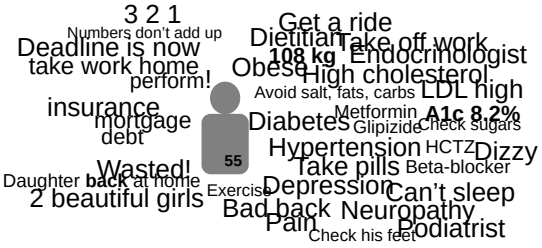
Poor fidelity to treatments is the patient's fault
Intentional noncompliance

Beliefs about the disease
and about the treatments

↓

Professional communication
Patient education
Behavioral interventions
Shared decision making

Pound et al. Soc Sci Med 2005



Collaborate to co-create a program that fits better

FIT

Intensify treatment

Victor Montori

A survey of 627 US primary care clinicians

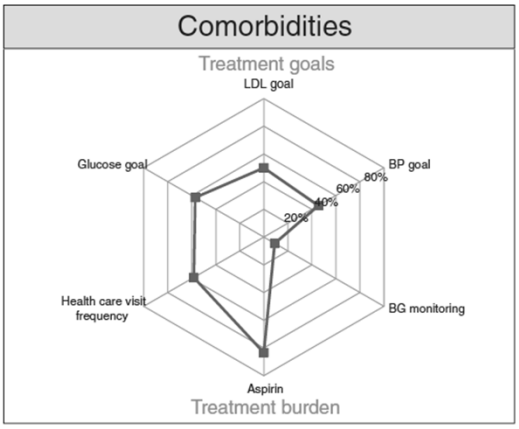
50% of my patients get too much care

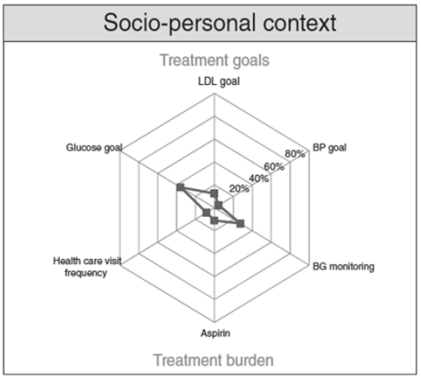
50% of primary care docs are too aggressive
60% of specialists are too aggressive

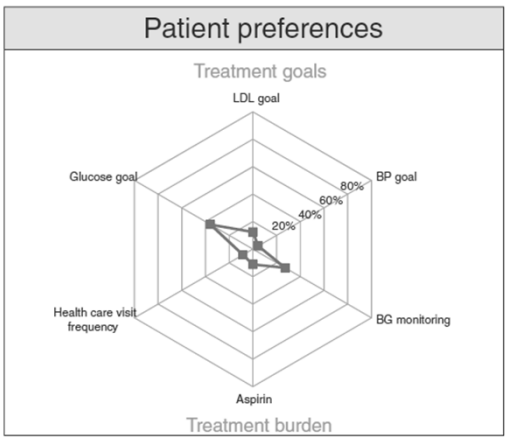
35% practice much more aggressively than what they would like

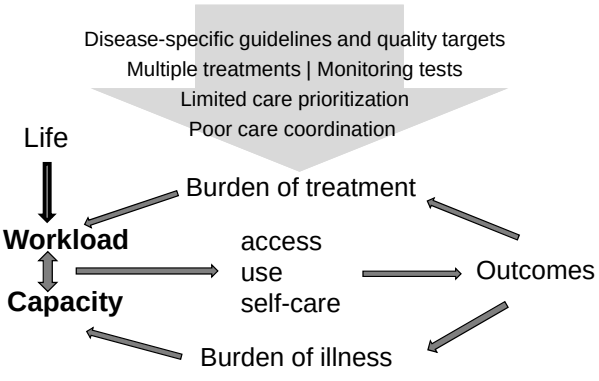
Sirovich BE et al. Arch Intern Med 2011

Evidence-based guidelines are disease-specific









Shippee N et al JCE 2012

Victor Montori

The work of being a chronic patient

Sense-making work

Organizing work and enrolling others

Doing the work

Reflection, monitoring, appraisal

The work of being a chronic patient

People with more chronic conditions attend more visits, get more tests, and more medicines

Shippee D, In press

2 hours/day spent on health-related activities

Jowsey and Yem. BMC Public Health 2012

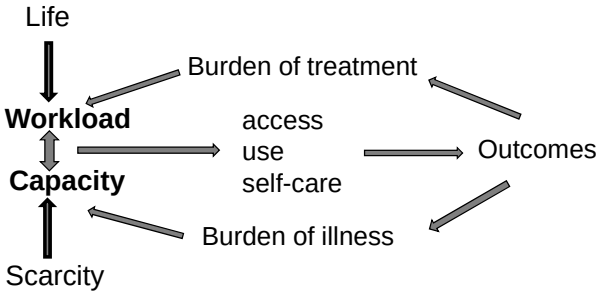
Of 83 workload discussions in 46 primary care visits (24 min): 70% left unaddressed

Bohlen et al. Diabetes Care 2011

Workload

Resilience
Literacy
Mental
Physical
Financial
Social
Environmental

Capacity



Shippee N et al JCE 2012

Minimally disruptive healthcare

Health care delivery designed to reduce the burden of treatment on patients while pursuing patient goals

To fully play the role they play

May CR, Montori VM, Mair FS. BMJ 2009; 339:b2803

Victor Montori

FIT

© Philip Dunn, 1987

More about MDM:
http://minimallydisruptivemedicine.org

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Victor Montori

Which silver bullet will you use now, Kemosabe?

Making choices that reflect patient preferences

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Learning objectives

- **To link the principle of evidence-based medicine to the practice of shared decision making**
- **To list the models of decision making consistent with EBM**
- **To describe elements of shared decision making that make it work in practice**

CFPC CoI Templates: Slide 1

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Disclosure of Commercial Support

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Potential for conflict(s) of interest:
None

CFPC CoI Templates: Slide 3

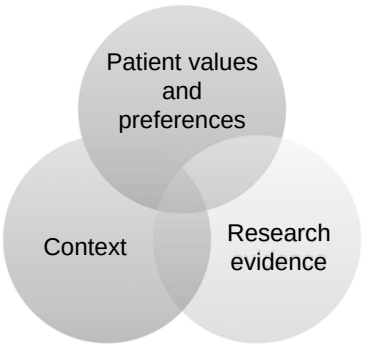
Mitigating Potential Bias

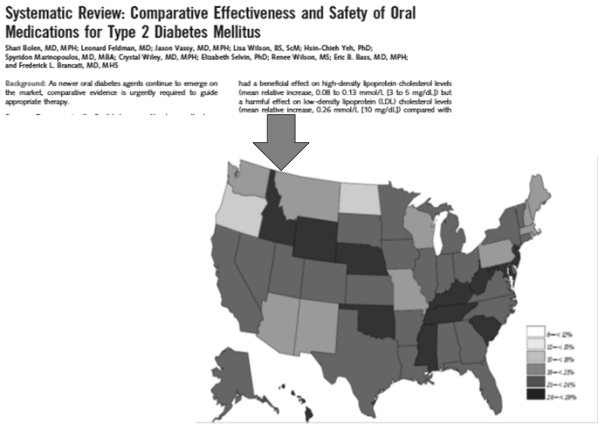
NONE

JUSTIFICATION

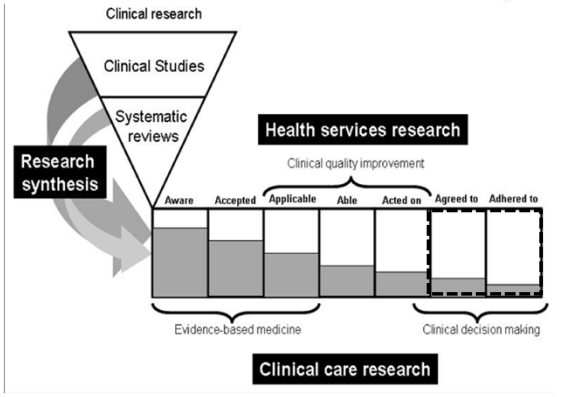
Victor Montori

Encounter Research





Shah ND et al N Engl J Med. 2010 363:2081-4.



Glasziou and Haynes ACP JC 2005

Wrong treatment?

Wrong person
Wrong diagnosis
Wrong procedure
Wrong preferences

FUNDAMENTALS

Decision making models

	Parental	Clinician-as-perfect agent	Shared decision-making	Informed
Choice talk	Implicit	Clinician	Team	Patient
Option talk	Informed consent	Clinician → Patient		
Deliberation	Clinician	Clinician	Joint	Patient
Decision talk	Clinician orders	Clinician recommends	Consensus	Patient requests
Consistent with EBM principles	No	Yes	Yes	Yes

Modified from Charles C et al

Victor Montori

Empathic decision making
Partnership
Dance across models
Support deliberation

The body of evidence

Systematic review of 115 RCTs

Compared to usual care, decision aids:
Increase patient involvement by 34% (+++-)
Increase patient knowledge of options by 13% (++++)
Increase consultation time by ~2.6 minutes
Reduce decisional conflict by ~7%
Reduce % undecided by 40%

No consistent effect on choice, adherence,
health outcomes or costs

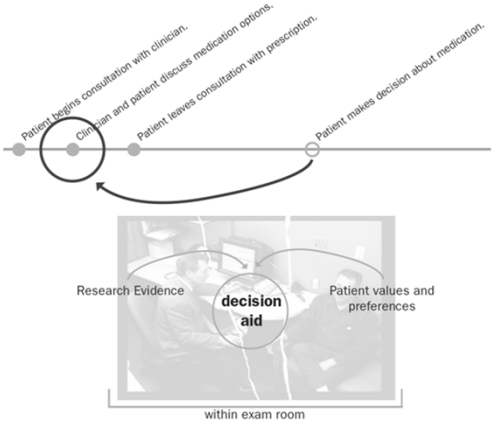
Stacey D et al. Cochrane review 2014

OUR EXPERIENCE

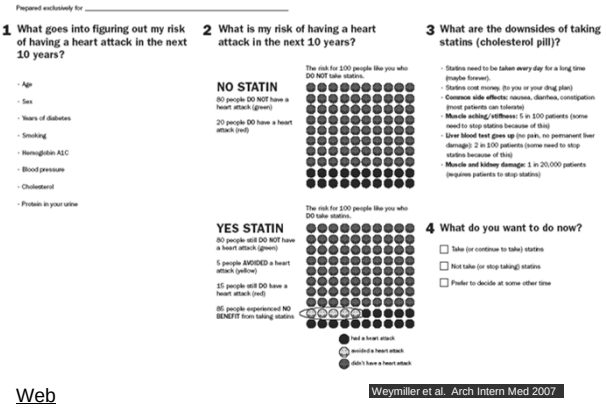
Our work

2004-2013
500+ clinicians at 50+ sites
2000+ patients
Patient and Family councils
Patient advisory group

Funders: Mayo, AHRQ, NIH, PCORI benefactors,
and foundations. Not for profit



Statin Choice



Web

Weymiller et al. Arch Intern Med 2007

Victor Montori

Compared to usual care,
patients using the decision aid were
22 times more likely
to have an accurate sense of their baseline risk and risk reduction with statins.

Weymiller et al. Arch Intern Med 2007

Depression Choice Trial

User-centered design with input from 24 stakeholders
10 primary care sites, 108 clinicians, 301 patients

Use of the Decision Aid Improved
Knowledge by 14% (p=.03)
Decisional conflict by 20% (p=.02)
Patient involvement by 50% (p=.002)

6-mo 50%↓ PHQ9 scores = 32% vs. 51% (p=.04)

Clinician satisfaction 64% vs. 87% (p<.001)

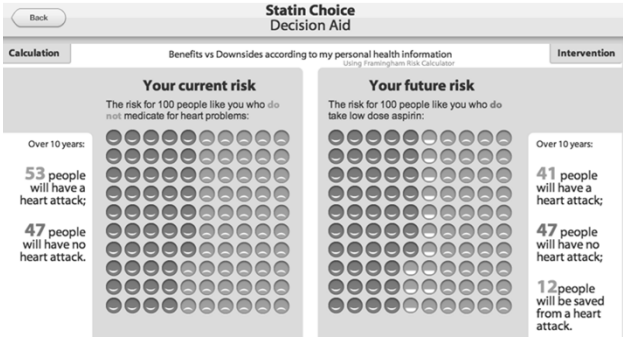
LeBlanc A et al

Summary of Mayo experience

Age: 40-92 (avg 65)
Primary care, ED, hospital, specialty care
74-90% clinicians want to use tools again
Adds ~3 minutes to consultation
60% fidelity without training
20% improvement in patient knowledge
17% improvement in patient involvement
Variable clinical outcomes

IMPLEMENTATION

Web-based tool



http://statindecisionaid.mayoclinic.org

Victor Montori

More about shared decision making:
http://shareddecisions.mayoclinic.org

montori.victor@mayo.edu @vmontori

Tina Korownyk

Big Busts & Rare Flashes of Brilliance

Menopause & Products for Women
Tina Korownyk

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty/Presenter:** [Tina Korownyk]
- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** Honorarium for this talk
  - **Consulting Fees:** None
  - **Other:** Employed by the UofA

Brilliantly Brief Objectives

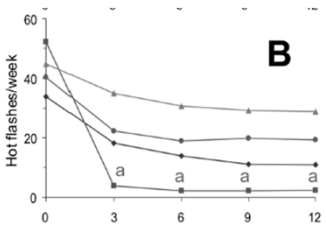
- Review evidence for traditional & alternative management of hot flashes in post menopausal women
- Review evidence around hormone therapy including timing and dosing of medications

A Brief History of 'Progress'

Year	Prevailing Idea	Treatment	Consequence
Long, long ago	Menopause – what's that?		Women are unhappy
Not as long ago	Hysteria	Time alone	Women are angry
More recently	Menopause = disease of deficiency	Estrogen	Happy but increased risk endometrial CA
~ 10 yrs after the estrogen debacle	Endometrial lining	Estrogen + Progestin	Happy but increased risk breast CA
2002	Synthetic BAD, Natural Good	Bio-identical Hormones	Some people making a lot of money
2013	?		

Botanicals- A nice little study

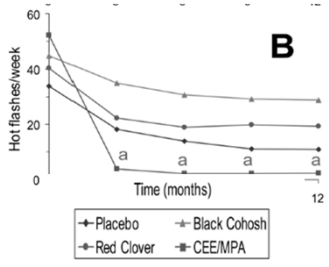
- Double blind, RCT 89 women, mean 53yrs of age, 12 mo



Menopause. 2009 ; 16(6): 1156–1166.

Botanicals- A nice little study

- Double blind, RCT 89 women, mean 53yrs of age, 12 mo

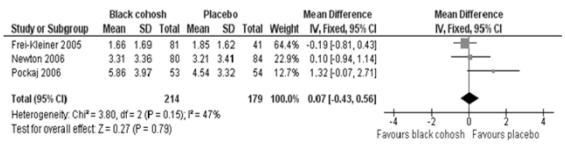


Menopause. 2009 ; 16(6): 1156–1166.

Tina Korownyk

Brilliant in Black?

Figure 4. Forest plot of comparison: 1 Black cohosh versus placebo, outcome: 1.1 Vasomotor symptoms: daily hot flush frequency.



393 women, three trials pooled
5 trials reported on this outcome, the other 2 reported hot flash / week – one found no benefit, the other found placebo was significantly better

Cochrane Database Syst Rev. 2012 Sep 12; 9:CD007244.

A Note on Herbal Supplements

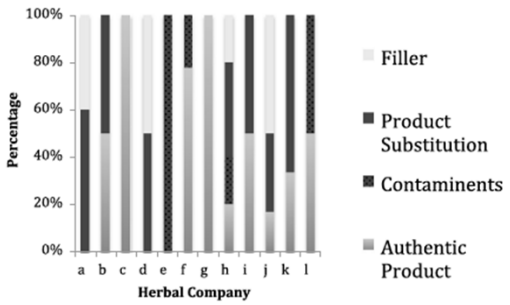
(& the problem with "placebo")

44 OTC herbal products in Canada or US:

- 48% of products tested contained product on label
  - 33% of these contained contaminants or fillers not on the label
- 32% of the samples had substituted another product instead
  - (ie there was no product on the label in the bottle)
- 21% had fillers (Rice/Soybean/Wheat)
  - 9% had ONLY rice or wheat filler
- Examples of contaminants found:
  - St. John's Wort → Only had Senna
  - A number of products contained Feverfew (a common weed) may increase risk of bleeding
  - Ginkgo → black walnut

Newmaster et al. BMC Medicine 2013, 11:222

44 products, 12 companies…



Newmaster et al. BMC Medicine 2013, 11:222

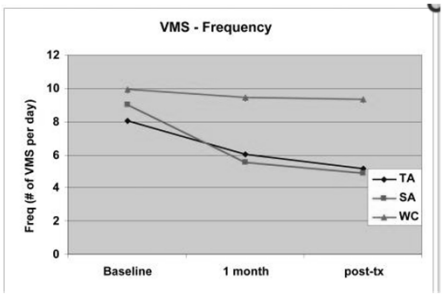
Another Flashy Cochrane Review:

Acupuncture:

- Vs HT: Three RCTs, 114 women
  - Acupuncture ↑hot flushes vs HT
  - (MD 3.18 flushes per day (CI 2.06 to 4.29)
- VS no intervention: 3 RCTs, 463 women
  - Significantly more effective in reducing hot flush frequency
  - SMD -0.50 (CI -0.69 to -0.31)
- Vs Sham acupuncture: 8 RCTs, 414 women
  - No difference
  - MD -1.13 flushes per day (CI -2.55 to 0.29)

1) Cochrane Database Syst Rev. 2013 Jul 30;7:CD007410

Sham & Tradition



"Both Traditional and Sham Acupuncture reduce VMS frequency and severity"

Menopause. 2012 Jan;19(1):54-61

Other ideas whose time has come (and gone)

- Yoga: Five RCTs, 582 participants[1]
  - No evidence for total menopausal symptoms, somatic symptoms, vasomotor symptoms, or urogenital symptoms.
- Omega-3[2]
- Veralipride[3]
- Stellate Ganglion Block[4]
- Audio-Based Paced Respiration Intervention[5]
- Cognitive-behavioral group treatment[6]
- Controlled flax interventions[7]

1) Evid Based Complement Alternat Med. 2012;2012:863905 2) Menopause. 2013 Aug 26. [Epub ahead of print 3) Menopause. 2013 Sep 23. [Epub ahead of print 4) Maturitas. 2013 Aug 20. 5) Music Med. 2013 Jan 1;5(1):8-14 6) Arch Womens Ment Health. 2013 Aug;16(4):325-32 7) **Menopause. 2013 Apr 8.**

Tina Korownyk

Brilliant ways to motivate postmenopausal women to clean

September 24, 2013

Featured in NEJM Journal Watch: Housework as a Sleep Aid During the Menopausal Transition?

By the NEJM Journal Watch Editors

For some women with vasomotor symptoms, household physical activity is associated with better-quality sleep, according to a study in *Menopause*.

1) Menopause: The Journal of The North American Menopause Society;20(9): 946-952.

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For some women with vasomotor symptoms, household physical activity is associated with better-quality sleep, according to a study in *Menopause*.

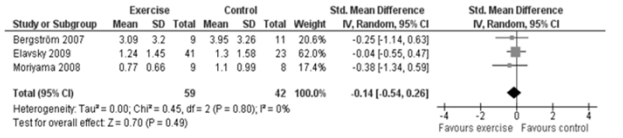
Consistently high Sports/Exercise activity associated with:[2]
better sleep quality [P < 0.01] & continuity [P = 0.02] [1]

Little benefit from household activity noted…

1) Menopause: The Journal of The North American Menopause Society;20(9): 946-952. 2) Sleep. 2013 Sep 1;36(9):1279-88. 3) Sleep. 2011 Jul 1;34(7):943-50 (basketball

Cochrane & Exercise

Figure 3. Forest plot of comparison: 1 Exercise versus control, outcome: 1.1 Hot flushes/night sweats



"Insufficient evidence"

RCT, 248 pts, exercise vs usual activity
Aerobic exercise 3x/week x 12 wk - No benefit vasomotor sx, mild improvement sleep.

Moderate evidence of No benefit.

Cochrane Database Syst Rev. 2011 May 11;(5):CD006108

Brilliant? Brisdelle

- 2 RCTs (614 & 570 pts), Paroxetine 7.5mg vs Placebo[1]
  - Multicentre, Double blinded, mean 54yrs, 11.3 Hot flashes / day, Daily awakenings due to VMS 3.6
  - ↓~ 1.25 hot flashes
  - minimal discontinuation sx
- Approved by FDA June 2013

- Recent network meta-analysis reports escitalopram likely superior for relief of hot flashes[2]
  - Significant flaws, not convincing

1) Menopause. 20(10):1027-1035, October 2013 2) J Gen Intern Med. 2013 Jul 26. [Epub ahead of print]

What works?

- Estrogen = 2.5- 3 ↓Hot flashes/d
- Gabapentin (300mg TID) = 2.05 ↓Hot flashes/d
- SSRI (mid dose)/ = 1.13 ↓Hot Flashes/d
- SNRI (ie Effexor 75mg qd)
- Clonidine (≤0.075mg BID) = 0.95 - 1.63 ↓Hot flashes/d
- ?Soy Isoflavone Extract (50-70mg/d)= 0.97-1.22 ↓
  - Mixed evidence, Endometrial safety with isoflavones?

JAMA 2006; 295: 2057-71

Hormone Therapy & Timing

1) WHI reanalysis: HT within 10 years of menopause NSS trend
   - ↓ CHD: HR 0.88 (0.54-1.43)
   - ↑ Stroke: HR 1.58 (0.81-3.05)
   - Limitations: Subgroup analysis; >130 statistical tests

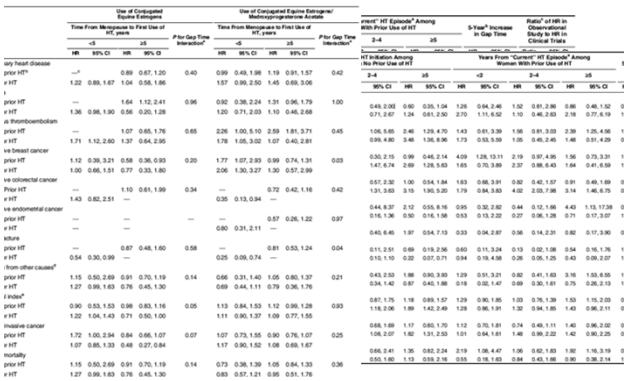
2) A second reanalysis (> 300 comparisons) reported ↑ breast cancer if HT started <5 years after menopause versus ≥5 years (p=0.03)

- "No noteworthy interactions with age, race/ethnicity, body mass index, prior hormone use, smoking status, blood pressure, diabetes, aspirin use, or statin use were found for the effect of estrogen plus progestin on CHD, stroke, or VTE." JAMA 2002

- **Evidence supporting the timing hypothesis of hormone therapy is poor.**
- Bottom line: Risk increases as you age.

Tina Korownyk

> 300 Tests



Surrogates, Theories & Real Stories
Topical vs Oral HT

- Oral estrogens ↑ TGs, CRP, SHBG & other surrogates[1]
  The clinical significance of this is unknown.

Weak evidence for reduced risk VTE with Transdermal HT.[4]
(4 case studies)[5]

Oral HT associated with 2.1 RR increase VTE.[5]
(10/10 000/yr to 21/10 000/yr)

1) Drug Design, Development and Therapy 2008:2 193–202 2) J Lab Clin Med, 1994 Jan;123(1):59-64 3) Circulation 2007;115
4) Obstetrics & Gynecology 2013:121(4); 887–890. 5) BMJ. 2008;336(7655):1227-31

Reflections on Dosing

Year	#pts	Comparators	Outcomes
1997	406	CEE 0.3mg. 0.625mg 1.25mg	Low dose – pos changes in BMD, lipids, no effect endometrial hyperplasia
1999	441	Estradiol + Norethisterone acetate 0.025/0.125mg, 0.05/0.25mg, 2/1mg	Similar sx relief
2001	2673	CEE+ MPA 0.625/2.5mg, 0.45/2.5mg, 0.45/1.5mg, 0.3/1.5mg	Similar sx relief all doses Trend for decrease breast pain/ bleed with lower dose
2002[4] (1 yr)	96	Estradiol + Norethisterone acetate 1/0.5mg, 2/1mg	Similar sx relief, low dose: ↓bleed (2% vs 23%) ↓breast pain (2% vs 15%)

1) Arch Intern Med. 1997 Dec 8-22;157(22):2609-15 2) Obstet Gynecol 1999 Jul;94(1):61 3) Maturitas 2002;26;41(2):123-31. 4) Fertil Steril 2001;75(6):1065

Preventative Measures

Factor	Effect on Breast Cancer
Combination HRT	RRI 24%[1]
Obesity	RRI 185% (comparing women > 82.2 kg with those < 58.7 kg in WHI cohort) [2]
Alcohol	No significant risk increase from one drink per day or less RRI 20% for 2 drinks vs. none RRI 40% for 3 drinks vs. None[3]
Diet	Most studies have found that a low-fat diet reduces risk
Smoking	Insufficient evidence
Physical Activity	RRR 30-40% if vigorous and more than 4 hours per week

1) JAMA 2002; 288(3):321-333. 2) **Cancer Epidemiol Biomarkers Prev** 2007; 16(12):2533-2547. **3) Ann Surg** 2003; 237(4):474-482. 4) **J Natl Cancer Inst** 2009; 101(6):384-398. 5) URL:http://www.cancer.gov/cancerinfo/pdq/prevention
McMaster Cancer Prevention Module 2010

G. Michael Allan

PSA Testing: A Shot in the Dark

Mike Allan
Evidence & CPD Team, ACFP
Associate Professor, U of A

Slide 1: Option A (Faculty with relationship(s) to declare)

Faculty/Presenter Disclosure

- **Faculty:** G. Michael Allan
- **Relationships that may introduce potential bias and/or conflict of interest:**
  - **None**

Objectives: Screening for Prostate Cancer

- Learn if Prostate cancer makes sense based on the criteria for appropriate screening
  1. Is Prostate cancer a common disease:
  2. Does Prostate Cancer have a high risk of mortality
  3. Does PSA or DRE clearly identify cancer (especially in high risk)
  4. What is the work-up for a positive test and what kind of risk does it care
  5. How effective are the interventions for the treatment of prostate cancer.
  6. Do those treatments have little risk?

Does Prostate Ca screening make sense?

- Screening works when
  1. A common disease:
  2. A high risk of mortality:
  3. Test clearly identifies cancer (esp high risk)
  4. Work-up for cancer has little risk
  5. Treatment is effective
  6. Treatment has little risk
- Prostate screening is
  1. ?
  2. ?
  3. ?
  4. ?
  4. ?
  5. ?

Allan GM1, Chetner MP, Donnelly BJ, Hagen NA, Ross D, Ruether JD, Venner P.Furthering the prostate cancer screening debate (prostate cancer specific mortality and associated risks). Can Urol Assoc J. 2011 Dec;5(6):416-21

Epidemiology of Prostate Ca

- Most common (non-skin) cancer among Canadian men
  - 24,600 men diagnosed/year
  - 4,300 men will dying/year
- Alberta: 2500 men will be diagnosed/year
- Lifetime probability of
  - developing prostate cancer is one in 7 men
  - dying from prostate cancer is one in 27 men

Allan GM1, Chetner MP, Donnelly BJ, Hagen NA, Ross D, Ruether JD, Venner P.Furthering the prostate cancer screening debate (prostate cancer specific mortality and associated risks). Can Urol Assoc J. 2011 Dec;5(6):416-21
Canadian Cancer Society. [updated 2010 May 19]. http://www.cancer.ca/Alberta-NWT/About%20cancer/Cancer%20statistics/Stats%20at%20a%20glance/Prostate%20 cancer.aspx?sc_lang=en&r=1

What does the meta-analysis say?

- 6 RCTs: 387,286 pts.
  - 5 studies provide data on mortality
- Screening not statistically significant reduction,
  - overall mortality (Risk Ratio 0.99, 0.97 to 1.01)
  - prostate cancer specific mortality (RR 0.88, 0.71-1.09)
- Heterogeneity (prostate cancer mortality) - important heterogeneity (I^2=55%; P=0.06)

BMJ. 2010 Sep 14;341:c4543. doi: 10.1136/bmj.c4543.

G. Michael Allan

Prostate Screening Studies: Why was there heterogeneity?

	Randomized to		Screening	Total F/U	Percent Screened*		Prostate Cancer Mortality (Rate Ratio unless noted)	
	Screening	No screening			Screened	Unscreened	Intention to Screen	Per Protocol
Norrkoping, Sweden[5,6]	1,494[†]	7,532	DRE q3 yrs x4 PSA q3 yrs x2[‡]	15 years (10 PSA) [‡]	83%[§]	na	1.04 (0.64, 1.68)[**]	na
Quebec City[7,8]	31,133	15,353	DRE + PSA PSA q yearly	11 years	23.6%	7.3%[††]	1.01 (0.76, 1.34)[‡‡] (risk ratio)	0.36 (0.19, 0.65) (risk ratio)
PLCO (USA)[9]	38,343	38,350	PSA q yr x 6 DRE q yr x 4	11.5 years	86%	52%	1.11 (0.83, 1.50)[§§] (risk ratio)	na
ERSPC (Europe)[10,11]	72,890	89,353	PSA q 4yrs (early DRE)	9 years	82.2%	15.4%[***]	0.80 (0.65, 0.98)	0.69 (0.51, 0.92)
Goteburg (Sweden)[12]	9,952	9,952	PSA q 2 yrs	14 years	76.1%	"low"	0.56 (0.39, 0.82)	0.44 (0.28, 0.68)

Allan GM1, Chetner MP, Donnelly BJ, Hagen NA, Ross D, Ruether JD, Venner P.Furthering the prostate cancer screening debate (prostate cancer specific mortality and associated risks). Can Urol Assoc J. 2011 Dec;5(6):416-21

Reduction in Prostate Cancer Mortality

Time	Number Needed to Screen	Number benefiting per 1000 screened	Number Needed to Treat
9 yrs	1410	0.7	48
12.8	565	1.8	33
14 yrs	293	3.4	12

- Based on 3 high quality studies
- Not dissimilar to other adopted screening programs
  - Like them, No difference in over-all mortality

N Eng J Med 2009;360(13):1320-8. Eur Urol. 2013 Oct;64(4):530-9. Lancet Oncol. 2010;11:725-32.

What are the problems with PSA?

- Positive PSA (≥4ng/ml) per round, based on age
  - 4.8% at age 55, 7.5% at age 59,
  - 12.4% at age 63 16.5% at age 67.
- Positive PSA (<10ng/ml) are 70% false positive
- False Negatives: If PSA <4, 15% will have Ca
  - Of those 15% (2% overall) will be high grade Ca
  - (median age = 69.4)

Br J Cancer. 2010;102:469-74. Ann Fam Med. 2009;7(3):212-22. N Engl J Med 2004;350:2239-46.

What are the problems with DRE?

- 17% of Prostate cancer were picked up by DRE when PSA was negative.
  - If PSA<3, then DRE sensitivity is 20% and PPV is 8.8%
- False positive rates for a single DRE = 6.4%
  - after 4 tests 17.6% or

Cancer J Clin 2010;60:70–98. Ann Fam Med. 2009;7(3):212-22.

What about false positives?

- Clearly false positives are common
- How to reduce them[1]
  - 37% - 40% positives are normal 1 yr later.
- What is the effect[2]:
  - Worry about cancer increases in false positive vs negative results (26% versus 6%, p<0.001).
- Bottom-line: frequently need to go to Biopsy, so what's the risk there.

JAMA. 2003;289(20):2695-700. 2) J Gen Intern Med. 2006;21(7):715-21.

What about Biopsies?

- The PLCO study reports 0.7% of patients had complications (infection, bleeding, clots and urinary difficulties) of positive screening.
- Biopsy (Rotterdam): hematuria >3 days (23%), pain (7.5%), fever (3.5%, most require antibiotics), hospitalizations (0.5%) and urinary retention (0.4%).
  - 0.15% core-needle breast biopsies cause infections requiring antibiotics

NEJM 2009;360(13):1310-9. Urology. 2002;60(5):826-30. Ann Intern Med. 2010;152:238-4

G. Michael Allan

What about interventions if positive?

- Treatment: every 10,000 men screened x14 yrs,
  - 34 prostate cancer deaths will be prevented at the cost of
  - 120 more men with impotence or sexual inactivity
  - 25 more men with urinary incontinence.
- Radical Prostatectomy vs observation RCT
  - 732 men with localized Prostate Ca, age 67, 7.8 PSA,
  - Mortality: 47% versus 49.9%, no stat diff
  - If high PSA >10 or tumor risk intermediate/high then 7-13% absolute improvement.

Eur J Cancer. 2010 Nov 17. [Epub ahead of print]. N Engl J Med 2012;367:203-13.

If screening, a few practical suggestions

- Single mildly elevated readings can be repeated (?3-6 months) as many will normalize
- Consistently elevated PSA over-time based on 2-3 test results, a rapidly rising PSA (velocity≥0.75 ng/mL/year) or a PSA doubling time<2 years: require

Recommended Risk Adjusted Prostate Specific Antigen (PSA) Cut-Off Values[6]		
Age (years)	PSA Cut-Off Values (ng/mL)	African-Canadians
40-49	2.5	2.0
50-59	3.5	4.0
60-69	4.5	4.5
70-79	6.5	5.5

TOP Prostate CPG 2011

Quality of Life

- The ERSPC study (162,243 pts) x 11 years
- Made a model from
  - Outcomes (e.g. prostate Ca mortality & biopsy harms)
  - Applied Quality of Life outcomes from other studies
  - Ran model with multiple analysis ("assumptions")
- Found: Over lifetime of 1000 men, PSA screening increases life-years by 73.
- Harms reduced QoL & and therefore life years by 23% (to 56 Quality Adjusted Life Years)
  - A lot depends on variation in analysis.

N Engl J Med 2012;367:595-605.

Does Prostate Ca screening make sense?

- Screening works when
  1. A common disease:
  2. A high risk of mortality:
  3. Test clearly identifies cancer (esp high risk)
  4. Work-up for cancer has little risk
  5. Treatment is effective
  6. Treatment has little risk
- Prostate screening is
  1. 24,600 Dx/yr (1 in 7 lifetime)
  2. 4,300 die/yr (1 in 27 lifetime)
  3. 70% false positive, 15% false negative
  4. Biopsy= Infection (NNH 28), admission (200), pain (14)
  5. Prostatectomy=observation
  6. Four have sexual dysfunction & one urinary incontinence (for every life saved).

So, What do guidelines Say

Guideline	Recommendation
Toward Optimized Practice	Suggest PSA testing be discussed
US Preventive Services Task Force	Recommends against PSA-based screening for prostate cancer.
American College of Physicians	Recommends clinicians inform men 50 - 69 years about the limited potential benefits and substantial harms of prostate cancer screening.
American Cancer Society	Recommends asymptomatic men with ≥ 10-year life expectancy have informed decision discussion: about uncertainties, risks, and potential benefits.

http://www.topalbertadoctors.org/cpgs/2073602 Ann Intern Med. 2013;158:761-769.

Wrap-up

- PSA screening can reduce Prostate cancer mortality (at best around 1 in 300 over 14 years)
- **BUT**
- The test is poor, the work-up has harms and the treatment has uncertain benefits and lots of harms.
- Future work will be in selective management and perhaps 5-HT drugs (Finasteride & Dutasteride)
  - If observation, 37% vs 45% progress over 3 yrs

Lancet 2012; 379: 1103–11

Mike Kolber

Probiotics:
Less difficile than you think

Mike Kolber BSc, MD, CCFP, MSc
University of Alberta Department of Family Medicine
DTC April 2014

Faculty/Presenter Disclosure

- **Faculty/Presenter(s): Michael R. Kolber**
- **Relationships with commercial interests:**
  - Pay from University of Alberta and Alberta Health
- Research and Speaking Fees
  - **Non-Profit Sources** (Alberta College of Family Physicians, Towards Optimized Practice)
  - **No funding from industry**

Disclosure of Commercial Support

- **Potential for conflict(s) of interest:**

  Michael R. Kolber receives grants from the Alberta College of Family Physicians.

For the **DTC conference**, the organization committee will pay for hotel rooms and travel expenses.

Objectives

- To facilitate understanding of the potential benefits and harms of probiotics in the treatment of GI and non GI diseases

What is a Probiotic?

- "living organisms, which when administered in adequate amounts confer a health benefit"
  - Bacteria: lactobacilli, bifidobacteria, non-pathogenic E. coli strains
  - Yeasts: saccharomyces boulardii

Canadian Digestive Health Foundation 2013
Curr Opin Gastroenterol 2013, 29:184 – 189

How do they work?

- "Bifidobacterium infantis 35624 prevents nuclear factor-kappa-B and interleukin (IL)-8 activation and inhibit the secretion of chemokine ligand 20 in response to Salmonella typhimurium, Clostridium difficile and Mycobacterium paratuberculosis"

Curr Opin Gastroenterol 2013, 29:184 – 189

Mike Kolber

Are all Probiotics similar?

- "Different probiotics have different microbiological characteristics that will inevitably impact on their efficacy".
  - "Need for health professionals to refer to individual RCTs and base their advice on the probiotic and symptom most relevant to each patient".

Curr Opin Gastroenterol 2013, 29:184

Are our patients using Probiotics?

- Small Canadian survey[1]
  - 35% taken probiotics: for "overall or digestive health"
  - Province most familiar with probiotics: British Columbia
- UK IBD patients: 43% (21% non-IBD)[2]
- Overall ~ $24 **B**illion / year
  - supplements = $5 Billion / year

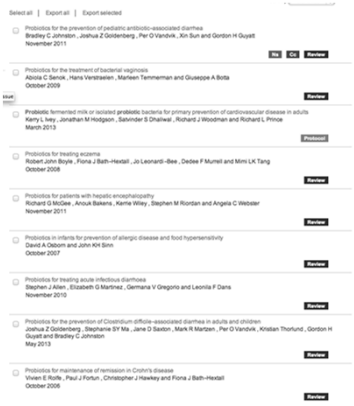
http://www.swissnatural.com/en/media/releases/new-study-says-canadians-puzzled-by-probiotic-health-benefits
[2]Inflamm Bowel Dis 2010;16:2099–2108

Gastroenterologists' Probiotic Knowledge

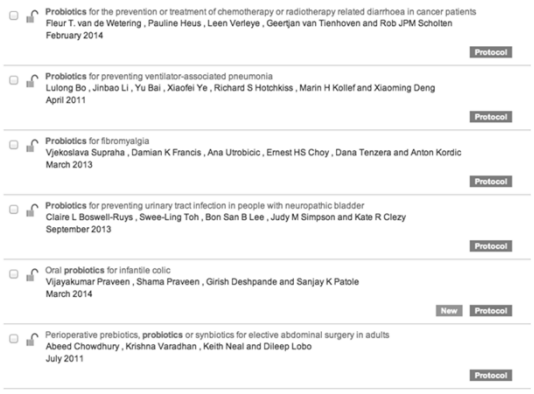
- 56 US Gastros:
  - 100% believe probiotics safe
  - 100% community GIs familiar with evidence
    - Only 85% academic
  - Recommend for IBS and CDAD
  - 7% state probiotics 'always effective'
- Canadian Gastro Constipation Guideline
  - 40% believe evidence supports probiotic use

J Clin Gastroenterol 2010;44:631–636
Can J Gastroenterol Vol 21 Suppl B April 2007

You want studies…



…we got studies!



Are Probiotics Safe?

- Fungemia, septicemia case reports[1,2]
- ↑ mortality in pancreatitis (NNK = 11)[3]
- AHRQ 2010: "*Lack of assessment or systematic reporting of AEs in studies*"
  - 40% of studies report "well-tolerated"
- Remaining 387 studies (24,615 patients):
  - RCTs show no signif ↑risk of the overall # of AEs
- "*…Despite the number of publications, the current literature is not equipped to answer questions on the safety of probiotic interventions with confidence*".

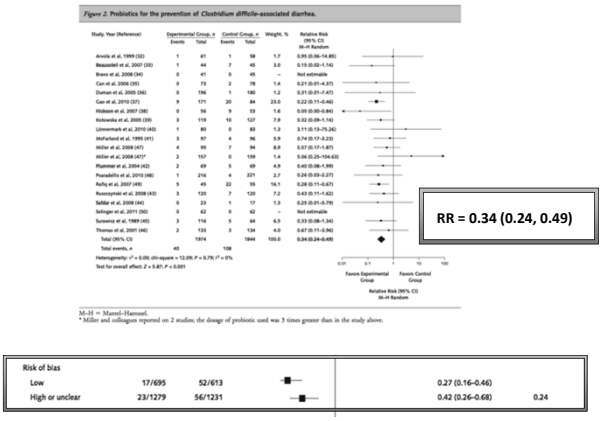
[1]AHRQ 2010 Safety of Probiotics to Reduce Risk and Prevent or Treat Disease
[2]Ann Int Med 2013 (158): 706 [3]Lancet 2008; 371: 651–59

Mike Kolber

Probiotics and *C diff.* Systematic Review 2012

- Meta-analysis: 20 RCTs, 3818 mostly adult inpatients[1]
  - different probiotics, variable treatment length (majority duration of antibiotic use + < 14 days)
- CDAD: placebo = 5.9%, probiotics = 2.0%
  RRR = 66%, ARR =3.9%, **NNT =26**
- Individual studies risk of bias: 7 low, 13 high/unclear
  - Allocation and missing data (CDAD rates)
- Results similar: high quality studies, adults / children, different probiotics, single or multiple species.

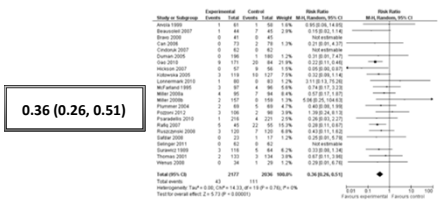
[1]*Ann Intern Med 2012;157(12):878*



[1]*Ann Intern Med 2012;157(12):878*

Probiotics and CDAD Updated SR: Cochrane 2013

- 23 RCTs, 4303 patients:
  - missed 2 papers, 1 2012 publication



Cochrane Systematic Reviews 2013, Issue 5. Art. No.: CD006095

Cochrane SR 2013 Sub-group analysis:

- Probiotics benefit similar in:
  - Inpatients or outpatients:
  - High or low risk of bias:
    - Low risk: "Product and placebo were provided by *Company X*. A research grant was provided by *Company X* to cover the pharmacy administration fees." No author is from the sponsoring agency
    - High Risk: "*Company Y* supported the study and produces the product. Primary author has financial relationship with the company funding the trials and producing the trial intervention".

23 Primary studies in Cochrane SR

- Largest study = 442 patients
  - 20 studies < 300 patients
- Heterogeneous groups: 8 excluded immunocompromised, CDAD < 3/12 (3), 3 studies on pediatrics
- Only 3 reported previous AAD / CDAD
- Rafiq 2007: 44% baseline CDAD rate
  - Never published, no response to requests for info

Cochrane Systematic Reviews 2013, CD006095

Picture of lots of small things

…What's New... 2012 study

- Placebo controlled RCT of *Saccharomyces boulardii on* 275 elderly Italian medical inpatients
  - duration of Abx + 7 days
- 79 years, 50% female, antibiotics ~ 10 days
- At 12 weeks: probiotics vs placebo:
  - AAD: 15% vs 13% OR = 1.16 (0.53–2.56)
  - CDAD: 3% vs 2% OR = 1.4 (0.23–8.55)
- Funding: hospital fund for independent research.
- Conclusion: ***single centre, small #s***
  → ***need larger multi-centre study***

Am J Gastroenterol 2012; 107:922

Mike Kolber

…Hold the phone…2013

- Large multi-centre RCT: 2981 elderly inpatients from 3 UK hospitals on antibiotics, randomized to *Lactobacilli and bifidobacteria* or placebo X 21 days
- 77 years, ~ 50% females
- High quality: AC, masked
- Funded: National Institute for Health Research
- At 12 weeks: compared to placebo, probiotics:
  - AAD (includes CDAD): 10.8% vs 10.4% RR=1·04 (·84-1·28)
  - CDAD: 0.8% vs 1.2% RR = 0·71 (0·34–1·47)

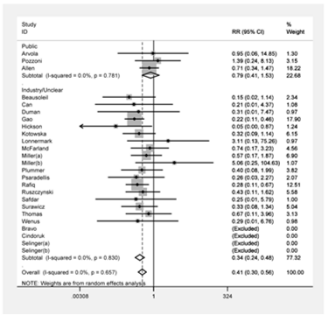
***Allen, Lancet* 2013; 382: 1249–57**

Shine the light…
All Probiotic CDAD studies Sept 2013

- 24 studies:
  - No one study influencing results
  - Funding:
    - 15 industry supported
    - 6 unclear funding
    - 3 publically funded

Kolber, Vandermeer, Allan Am J Gastro 2014 *in press*

Funding Influence of Results



Industry supported / unclear funded studies were > twice as likely to report (RR: 2.32 (1.1, 4.9) that probiotics ↓ CDAD rates compared to publically funded studies.

Probiotics and CDAD

- Funding may influence the results of probiotic trials more than the probiotic used or type of patients enrolled.
- Future studies should disclose funding sources
- Systematic reviews should specifically analyze the influence of funding on their results.

Probiotics for
Antibiotic associated Diarrhea (AAD)

- JAMA 2012 SR:
  - 82 RCTs: probiotic + antibiotic

eFigure 1. PubMed Search Strategy

probiotic* OR prebiotic* OR synbiotic*
NOT
animals NOT humans

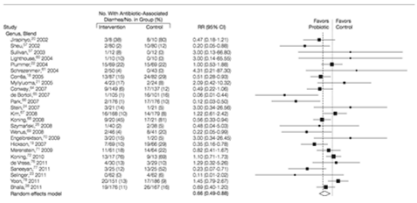
Note: The search strategy was designed to find all research studies on probiotics and was not restricted to specific outcomes, study designs, interventions, or genera.

HIGH RISK OF BIAS: few reported AE, sequence generation
    - 84% industry sponsored or unclear
  - Mean number of patients ~ 160
  - 63 RCTs reported diarrhea rates, 43 studies placebo controlled
    - Sub-group analysis: strains, age (adults, elderly, peds), inpatient / outpatient, funding

JAMA. 2012;307(18):1959

Probiotics for AAD Results

- High I^2 (54%)--> but meta-analyzed anyways



Concluded: probiotics ↓ AAD NNT=13

"More research is needed to determine which probiotics are associated with the greatest efficacy and for which patients receiving which specific antibiotics".

JAMA. 2012;307(18):1959

Mike Kolber

Probiotics and IBD

- Crohn's: few very small studies, no benefit[1]
- *Ulcerative Proctitis: rectal E. coli vs placebo: no diff CDA*[2]
- Ulcerative Colitis:
  - Maintaining remission: (relapses @ 1 year):
    - 40.1% probiotics vs 34.1% 5-ASA: OR 1.33; 0.94 to 1.90[5]
  - Inducing remission:
    - 5-ASA vs E.coli → favor 5-ASA (NSS)[4]
    - VSL-3 vs placebo (added to existing therapy) → favor VSL-3
- Pouchitis: maintaining remission: VSL-3 superior to placebo[6]
- Issues: sub-optimal 5-ASA doses,[3,4] no remission → removed from LT analysis,[4] wide non-inferiority margins,[4] not blinded, ? AC, incomplete reporting[5,] funding bias, ITT not beneficial → report PP

[1]Cochrane 2008 CD006634 2J Clin Gastro 1997; 25 (4): 653-8
[3]Aliment Pharmacol Ther 1997; 11: 853, [4]*Lancet* 1999; **354:** 635
[5]Cochrane *2011, No.: CD007443* [6]*Cochrane* 2010 No.: CD001176.

Probiotics and IBS

- Systematic Review: 19 RCTs (placebo or no treatment), 1650 patients[2]
- 10 RCTs (918 patients): reported dichotomous outcomes
  - symptoms max improved or 'cured'
  - RR = 0.71 (0.57, 0.88), NNT = 4
- Significant heterogeneity, ? Publication bias, 0 AEs reported in 6 trials!
- Jadad scores ≥ 4: less benefit; RR = 0.86 (0.71, 1.03)[2,3]

[2]*Moayyedi, Gut 2010;59:325e332,* [3]*van Zanten, ACP 2010*

Probiotics and IBS 'Best' Study

- Multi-centre placebo controlled RCT of 362♀ from 20 primary care centres in UK
- *Bifidobacterium 10^6, 10^8 or 10^{10} vs placebo*
- Patient recorded symptoms x 4 weeks
- *JADAD 5/5: can't find AC*
- *Funding: study funded by probiotic producer, employs 4/9 authors*
- *Results: Only Bifido 10^8 improved IBS symptoms*

Am J Gastroenterol 2006;101:1581–1590

Why other doses did not work

- Each treatment provided in an identical capsule
- "clearly showed that the highest dose formulation, "coagulated" into a firm glue-like mass which was resistant to acid and intense, prolonged agitation, a phenomenon that can be explained by the intensely hygroscopic nature of this organism

Am J Gastroenterol 2006;101:1581–1590

Probiotics for Everything!

Outcome	Significant Finding	Notes
Bacterial vaginosis[1]	Insufficient evidence	probiotic + Abx ↓ physician reported outcomes
Hepatic Encephalopathy[2]	No difference in mortality, hospitalization, other outcomes	'Further studies needed' (7 RCTs, 550 patients)
Eczema[3]	No difference: parental scores of child's eczema	Investigators reported eczema improved
URI symptoms[4]	Prevention: ↓ URI episodes (NNT 12) Treatment: hospitalized children ↓ URIs (NNT 30)	Heterogeneous results
Gestational DM prevention[5]	One study (256 women): ↓ Gest DM	No diff in fetal outcomes
Sepsis Prevention post Liver Transplant[6]	Bowel decontamination, probiotics, prebiotics, prebiotics + probiotics…	Overall 32% infection rate

[1]*Cochrane* 2009 CD006289. [2]*Cochrane* 2011 CD008716, [3]*Cochrane* 2008 CD006135
[4]*Cochrane* 2011 CD006895, [5]*Cochrane* 2014 CD009951, [6]Cochrane 2014CD006660

Probiotic Summary

- Probiotics are commonly used by our patients and can be costly:
  - $1 (Bio K), 3$ (Tuzen), $8 (VSL-3) / day
- May confer a benefit for CDAD / AAD, and every other disease known to mankind…but may have funding influence and other biases
- If using for chronic condition: try n of 1 study and if no difference → stop

Val Montessori

STI's: Keeping Your Gun in Your Holster

Val Montessori
Division of Infectious Diseases
St. Paul's Hospital

Disclosure of Commercial Support

- **Advisory board meetings for:**
  - **Bristol Myers Squibb**
  - **Pfizer**
  - **Tibotec**
- **Lectures/CME for Merck**

Learning Objectives

- Develop an awareness of increasing antibiotic resistance in gonorrhea and current appropriate therapy
- Become familiar with the changing epidemiology of syphilis and persistent varied clinical presentations of syphilis
- Be informed of the new HIV testing currently available and testing algorithms aimed at earlier diagnosis

Pathogen Resistance and Persistance - Guns Blazing!

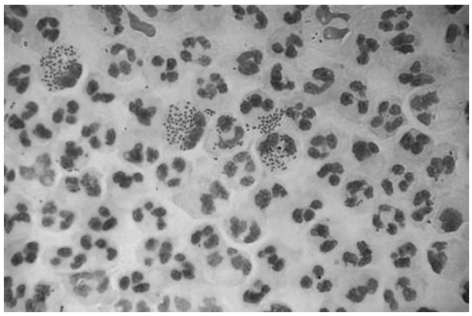
1. Gonococcus – resistance to antibiotics
2. Syphilis – it's everywhere!
3. New Testing for HIV

Sources

- **Canadian Guidelines on Sexually Transmitted Infections, January 2010**
- Updated online www.phac-aspc.gc.ca

- **CDC Sexually Transmitted Diseases Treatment Guidelines, 2010**
- Updated online www.cdc.gov
  - **February 15, 2013 / 62(06);103-106**

Resistance in Gonorrhea

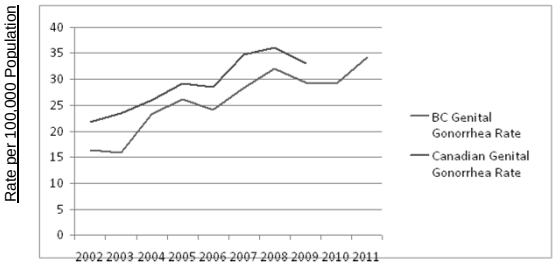


Val Montessori

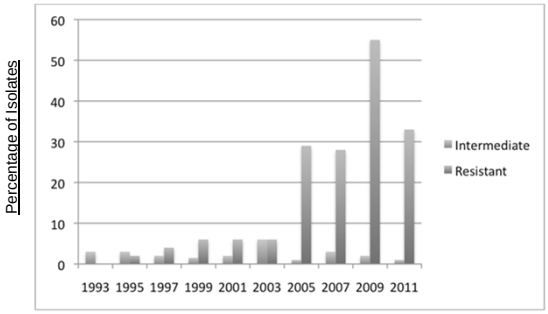
Antibiotic resistance in GC "We need new bullets!"

- CDC developed Gonococcal Isolate Surveillance System (GISP) in 1986
  - **Increasing quinolone resistance**
  - **Increasing cefixime resistance**
  - **Increasing tetracycline resistance**
- **GC cases have doubled in the past 10 years**
- **Molecular testing has become available**

Rate of GC in BC and Canada



GC Resistance to Cipro in BC



Diagnostic Testing

- Molecular testing
  - Nucleic Acid Amplification testing (NAAT)
    - More sensitive than culture
    - Use to screen asymptomatic patients
    - In high risk patients such as Men who have Sex with Men (MSM) may use both NAAT and culture

Diagnostic testing

- **<u>Culture is preferred</u>**
- Especially important if:
  - Patient is MSM
  - Concern about treatment failure
  - Patient traveling from another area
  - Evaluating possible PID
  - Pharyngeal infection
  - Sexual assault
- Repeat culture after treatment if:
  - Not treated with ideal therapy
  - Previous treatment failure
  - Persistent symptoms

Treatment for GC

MMWR August 10, 2012 / 61(31);590-594

- **Treatment of choice:**
  - **Ceftriaxone 250 mg IM**
- **GIVE WITH A SECOND AGENT**
- either 1 g of azithromycin as a single oral dose or 100 mg of doxycycline orally twice daily for 7 days even EVEN IF NAAT TESTING FOR CHLAMYDIA IS NEGATIVE
- **Goal is to delay development of further resistance in GC**

- azithromycin as the second antimicrobial is preferred
  - convenience and compliance advantages of single-dose therapy
  - substantially higher prevalence of gonococcal resistance to tetracycline than to azithromycin among GISP isolates
    - particularly in strains with elevated cefixime MICs.

- **Alternatives:**
  - **Cefixime 800 mg po**
    - A 400-mg oral dose of cefixime does not provide bactericidal levels as high, nor as sustained as does an intramuscular 250-mg dose of ceftriaxone, and demonstrates limited efficacy for treatment of pharyngeal gonorrhea
    - **GISP isolates in MSM and US West showing increased MICs to Cefixime**

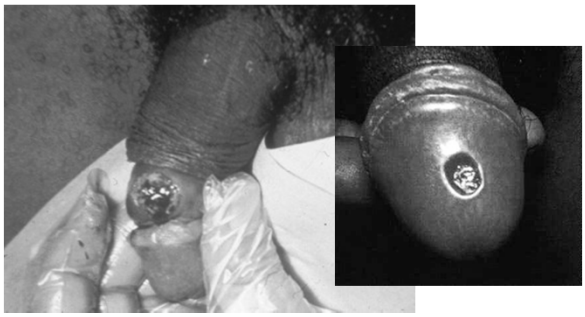
Alternatives

- **Quinolone (ciprofloxacin 500 mg po or ofloxacin 400 mg po) if org known to be sensitive or local quinolone resistance < 5%**
- **Azithromycin 2 grams po single dose**

Chlamydia

- treatment failure may be more common for azithromycin than for doxycycline
- However, adherence rates with doxycycline are a concern
- Test of cure still not recommended (except in pregnancy) but RETEST AT 3 MONTHS

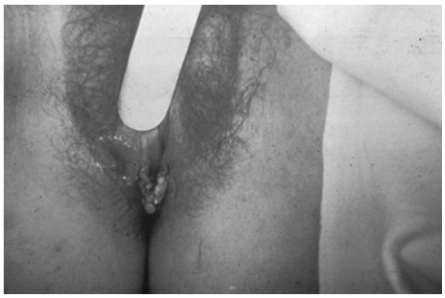
Primary Syphilis—Penile Chancre "Wounds on the Weapon"



Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Clinical Manifestations

Primary Syphilis—Labial Chancre



Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

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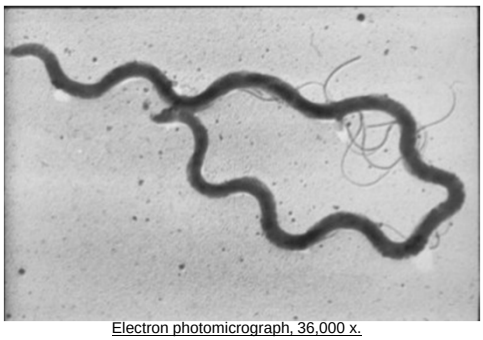
Pathogenesis

Treponema pallidum



Electron photomicrograph, 36,000 x.

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Epidemiology

- Syphilis in BC
  - 2012 the rate was the highest it has been in over 30 years
  - predominantly in MSM
  - 60% of syphilis diagnoses occur in individuals with HIV infection.
- Syphilis in China
  - N Engl J Med 2010; 362:1658-1661
  - In 2008, an average of more than 1 baby per hour was born with congenital syphilis in China, for a total of 9480 cases

Syphilis in BC

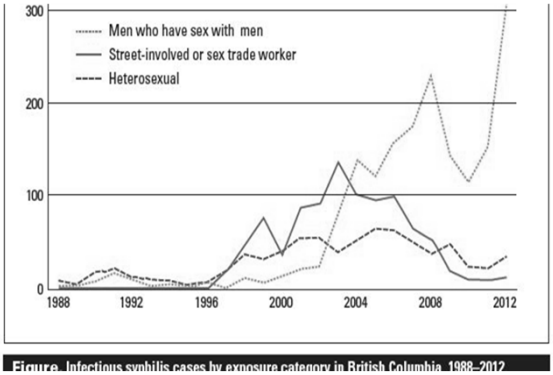
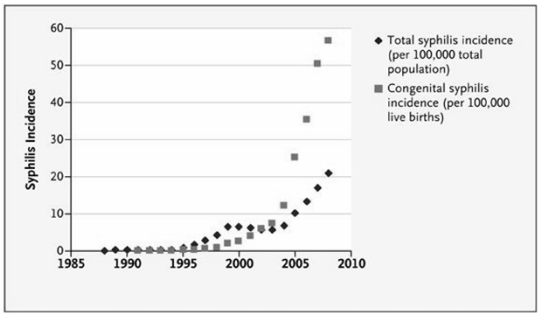


Figure. Infectious syphilis cases by exposure category in British Columbia, 1988–2012

Reported Overall Incidence of Syphilis per 100,000 Population and Incidence of Congenital Syphilis per 100,000 Live Births in China.



Tucker JD et al. N Engl J Med 2010;362:1658-1661.

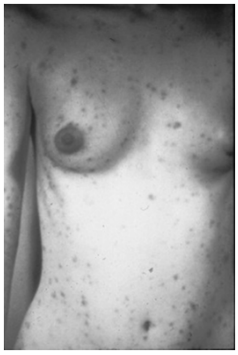
Clinical Manifestations

Secondary Syphilis

- Secondary lesions occur several weeks after the primary chancre appears; and may persist for weeks to months.
- Primary and secondary stages may overlap
- Mucocutaneous lesions most common
- Clinical Manifestations:
  - Rash (75%–100%)
  - Lymphadenopathy (50%–86%)
  - Malaise
  - Mucous patches (6%–30%)
  - Condylomata lata (10%–20%)
  - Alopecia (5%)
  - Liver and kidney involvement can occur
  - Splenomegaly is occasionally present
- Serologic tests are usually highest in titer during this stage.

Clinical Manifestations

Secondary Syphilis—Papulosquamous Rash

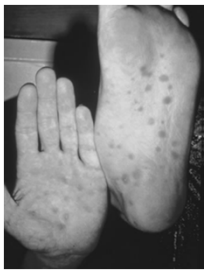


Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

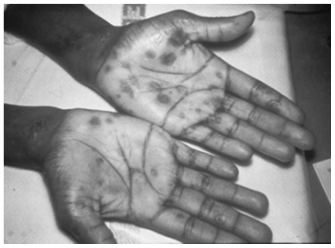
Val Montessori

Clinical Manifestations

Secondary Syphilis—Palmar/Plantar Rash



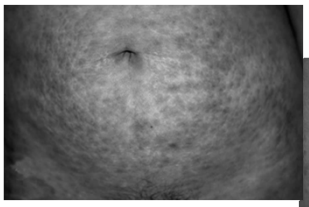
Source: Seattle STD/HIV Prevention Training Center at the University of Washington, UW HSCER Slide Bank



Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Clinical Manifestations

Secondary Syphilis—Generalized Body Rash



Source: Cincinnati STD/HIV Prevention Training Center

Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Clinical Manifestations

Latent Syphilis

- Host suppresses infection, and no lesions are clinically apparent
- Only evidence is a positive serologic test
- May occur between primary and secondary stages, between secondary relapses, and after secondary stage
- Categories:
  - Early latent: <1 year duration
  - Late latent: ≥1 year duration

Clinical Manifestations

Neurosyphilis

- May occur at any stage of syphilis
- Can be asymptomatic
- Early neurosyphilis occurs a few months to a few years after infection
  - Clinical manifestations can include acute syphilitic meningitis, meningovascular syphilis, and ocular involvement
- Ocular involvement can occur in early or late neurosyphilis.
- In BC:
- **1992 the neurosyphilis rate was 0.03 per 100000 population**
- **2012 the rate was 0.8 per 100000 (27-fold increase)**

Diagnosis

Laboratory Diagnosis

- Identification of *Treponema pallidum* in lesion exudate or tissue
  - Darkfield microscopy
  - Tests to detect *T. pallidum*
    - *Direct Fluorescent Antibody Test*
    - *New PCR currently being evaluated by BCCDC*
- Serologic tests to allow a presumptive diagnosis
  - Nontreponemal tests
  - Treponemal tests

BCCDC Syphilis Contacts

Public health nurse: 604 707-5607

Physician: 604 707-5606

Val Montessori

HIV Testing "Finding the Infectious Saturday Night Special"

- New test available
- New testing algorithm and guidelines forthcoming

HIV in BC

- 1/4 of Canadians living with HIV are unaware that they are infected.
  - 3,500 people in British Columbia
- about 65% of diagnoses occur after our patients should already be on treatment,
- 17% having advanced disease at the time of diagnosis

- Gustafson R. 5 July 2012.
- Rank C, et al. Advanced HIV disease at time of diagnosis in British Columbia 1995-2008. BC Centre for Disease Control Special Report, 2011.

New 4th Generation Testing for HIV

- fourth-generation assays have greater sensitivity because of their ability to detect p24 antigen as well as conventional HIV antibodies.
- third-generation assays: HIV antibodies can be detected in most individuals within 3-4 weeks of viral transmission.
- early antigen recognition with fourth-generation assays reduces the window period for detection by approximately 5 days

Cost Effectiveness of Testing

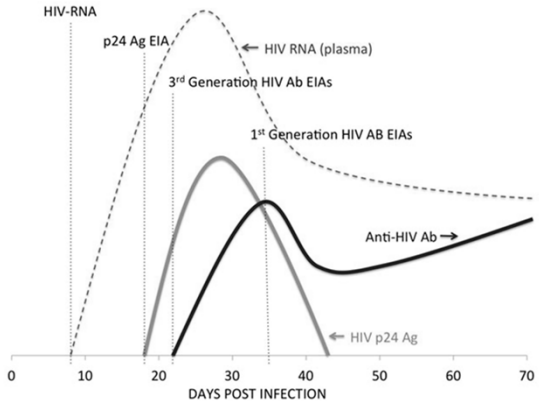
- Evidence supports expanded HIV testing even when the HIV prevalence is as low as 0.5-2 cases per 1000
- Vancouver at 12/1000 diagnosed prevalence,
- BC at 2.2/1000.

- Qaseem A, et al Ann Intern Med. 2009;150:125-131
- Gustafson R. : BCCDC prevalence. 22 June 2012.

HIV transmission

- The acute infection stage is the first 6-8 weeks after infection.
- individuals are highly infectious and more likely to transmit the virus to others.
- 11%-49% of all transmission occur during the acute infection stage.

- Brenner B.G. et al. (2007). High rates of forward transmission events after acute/early HIV-1 infection. *Journal of Infectious Diseases,* 195(7):951–9.



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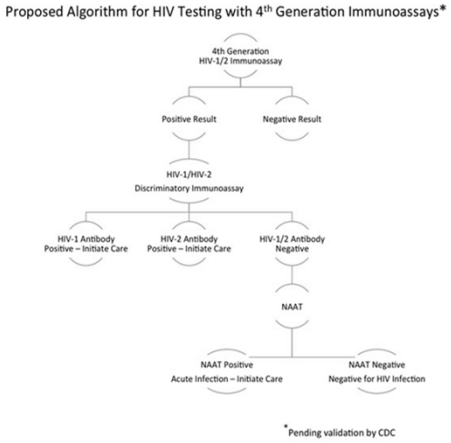

Summary #1 - Gonorrhea

- **Increasing resistance**
- **Ceftriaxone 250mg IM PLUS AZITHROMYCIN 1 gram is preferred therapy**

Summary #2 – Syphilis

- Increasing incidence in MSM in BC
- Increasing incidence worldwide including China

Summary #3 HIV Testing

- Newer tests have shorter window period
- Newer testing algortihms will be forthcoming

Mike Kolber

Adult Vaccines
A silver or a Trojan Horse

Mike Kolber BSc, MD, CCFP, MSc
DTC April 2014
Department of Family Medicine
University of Alberta

Faculty/Presenter Disclosure

- **Faculty/Presenter(s): Michael R. Kolber**
- **Relationships with commercial interests:**
  - Pay from University of Alberta and Alberta Health
- Research and Speaking Fees
  - **Non-Profit Sources** (Alberta College of Family Physicians, Towards Optimized Practice)
  - **No funding from industry**

Adult Vaccine Objectives

- To understand the potential benefits and harms of commonly used adult vaccines including:
  - Influenza Vaccine
  - Pneumococcal vaccine
  - Pertussis
  - Varicella zoster vaccine

"Kolber's Quadruple C Curriculum"

- **C**oncrete Evidence
- **C**ommon Sense
- Patient **C**hoice: once informed
- **C**ost

Vaccines are Tricky…

- More than you may benefit
- Outbreaks are not predictable
- International travel = disease transmission
  - measles post 2010 Olympics, Fraser Valley 2014
- Funny stats: vaccine effectiveness (1-RR)
  - Few RCTs giving NNTs

…And they work

Disease	Vaccine Introduced	Peak Annual number of cases (pre-vaccine)	Peak Annual number of cases 2000-2004 (post vaccine)
Diphtheria	1926	9,010	1
Haemophilis influenza type b (Hib)	1986	526	17
Measles	1963, MMR for all 1983, 2 dose MMR 1996	61,370	199
Mumps	1969, MMR for all 1983, 2 dose 1996	43,671	202
Pertussis	whole cell 1943 acellular 1997	19,878	4,751
Polio	1955 (IPV)	1,584	0
Rubella	1969, MMR for all 1983 2 dose 1996	37,917	29

http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-02-eng.php

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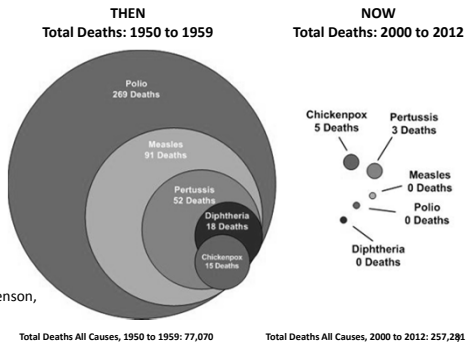
Vaccine Preventable Disease Mortality in Alberta – Then and Now



From Larry Swenson, AH 2013

Recommended Adult Vaccines

Table 1: Adult immunization - recommendations for routine immunization in healthy adults at low risk

Vaccine	Recommendations for routine immunization
Diphtheria Tetanus	Primary series for previously unimmunized adults Booster dose every 10 years
Herpes zoster (shingles)	60 years of age and older - 1 dose 50 to 59 years of age - may be given 1 dose
HPV	Women up to and including 26 years of age - bivalent (HPV2) or quadrivalent (HPV4) vaccine Men up to and including 26 years of age -HPV4 vaccine
Measles Mumps	Susceptible adults born in or after 1970 - 1 dose Born before 1970 - consider immune
Meningococcal conjugate	Adults up to and including 24 years of age not immunized in adolescence - 1 dose
Pertussis	One dose of acellular pertussis-containing vaccine (Tdap) in adulthood Adults who will be in close contact with young infants should be immunized as early as possible
Pneumococcal 23-valent polysaccharide (Pneu-P-23)	65 years of age and older - 1 dose
Polio	Primary series for previously unimmunized adults when a primary series of tetanus and diphtheria toxoid-containing vaccine is being given or with routine tetanus and diphtheria-toxoid containing vaccine booster doses
Rubella	Susceptible adults - 1 dose If vaccine is indicated, pregnant women should be immunized after delivery
Varicella (chickenpox)	Susceptible adults up to and including 49 years of age - 2 doses; if previously received 1 dose should receive a second dose Known seronegative adults 50 years of age and older - 2 doses - routine testing is not advised

TABLE 4: Recommended recipients of influenza vaccine for the 2012-2013 season*

People at high risk of influenza-related complications or hospitalization

- Adults (including pregnant women) and children with the following chronic health conditions:
  - cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma);
  - diabetes mellitus and other metabolic diseases;
  - cancer, immune compromising conditions (due to underlying disease and/or therapy);
  - renal disease;
  - anemia or hemoglobinopathy;
  - conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration;
  - morbid obesity (BMI≥40); and
  - children and adolescents with conditions treated for long periods with acetylsalicylic acid.
- Residents of any age who are residents of nursing homes and other chronic care facilities.
- People ≥65 years of age.
- **All children 6 to 59 months of age.**[1]
- Healthy pregnant women (the risk of influenza-related hospitalization increases with length of gestation, i.e. it is higher in the third than in the second trimester).
- Aboriginal peoples.

People capable of transmitting influenza to those at high risk

- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications.
- Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):
  - household contacts of individuals at high risk, as listed in the section above;
  - household contacts of infants <6 months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine; and
  - members of a household expecting a newborn during the influenza season.
- Those providing regular child care to children ≤ 59 months of age, whether in or out of the home.[1]
- Those who provide services within closed or relatively closed settings to persons at high risk (e.g. crew on a ship).

Others

- People who provide essential community services.
- People in direct contact during culling operations with poultry infected with avian influenza.

* NOTE: Healthy persons aged 5 to 64 years without contraindication are also encouraged to receive influenza vaccine even if they are not in one of the priority groups.

CANADA COMMUNICABLE DISEASE REPORT
CCDR
OCTOBER 2013 • VOLUME 39 • ACS-4
ISSN 1481-8531

An Advisory Committee Statement (ACS)
National Advisory Committee on Immunization (NACI)

STATEMENT ON SEASONAL INFLUENZA VACCINE FOR 2013–2014

- To ↓morbidity and mortality associated with influenza, immunization programs should focus on those:
  - high risk of influenza-related complications,
  - capable of transmitting influenza to individuals at high risk of complications
  - who provide essential community services

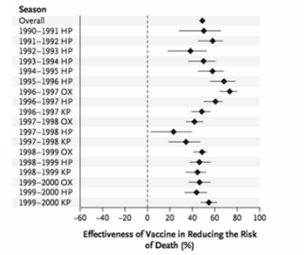
Influenza Vaccine: > 65 years olds

Influenza Vaccine Evidence "↓Mortality by ~ 50%"

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 4, 2007 VOL. 357 NO. 14

Effectiveness of Influenza Vaccine in the Community-Dwelling Elderly

Kristin L. Nichol, M.D., M.P.H., M.B.A., James D. Nordin, M.D., M.P.H., David B. Nelson, Ph.D., John P. Mullooly, Ph.D., and Eelko Hak, Ph.D.



Nichol et al. N Engl J Med 2007;357:1373

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Influenza Vaccine
Mortality ↓ from Cohort studies is Likely Biased

- Healthy user effect:
  - Those choosing vaccination are different than those that do not choose vaccination
    - Mortality benefit exists outside influenza season[1]
    - Adjust for other important confounders (functional and socioeconomic status) → Mortality benefit disappears[1]
  - Magnitude of benefit: mortality reduction >> influenza hospital admission reduction > respiratory comps reduction > influenza incidence reduction[1,2,3]

[1]Eurich Am J Respir Crit Care Med 2008; 178: 527, [2]Doshi BMJ 2013;346:f3037, [3]Jefferson, Cochrane 2010, Issue 2. Art. No.: CD004876.

Vaccines for preventing influenza in the elderly (Review)

Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE

Cochrane 2010, Issue 2. Art. No.: CD004876. DOI: 10.1002/14651858.CD004876.pub3.

Cochrane 2010 Conclusion

- "Due to… low quality of non-RCTs and the likely presence of biases … firm conclusions potentially misleading, …unable to reach clear conclusions about the effects of the vaccines in the elderly.
- To resolve uncertainty, an adequately powered publicly-funded randomized, placebo-controlled trial run over several seasons should be undertaken.

Cochrane 2010, Issue 2. Art. No.: CD00487

RCT: Influenza Vaccine and Elderly Community dwellers

- 1838 generally healthy patients
  - 67 years, 55% female, 30% co-morbidities
  - 87% no previous vaccine
- Double blinded RCT: TIV vs placebo
- Publically funded

Govaert, JAMA. 1994;272:1661

Outcomes

Outcome	Placebo	Vaccine	ARD	Vaccine Effectiveness (1-RR)	Number Needed to Vaccinate (NNV) or harm (NNH)
Influenza (clinical + serology / culture)	4.2%	1.7%	2.5%	60%	**40**
Local Adverse Events	7.3%	17.5%	10.2%		**10**
Systemic Adverse Events	9.4%	11%	1.6%		**NSS**
Mortality	Not recorded		-		-

Govaert JAMA 1994;272:1661 Govaert BMJ 1993;307:988

Nursing Home RCT

- 614 nursing home residents randomized to:
  - Combinations of TIV, live intranasal (LIV), placebo
- Low quality: ? randomization, no AC, under powered for multiple comparisons, stratified by co-morbidities / activity, industry
- Only **TIV PLUS LIV** ↓ influenza
  - 4.6% vs 12.8% placebo, NNT = 13

Rudenko, Vaccine 2001; 19: 308

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Influenza Vaccine in Healthy Adults

Meta-Analysis Influenza Vaccine Healthy Adults (16-65 years)

- 17 RCTs (38,800 patients) of TIV vs placebo / no tx

	Influenza Rates Vaccinated	Influenza Rates Placebo	Vaccine Effectiveness (1-RR)	ARD	NNV
Vaccine Matches	1.2%	4.1%	~ 70%	2.9%	**35**
Vaccine Does not match	1.1%	2.4%	~ 55%	1.3%	**77**

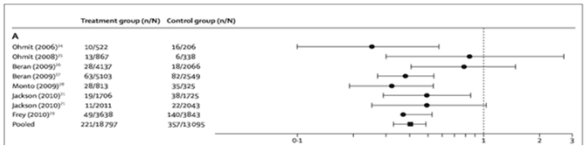
- Limitations: most 1 flu season, included HCWs, kids (20%), epidemics 30 yo
- Number of days ill: ↓ 0.5 days (matched), ↑ 2/3 day (no match)

  - Pneumonia: 1 trial (1970): no difference
  - Hospitalizations 2 trials: no difference
  - Mortality: not reported

Jefferson, *Cochrane* 2010; (7):1-119. CD001269.

Lancet ID 2012 SR TIV in Adults

- 8 studies, 31892 adults, not separated by matching
- Different outcomes (no ILIs or sick days), influenza (PCR or culture (no serology), later search → different studies
- Influenza: placebo = 2.7%, vaccine = 1.2%, VE = 55%, **NNV = 67**



Lancet Infect Dis 2012; 12: 36–44

Best RCT on Healthy Adults

- RCT (TIV vs placebo) > 1100 American factory workers randomized over 2 flu seasons:

Year	Influenza Rate (%) Placebo	Influenza Rate (%) Vaccine	P value	1-RR	ARD	NNV
1 (**poor vaccine match**)	4.4	2.2	0.33	50%	NSS	-
2 (**good vaccine match**)	**10**	1.4	0.001	85%	8.8	**12**

- Minimal impact on work days lost or physician visits
- Hospitalizations: no difference
- Mortality: not recorded

Bridges, JAMA. 2000;284:1655-1663

Influenza vaccine Best Evidence

Population	Vaccine Effectiveness	Number needed to vaccinate to prevent 1 case of influenza
Healthy Adults: well matched vaccine	~ 80%	**12 – 35**
Healthy Adults: poor matched vaccine	~ 50%	**77 or higher**
Healthy Adults: irrespective of match	~ 55%	**67**
Elderly community dwellers	~ 60%	**40**
Elderly Nursing Home	~ 65%	**TIV + LIV = 13**

THE LANCET Infectious Diseases

Pneumococcal Vaccine

Mike Kolber

Pneumococcal Vaccine (PPV) Recommendations

- Everyone @ 65 years once
- 19 – 64 yrs + ↑ risk of invasive pneumonia (IPD):
  - LTC facility
  - Lifestyle: alcoholism, homeless or IVDU, smokers
  - Co-morbidities: cirrhosis, nephrotic syndrome, asthma
- Immunosuppressed: asplenic, HIV, sickle cell, immunosupps: give and boost in 5 years
- 380 cases IPD Alberta 2012

Can Immun Guide, http://www.ahw.gov.ab.ca/IHDA_Retrieval
MMWR 2010 Vol. 59 / No. 34

Pneumococcal Vaccine Overall Results

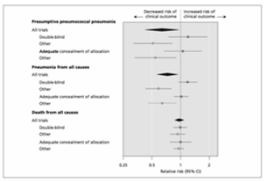
	Placebo risk (%)	Vaccine risk (%)	ARD	NNT
Pneumonia (all) 16 RCTs, 47,734 pts	6.2	4.3	1.9	**53**
Invasive PD 11 RCTs, 36,489 pts	0.36	0.08	0.28	**358**
Mortality 14 RCTs, 47560 pts	4.4	4.2	0.2	**NSS**

Pneumonia: **HI + co-morbid: 4000 patients: 8.5% vax vs 9% (NSS), NNV ~ 200**
HI + healthy: 29,000 patients: 4.4 vs 5.7% NSS, I^2 = 93%
IPD: **HI + co-morbid: 3200 patients: IPD: 4 cases vax vs 2 control**
HI + healthy: 28,000 patients: IPD: 9 vax, 47 control (NNV ~ 400)
Mortality: **HI + co-morbid: 3600 patients: 14.6% vax vs 12.8% (NSS)**
HI + healthy: 32,000 patients: 3.8% vs 4.1% (NSS)

Cochrane 2013, Issue 1. Art. No.: CD000422 HI = high income country

Pneumococcal Vaccine works for pneumonia in certain:

- **People**: Miners and soldiers* (1945) > elderly with co-morbidities (NS)
- **Place**: Africa, New Guinea > Europe, N. America (NS)
- **Things:** lower quality studies > high quality (NS)



*None were double-blinded
CMAJ 2009; 180(1): 48

Pneumococcal Vaccine: Special groups

- **Does pneumovax prevent recurrent pneumonia?**[1]
  - 50-85 yo Swedes w pneumonia → RCT PPV vs placebovax
  - @ 3 years stopped: no diff in pneumonia (vax 19% vs 16%), pneumococcal pneumonia (~5%) or mortality (~ 8%)
- **COPD:** SR 6 RCTs, 1372 patients[2]
  - @ ~ 2 years: ↓ pneumonia: 0.72 (0.51, 1.01), NNT = 17
  - AECOPD or admissions: no diff (2 studies, 216 pts)
  - Mortality: no diff (3 studies (~ 900 pts) @ 4 years)

[1]*Ortqvist, Lancet 1998; 351: 399–403*
[2]*Walters, Cochrane 2010, Issue 11. Art. No.: CD001390*

Pertussis cases Canada

Table 1. Reported cases of pertussis in Canada by year and age group, 2005 to 2011.

Year	All Ages	Less than 1	1 to 4 years	5 to 9 years	10 to 14 years	15 to 19 years	20 to 24 years	25 to 29 years	30 to 39 years	40 to 59 years	60 years or Greater	Age Unspecified
2005*	2493	275	406	321	739	199	58	49	167	235	42	2
2006*	2346	359	650	324	406	125	55	52	115	212	43	5
2010†	759	141	124	111	124	60	31	25	42	85	16	0
2011†	676	146	145	106	103	37	18	13	43	45	17	3

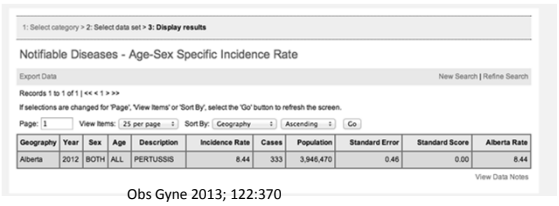
*Data obtained from the Canadian Notifiable Diseases Surveillance System.
†Based on preliminary data.

2012: ~ 4500 cases Canada, ~ 45,000 cases US

MacNeil, Vaccine 2014, Obs Gyne 2013; 122:370

Pertussis in Alberta 2013

- 2013 Alberta outbreaks (including HCW)
- 15 – 20% < 1 yo
- Normally 1-3 deaths / year in Canada
  - 2 deaths Alberta in 2012 (both < 1 yr)
- All 10 2012 California deaths < 2 months old


1: Select category > 2: Select data set > **3: Display results**

Notifiable Diseases - Age-Sex Specific Incidence Rate

Export Data | New Search | Refine Search

Records 1 to 1 of 1 | << < 1 > >>

If selections are changed for 'Page', 'View Items' or 'Sort By', select the 'Go' button to refresh the screen.

Page: 1 View Items: 25 per page Sort By: Geography Ascending Go

Geography	Year	Sex	Age	Description	Incidence Rate	Cases	Population	Standard Error	Standard Score	Alberta Rate
Alberta	2012	BOTH	ALL	PERTUSSIS	8.44	333	3,946,470	0.46	0.00	8.44

View Data Notes

Obs Gyne 2013; 122:370

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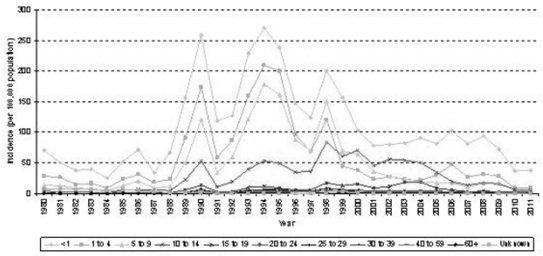
Pertussis Incidence
Highest in youngest

Figure 2. Reported incidence (per 100,000 population) of pertussis in Canada by year and age group, 1980 to 2011*.

Top of Page



*Case data obtained from the Canadian Notifiable Disease Surveillance System. Population data obtained from Statistics Canada July 1st annual estimates. Data for 2009 to 2011 are preliminary.

Recommendation 2013

- All adults receive pertussis vaccine booster once
- Pregnancy:
  - US: vaccinate (TdaP) all pregnant women 27-36 weeks gestation (each pregnancy) OR vaccinate post partum[1]
  - CAN: if no adult TdaP → vaccinate post partum[2]
  - NACI reviewing Tdap for pregnant women[3]
    - consider vaccination in pregnancy during outbreak
- RCTs underway to determine whether maternal vaccination prevents pertussis

[1]Morbidity and Mortality Weekly Report Feb 22, 2013
[2]Can Fam Phys 2013; 59: 497 [3]Can Fam Phys 2014; 2: 138
3http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pert-coqu-eng.php#a4

Zoster vaccine
"60 / 360 @ 60"

- **> 60 year olds[1,2]**
  - Shingles NNT ~ **60** over 3 yrs to prevent 1 case
  - PHN NNT ~ **360** over 3 yrs to prevent 1 PHN
- **50-59 years[3]**
  - Shingles NNT = 71 over 3 years to prevent 1 HZ

[1]Oxman et al. NEJM 2005;352:2271
Schumader, Clin Inf Dis 2012:55: 1320
Schmader et al. Clin Infect Dis 2012;54(7):922

MERCK

Quadruple C Curriculum
1. **Concrete Evidence**

- Influenza:
  - Healthy Adults: works better if matches (NNV = 12) then if not matched
  - Elderly: community dwellers: NNT = 40
  - Nursing home: TIV + LIV: NNT = 13
- Pneumococcal: ↓ pneumonia or IPD (but not in elderly N. American with co-morbidities or high quality studies
- Pertussis: infants and outbreaks
  - vaccinate yourself (HCWs) and adults (Td-DaP)
  - Coming soon - vaccinate pregnant females 3rd tri (TdaP)
- Zoster: "60 / 360 @ 60"

Quadruple C Curriculum

2. Common Sense:
- Can't predict outbreaks
- Vaccine effectiveness driven by baseline rates of disease
- Value vaccines for diseases with potentially serious sequelae

3. Patient Choices:
- Dispel myths: autism and MMR, causes illness

4. Costs:
- Zostavax ~$200
- ? costs of others

Thank you!

- mkolber@ualberta.ca

- Special Thanks:
  - Influenza: Darren Lau (PhD)
  - Pertussis: Kelly Flynn (RN), Sara Forgie (MD, FRCPC)
  - Zoster: Tony Nickonchuk (Pharm)

Val Montessori

Emporiatrics: When you Hi Ho Silver Away

Val Montessori
Division of Infectious Diseases
St. Paul's Hospital

Disclosure of Commercial Support

- **Advisory board meetings for:**
  - **Bristol Myers Squibb**
  - **Pfizer**
  - **Tibotec**
- **Lectures/CME for Merck**

Learning Objectives

- Develop an approach to diagnosis and treatment of fever in the returning traveler
  - Be aware of importance of
    - Region traveled
    - Exposure history
    - Incubation periods of various travel-related infections
- Develop an understanding of effective prevention and treatment of traveler's diarrhea

Travel and Infectious Diseases

- The Febrile Returned Traveler
- When you've just gotta go - traveler's diarrhea

Outline

- Incidence of syndromes & diseases causing fever in travelers
- Diagnostic clues: – region traveled
  – exposure history
  – incubation periods
- Initial investigations +/- serologies
- Empiric treatment after malaria excluded?
- Traveler's diarrhea - prevention and treatment

Travel-related Illness

	Frequency
• travelers reporting any illness	~ 20-70 %
• seek medical attention	~ 1-5 %
• develop fever	~ 3 %
• die	~ 1/100,000

J Infect Dis 1987;156:84
NEJM 2002;347:505

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Incidence Rate Per Month of Travel-related Health Problems in Developing Countries

	% of travelers
Traveler's diarrhea	20-60%
Malaria (no prophylaxis, West Africa)	3%
Dengue	1%
Animal bite (rabies risk)	0.5%
Hepatitis A	0.04%
Typhoid (South Asia)	0.03%
Cholera	0.0003%
Japanese B encephalitis	0.0001%

J Travel Med 2008;15:145

Fever in Returned Travelers: Dx'ic Groups

GeoSentinel Surveillance Network
Febrile patients 28% (6,957 of 24,920)

N= 6,957	%*
• systemic febrile illness	35
• acute diarrheal disease	15
• respiratory illness	14
• genitourinary diagnosis	4
• dermatologic diagnosis	4
• unspecified febrile illness	22
• other diagnoses	10

Clin Infect Dis 2007;44:1560 *may be > 1 diagnosis (>100%)

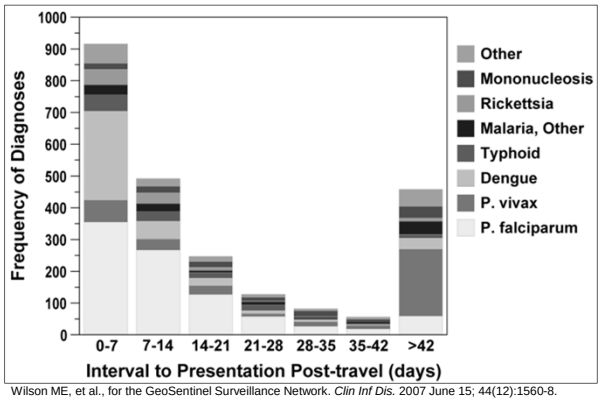
Fever in Returned Travelers: Dx'ic Groups

GeoSentinel Surveillance Network (n= 6,957)

	%
Systemic febrile illness:	35
• malaria	21
• dengue	6
• enteric fever (*Salmonella*)	2
• rickettsia	2
• mono syndrome*	1
• other	3

Clin Infect Dis 2007;44:1560 *EBV, CMV, HIV, or toxo

Frequency of Systemic Febrile Illnesses based on Interval to Presentation to a GeoSentinel Site



Wilson ME, et al., for the GeoSentinel Surveillance Network. *Clin Inf Dis.* 2007 June 15; 44(12):1560-8.

Febrile Illness Incubation Periods

1) Fever onset > 3 weeks after leaving endemic zone, then unlikely to be:
- dengue
- rickettsial infection
- viral hemorrhagic fevers (e.g. yellow fever)

2) Fever onset > 6 weeks after leaving endemic zone, then possibilities include:
- malaria
- hepatitis B, E
- TB, others

• *CDC Health Information for International Travel 2014 (Yellow Book)*
• *NEJM 2002;347:505*

Febrile Traveler: History for Assessing Risks

1. Regions traveled:
   - travel dates, symptom onset, urban/rural
2. Exposure history — Infection
   - fresh water — schistosomiasis, leptospirosis
   - sexual/blood — HIV, HBV, other STDs
   - insect bites — malaria, dengue, tick typhus, trypanosomiasis
   - animals & bites — Q fever, rabies
   - caves — histoplasmosis
3. Immunizations and Malaria prophylaxis

Val Montessori

Fever in Travelers: Initial Investigations

- CBC, differential, and platelet count
- malaria blood smears (thick & thin) daily x 3, ***plus*** rapid diagnostic test (RDT, "dipstick" antigen detection test)
- blood cultures (+/- urine & stool cultures)
- liver enzymes & function tests
- urinalysis, creatinine
- chest X-ray

• *CDC Health Information for International Travel 2014 (Yellow Book)*
• *NEJM 2002;347:505*

Malaria Smear Turn Around Times (hours)

	Ordered as STAT	Ordered as Routine
Life Labs	4 (?)	8
BC Biomedical Lab	4 (?)	8
Vancouver General Hosp	1	2-4
St. Paul's Hosp	1	2-4
Richmond General Hosp	1	2-4
Surrey Memorial	1	2

Serology in the Returned Febrile Traveler

If relevant, based on exposure, incubation period, and clinical presentation:

- dengue
- other viral: e.g. HIV, hepatitis A, B, E
- rickettsioses and ehrlichioses (*Ehrlichia chaffeenisis* and *Anaplasma phagocytophilum*)
- leptospirosis
- schistosomiasis
- brucellosis

NEJM 2002;347:505

Pitfalls in Febrile Traveler Evaluation

- ~10% of malaria patients afebrile on presentation
- malaria may have prominent headache, GI, or respiratory symptoms
- malaria may occur despite history of malaria prophylaxis adherence
- *P. falciparum* malaria may progress rapidly; need short turn around time on testing; hospitalize
- malaria Dx missed on 1st visit for 59% (Rx delay 7.6d)
- "cosmopolitan infections" (e.g. pneumonia, pyelonephritis) may get overlooked

Clin Infect Dis 1998;27:142

Infection	Diagnosis	Empiric Rx
• Malaria	blood smear & rapid test	no
• Dengue	serology	supportive only
• Enteric fever	blood C&S	possibly (ceftriaxone, or azithro, avoid cipro for Indian subcontinent)
• Rickettsioses	serology	doxycycline
• Ehrlichioses	serology	doxycycline
• Leptospirosis	serology	doxycycline, or ceftriaxone, or IV penicillin

INTERNATIONAL
Herald Tribune
THE NEW YORK TIMES
MONDAY, AUGUST 27, 2001

Fake malaria pills haunt Asians

Fatalities grow as people use cheap but worthless 'drugs'

Val Montessori

Substandard & Counterfeit Drugs Manafactured in Developing Countries

- **Substandard antimalarials:**
  - Africa 48%
  - Asia 32%
- **Counterfeit drugs worldwide:**
  - 10% of global pharmaceutical market
  - annual criminal sales $35 billion
  - 192,000 patient deaths in China 2001

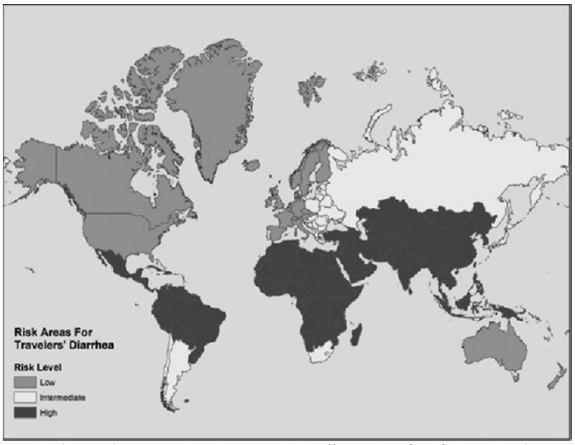
PLoS Med 2005;2(4):e100
PLoS Med 2006;3(6):e197 *PLoS ONE 2008;3(5):e2132*

Travel Medicine Websites

- CDC Traveler's Health Homepage http://www.cdc.gov/travel
- CDC Traveler's Health Yellow Book http://www.cdc.gov/yellowbook
- WHO International Travel Health Homepage http://www.who.int/ith/en
- Committee to Advise on Tropical Medicine and Travel (CATMAT) http://www.publichealth.gc.ca

Traveler's Diarrhea

- 50% of travelers affected in some areas



CDC Health Information for International Travel 2014. Found at http://wwwn.cdc.gov/travel/YellowBookListofMaps.aspx.

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Traveler's Diarrhea

- 80% bacterial, 15% viral, 5% other
- Bacterial
  - Enterotoxogenic *E. coli* – gastroenteritis
  - Salmonella – gastroenteritis
  - Shigella – dysentery, small volume mucopurulent
  - Camplyobacter – dysentery
  - *S. aureus* – acute vomiting
- Viruses
  - Norovirus
- Parasitic

Current Medical Diagnosis and Treatment, 2007.

Other Enteric Pathogens

- **Vibrio spp.**
  - *Vibrio parahaemolyticus & Vibrio cholerae*
    - associated with eating raw/partially cooked seafood
- **Other**
  - *Aeromonas hydrophila, Plesiomonas shigelloides, Yersinia enterocolitica*

General Features

- Benign, self-limited disease
- One week into travel
- Prophylaxis recommended
  - For inflammatory bowel, HIV, IBS, immunosuppression: give prophylaxis
- In others: treat symptomatically

Current Medical Diagnosis and Treatment, 2007.

E coli induced Diarrhea

- Enterotoxigenic E. coli
  - Express two plasmid-encoded toxins: heat labile (LT) and heat stable (ST)
- Enteroadherent E. coli
  - Defined by their adherence properties to cells in culture
- Enteroinvasive E. coli
  - Have plasmids that encode "invasive proteins"
  - Proteins are necessary for virulence and bacterial invasion into gut mucosa
- Enteropathogenic E. coli
  - Mechanisms are not defined; uncommon in the US
- Shiga toxin–producing E. coli
  - Produce Shiga-like toxins that are cytotoxic for cells in culture
  - Genes for these toxins are located on bacteriophages
  - Known causes of HUS/TTP

E coli Pathogens

- Enterotoxigenic Escherichia coli (ETEC)
  - most common cause of TD worldwide
  - large inoculum necessary to produce disease
  - watery diarrhea associated with cramps
  - fever may be low grade or absent
- Enteroaggregative E. coli (EAEC)
  - up to 25% of cases
  - resemble ETEC in presentation & response to abx

Preventive Measures

- For travelers to high-risk areas, several approaches may be recommended that can reduce but never completely eliminate the risk for TD. These include—
- Instruction regarding food and beverage selection
  - Use of agents other than antimicrobial drugs for prophylaxis
  - Use of prophylactic antibiotics for select high risk patients
  - Carrying small containers of hand-sanitizing solutions or gels (containing at least 60% alcohol) may make it easier for travelers to clean their hands before eating

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Food and Beverage Selection

- freshly cooked and served piping hot
- avoid beverages diluted with nonpotable water and foods washed in nonpotable water, such as salads.

- Other risky foods include raw or undercooked meat and seafood, and unpeeled raw fruits and vegetables.
- Safe beverages include those that are bottled and sealed, or carbonated.
- Boiled beverages and those appropriately treated with iodine or chlorine may also be safely consumed.

Nonantimicrobial Drugs for Prophylaxis

- Bismuth subsalicylate (BSS) (Pepto-Bismol).
- Studies from Mexico have shown this agent (taken daily as either 2 oz of liquid or two chewable tablets four times per day) reduces the incidence of TD from 40% to 14%.
- BSS commonly causes blackening of the tongue and stool and may cause nausea, constipation, and rarely tinnitus.
- BSS should be avoided by travelers with aspirin allergy, renal insufficiency, and gout, and by those taking anticoagulants, probenecid, or methotrexate.

Yellow Book 2014

JAMA. 1987 Mar 13;257(10):1347-50. Prevention of travelers' diarrhea by the tablet formulation of bismuth subsalicylate. DuPont HL, Ericsson CD, Johnson PC, Bitsura JA, DuPont MW, de la Cabada FJ.

Nonantibiotic Prophylaxis

- Caution should be used in administering BSS to children with viral infections, such as varicella or influenza (Reye syndrome).
- BSS is not recommended for children <3 years of age. Studies have not established the safety of BSS use for periods >3 weeks.
- The use of probiotics, such as Lactobacillus GG and *Saccharomyces boulardii*, has been studied in the prevention of TD in limited numbers of subjects. Results are inconclusive
  - ?partially because standardized preparations of these bacteria are not reliably available.

Antibiotic Prophylaxis

- For high risk patients (eg immunosuppressed)
- Increasing resistance is problematic with Septra, doxycyline, quinolones
  - Rifaximin 200 BID with lunch / dinner
  - Cipro 250 BID

DuPont H. Bacterial Diarrhea. *NEJM* 2009;361:1560-1569

Travelers' Diarrhea - Vaccine

- oral,inactivated cholera vaccine, Dukoral approved in Canada in 2003
- Killed whole cell *Vibrio cholerae* and non-toxic, recombinant toxin B-subunit
  - Toxin B subunit gives moderate protection against diarrhea from ETEC

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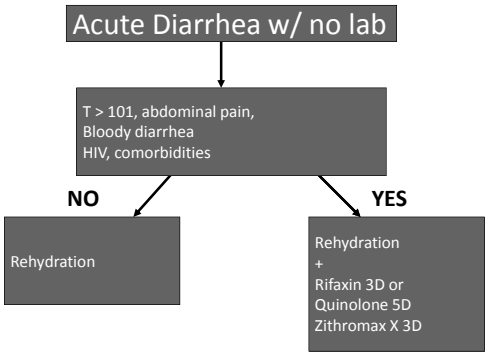
Cholera and ETEC

- Overall efficacy approx. 60 - 80% against cholera
- Many ETEC strains produce toxin similar to cholera toxin so some protection with Dukoral
  - Approx. 50% effective against ETEC and as ETEC do not cause all travelers' diarrhea overall protection of 25%
    - (24% vs 31%)
    - $75
    -

Dukoral

- Not widely recommended
- Most travelers' diarrhea self-limited
- Might lead to false sense of security
- Consider in:
  - Chronic illness
  - Increased risk for TD (gastric hypochlorydria, young children >2)
  - Immunosuppressed

Vaccines for preventing enterotoxigenic Escherichia coli (ETEC) diarrhoea
Ahmed T et al Editorial Group: Cochrane Infectious Diseases Group
Published Online: 5 JUL 2013 DOI: 10.1002/14651858.CD009029.pub2



Adapted from: Figure 14-1 and 14-6, 559. Current Medical Diagnosis and Treatment, 2008

Clin Infect Dis. (2001) 33 (11): 1807-1815. doi: 10.1086/323814 Rifaximin vs Ciprofloxicin

Therapy for Diarrhea

- With sugar and salt (raw sugar or molasses can be used instead of sugar)
  - 1 liter (.3 gallon) of clean water
  - 1/2 tsp SALT
  - 8 level tsps sugar or substitute
  - Need 3 L/ D, drink q5 min
  - BRAT diet: Bananas, rice, applesauce, toast

Werner D. Where There is No Doctor: A Village Healthcare Handbook for Africa, p161.

DuPont H. Bacterial Diarrhea. *NEJM* 2009;361:1560-1569

Persistent Diarrhea

- Suggest protozoan parasites as the etiology.
- Parasites as a group are the pathogens most likely to be isolated from patients with persistent diarrhea
- Parasites may also be the cause of persistent diarrhea in those already appropriately treated for a bacterial pathogen.
- Intestinal parasites include *Giardia* (most common) as well as *Cryptosporidium parvum*, *Entamoeba histolytica*, *Isospora belli*, *Microsporidia*, as well as *Cyclospora cayetanensis*.
- Also consider c.dif., sprue

Giardia

- Suspicion for giardiasis should be particularly high when upper gastrointestinal symptoms predominate.
- Untreated, symptoms may last for months even in the immunocompetent host.
- The diagnosis can often be made through stool microscopy.
- Given the high prevalence of *Giardia* in persistent travelers diarrhea, empiric therapy is a reasonable option in the appropriate clinical setting after negative stool microscopy and in lieu of duodenal sampling

CDC Yellow Book 2014

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Postinfectious Phenomena

- At least 3 months of symptoms, with an onset of symptoms at least 6 months previously.
- Recurrent abdominal pain or discomfort associated with two or more of the following features:
  - Improvement with defecation
  - Onset associated with a change in the frequency of stool
  - Onset associated with a change in form (appearance) of stool

Summary

- Fever in a returned traveler is a **medical emergency** (until proven otherwise)
- Prompt evaluation and rapid lab tests including malaria smears required
- Most important treatable infections: malaria, intestinal, respiratory & GU infections. Occasionally typhoid, rickettsial infection, and others.

Summary

- Acute Travelers' Diarrhea
  - Common - bacterial
  - Avoidance is key
  - Supportive care
  - Self initiated antibiotics
- Persistent Diarrhea
  - Parasitic
  - Postinfectious

G. Michael Allan

Vitamin D: Riding off into the Sunshine
Or
Vital Vitamin or Hopeful Hype

G Michael Allan
Associate Professor, Dept of Family Medicine, U of A
Director of the Evidence & CPD Program, ACFP

Slide 1: Option A (Faculty with relationship(s) to declare)

Faculty/Presenter Disclosure

- **Faculty:** G. Michael Allan
- **Relationships that may introduce potential bias and/or conflict of interest:**
  - **None**

SMART Objectives Vitamin D

- Vitamin D Level: Learn why testing Vitamin D is not necessary and should not be done without specific bone disease.
- Vitamin D Treatment: Although we will show that low levels of Vitamin D are associated with all sorts of outcomes, we will review evidence showing that Vitamin D treatment has no effect on (and should not be given for) prevention or treatment of
  - Upper Respiratory Tract Infection
  - Depression
  - Diabetes
  - Rheumatoid Arthritis (as an example),
  - MS
  - Cancer
- Vitamin D treatment: we will review evidence showing that Vitamin D treatment has may have benefit older patients in (and can be given for) prevention of
  - Bones-fractures
  - Falls in frail elderly
  - Mortality

What we'll cover.

- Vitamin D Level
- Testing for Vitamin D
- Vitamin D
  - Bones-fractures
  - Falls
  - Mortality
  - Upper Respiratory Tract Infection
  - Depression
  - Diabetes
  - Rheumatoid Arthritis (as an example),
  - MS
  - Cancer
- Dosing (and Type) of Vitamin D

What levels do we need?

Our Lab print out says,…

- <25 nmol/L severe deficiency
- 25-80 moderate to mild deficiency
- 80-200 optimum levels
- >200 toxicity possible

Institute of Medicine

- ≤ 30 nmol/L at risk relative to bone health
- 30-50 nmol/L some, but not all, are potentially at risk for inadequacy
- ≥ 50 nmol/L practically all persons are sufficient
- >75 nmol/L not consistently associated with increased benefit.
- >125 nmol/L may be reason for concern

Dietary Reference Intakes for Calcium and Vitamin D. Institute of medicine 2011. (page 13-14)

Vitamin D Levels in Canada

What is the prevalence of Low Vitamin D level (age ≥9)

Level	Percent (CI)
<40nmol/L	13% (10-16)
≥40nmol/L	87% (84-90)

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Some good, A lot Better?

- 2258 women RCT of annual 500,000 (oral) yearly in autumn for 3-5 years.
  - Falls up: 74% vs 68% (6% more)
  - Fractures up: 14% vs 11% (3% more)
  - Most harm in first 3 months when Vit D levels >90
- Other RCT (9400 pts), given 300,000 IU (IM) yearly every autumn for 3 years
  - Fractures up (hip # significant, 0.5% worse)

JAMA. 2010;303:1815-22. Rheumatology (Oxford) 2007;46:1852-7.

Vitamin D & MS: Background

- Theory:
  - Farther from equator = higher risk Vit D Defi
  - Farther from Equator = higher risk of MS
  - Vit D has some role in immunity
- Evidence: n=~180,000 people, 173 cases
  - Vit D supplements vs none: RR=0.59 (0.38-0.91) for developing MS
  - Vit D from Food: No association

Neurology 2004;62:60-5.

Evidence-Treatment of MS

- Systematic Reviews & Meta-Analyses:
  1. Cochrane: only 1 RCT[1]
  2. Five RCTs, too heterogeneous for MA[2]
  3. Five RCTs, no significant difference relapse rate[3]
- Looking at RCTs: small, short RCTs, often open-label.
  - One Positive: effect on surrogate end points[4]
  - One Negative: High vs Low dose increased "expanded disease severity scale" & numerically more relapses (4 vs 1)[5]
  - Three found no effect[6-8]

[1]Cochrane 2010;12:CD008422. [2]Neuroepidemiology 2013;40:147-53. [3]Mult Scler. 2013 May 22. ePub [4] J Neurol Neurosurg Psychiatry 2012;83:565e571. [5]Neurology 2011;77:1611-8. [6]Neurology 2010;74:1852-9. [7]kampman Mult Scler. 2012 Aug;18(8):1144-51. [8]Immunol Invest. 2011;40(6):627-39.

Vitamin D and MS Summary

- Low serum vitamin D levels may increase risk of developing MS
  - Correlation ≠ causation
- Current evidence does not support Vit D supplements to treat MS

Rheumatoid Arthritis

- Cohorts
  - 29,368 women, 11 yrs, 152 got RA:[1]
    - Highest vs lowest third, RR 0.67, (0.44–1.00)
  - Nurses Health Study[2]: 186,389 women, 22 yrs: Overall no link
    - Increase supp associated with Increase risk: 2.3 (1.1, 5.1)
- Systematic reviews[3] acknowledge that the
  - weaker evidence seems to draw some association
    - Remember: Healthy user effect
  - But stronger evidence (e.g. cohort) is no supportive
  - RCT is needed.
- WHI:[4] 36,282 women (mean age 62) x 5.1 years. Two parts,…
  - RCT: 400 IU of vitamin D3 (+ Ca) or placebo, RR was 1.04 (0.76, 1.41)
  - Cohort: Higher total intake Vit D, seemed to have higher risk of RA

1. Arthritis Rheum. 2004 Jan;50(1):72-7. 2) Ann Rheum Dis 2008;67:530–535. 3) Autoimmun Rev 2012; 12:127–136. Semin Arthritis Rheum2011; 40:512-531. 4) Rheumatol Int (2012) 32:3823–3830

Vitamin D as RA treatment

- RCT 117 RA (on methotrexate) pts took 50,000 IU weekly Vitamin D x 12 weeks in Iran
  - No difference (some better, some worse)
- RCT 121 RA (on treatment) pts took 500 IU a day x 12 weeks in India – Open Label
  - No diff in primary outcome (time to pain relief) or degree of pain relief at onset of pain relief (both identical)
  - Higher median pain relief score at 12 wks (50% vs 30%).
- RCT 50 RA pts took 100,000 IU per day x 1 yr (in Sweden – 40+ years ago).
  - "objective & subjective improvement" 67% (Vit D) vs 36%, p<0.01 (NNT 4)

1) Rheumatol Int (2012) 32:2129–2133. 2) Int. J Rheum Dis 2011; 14: 332–339. 3) Scand J Rheumatology 1973;2: 173-176.

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Vitamin D & RA: Summary

- Does Vitamin D prevent RA:
  - Nothing (or maybe increase with Supplement)
- Can Vitamin D be used to Treat RA:
  - Evidence is poor and conflicting. Can not support the use of Vitamin D for RA.
- Bottom-Line: Vitamin D does not appear to offer any benefit in the prevention or treatment of RA.

Vitamin D & Depression:
Are low levels associated with depression?

- Meta-analysis of observational data: 31,242 pt
  - Low Vit D risk is 1.3 to 2.2 (across diff study types)
  - Issues: Lots of heterogeneity, borderline stat sign,
  - Bottom-Line: There appears to be an association between low Vitamin D and Depression.
- Many studies looked at mental health (MH) not depression (so harder to find differences)
  - People in general, gave Vit D and measure MH, or
  - People with low Vit D, Gave Vit D, measure MH

Brit J Psych 2013; 202: 100–107.

Vitamin D & Depression:
Does Vitamin D improve Mental Health

- Negative:
  - Secondary outcome US Bone trial 489 pts:
    - No effect (ns 4% better change). Moderate quality
  - Healthy young adults, Australia, 128pts
    - No effect (mood or anxiety). Good quality.
    - Asked if blinded 74-77% thought they got placebo.
  - Secondary outcome, osteoporosis, Australia 2258 pts
    - No effect (4 measures), moderate quality
  - Norway, mean age 54, 243 pts
    - No effect (4 measures), good quality

1) Menopause. 2012; 19(6): 697–703. 2) PLoS ONE 2011; 6(11): e25966. 3) Brit J Psych (2011) 198, 357-364. 4) Brit J Psych (2012) 201, 360–368.

Vitamin D & Depression:
Does Vitamin D improve Mental Health

- Positive: Lots of flaws (e.g. drop-out ≥24%)
  - Two poor trials in one. 130 pts in both. Toronto[1]
    - Small effect: 0.6 to 1.5 better on 16 pt scale.
  - Norwegian,[2] overweight-obese, 441 pts,
    - Maximum 1.5 change on Beck Inventory.
- Possible worse: WHI[3] 36,282 women, x 3 years
  - 2263 did final depression questionnaire (Burnam)
  - Mean scores: trend worse. Cut-off to depression: same or worse for Vit D, Antidepressant use equal.
- Sum-up: 4 show no effect, 2 show small effect, and 1 shows possible worsening.

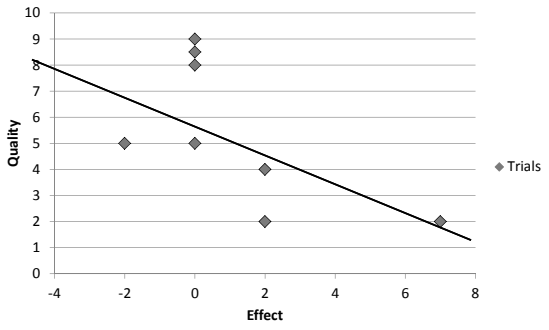
1) Nutrition Journal 2004, 3:8 2) J Int Med 2008 264: 599-609. 3) Am J Epidemiol. 2012;176(1):1-13

Vitamin D & Depression:
Does Vitamin D improve Depression

- 489 patients, Secondary outcome was mood.
  - Sub-population of 57 depressed women:
    - End: 29% less Placebo vs 23% less Vitamin D.
- Iran, 120 patients, Vit D <40 nmol/L, beck ≥17,
  - IM injections of 300,000 and 150,000 IU (one dose) or no treatments. X 3 months
  - Quality poor: Random # tables, unclear (unlikely) AC, no power calc, no blinding, 9.2% withdrew, per protocol
  - Mean BECK scores improved 9.3, 6.8, 2.1, $p < 0.001$
  - Percent who got <10 on Beck: 26%, 17%, 3%.

1) Menopause. 2012 June ; 19(6): 697–703. 2) J Clin Psychopharmacol 2013;33: 378-385

As quality Improves, Effect Less.



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Vitamin D & Depression: Summary

- **Bottom-line**
- Does Vitamin D prevent or improve anxiety or mental well-being scores in general population (even when Vitamin D levels low)?
- NO
- Does Vitamin D treat depressed patients?
- Unclear: Poor, conflicting evidence

Vitamin D and URTI

- A large cohort study suggests that RTI are more common in low Vitamin D levels[1]
  - Lowest vs highest third, Odds ratio 1.36 (1.01-1.84).
- Two Meta-analyses[2]: Vitamin D decrease RTI.
  - Pooled regardless of population, outcomes, quality, etc
  - "Results indicate that vitamin D has a protective effect against RTI, ... Due to heterogeneity of included studies and possible publication bias in the field, these results should be interpreted with caution."
- One Meta-analysis pooled studies with healthy populations, used relative risks and found no difference.[3]

1) Arch Intern Med. 2009;169(4):384-390. 2) PLoS One 2013; 8 (6): e65835. J Pharmacol Pharmacother. 2012;3(4):300-3. 3) Scand J Infect Dis. 2013;45(9):696-702.

Vitamin D & URTI

- 2259 patients (mean age 58, 60% male) x17 months.
  - Sub-study of 759 for more detailed URTI info
  - No difference in # of illnesses or days ill for URTI or cold
- 162 adults (mostly female, mean 59) x12 wks.
  - No diff in percent with, duration or severity of URTI.
- 164 Finnish male military recruits (age 18-28).
  - No difference in days absent or symptoms
- 322 employees university or health care x18 months.
  - No difference in mean number of URTI/person, number of days of missed work/episode, duration of symptoms, severity.

1) Rees JR, et al. Clin Infect Dis. 2013 Sep 6. Pub online 2) Epidemiol. Infect. (2009), 137, 1396–1404. 3) The Journal of Infectious Diseases 2010; 202(5):809–81. 4) 4) JAMA. 2012;308(13):1333-1339

Vitamin D and Flu

- 430 Japanese, children, mean age 10, male 56%,
  - 22.3 % withdrawn X 4 months (winter).
  - NNT 13, p=0.04
  - Selective reporting Examples
    - Influenza A (not influenza overall) as primary outcome
    - RR =0.5806, 0.3385-0.9961 (p=0.0484). They rounded down 0.34-0.99, p=0.04

	Vitamin D		Placebo		Fischer
	n=167	%	n=167	%	
Influenza A	18	11%	31	19%	0.06
Influenza B	39	23%	28	17%	0.17
Influenza Like Illness	8	5%	9	5%	
Total	65	38.9%	68	40.7%	0.82

Am J Clin Nutr 2010;91:1255–60.

Vitamin D and Other RTI Infection

- Other RTI: 2 studies
  - 140 immune def (and/or frequent RTI?) patients
    - Lower RTI score but not validated) & hard to apply
  - Secondary analysis of osteoporosis study (5292 pts)
    - No difference in reporting of infection or Abx use.
- Pneumonia: 2 studies
  - Kabul Afghanistan, 453 children (mean 13 months), x3 months.
    - Did not decrease the duration of the original pneumonia.
    - ≥1 new pneumonia, 45% vs 58%, NNT 8, p=0.01 (inconsistent with ≥2)
  - Kabul Afghanistan, 3060 children, 1-11 months, x18 months
    - First ever pneumonia clinically and/or radiographically : No difference
    - Inconsistent repeat pneumonia: X-ray confirmed worse Vitamin D 1.68

1) BMJ Open 2012;2:e001663. 2) Age and Ageing 2007; 36: 574–592. 3) Trop Med Int Health. 2010 Oct;15(10):1148-55. 4) Lancet 2012; 379: 1419–27

Vitamin D and URTI

- Bottom-Line: While Vitamin D levels seem association with RTI, Giving Vitamin D does not reduce URTI, RTI or pneumonia.

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Fractures

- Five Systematic Reviews 11-45 RCTS
  - Hip fracture: RR 0.84, (0.73-0.96)
  - Non-vertebral fracture: RR 0.95 - 0.88 (varies)
- Bottom-Line: Vitamin D, at dose of ≥800 IU, with calcium, reduces fracture risk. If the risk of fracture is 15% over 10 years, the NNT is approximately 45 (at best).

Cochrane Database Sys Rev 2009;2: CD000227 Ann Intern Med. 2011;155:827-38. Arch Intern Med. 2009:169:551-61 NEJM 2012:367:40-9. Bolland MJ Lancet Diabetes Endocrinol 2014

Meta-analyses

- 7 Meta-analyses
  - Dog's breakfast: works, doesn't, only this subgroup, overall number of falls, individuals who fall, etc
- Bottom-Line: Vitamin D in elderly patients may decrease the number of falls. A positive estimate would be that 1 in 11 to 1 in 15 patients will avoid a fall because of Vitamin D.

Cochrane 2009;2:CD007146. Cochrane 2010;1:CD005465. Can Geriatric J 2011;14(4):93-9. Ann Intern Med 2010;153:815-25. J Clin Endocrinol Metab 2011;96(10):2997-3006. J Am Geriatr Soc 2010;58(7):1299-1310. BMJ 2009;339:b3692. IOM (Institute of Medicine). 2011. *Dietary Reference Intakes for Calcium and Vitamin D.* Washington, DC: The National Academies Press.

What about over-all Mortality

- 5 Meta-analysis: Always secondary outcome
  - >80,000 people, 2 yrs: 0·96 (0·93–1·00) p=0·04
- Bottom-Line: Vitamin D does not increase mortality. It may decrease mortality but the effect is very small and inconsistent. If it does, best estimates are NNT of 150-900 over 2-3 yrs

Cochrane 2011; 7: CD007470. ArchInternMed 2007;167:1730-7. J Clin Endocrinol Metab 2012 97 2670-81. J Clin Endocrinol Metab 2011;96:1931-42. Bolland MJ Lancet Diabetes Endocrinol 2014

Cancer & CVD overview

- No convincing evidence, almost 50,000 studied
  - RR for CHD: 1.02 (0.93 – 1.13)
  - RR for Cancer: 0.99 (0.93 – 1.05)

IOM & Ann Intern Med. 2011;155:827-38. . Bolland MJ Lancet Diabetes Endocrinol 2014

SALT WATER

Love and Marriage
go together like a horse and carriage

PETER LOEWEN
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Faculty of Pharmaceutical Sciences
The University of British Columbia
Vancouver General Hospital

OBJECTIVES

After participation and upon further reflection, learners will be able to:

1. Overview the current state of evidence for the effects of sodium intake reduction on cardiovascular disease.
2. Describe a rational approach to advising heart failure patients about sodium intake.
3. Name key features of the most current guidelines on hyponatremia management.

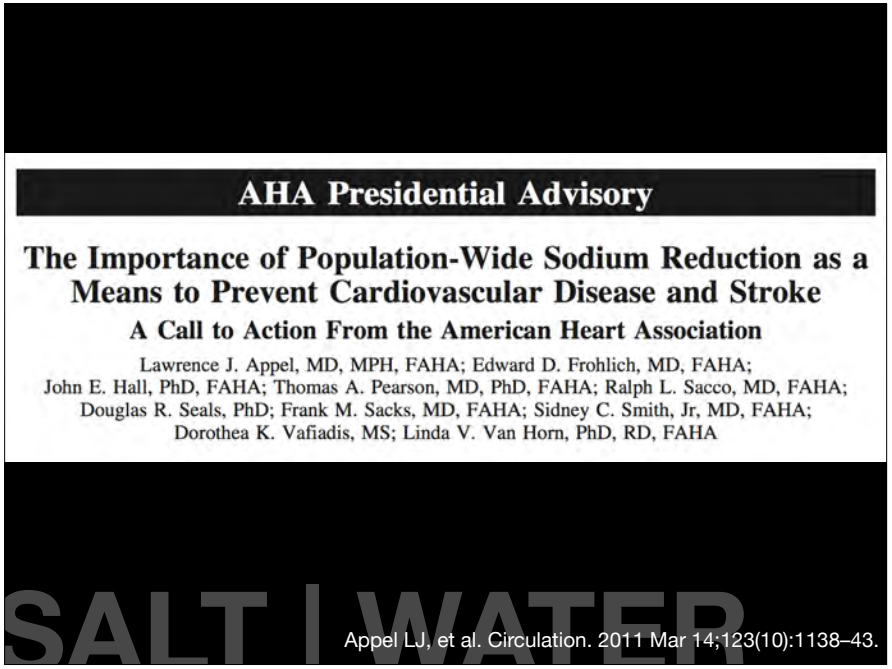
SALT | WATER

COI

SALT | WATER

SALT BP

Peter Loewen



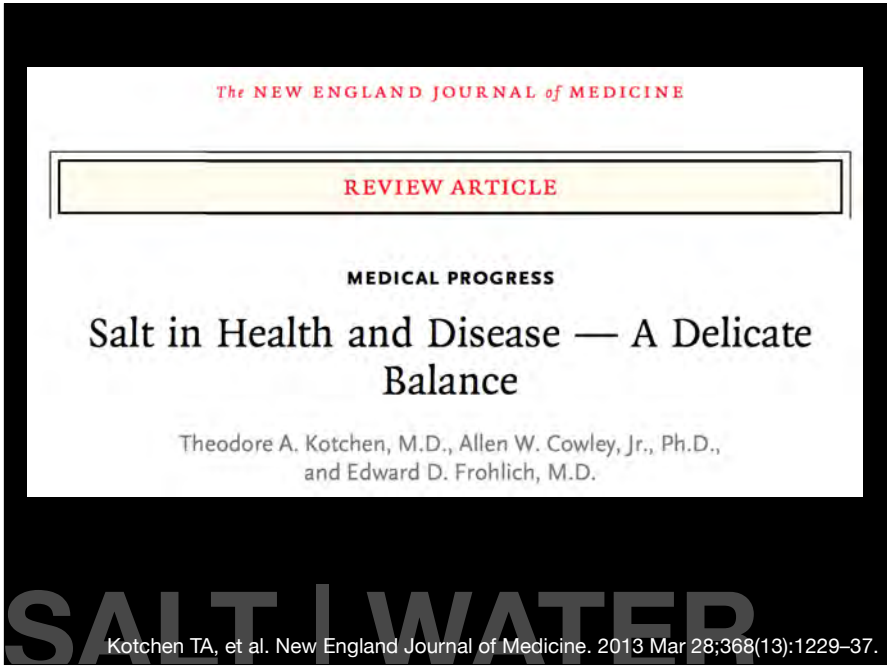
AHA Presidential Advisory

The Importance of Population-Wide Sodium Reduction as a Means to Prevent Cardiovascular Disease and Stroke

A Call to Action From the American Heart Association

Lawrence J. Appel, MD, MPH, FAHA; Edward D. Frohlich, MD, FAHA; John E. Hall, PhD, FAHA; Thomas A. Pearson, MD, PhD, FAHA; Ralph L. Sacco, MD, FAHA; Douglas R. Seals, PhD; Frank M. Sacks, MD, FAHA; Sidney C. Smith, Jr, MD, FAHA; Dorothea K. Vafiadis, MS; Linda V. Van Horn, PhD, RD, FAHA

Appel LJ, et al. Circulation. 2011 Mar 14;123(10):1138–43.



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

Salt in Health and Disease — A Delicate Balance

Theodore A. Kotchen, M.D., Allen W. Cowley, Jr., Ph.D., and Edward D. Frohlich, M.D.

Kotchen TA, et al. New England Journal of Medicine. 2013 Mar 28;368(13):1229–37.

Reduced Dietary Salt for the Prevention of Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials (Cochrane Review)

Rod S. Taylor[1], Kate E. Ashton[2], Tiffany Moxham[3], Lee Hooper[4] and Shah Ebrahim[5]

BACKGROUND
Although meta-analyses of randomized controlled trials (RCTs) of salt reduction report a reduction in the level of blood pressure (BP), the effect of reduced dietary salt on cardiovascular disease (CVD) events remains unclear.

METHODS
We searched for RCTs with follow-up of at least 6 months that compared dietary salt reduction (restricted salt dietary intervention or advice to reduce salt intake) to control/no intervention in adults, and reported mortality or CVD morbidity data. Outcomes were pooled at end of trial or longest follow-up point.

RESULTS
Seven studies were identified: three in normotensives, two in hypertensives, one in a mixed population of normo- and hypertensives and one in heart failure. Salt reduction was associated with reductions in urinary salt excretion of between 27 and 39 mmol/24 h and reductions in systolic BP between 1 and 4 mm Hg. Relative risks (RRs) for all-cause mortality in normotensives (longest follow-up—RR: 0.90, 95% confidence interval (CI): 0.58–1.40, 79 deaths) and hypertensives (longest follow-up RR 0.96, 0.83–1.11, 565 deaths) showed no strong evidence of any effect of salt reduction CVD morbidity in people with normal BP (longest follow-up: RR 0.71, 0.42–1.20, 200 events) and raised BP at baseline (end of trial: RR 0.84, 0.57–1.23, 93 events) also showed no strong evidence of benefit. Salt restriction increased the risk of all-cause mortality in those with heart failure (end of trial RR 2.59, 1.04–6.44, 21 deaths). We found no information on participant's health-related quality of life.

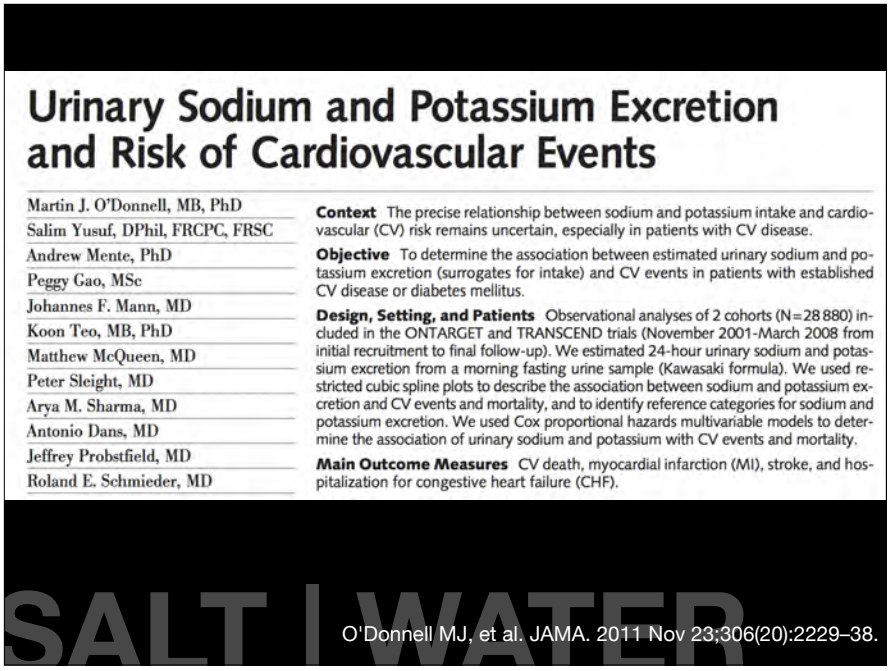
CONCLUSIONS
Despite collating more event data than previous systematic reviews of RCTs (665 deaths in some 6,250 participants) there is still insufficient power to exclude clinically important effects of reduced dietary salt on mortality or CVD morbidity. Our estimates of benefits from dietary salt restriction are consistent with the predicted small effects on clinical events attributable to the small BP reduction achieved.

Keywords: blood pressure; cardiovascular disease; diet; hypertension; meta-analysis; salt; sodium; systematic review

A more detailed review has been published and will be updated in the Cochrane Database of Systematic Reviews (Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease. Cochrane Database of Systematic Reviews (CDSR) 2011, Issue 7 (see www.thecochranelibrary.com for information). This is a version of a Cochrane review, which is available in The Cochrane Library. Cochrane systematic reviews are regularly updated to include new research, and in response to feedback from readers. The results of a Cochrane review can be interpreted differently, depending on people's perspectives and circumstances. Please consider the conclusions presented carefully. They are the opinions of review authors, and are not necessarily shared by The Cochrane Collaboration.

American Journal of Hypertension, advance online publication 6 July 2011; doi:10.1038/ajh.2011.115

Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of CV disease: a meta-analysis of RCTs (Cochrane review). 2011.



Urinary Sodium and Potassium Excretion and Risk of Cardiovascular Events

Martin J. O'Donnell, MB, PhD
Salim Yusuf, DPhil, FRCPC, FRSC
Andrew Mente, PhD
Peggy Gao, MSc
Johannes F. Mann, MD
Koon Teo, MB, PhD
Matthew McQueen, MD
Peter Sleight, MD
Arya M. Sharma, MD
Antonio Dans, MD
Jeffrey Probstfield, MD
Roland E. Schmieder, MD

Context The precise relationship between sodium and potassium intake and cardiovascular (CV) risk remains uncertain, especially in patients with CV disease.

Objective To determine the association between estimated urinary sodium and potassium excretion (surrogates for intake) and CV events in patients with established CV disease or diabetes mellitus.

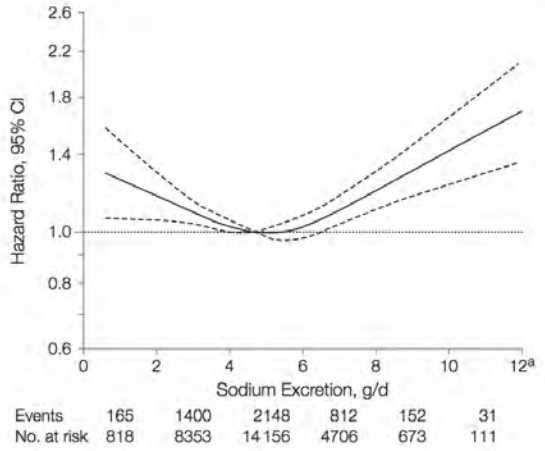
Design, Setting, and Patients Observational analyses of 2 cohorts (N=28 880) included in the ONTARGET and TRANSCEND trials (November 2001-March 2008 from initial recruitment to final follow-up). We estimated 24-hour urinary sodium and potassium excretion from a morning fasting urine sample (Kawasaki formula). We used restricted cubic spline plots to describe the association between sodium and potassium excretion and CV events and mortality, and to identify reference categories for sodium and potassium excretion. We used Cox proportional hazards multivariable models to determine the association of urinary sodium and potassium with CV events and mortality.

Main Outcome Measures CV death, myocardial infarction (MI), stroke, and hospitalization for congestive heart failure (CHF).

O'Donnell MJ, et al. JAMA. 2011 Nov 23;306(20):2229–38.

Peter Loewen

Figure 1. Estimated 24-Hour Urinary Excretion of Sodium and Composite of Cardiovascular Death, Stroke, Myocardial Infarction, and Hospitalization for Congestive Heart Failure



SALT | WATER

O'Donnell MJ, et al. JAMA. 2011 Nov 23;306(20):2229–38.

Dietary Sodium Intake and Cardiovascular Mortality: Controversy Resolved?

Michael H. Alderman[1] and Hillel W. Cohen[1]

Universal reduction in sodium intake has long been recommended, largely because of its proven ability to lower blood pressure for some. However, multiple randomized trials have also demonstrated that similar reductions in sodium increase plasma renin activity and aldosterone secretion, insulin resistance, sympathetic nerve activity, serum cholesterol, and triglyceride levels. Thus, the health consequences of reducing sodium cannot be predicted by its impact on any single physiologic characteristic but will reflect the net of conflicting effects. Some 23 observational studies (>360,000 subjects and >26,000 end points) linking sodium intake to cardiovascular outcomes have yielded conflicting results. In subjects with average sodium intakes of less than 4.5 g/day, most have found an inverse association of intake with outcome; in subjects with average intakes greater than 4.5 g/day, most reported direct associations. Finally, in two, a "J-shaped" relation was detected. In addition, three randomized trials have found that heart failure subjects allocated to 1.8 g of sodium have significantly increased morbidity and mortality compared with those at 2.8 g. At the same time, a randomized study in retired Taiwanese men found that allocation to an average intake of 3.8 g improved survival compared with 5.3 g. Taken together, these data provide strong support for a "J-shaped" relation of sodium to cardiovascular outcomes. Sodium intakes above and below the range of 2.5–6.0 g/day are associated with increased cardiovascular risk. This robust body of evidence does not support universal reduction of sodium intake.

Keywords: *blood pressure; cardiovascular disease; cardiovascular morbidity; cardiovascular risk; diabetes; dietary; hypertension; J-shaped relation; mortality; sodium intake; sodium reduction; sodium restriction*

American Journal of Hypertension, advance online publication 25 May 2012; doi:10.1038/ajh.2012.52

SALT | WATER

Alderman MH, Cohen HW. Am J Hypertens. 2012 Jul 1;25(7):727–34.

J

SALT | WATER

Alderman MH, Cohen HW. Am J Hypertens. 2012 Jul 1;25(7):727–34.

SALT

HF

Peter Loewen

7.3.1.3. SODIUM RESTRICTION: RECOMMENDATION

CLASS IIa

1. **Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms. *(Level of Evidence: C)***

2013 ACCF/AHA Guideline for the Management of Heart Failure. Journal of the American College of Cardiology. 2013 Oct 15;62(16):e147–239.

SALT | WATER

Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis

James J DiNicolantonio,[1] Pietro Di Pasquale,[2] Rod S Taylor,[3] Daniel G Hackam[4]

► Additional materials are published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2012-302337).

[1]Wegmans Pharmacy, Ithaca, New York, USA
[2]Chief Division of Cardiology, "Paolo Borsellino", G.F. Ingrassia Hospital, Palermo, Italy
[3]Peninsula Medical School, University of Exeter, Exeter, UK
[4]Division of Clinical Pharmacology, Department of Medicine, and Departments of Clinical Neurological Sciences and Epidemiology & Biostatistics, University of Western Ontario; Stroke Prevention and Atherosclerosis Research Centre (SPARC), Robarts Research Institute, and the Premature Atherosclerosis

ABSTRACT

Context A low sodium diet has been proposed to reduce the risk of heart failure (HF) hospitalisations and is currently advocated in consensus guidelines, yet some evidence suggests adverse neurohumoral activation for sodium restriction in the HF setting.

Objectives To evaluate the effects of a restricted sodium diet in patients with systolic HF.

Data sources A systematic review and meta-analysis of randomised trials OVID MEDLINE, PubMed, Excerpta Medica (Embase), the Cochrane Controlled Trials Register, Scopus, Web of Science and Google Scholar were searched up to April 2012.

Study selection Two independent reviewers selected studies for inclusion on the basis of a randomised controlled trial design that included adults with systolic HF receiving a restricted salt diet or control diet and reporting mortality (all-cause, sudden death or HF-related) and HF-related hospitalisations.

Data extraction and analysis Descriptive and

North American and European guidelines for the management of HF consistently advise dietary sodium restriction for patients with both systolic HF and HF with preserved ejection fraction.[6] US guidelines recommend an intake of 2–3 g/day with further restriction (below 2 g/day) to be considered in moderate to severe HF. These recommendations are based on level C evidence, that is, expert consensus opinion and results from observational studies. Therefore, a comprehensive systematic review of randomised trials was undertaken comparing sodium-restricted diets with non-restricted diets in patients with systolic HF.

METHODS

A systematic review of the available literature according to the PRISMA guidelines for the conduct of systematic reviews of intervention studies was performed.[7]

Dinicolantonio JJ, et al. Heart. 2013 Mar 12.

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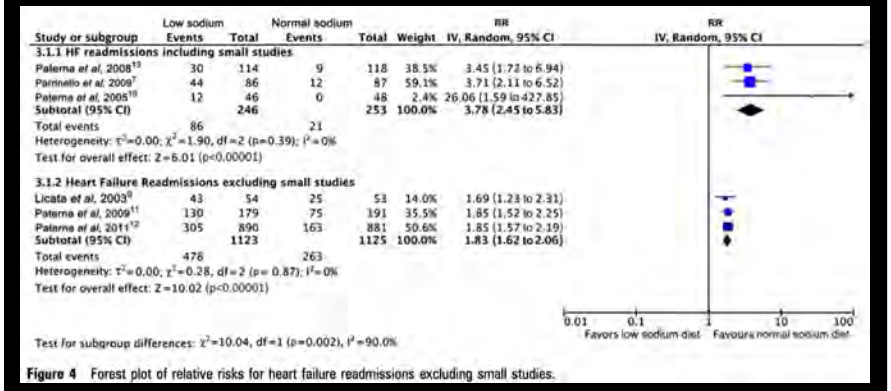

Figure 4 Forest plot of relative risks for heart failure readmissions excluding small studies.

Dinicolantonio JJ, et al. Heart. 2013 Mar 12.

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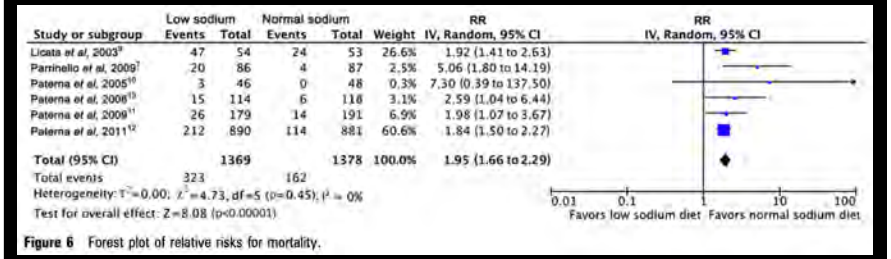

Figure 6 Forest plot of relative risks for mortality.

Dinicolantonio JJ, et al. Heart. 2013 Mar 12.

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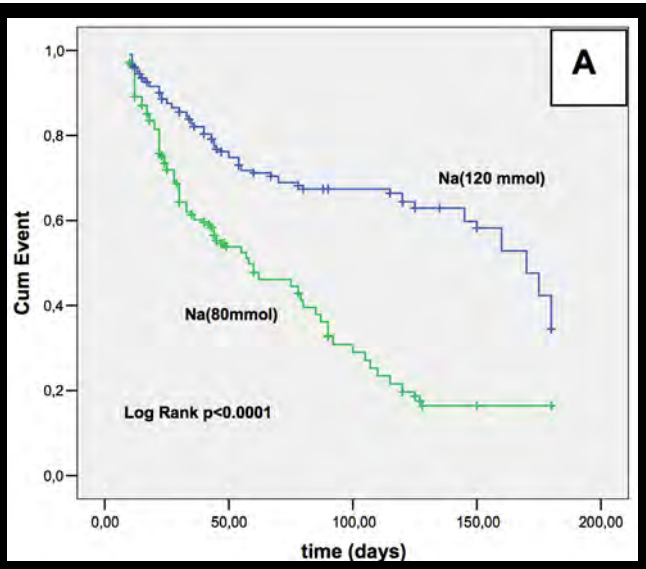


Paterna S, et al. The American Journal of Cardiology. 2009 Jan 1;103(1):93–102.

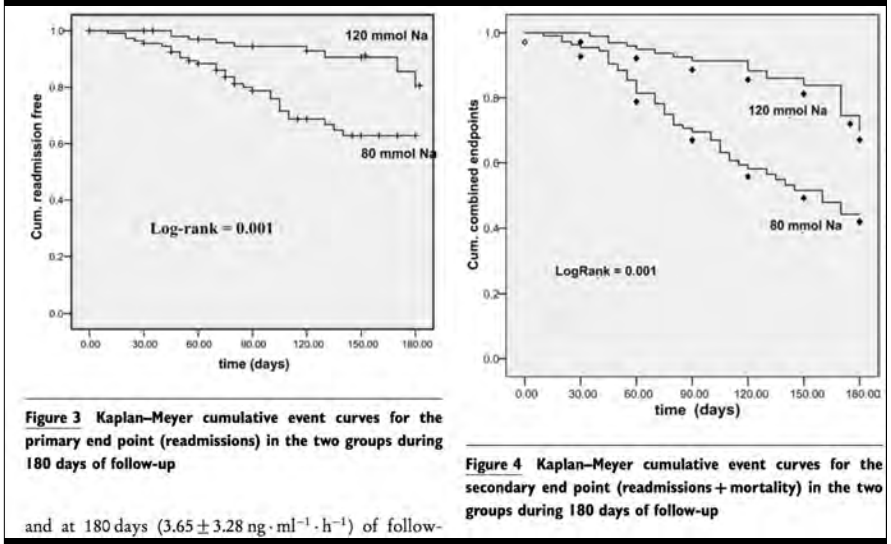


Figure 3 Kaplan–Meyer cumulative event curves for the primary end point (readmissions) in the two groups during 180 days of follow-up

Figure 4 Kaplan–Meyer cumulative event curves for the secondary end point (readmissions + mortality) in the two groups during 180 days of follow-up

and at 180 days (3.65 ± 3.28 ng · ml^{-1} · h^{-1}) of follow-

Paterna S, et al. Clinical science. 2008;114:221–30.

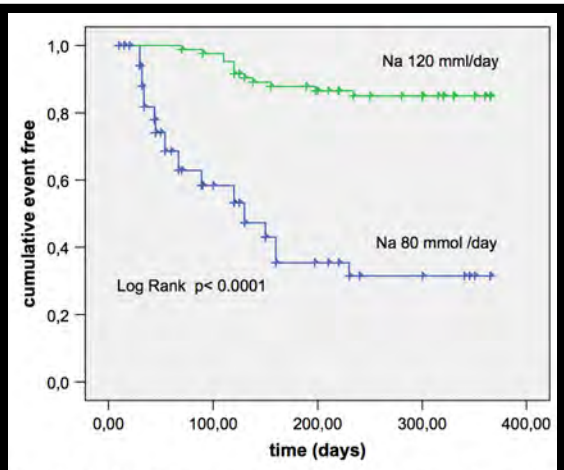


Fig. 1. Kaplan-Meier cumulative event curves for primary end point (hospital readmission) in the 2 groups during 1-year follow-up. Na 120 mmol (2.8 g)/day vs. Na 80 mmol (1.8 g)/day.

Parrinello G, et al. Journal of Cardiac Failure. 2009 Dec;15(10):864–73.

Contemporary Reviews in Cardiovascular Medicine

Dietary Sodium Intake in Heart Failure

Divya Gupta, MD; Vasiliki V. Georgiopoulou, MD; Andreas P. Kalogeropoulos, MD, PhD; Sandra B. Dunbar, RN, DSN; Carolyn M. Reilly, RN, PhD; Jeff M. Sands, MD; Gregg C. Fonarow, MD; Mariell Jessup; Mihai Gheorghiade, MD; Clyde Yancy, MD, MSc; Javed Butler, MD, MPH

Gupta D, et al. Circulation. 2012 Jul 24;126(4):479–85.

Peter Loewen

"there are no conclusive data suggesting that the sodium intake recommended for the general population is unsafe for HF patients in the current era of medical therapy."

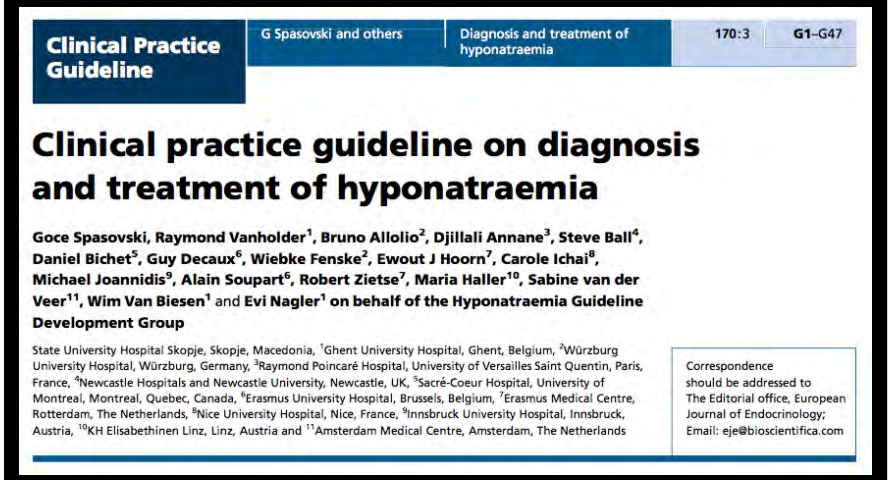
"Currently, there are insufficient data to endorse any specific level of sodium intake with certainty, and differences among the various HF subpopulations are not known. Effects of sodium restriction in nonwhite HF patients and those with preserved ejection fraction are virtually unknown."

SALT | WATER

Gupta D, et al. Circulation. 2012 Jul 24;126(4):479–85.

SALT

[↓Na+]



Clinical Practice Guideline

G Spasovski and others | Diagnosis and treatment of hyponatraemia | 170:3 | G1–G47

Clinical practice guideline on diagnosis and treatment of hyponatraemia

Goce Spasovski, Raymond Vanholder[1], Bruno Allolio[2], Djillali Annane[3], Steve Ball[4], Daniel Bichet[5], Guy Decaux[6], Wiebke Fenske[2], Ewout J Hoorn[7], Carole Ichai[8], Michael Joannidis[9], Alain Soupart[6], Robert Zietse[7], Maria Haller[10], Sabine van der Veer[11], Wim Van Biesen[1] and Evi Nagler[1] on behalf of the Hyponatraemia Guideline Development Group

State University Hospital Skopje, Skopje, Macedonia, [1]Ghent University Hospital, Ghent, Belgium, [2]Würzburg University Hospital, Würzburg, Germany, [3]Raymond Poincaré Hospital, University of Versailles Saint Quentin, Paris, France, [4]Newcastle Hospitals and Newcastle University, Newcastle, UK, [5]Sacré-Coeur Hospital, University of Montreal, Montreal, Quebec, Canada, [6]Erasmus University Hospital, Brussels, Belgium, [7]Erasmus Medical Centre, Rotterdam, The Netherlands, [8]Nice University Hospital, Nice, France, [9]Innsbruck University Hospital, Innsbruck, Austria, [10]KH Elisabethinen Linz, Linz, Austria and [11]Amsterdam Medical Centre, Amsterdam, The Netherlands

Correspondence should be addressed to The Editorial office, European Journal of Endocrinology; Email: eje@bioscientifica.com

SALT & WATER

Spasovski G, Eur J Endocrinol. 2014 Feb 4;170(3):G1–G47.

Tina Korownyk

Pediatric Myths & Other Bedtime Stories

Tina Korownyk

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** Tina Korownyk
- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** Honorarium for giving this talk
  - **Consulting Fees:** None
  - **Other:** None

Learning Objectives

- Review evidence on recent "hot topics" in pediatrics

Probiotics To Prevent Infant Crying

- "This study is ground breaking as it shows that (this) product should be given to all babies from birth.. Not only does it reduce suffering in babies and parents, but it also saves the families and societies costs."
- Company President

Probiotics to Prevent Infant Crying

- RCT 554 healthy infants (~50% breastfed),
- Lactobacillus reuteri DSM 17938 vs placebo qd [1]
- At 3 mos, (468 infants analyzed – no ITT) significant ↓ in mean daily
  - Crying duration (38 vs 71 mins, p<0.01)
  - Regurgitations (2.9 vs 4.6, p<0.01)
  - Evacuations per day (4.2 vs 3.6; p<0 .01)
  - Reported ultimate savings to society ~$260 USD / pt
- 1 Sys revs included crying prevention studies (2013)[2]
  - 7 RCTs: 2 benefit, 5 no benefit (1440 infants, heterogeneous interventions).
  - Benefit: 1) 20 premature babies on formula supplemented with probiotics[3]
  - 2) Secondary outcome, 94 babies, formula supplemented[4]
- Bottom Line: Overrated
  (next chapter in "Selling Sickness"?)

1) JAMA Pediatr 2014;168(3):228-233. 2) *JAMA Pediatr.* 2013;167(12):1150-1157. 3) J Pediatr. 2008 Jun;152(6):801-6, 4) Br J Nutr. 2012 Jun;107(11):1616-22.

Probiotics for Colic

2 Systematic Reviews 2013[1]

1) 3 RCTs, 220, 1° breastfed infants, probiotics ↓ crying by ~1hr /d
  - 2/3 industry sponsored,(BioGaia AB) L reuteri DSM 17938 5 drops/d
  - the 3rd non blinded, no AC or ITT

2) 12 RCTs, 5 for colic, 3/5 positive (as above), 2/5 negative [2]
  - Of the 2 negative, one positive for ↓ irritability but not crying (53 infants), the other included only 9 infants

2 RCTs of Interest: Infants <5mo, Probiotic or Placebo, Primarily breastfed

1) 80 infants, 1° outcome - >50% reduction in crying[3]
  - 7 days, NNT = 7, 14 days NNT = 2

2) 50 infants, 1° outcome – crying time, trend to benefit at all times, sign at 21 days. [4]
  - 2° outcome - >50% ↓ crying. sign at all timelines, At 7 days, NNT = 3.

Bottom Line: Interesting.

Awaiting further information. 6 trials registered investigating BioGaia product.[6]

*Placebo response rates for colic from 5-83%[5]

1) BMC Pediatr 2013;13:186. 2) *JAMA Pediatr.* 2013;167(12):1150-1157.3) J Pediatr 2013;162:257-62. 4) Pediatrics. 2010 Sep;126(3):e526-33 5) Curr Opin Pediatr 2010;22:791-7. 6) Clinical trials.gov

Tina Korownyk

A Mother's Love

- RCT 69 children aged 7-12 years, venipuncture, randomized to three groups:[1]
  A) No distraction
  B) the soothing love and and caress of your mother
  C) cartoon on TV
- Pain scores rated on validated scale from 0-100
  - Mother's love no different than control (ie nothing)
  - TV group had significant reduction in pain scores
    - 8 vs 23 on 100 point scale, p=0.037
    - (Minimum clinically sign difference ~ 10)[2]
- Bottom Line: Definitely Overrated

1) Arch Dis Child 2006;91:1015–1017 2) Ann Emerg Med. 2001 Jan;37(1):28-31.

Surgery to Improve Sleep

- RCT, Multicentre, US, 464 kids, 5-9 yrs with Obstructive sleep apnea, randomized to early adenotonsillectomy vs watchful waiting.
- At 7 months,
  - Non-significant improvement in 1° outcome: attention & executive fn score
  - Consistent, significant improvement in:
  - Behavioural rating scores (connors' & BRIEF)
  - Sleep & QOL scores
  - Surgery group more likely to have normalization of OSA (79% vs 46%, p<0.001) NNT = 4
- Bottom Line: Underrated.

1) N Engl J Med 2013;368:2366-76 http://download.journals.elsevierhealth.com/pdfs/journals/0022-3476/PIIS0022347613010846.pdf
2) Cochrane Database Syst Rev. 2009 Apr 15;(2):CD003136. 3) Pediatrics 2002;109;e69.

Vitamin D for All

(particularly older children)

- Institute of Medicine recommends 400IU/day for all children[4]
- Canadian Pediatric Society
- "Vitamin D deficiency linked to: osteoporosis; asthma; rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases; diabetes; disturbed muscle function; resistance to tuberculosis; and the pathogenesis of specific types of cancer."
- Vitamin D Levels (25 OHD): 2-12yr olds in Edmonton: 34% < 40 nmol/L, 90% <75 nmol/L[1]
  - 2-3 yr olds in Toronto: 32% < 50 nmol/L, 82% <75nmol/L[2]
  - (similar numbers in Qatar, Middle East and North Africa)
- Rickets in Canada: 2.9 / 100 000 children.[3]
  - 9/100 000 if <1 year,
  - 0.3/100 000 if 2-7 years of age

1) Can J Public Health 2005;96:443-9 2) Paediatr Child Health. 2011 Feb;16(2):e11-5. 3) CMAJ. 2007 Jul 17;177(2):161-6. 4) IOM 2010 report on Ca and Vitamin D www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx 5)

Vitamin D deficiency and wheeze?

- ***Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age.** Am J Clin Nutr. 2007 Mar;85(3):788-95.
- **Maternal antioxidant intake in pregnancy and wheezing illnesses in children at 2 y of age.** Am J Clin Nutr. 2006 Oct;84(4):903-11.
- **Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children.** Am J Respir Crit Care Med. 2006 Sep 1;174(5):499-507.
- **Early childhood wheezing symptoms in relation to plasma selenium in pregnant mothers and neonates**. Clin Exp Allergy. 2007 Jul;37(7):1000-8.
- **Fish intake during pregnancy and the risk of child asthma and allergic rhinitis - longitudinal evidence from the Danish National Birth Cohort.** Br J Nutr. 2013 Oct;110(7):1313-25.
- **Consumption of artificially-sweetened soft drinks in pregnancy and risk of child asthma and allergic rhinitis.** PLoS One. 2013;8(2):e57261. 2013 Feb 27.

Vitamin D for All

- Systematic Review, 6 RCTs, (343 participants), no benefit vit D supplementation on bone density in healthy children[1]
- RCT 3046 infants (1-11mo) Kabul, 100 000IU D3 vs placebo q3mo.
  - No difference pneumonia RR 1.06 (0.89-1.27)[2] or diarrhea HR 1.05 (0.98,1.17)[3]
- Do IT Trial – 1st RCT to assess supplementation Vit D 400IU or 2000IU/day in 1-5yrs to assess for ↓ URTI/Asthma – ongoing.[4]
- Bottom Line: Overrated. No consistent RCT data demonstrating that supplementation improves outcomes in children.

1) Cochrane Database Syst Rev. 2010 Oct 6;(10):CD006944. ***2)*** Lancet. 2012 Apr 14;379(9824):1419-27. 3)Pediatrics 2013 Oct;132(4):e832-40. 4) BMC Pediatr. 2014 Feb 8;14(1):37. 5) *Arch Dis Child 2012;**97:952-954 6)*** CMAJ. 2007 Jul 17;177(2):161-6.

Vitamin D for All

- Cohort Data: Rickets
  - UK, ↓ from 120 to 49/100 000 cases over 4 yrs, following program implementation, despite only 17% ↑ supplement uptake, high risk population[5]
  - Canada 2004/05 – Of 105 cases, none in breastfed babies supplemented with Vit D.
  - Of those with rickets: Incidence highest in NWT and Nunavet (15x higher for older children),
    - 89% had darker skin
    - 94% breastfed
    - 76% of mothers reported drinking NO milk pre or postnatally[6]

Tina Korownyk

Money

- RCT, 285 children, Singapore, 6-12 yrs[1]
- Intervention: Pedometer x 9 mo with an 8000step/d goal, reward (~$25CDN) for achieving goal at least ½ the days/mo, every mo. Additional lotteries for ~$100CDN
- Control: Usual activities, sealed pedometer for last wk
- Results:
- Intervention group ~1000 more steps/day
  - (8660 vs 7767, p=0.01)
- More in intervention reached goal of 8000 steps/d
  - (24.4% vs 1.9%) NNT = 5
- Non-sign trend to improvement in QOL scores, BMI & 6 min walk test

- Time spent in moderately vigorous PA inversely associated with cardiac risk factors
- Observational data suggests that to prevent onset of risk factors, adolescents need ~90min/d moderate vigorous PA[2,3]

- Bottom Line: Underrated

1) J Pediatr. 2013 Jul;163(1):167-72. 2) BMC Pediatr. 2014 Feb 14;14(1):42. 3)Lancet 2006;368:299–304

Flax

- 4 wk blinded RCT, 32 children, 8-18 yrs, elevated LDL (3.5 - 5.0mmol/L) and family history of hyperlipidemia[1]
  - 2 muffins and 1 slice bread/d with flaxseed (30g/d)
  - 2 muffins and 1 slice bread/d with whole-wheat flour
- Flaxseed group: ↓ HDL (0.19mmol/L), p=0.001
  - ↑ TGs (0.33 mmol/L), p=0.02
  - No change in total Cholesterol or LDL
- Non-significant Increase in BMI and cal/day noted in both groups
- No patient oriented outcomes

- Bottom Line: Overrated

1) JAMA Pediatr. 2013;167(8):708-713.

B blockers for Infant Hemangiomas

- 2008 – 2 cases of severe infant hemangioma started on propranolol for cardiac concerns, dramatic improvement noted in hemangioma. 11 cases reported in total.[1]

- RCT 40 children 9 wks to 5 yrs facial or disfiguring hemangiomas. Propranolol 2mg/kg/d vs placebo. Significant improvement in volume, color and elevation with propranolol[2]
- Retrospective study propranolol 2mg/kg/day (divided bid), 635 infants (16 days to 3 yrs) with IH.[3]
  - Efficacy (>26% regression) seen in 91%
  - 26% resolved completely
  - 2% had side effects (3 diarrhea, 4 hyperkalemia, 2 bradycardia)
- Cardiac workup and monitoring in all cases, side effects still being investigated, multinational trial ongoing.

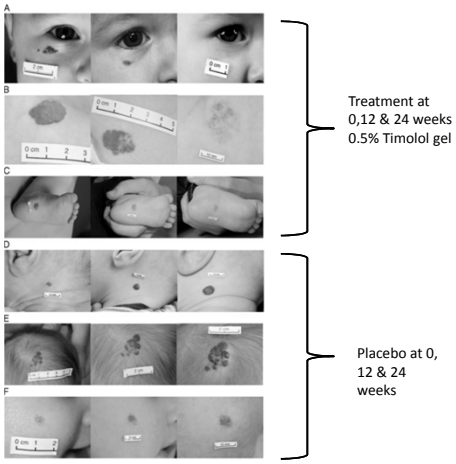
1) N Engl J Med. 2008 Jun 12;358(24):2649-51. 2) Pediatrics 2011;128:e259-e66. 3) Pediatr Dermatol. 2014 Mar 6. doi: 10.1111/pde.12308. 4) Arch Dermatol 2010; 146: 564-565 5) Pediatric Dermatology Vol. 30 No. 2 245–249, 2013 5). 6) Arch Ophthalmol 2010; 128: 255-256. 7) Arch Ophthalmol 2011; 129: 377-379. 8) Pediatrics. 2013 Jun;131(6):e1739-47

B blockers for Infant Hemangiomas

- First case report of Topical Timolol 2010[4]
- Case report 11 infants with less severe IH, topical Timolol 0.5% gel[5]
  - 7 virtual complete resolution, sign improvement in other 4
  - No s/es reported, systemic absorption unknown
  - A number of other case reports with similar outcomes[6,7]

- 2013 Blinded, RCT, topical 0.5% timolol gel vs placebo, 24 weeks, 41 infants, mean age 9 weeks
  - Significant improvement in size/volume change noted at 12 weeks, ITT analysis
  - Treatment group significantly more likely to be rated 0 for redness at 24 weeks (47% vs 6%, NNT = 3)
- No reported A/Es

- Bottom Line: Interesting.



Thanks for your questions and discussion.

Thanks for completing your course evaluations.

HAVE A SAFE TRIP HOME

We hope to see you next year!