23rd ANNUAL DRUG THERAPY DECISION MAKING COURSE

Encouraging Healthy Skepticism

April 20th and 21st, 2012

Fairmont Waterfront Hotel
Vancouver, B.C.

Saturday Syllabus

SKEPTICEMIA

When skepticism gets into your blood

There is no cure

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

“A truth's initial commotion is directly proportional to how deeply the lie was believed. It wasn't the world being round that agitated people, but that the world wasn't flat. When a well-packaged web of lies has been sold gradually to the masses over generations, the truth will seem utterly preposterous, and its speaker a raving lunatic."

- Dresden James

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
Mike Kolber, Assoc. Prof., Family Medicine, University of Alberta
Tina Korownyk, Asst. Prof., Family Medicine, University of Alberta
Stephen Setter, Assoc. Prof., Pharmacy, Washington State University, Spokane WA

Local Faculty

Roxane Carr, Clinical Pharmacy Specialist, CWHC
Peter Chan, Clin. Prof., Medicine, Psychiatry, UBC
Tom Elliott, Clin. Assoc. Prof., Medicine, Endocrinology, VGH
Rob Enns, Clin. Prof., Medicine, Gastroenterology, UBC & PHC
Jonathan Fleming, Assoc. Prof., Medicine, Psychiatry, UBC
Shahin Jamal, Clin. Asst Prof., Medicine, Rheumatology, UBC & VA
Jason Kong, Clin. Asst. Prof., Medicine, Endocrinology, UBC & VA
Peter Loewen, Assoc. Prof., Pharmaceutical Sciences, UBC & VCH
Andrew Merkur, Clin. Asst. Prof., Dept. of Ophthalmology and Visual Sciences, UBC & VA
Val Montessori, Clin. Assoc. Prof., Medicine, Infectious Diseases, UBC & PHC
Natasha Press, Clin. Assoc. Prof., Medicine, Infectious Diseases, UBC & PHC
Kam Shojania, Clin. Prof., Medicine, Head, Division of Rheumatology, UBC & PHC
Johanna Trimble, BC Patient Voices Network, Patient Safety Advisory Council, VCH
Adil Virani, Assoc. Prof, Pharmaceutical Sciences, UBC, & Director, LMPS

CWHC - Children's and Women's Health Centre
FHA – Fraser Health Authority
PHC – Providence Health Care
UBC – University of British Columbia
VA - Vancouver Acute
VCH - Vancouver Coastal Health
LMPS - Lower Mainland Pharmacy Services, FHA, PHSA, PHC, VCH

23rd Annual
Drug Therapy Decision Making Course
Saturday, April 21, 2012

07:30 Registration coffee and muffins

Chair - Bob Rangno and James McCormack

"1 head, 2 eyes, with multiple issues"

08:30	How to critically appraise an RCT in 10 min	James McCormack
08:50	Macular degeneration – "I'd rather have needles in my eyes"	Andrew Merkur
09:10	Menopause therapeutics – when 1 hot flash is 2 many	Tina Korownyk
09:30	Questions	
09:50	Refreshment Break	

"It's not about treating numbers"

10:10	Diabetes is a condition, not a disease or number	Tom Elliott
10:30	BP - Accurate diagnosis, targets and choices	Bob Rangno
10:50	Questions	
11:20	Hypothyroid and TSH – what to do with asymptomatic numbers	Jason Kong
11:40	Questions	
11:50	Lunch	

"To infinity and beyond"

12:40	Insomnia—Count the sheep's legs and divide by 4	Jonathan Fleming
13:00	What antibiotics can family docs count on and for how long?	Tina Korownyk and James McCormack
13:30	Questions	
13:50	Stump the EBM Panel and be a Therapeutics Millionaire	The Gang plus the Audience
15:00	The End	

Therapeutics Philosophy

Get Your Doctor to Treat You Right

Train your doctor to be your doctor, not your salesperson.

Published blog on January 7, 2012 by Alice Dreger in Fetishes I Don't Get

1. **"Thou shalt treat according to the level of risk rather than level of risk factor."**
   In medicine, a risk factor is a trait that increases the likelihood of having something really bad happen to you. For example, having a high level of triglycerides is a risk factor for having a heart attack. (That means that having high triglycerides increases the likelihood you will suffer a heart attack.) But you want your doctor to try to prevent what's really bad - the heart attack - not just treat your triglyceride level. Why? Because lowering your triglyceride level with some prescription drug won't actually decrease your risk of a heart attack. Doctors need to treat what really matters to you, the patient, not what is merely measurable *in* you.
2. **"Thou shalt exercise caution when adding drugs to existing polypharmacy."**
   It's generally a bad idea to give a patient another drug when a patient is already on a drug. Doing so increases the risk of bad interactions between the drugs. It also increases patient confusion, thereby again increasing risk. So adding one drug doesn't just introduce the risks named on the pamphlet you get with that drug, because the body is a complex machine, drug interactions are poorly understood, and humans on lots of drugs make mistakes in the use of those drugs.
3. **"Thou shalt consider benefits of drugs as proven only by hard endpoint studies."**
   This is similar to the first commandment because it reminds the physician that what you really care about are "hard endpoints" - things like heart attacks and strokes, not things like levels of cholesterol and triglycerides. A particular drug might make your labs look really great, but it's not a good drug if it doesn't actually improve your health in the ways that matter (for example, reduction of risk of a major disease, or reduction of risk of death.) A drug might increase your bone density, but if it doesn't reduce your risk of fracture, who cares that your bones are denser?

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

   Again, "surrogate endpoints" are things like blood pressure readings, as opposed to "hard endpoints" like heart attacks and strokes. It doesn't actually matter what your blood pressure is if your blood pressure doesn't hurt you. We use blood pressure readings as a surrogate for what we really care about. It's worth measuring, but we should not treat high blood pressure with a drug unless that particular drug is shown to achieve what we really care about: reduction of risk of heart attacks and strokes.

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

   Sometimes consensus groups come up with "treatment targets" that tell physicians what patients' lab numbers should look like. But physicians need to take individual patients' bodies, lives, and needs into account. An example: a consensus committee might issue a treatment target for glucose (blood sugar) control. They might say everyone should have low blood sugar. But imagine a patient who is an 80-year-old woman who has been falling a lot. Lowering that woman's blood sugar could increase her risk of a big bone fracture from a fall. So she should not be treated glibly according to a Treatment Target that might be perfectly reasonable for an otherwise healthy 30-year-old woman. Physicians and patients should especially beware any consensus issued by a committee of people who have had financial ties to drug and device makers.

6. **"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 they daily clientele."**

   This is a complicated way of again reminding physicians what should matter: actual reduction of risk of the things their own real patients really care about and are really likely to suffer from. Relative Risk Reduction is another way drug companies often fool physicians and patients into thinking a drug is better than it really is.

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

   The phrase "numbers needed to treat" refers to how many patients a doctor needs to treat with a particular intervention in order to have one patient's outcome improve. This concept acknowledges that not every intervention benefits every patient. In fact, there's a "number needed to harm" for each drug, too, but you don't often hear about either stat from your doctor. Yet for many medical interventions, you have to treat a relatively large number of people to benefit just one, but you're introducing ALL of them to the risks of that intervention. You might think from pharmaceutical ads that a drug for heartburn will lower your risk of esophageal cancer. But the truth is that probably dozens if not hundreds of people will have to take the drug before just ONE of those people has cancer prevented by the drug, while ALL of you on the drug will bear all of the risks of the drug. Note that this commandment also refers to treatment cost, an idea that is supposed to offend us Americans. But the truth is we are already rationing healthcare in this country, and it would be better if we thought rationally about how much money it makes sense to prevent, say, one death from cancer. If we keep ignoring that calculation, we'll kill a lot more people than we save.

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

   These days, detailmen are actually often women - perky, young, blond women chosen because they still carry their cheerleader looks from high school. They are the representatives from drug and device makers who come to seduce your doctor into using their products on your body, so that profit can ensue. Drug and device makers also like to whisk your doctor off to "educational symposiums" where they are wined, dined, and sold the idea of using more of the companies' products. Profit is the only endpoint these companies really care about, so they will take all the risks they need to in order to achieve that endpoint, including treating your life as an acceptable risk. If you are at your doctor's office and you see detailmen or their paraphernalia (pens, mugs, posters, videos, etc. produced by these companies), you can assume your body is being used as an endpoint

by a corporation that doesn't care what really happens to you. So ask yourself: how much does your doctor really care about you?

9. **"Thou shalt share decisions on treatment options with the patient in the light of estimates of the individual's likely risks and benefits."**
   Your doctor needs to talk to you about what YOU are trying to achieve with your medical care. Then she or he needs to discuss with you the reasons and evidence for the options being offered to you. She or he really should be educating you about all the things we've covered so far: risk factor versus risk, surrogate endpoints, unknown drug interactions, etc. You can start this conversation by telling your doctor about what exactly you're trying to achieve in a given office visit. For example, you might say in a yearly exam, "I would rather live a healthy life than a longer life, so I'm only interested in tests, procedures, and interventions that are likely to give me good health, not those that will necessarily keep me alive longer but make me feel unhealthy during those years." Or at a sick visit, you might say, "I didn't come for a prescription. I came to try to figure out why I feel sick, and what I can expect in terms of healing. I only want a prescription if I really need one to get better. I would rather suffer the symptoms of this thing than take the risk of a drug that's just going to treat the symptoms and increase my risk of ‘side effects.'
10. **"Honour the elderly patient, for although this is where the greatest levels of risk reside, so do the greatest hazards of many treatments."**
    This one is self explanatory, but too often ignored.

Don't be a consumer. Be a patient patient, and teach your doctor to be a patient doctor who thinks about what you really need from her or him. Do that, and you'll give your doctor a better life, too.

Alice Dreger *is a Professor of Clinical Medical Humanities and Bioethics at Northwestern University's Feinberg School of Medicine in Chicago*

Let's recap

- Look at the Abstract
- Read the title
- Look at what was studied
- Look at the outcomes
- Read the conclusions

Let's recap

- Random
- Blind
- Allocation
- Intent
- Follow
- Conflicts

Let's recap

- Differences between groups
- Baseline characteristics

Let's recap

- Primary outcomes
- Other outcomes
- Differences
  - Absolute numbers
  - Relative numbers
  - Confidence intervals

Let's recap

- Adverse outcomes
- Any other outcomes
- Differences
  - Absolute numbers
  - Relative numbers
  - Confidence intervals

Randomised
Non-blinded
Allocation concealment?
Intention-to-treat
Follow-up

N=10,251 - 3.5 years

Age 62, Female 38%, Diabetes 10 years, Previous CV event 35%, White 65%, Smoker14%, BMI 32, BP136/75, A1C 8.3, Total Chol 183

	Intensive therapy	Standard therapy	Hazard Ratio	Hazard Ratio 95% CI
Primary outcome (%)	6.9	7.2	0.90	0.78-1.04
Death (%)	5.0	4.0	1.22	1.01-1.46
Non-fatal MI (%)	3.6	4.6	0.76	0.62-0.92
Non-fatal stroke (%)	1.3	1.2	1.06	0.75-1.50
CHF (%)	3.0	2.4	1.18	0.93-1.49
Hypoglycemia (%)	10.5	3.5		
Serious adverse event	2.2	1.6		
Weight gain >10kg	27. 8	14.1		

Andrew Merkur

Macular Degeneration – I'd Rather Have Needles in my Eyes

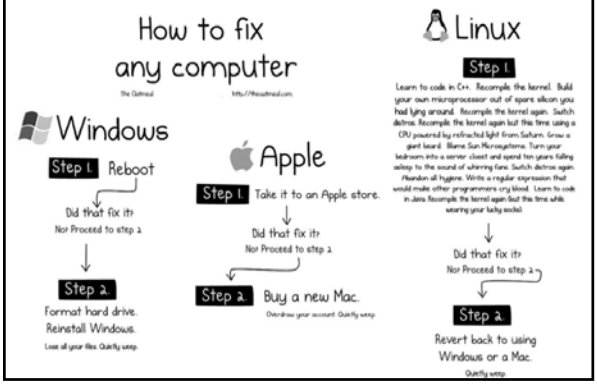
23rd Annual Drug Therapy Decision Making Course

Andrew Merkur, MD, FRCSC
Assistant Professor University of British Columbia
Department of Ophthalmology and Visual Sciences
Vitreoretinal Division

West Coast Retina Consultants

UBC

IT for guys like me…….



Epidemiology

NIH Data on AMD in USA

Age,	Cataract		Advanced AMD		Intermediate AMD		Glaucoma	
Years	Persons	(%)	Persons	(%)	Persons	(%)	Persons	(%)
40-49	1,046,000	2.5%	20,000	0.1%	851,000	2.0%	290,000	0.7%
50-59	2,123,000	6.8%	113,000	0.4%	1,053,000	3.4%	318,000	1.0%
60-69	4,061,000	20.0%	147,000	0.7%	1,294,000	6.4%	369,000	1.8%
70-79	6,973,000	42.8%	388,000	2.4%	1,949,000	12.0%	530,000	3.9%
≥80	6,272,000	68.3%	1,081,000	11.8%	2,164,000	23.6%	711,000	7.7%
Total	20,475,000	17.2%	1,749,000	1.5%	7,311,000	6.1%	2,218,000	1.9%

Economic Burden of Disease

TABLE 7. YEARLY ECONOMIC LOSS TO THE GROSS DOMESTIC PRODUCT (GDP) IN THE UNITED STATES FROM THE SEQUELAE OF AGE-RELATED MACULAR DEGENERATION (ARMD)

CATEGORY	PATIENT ≥65 YEARS OLD	PATIENTS <65 YEARS OLD
A. WET (NEOVASCULAR) ARMD		
Per capita salary loss for those employed	$11,856	$11,856
People employed	104,400	41,922
Total salary reduction loss	$1.237 billion	$497 million
Jobs lost from neovascular ARMD	52,200	65,212
Average job salary	$31,182	$31,182
Total salary loss	$1.628 billion	$2.033 billion
Subtotal all losses	$2.866 billion	$2.530 billion
Total GDP loss from wet ARMD = $5.396 billion		
B. DRY ARMD		
Per capita salary loss for those employed	$9,378	$9,378
Employed with mild visual loss	240,900	548,824
Total salary reduction loss	$2.259 billion	$5.147 billion
Jobs lost from dry ARMD and mild visual loss	120,450	424,375
Average job salary	$31,182	$31,182
Total salary loss	$3.756 billion	$13.233 billion
Subtotal all losses	$6.015 billion	$18.380 billion
Total GDP loss from dry ARMD = $24.395 billion		
TOTAL GDP LOSS FROM WET + DRY ARMD = $29.791 BILLION		

Data from references 1, 6, and 39 through 42.

Morbidity of Disease

TABLE 4. TIME TRADEOFF UTILITY VALUES ASSOCIATED WITH VISUAL ACUITY LEVELS IN THE BETTER-SEEING EYE

VISUAL ACUITY	UTILITY VALUE
20/20 in each eye permanently	1.00
20/20 (20/20 to 20/25 in the other eye)	0.97
20/20 (≤20/40 in the other eye)	0.92
20/25	0.87
20/30	0.84
20/40	0.80
20/50	0.77
20/70	0.74
20/100	0.67
20/200	0.66
20/300	0.63
20/400	0.54
Counting fingers (20/800)	0.52
Hand motions	0.35
Light perception	0.35
No light perception	0.26
Death	0.00

Adapted from Brown MM, et al.[4]

Age-related macular degeneration

GROUP 3	
Dialysis, home	0.56[33]
ARMD, severe*	**0.47***
GROUP 4	
ARMD, very severe*	**0.39***
Prostate cancer, advanced (uncontrolled pain; bladder, bowel and sexual function abnormal; depression, severe fatigue)	0.35[31]
Stroke, severe (bedridden, incontinent, and requiring constant care, at 6 months)	0.34[27]
Total blindness (NLP OU)	0.26[35]
Stroke, severe, with aphasia	0.26[36]
Stroke, severe, total paralysis (at 10 years)	0.20[37]

Etiology

Age-related macular degeneration

Non-Modifiable Risk Factors:

- Genetic:
  - accounts for ~80% disease
- Age:
  - see upcoming slides
- Gender:
  - OR: 1.43

Modifiable Risk Factors:

- Smoking:
  - OR: 3.5 (never vs current)
- BMI:
  - OR: 1.93 (obese vs non-obese)

Andrew Merkur

What really is AMD? Genetic!!!!!

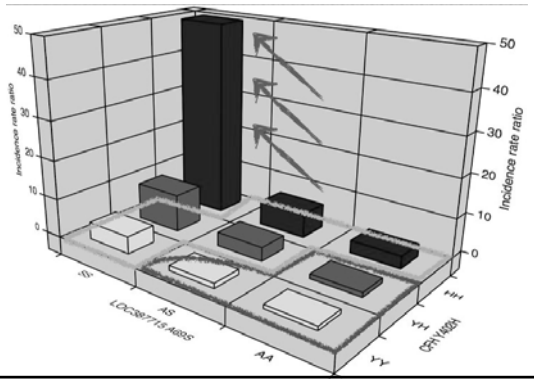
- Many in this room are heterozygous or homozygous for the disease GENES!!!
- We are born with this ***active*** polygenetic disease
- We may have a family history or not
- If HTZ / HMZ then we are diseased from birth
- It is the best characterized and understood polygenetic disease in humans

Basic Genetics of AMD

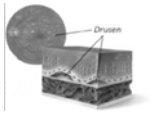
Table 1—Odds ratios of individual risk factors for geographic atrophy/choroidal neovascularization in age-related macular degeneration

Risk factor	Prevalence
CFH factor[18] (H2 and H4 combinations alone)	0.302
4.33 (one of H1/H3/H5–8 and one of H2/H4)	0.495
17.97 (H1, H3, and H5–8 combinations alone)	0.203
ARMS2 factor (rs10490924)[21] #1130	
1 for GG	0.593
2.7 for TG	0.390
8.2 for TT	0.017
C3 factor (rs2230199)[19] #3864	
1 for CC	0.712
1.7 for GC	0.237
2.6 for GG	0.051
mt factor (mtA4917G)[34] #527	
1 for A	0.910
2.16 for G	0.090
Smoking factor[35] #4016, #4094	
1 for never	0.440
1.46 ex-smoker	0.370
3.14 current smoker	0.190

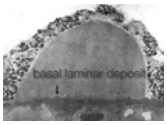
Pathophysiology / Pathobiology of the A69S and CFH

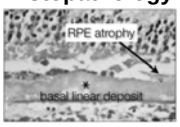


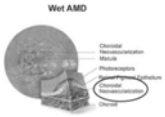
Clinical Phenotype



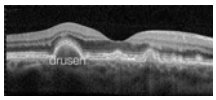
Histopathology

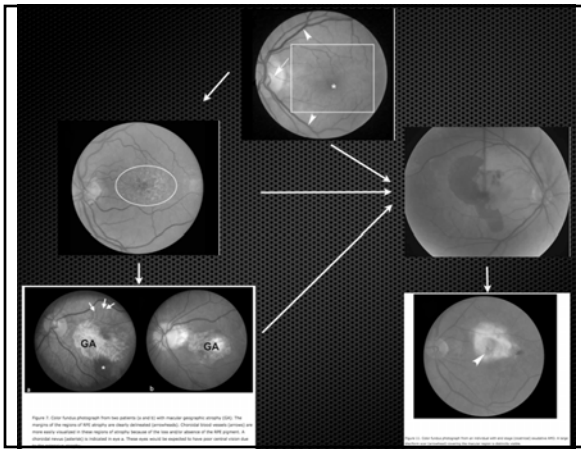






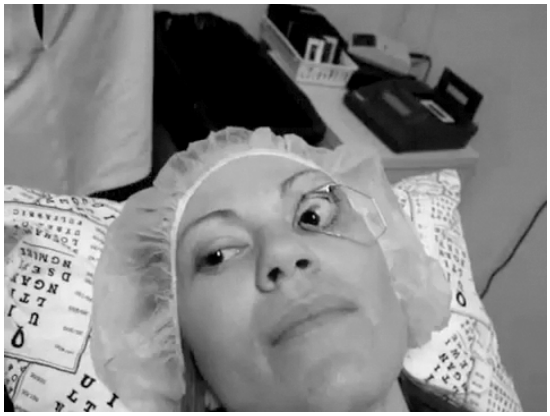
Next Generation Imaging



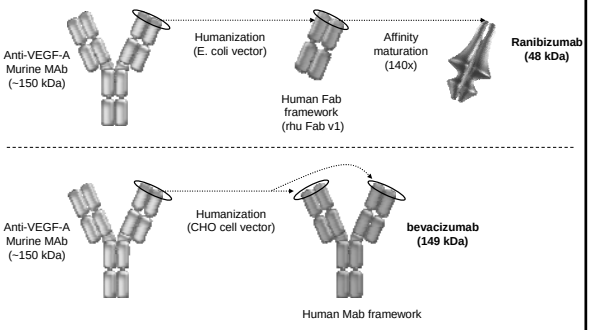


Intravitreal Injections

Andrew Merkur



Ranibizumab and Bevacizumab: Developed on Parallel Timelines for Different Indications



Ranibizumab and Bevacizumab: Different Drugs

	LUCENTIS RANIBIZUMAB		AVASTIN bevacizumab
Compound	Fully humanized monoclonal antibody fragment	VS	Humanized anti-VEGF monoclonal, full-length antibody
Indication	Indicated for wet-AMD	VS	Indicated for colorectal cancer
PK / PD	Smaller antibody fragment (Fab, 48kDa) Shorter systemic half-life ~2 hrs	VS	Full size IgG Avastin (149kDa) Longer systemic half-life ~20 days
Handling / Back-ground	Developed specifically for wAMD and ophthalmology Single use vial Manufactured to specifications for intravitreal use	VS	No dose finding and no clinical development program for ophthalmic use Vials split into many doses Manufactured to specifications for intraveneous use
Clinical database	Extensively studied in randomized trials with more than 7,500 patients Fully characterized safety profile Risk Management Plan in place	VS	No level 1 clinical efficacy and safety evidence for ophthalmic use No clinically relevant safety data Off-label use

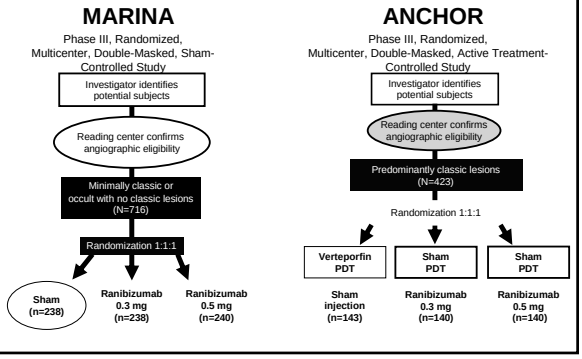
Levels of Evidence Ranibizumab Trials

LEVEL 1	Strong evidence: Well-designed, controlled RCTs	ANCHOR & MARINA, PIER, SAILOR Cohort 1, EXCITE n = 4054
LEVEL 2	Substantial evidence: Clinical trials with certain flaws e.g. absence of control group or short follow-up period	SUSTAIN* n = 531
LEVEL 3	Relatively weak evidence: Non-comparative studies without controls, descriptive studies, panel consensus or expert opinion	PrONTO (Small, open label) n = 40

*SUSTAIN level 2 because only interim analysis available when guidelines were created

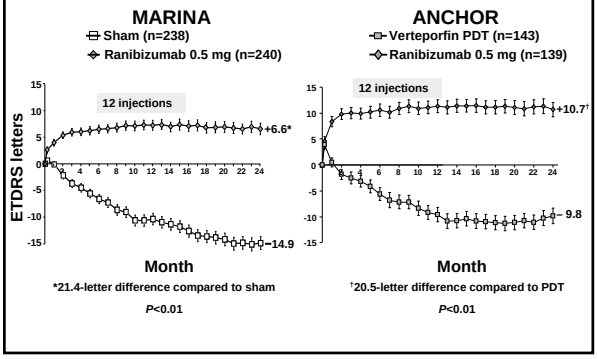
LEVEL 1

MARINA and ANCHOR Trial Design



LEVEL 1

Ranibizumab Phase III Trial Results At Month 24



*21.4-letter difference compared to sham
P<0.01

†20.5-letter difference compared to PDT
P<0.01

Andrew Merkur

LEVEL 1

25

PIER
Study design

Phase IIIb, multicenter, double-masked, sham-controlled, 2-year study investigating quarterly Ranibizumab

Investigator determines eligibility

Subfoveal CNV (all lesion types) secondary to AMD

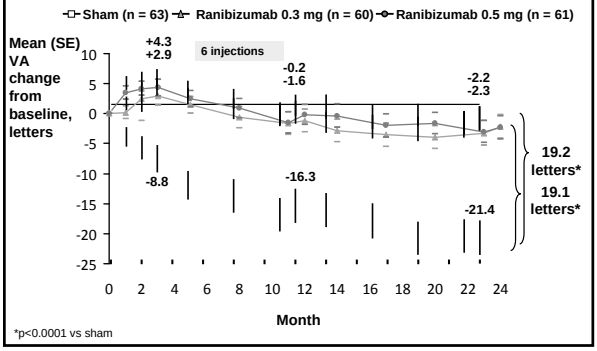
Randomized 1:1:1

- **Sham injection (n = 63)**
- **Ranibizumab 0.3 mg (n = 60)**
- **Ranibizumab 0.5 mg (n = 61)**

AMD, age-related macular degeneration
CNV, choroidal neovascularization

LEVEL 1

PIER
Primary efficacy endpoint: Mean VA change from baseline over time



*p<0.0001 vs sham

LEVEL 3

PrONTO
Study design

Two-year, open-label, prospective, non-randomized, single-center, investigator-sponsored study

Investigator determines eligibility

Subfoveal CNV (all lesion types) secondary to AMD; OCT CRT ≥300 µm (N = 40)

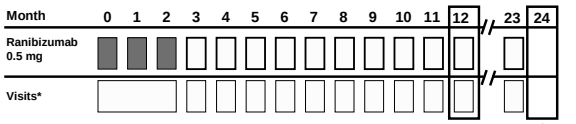
Ranibizumab 0.5 mg at baseline, Month 1, and Month 2

Monthly assessments and individualized OCT-guided Ranibizumab retreatment as necessary

AMD, age-related macular degeneration; CNV, choroidal neovascularization
CRT, central retinal thickness
OCT, optical coherence tomography

LEVEL 3

PrONTO
Treatment schedule



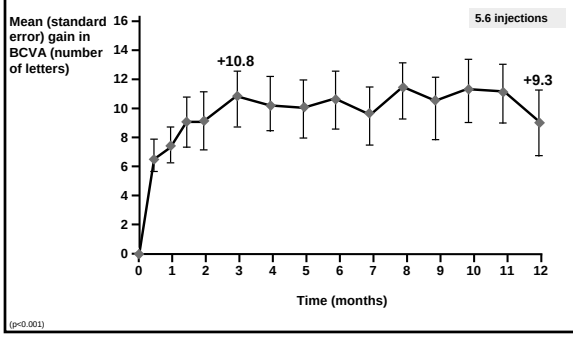
*Ophthalmologic examinations were carried out on Days 0, 14, 30, 45, and 60 then monthly thereafter; after the first 2 injections; OCT imaging and fundus photography was carried out on Days 0, 1, 2, 4, 7, 14, and 30 then monthly thereafter; Fluorescein angiography was performed at baseline, month 1, month 2, month 3, and every three months thereafter.

Primary endpoint

- ☐ ■ **Additional Ranibizumab injections were given if any of the following changes were observed between visits**
  - **loss of ≥5 letters with OCT evidence of fluid in the macula**
  - **increase in OCT CRT of ≥100 µm**
  - **new macular hemorrhage**
  - **new area of classic CNV**
  - **evidence of persistent fluid on OCT ≥1 month after previous injection**

LEVEL 3

PrONTO
Mean VA change from baseline over time (key efficacy endpoint)



(p<0.001)

LEVEL 1

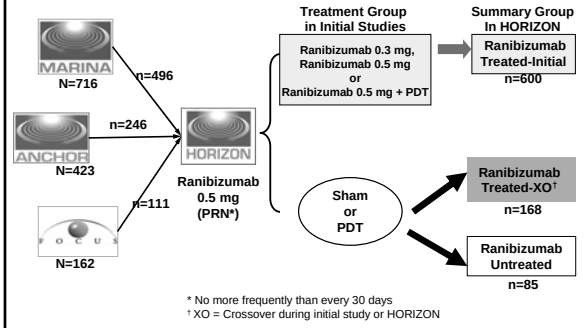
HORIZON

- **Open-label, multicenter Phase IIIb extension study**
- **Evaluate the long-term safety and efficacy of ranibizumab administered PRN to patients with AMD-related CNV who completed the 2-year treatment phase of MARINA, ANCHOR, or FOCUS**

Andrew Merkur

LEVEL 1

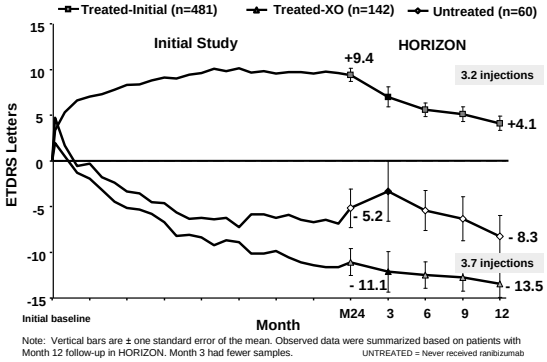
HORIZON
Study design



* No more frequently than every 30 days
† XO = Crossover during initial study or HORIZON

LEVEL 1

HORIZON
Mean Change in Visual Acuity (Month 12 Follow-up)



Note: Vertical bars are ± one standard error of the mean. Observed data were summarized based on patients with Month 12 follow-up in HORIZON. Month 3 had fewer samples.

UNTREATED = Never received ranibizumab

Study	Level of Evidence	Dosing Strategies Employed	Key Takeaways
MARINA	1	3 loading does + Monthly maintenance	Loading dose is essential Monthly dosing provides rapid improvement in VA sustained over 24 months
ANCHOR	1	3 loading does + Monthly maintenance	Loading dose is essential Monthly dosing provides rapid improvement in VA sustained over 24 months
PIER	1	3 loading does + Quarterly maintenance	Loading dose is essential Fixed quarterly dosing provides inferior outcomes vs. monthly
EXCITE	1	3 loading doses + Monthly maintenance dosing & 3 loading doses + Quarterly maintenance dosing	Loading dose essential Monthly dosing provides superior results to quarterly, even at lower dose
PrONTO	3	3 loading does + Quarterly maintenance (very small, single centre trial)	Loading dose essential PRN dosing assessments, with very aggressive anatomical & functional monitoring schedule may provide sustained VA improvements
SAILOR	1	3 loading doses + PRN* maintenance dosing	Loading dose essential PRN dosing based on anatomical AND functional assessments produced inferior outcome vs. monthly dosing – results in loss of initial VA gain
SUSTAIN	2 (n=69)	3 loading doses + PRN* maintenance dosing	Loading dose essential PRN dosing results in some loss of initial VA gain Mandatory monthly exams may help to optimize outcome
HORIZON	1	3 loading doses + PRN* maintenance dosing	Loading dose is essential A loosely designed PRN maintenance schedule results in substantial VA loss/loss of initial gains (even after 24 monthly treatments) Delayed treatment initiation associated with poor outcome

Conclusions

- Ranibizumab is the gold standard treatment of wet AMD
- Ranibizumab treatment initiation with three consecutive monthly injections, followed by continued monthly injections, has provided the best VA outcomes in pivotal trials
- If continued monthly injections are not feasible after three consecutive loading doses, a flexible strategy appears viable, if done in conjunction with monthly monitoring
- Continuous careful monitoring with flexible retreatment may help minimize vision loss

Bevacizumab

- **Bevacizumab has not been approved by Health Canada for ocular use**
- **No Level 1 systemic or ocular bevacizumab data**
- **Roche discourages ocular use**

CATT TRIAL
Design

- **4 Treatment Arms:**

Lucentis 0.5mg monthly	Lucentis 0.5mg PRN*
Avastin 1.25mg monthly	Avastin 1.25mg PRN*

*one induction dose, PRN according to MD discretion

- **Primary outcome measure:**
  - **Mean change in VA (ETDRS) after 1 year. Non-inferiority limit of 5 letters**
- **Secondary outcome measures:**
  - **Number of treatments**
  - **Mean VA change after 2 years**
  - **3-line change in VA (15 letters on ETDRS chart)**
  - **Change in sub-retinal and intra-retinal fluid on OCT**
  - **Change in lesion size on FA**
  - **Incidence of adverse events**
  - **Comparison of cost of treatments**

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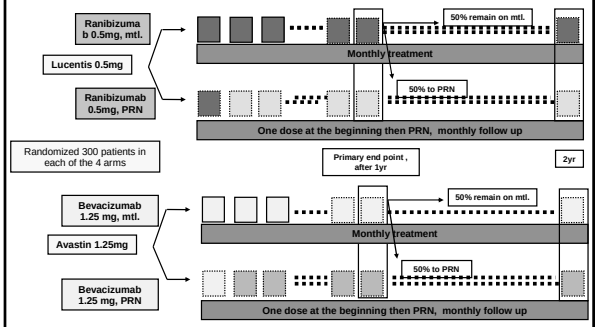
CATT TRIAL Design



CATT Considerations: Blinding

Partial un-blinding:

- **Coordinators are UNBLINDED (bevacizumab supplied in masked syringes, ranibizumab supplied in trade vials)**
- **Patients are UNBLINDED because of co-pay**
- **Investigators are BLINDED – risk of becoming UNBLINDED**

CATT Considerations Trial Design

Non-inferiority trial vs. direct comparison

<5 letter variance in outcome considered "non-inferior"

Running non-inferiority trials & achieving statistical significance difficult

Design significantly different from registration trials therefore limits comparability (can't extrapolate)

Study population, concomitant therapy, outcome measures

Eyes with relatively good VA at baseline can be included - favours a higher VA, ie, after 1yr.

No sham injections for patients who do not meet re-treatment criteria

Vial-Splitting Bevacizumab and Endophthalmitis: Jeopardizing Patient Safety

- **Bevacizumab vial volume is split into multiple doses by compounding pharmacies or clinic staff to treat AMD.**
- **Multi-dosing of the single use vial may lead to serious eye infections which can occur from:**
  - **microbial or viral contamination of vials while multi-dosing through improper handling techniques.**
- **Single-dose vials do not contain added preservatives like multi-dose vials do and, consequently, are designed for immediate disposal after use**

Canadian Bevacizumab Ocular Adverse Events

- **Intraocular inflammation associated with particular lots of bevacizumab used for intravitreal injection**
  - 2 clusters of reported adverse events (intraocular inflammation) reported in Canada in 2008
  - 117 patients; 14 centers

DHCP letter sent in Canada, US and some EU countries

- **Health Canada is aware of bevacizumab adverse event under-reporting**
  - **Health Canada spokesperson Philippe Laroche: "Estimating the adverse event rate for intravitreal bevacizumab would be inherently inaccurate because "adverse reactions remain underreported, and patient exposure is unknown"**

Pharmacoeconomics

Andrew Merkur

Cost Analysis

- **Cost / VA line-year:**
  - **$21 PRP in PDR**
  - **$33 SB for RD**
  - **$100 most vitrectomy indications**
- **QALY:**
  - **$2000 vitrectomy for complex diabetic complications**
  - **$4500 for ERM**
  - **$125,000 for 2 year Ranibizumab protocol style**

Cost / Line-year Various Treatments

Table 6. Summary Comparison of Cost per Line-Year

	1 Yr	2 Yrs
Ranibizumab*[1,2]	474/766	827/1532†
PIER[3]	505	707‡
PrONTO[4]	344	611
Bevacizumab[5–9]	84	—
PDT/TA[27,28]	104–269	—
PDT/ranibizumab[12,13]	355–679	1326
PDT/bevacizumab[11,15]	90	—
Triple[33]	71	—
VEGF Trap[17]	467	—

Ethical Question

What degree of differential treatment effect would justify a 200% or more cost premium?

References

1 - Ranibizumab Canadian Product Monograph, 2009
2 - Mitchell P et al. Br J Ophthalmol. Published online 13 May 2009. 10.1136/bjo.2009.159160
3 - Rosenfeld et al, N Engl J Med 2006; 355: 1419
4 - Brown et al, N Engl J Med 2006; 355: 1432
5 - Regillo et al. Am J Ophthalmol 2008; 145: 239-248
6 - 2008 AAO/ ASRS U of T Scientific Update
7 - Fung et al. Am J Ophthalmol 2007; 143: 566-583
8 - Boyer et al. Ophthalmology 2009; 143: 1731-1739
9 - Ferrara et al. Retina 2006; 26: 859-870
10 - Chen et al. J Mol Biol 1999; 293: 865-881
11 - Csaky & Cousins DVD. McGill 2009. Section 5: Bevacizumab is not the same as Ranibizumab Therapy
12 - Csaky & Cousins. VEGF Inhibitors in the Treatment of CNV Secondary to AMD. McGill. 2009
13 - Berger & Sharma. U of T Scientific Update. September 2009
14 - CanadaVigilance@hc-sc.gc.ca
15 - Health Canada Endorsed Safety Information on bevacizumab
16 - ASHP Guidelines on ophthalmic preparations.
17 - Paparella S. (2006 Oct) "The risks associated with the use of multi-dose vials", Journal of Emergency Nursing, 32(5):428-430
18 - http://emedicine.medscape.com/article/799431-overview
19 - Trissel LA. An update on USP chapter 797: the new national standard for sterile preparation. Available at: http://www.ashpadvantage.com/website_images/pdf/hospira797.pdf. Accessed December 21 2008.
20 - Georgopoulos et al. BJO 2009.
21 - http://www.rcophth.ac.uk/
22 - http://www.med.upenn.edu/cpob/studies/documents/CATTMOPSept2008.pdf.

Canadian Consultant Panel Feedback: April 2009

MENOPAUSE
The death of an ovary (or two)…

Dr. Tina Korownyk
Assistant Professor, Dept of FM
University of Alberta

Hot Flashes

- Most common symptom related to menopausal transition. (?)*
- Experienced by more than 50% of menopausal women

Nelson H, Haney E, Humphrey L, et al. Management of Menopause-related Symptoms: Evidence Report/Technology Assessment No. 120; Rockville, Md: Agency for Healthcare Research and Quality; 2005.

Hot Flashes

All of the following are effective treatments for Hot Flashes, except:

1) Red Clover
2) Gabapentin
3) SSRI's
4) Clonidine
5) Soy Isoflavone Extract

Hot Flashes

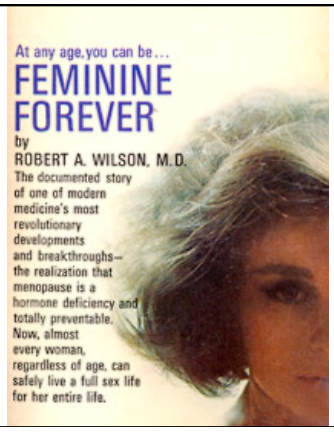
- Red Clover
- Well-designed Meta-analysis of 43 RCT's[1]
- Placebo = Red Clover, Methyldopa, Bellergal.
- Things that work
  - SSRI/SNRI (mid dose)= 1.13 ↓Hot Flashes/d (vs placebo)
  - Clonidine (≤0.075mg BID) = 0.95 - 1.63 ↓Hot flashes/d
  - Gabapentin (300mg TID) = 2.05 ↓Hot flashes/d
  - Soy Isoflavone Extract (50-70mg/d)= 0.97-1.22 ↓
- Endometrial safety with Isoflavone still unresolved.
- Estrogen best (2.5-3 ↓ Hot flashes/d)[2]

1) JAMA 2006; 295: 2057-71. 2) JAMA 2004;291:1610-1620.

Estrogen Benefits…

- Sys Rev, 192 RCTS, management of Menopause sx
- Conclusive only for estrogen (vasomotor & urogential sx)
- Trials limited in many ways:
  - Use of highly selected, small samples of women
  - Short durations
  - Inadequate reporting of loss to follow up, contamination, methods of analysis, and adverse events
  - Industry sponsorship
  - Outcomes often not standardized or validated (**92** measures of menopausal symptoms were reported)

1) Nelson H, Haney E, Humphrey L, et al. Management of Menopause-related Symptoms: Evidence Report/Technology Assessment No. 120; Rockville, Md: Agency for Healthcare Research and Quality; 2005.



Estrogen's Fall from Grace (again and again)

- 1965- Cosmopolitan "Oh what a lovely pill"
- 1975 – Increased risk of endometrial ca
- 1980s-1990s– Addition of progestins prevents endometrial ca (also prevents osteoporosis and decreases CAD by 35-50%[1,2])
  - Evidence from observational studies, small RCTs and surrogate endpoints.
- 1995-99 – 58 million ➔ 90 million prescriptions[3]
- 2002 – WHI – increased risk of breast ca, CAD and stroke[4]
- 2003 – 57 million prescriptions[3]

1) Ann Intern Med. 1992;117(12):1016-37. 2) Prev Med. 1991;20(1):47-63. 3) JAMA. 2004;291:47-53. 4) JAMA 2002; 288(3): 321-333.

The Media: Women's Health Initiative

- TV Evening News (September 24, 2003)
  - 41% increase in stroke
  - 29% increase in MI
  - Double rate of VTE
  - 26% in Breast Ca
  - No benefits mentioned
- Actual Risk per 10,000 (JAMA 288(3):321-33)
  - 8 strokes in 10,000 p. y.
  - 7 MI's in 10,000 p. y.
  - 18 VTE in 10,000 p. y.
  - 8 Breast Ca in 10,000
  - 6 Colorectal Ca & 5 Hip Fractures Less/10,000

CEE vs CEE+ MPA

Outome	HR Estrogen[1] 6.8 yrs	HR E+P[2] 5.2 yrs
CHD	0.91	1.29
Breast CA	0.77 CI (0.59-1.01)	1.26[3-6] CI (0.83-1.92)
Stroke	1.39	1.41
VTE	1.34	2.13
Colorectal CA	1.08	0.63
Hip Fracture	0.61	0.66

Composite outcomes total CVD with estrogen alone: 1.12 (1.01-1.24)

"CEE should not be recommended for chronic disease prevention in postmenopausal women"

1) JAMA. 2004 Apr 14;291(14):1701-12 2) JAMA 2002; 288(3): 321-333. 3) JAMA 2000;283:485-491. 4) J Natl Cancer Inst. 2000;92:328-332. 5) N Engl J Med 1995;332:1589-1593. 6) Int J Cancer 1999;81:339-344

Bioidentical Hormones, Faulty Conclusions &"1000s of studies"

- Conclusion: Continuous combined provera ↑ breast cancer risk, CVD…
- Therefore: Switch to bioidentical progesterone
- In vitro, primates, +++ Surrogate data (lipids, coronary plaques..)
- Many studies are too small (<25 patients) to provide any meaningful information[1-3]

Menopause. 2002;9(4):253-63. 2) Obstet Gynecol. 1989;73(4):606-12. 3) J Am Coll Cardiol. 2000;36(7):2154-9.

So we're all on the same page…

- **Bioidentical HT** – compounds that have the exact chemical structure as hormones produced in the body. May be "natural" or "synthetic"
- **Health Canada/FDA approved BHT** – carefully controlled and regulated
  - 17β-estradiol: pills, patches, sprays, creams, gels & vaginal tablets,
  - micronized progesterone: oral or vaginal
- **Compounded BHT** – plant derived, specifically compounded for individual patients. Often combinations of estrogens and progesterone. Not Health Canada/FDA approved.

Mayo Clin Proc. 2011;86(7):673-680.

Are Bioidentical Hormones Safer or More Efficacious than Synthetic Versions in HRT?[1]

	Symptoms	Tolerability	Breast Ca	CVD
RCT	2 No diff PEPI 875 pts 23 pts	2 PEPI – diff in bleeds 23 women - bleed	0	2 Surrogate Markers
Cohort/Case Control	1	1	1	1 (VTE)
Cross-sectional Survey	1	1	0	
Case Series/ Case Reports				
Expert Opinion	+++	+++	+++	+++

Postgrad Med. 2009 Jan;121(1):73-85. Review

Symptoms/Tolerability

1) RCT 875 women placebo, CEE + cyclical MPA vs CEE + cyclical MP[3]
   - No diff symptoms
   - 11% vs 4% had 1-1.5 episodes excess bleeding over 6 mo with MPA.
2) Cross-sectional survey 176 women previously tx with MPA, switched to progesterone for 1-6 mo[1]
   - Bias towards progesterone
   - Sign benefit with sleep, anxiety, depression, bleeds

1) J Womens Health Gend Based Med. 2000 May;9(4):381-7 2) Menopause. 2002 Jul-Aug;9(4): 253-63. 3) Obstet Gynecol. 2002 Nov;100(5 Pt 1):853-63. 4) Obstet Gynecol. 1989 Apr;73(4): 606-12

CHD

1) PEPI trial, 3 yrs, 875 women[1]
   - MP assoc with sign increase HDL - <0.1mmol/L
   - No clinical outcomes
2) Case Control 271 cases VTE vs 610 controls[2]
   - No diff MP vs MPA

1) JAMA. 1995 Jan 18;273(3):199-208 2) Circulation. 2007 Feb 20;115(7):840-5 3) 2) J Am Coll Cardiol. 2000 Dec;36(7):2154-9

Breast Cancer

1) No RCTs directly compare progesterone to synthetic progestins
2) 1 Cohort, 8.1 years (reported as 2)[1,2]
   - 80 377 postmenopausal women, France, f/u 8.1
     - E + P **129/40,537PY = 0.32%**
     - E + other progestagens **527/104,243PY = 0.51%**
     - **Diff = 0.19%**
     - **Results at risk of selection bias**

1) Breast Cancer Res Treat (2008) 107:103–111 2) Int J Cancer. 2005 Apr 10;114(3):448-54

Bottom Line on BHT

- SOGC does not encourage these hormones based on lack of evidence of benefit and unknown long-term risk.[1]
- SOCG and others[2] recommend against compounding of bioidentical hormones.

Patients desiring treatment should be advised there is no convincing evidence that bioidentical hormones are different from synthetic HRT.

1) http://www.sogc.org/health/health-menopause_e.asp
2) http://menopauseandu.ca/therapies/bioidentical-hormone-therapy_e.aspx

Lifestyle & Bottom Lines

- Cochrane sys review – 6 RCTs, 276 women, no benefit of exercise on vasomotor sx.[1]
  - Non sign trend HRT>exercise>placebo
  - Observational studies suggest limited benefit with lifestyle interventions
- Pharmacologic Options: Estrogen, Clonidine, Gabapentin, SSRI/SNRI

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

Diabetes is a condition, not a disease....

Tom Elliott MBBS, FRCPC

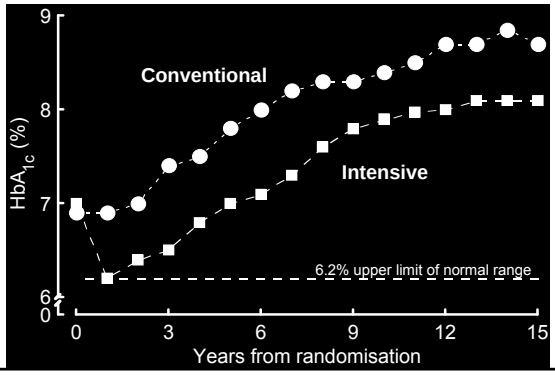
medical director, bcdiabetes.ca
skeptic, medicalmyths.ca
straight-talker, rateyourmd.com vs rateyourpatient.ca
cycling enthusiast
Canucks fan, passittobulis.com

Take home messages

- Diabetes is caused by progressive insulin deficiency
- Lower is not better
- Metformin then insulin +/- GLP-1 rules
- Once is better than twice daily

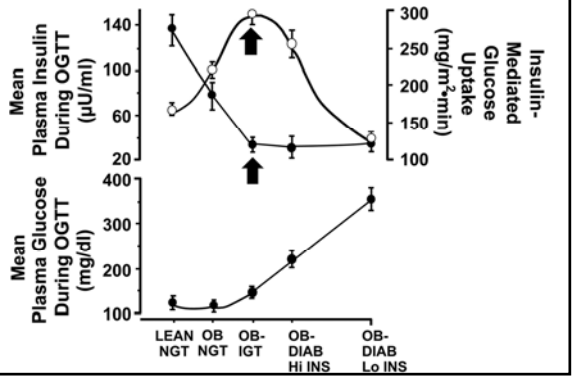
Type 2 Diabetes is progressive

(ukpds 1998)



Type 2 & its progression is caused by insulin deficiency

DeFronzo 2009 http://diabetes.diabetesjournals.org/content/58/4/773.full



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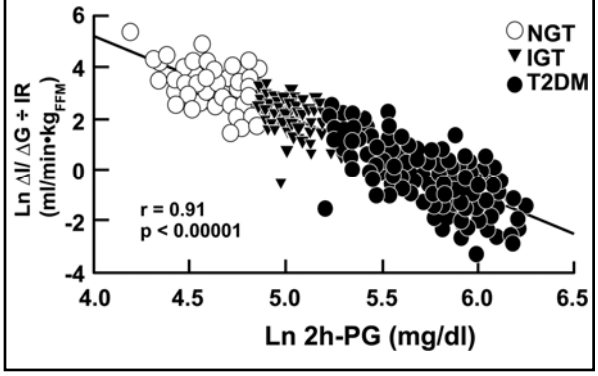
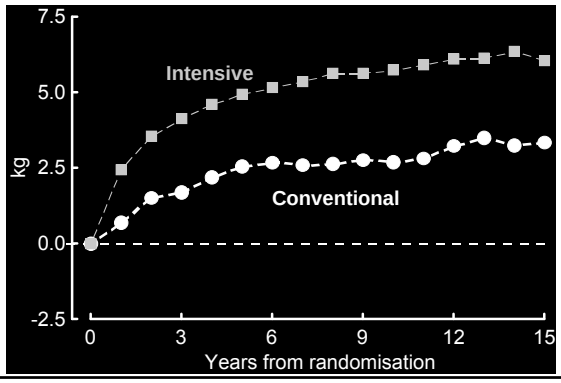


ACCORD & ADVANCE are a bust

nejm.org/doi/full/10.1056/NEJMe0804182

Outcome (intensive vs. standard)		
Median glycated hemoglobin at study end (%)	6.4 vs. 7.5†	6.4 vs. 7.0†
Death		
From any cause (%)	5.0 vs. 4.0†	8.9 vs. 9.6
From cardiovascular causes (%)	2.6 vs. 1.8†	4.5 vs. 5.2
Nonfatal myocardial infarction (%)	3.6 vs. 4.6†	2.7 vs. 2.8
Nonfatal stroke (%)	1.3 vs. 1.2	3.8 vs. 3.8
Major hypoglycemia requiring assistance (ACCORD), or severe hypoglycemia (ADVANCE) (%/yr)	3.1 vs. 1.0†	0.7 vs. 0.4
Weight gain (kg)	3.5 vs. 0.4	0.0 vs. −1.0†

UKPDS weight change



bcdiabetes.ca treatment philosophy

evidence-based medicine

simplicity & economics

"get your diabetes over with before breakfast"

- Once daily testing
- Once daily medication

Lifestyle therapy is always #1

If A1c is above target ask:
"have you been good"

diet "nothing is forbidden"
"everything you eat (except fat) turns to sugar
"your body can only handle a moderate amount of starch/carb/junk food"

Exercise – get out your prescription pad & prescribe
"graded exercise program"

Testing in all except

needle phobia & A1c to target at diagnosis

needle phobia & A1c < 8.5 no insulin or secretagogues

Testing schedule

Default: before breakfast daily
- reduce to M/W/F once A1c to target for 6 months
- reduce to once weekly once A1c to target for 12 months

Consider: 2 hr pc testing
- meal-planning/carb-counting
- for rapid insulin titration

Consider: before meal testing
- for corrections

Pharmacotherapy

http://www.bcdiabetes.ca/handouts?folder=For+Physicians&folder=Diabetes

medication is added step-wise until blood sugar targets reached. Medication is only stopped if ineffective or unacceptable side-effects or if insulin therapy leads to acceptable control (exception metformin - never stopped, see below).

Glycemic targets: general

in hospital	FBS 5.0-10.0
NH or age >85:	A1c < 9.0, FBS 5.0-10.0
age 75-84:	A1c < 8.0, FBS 5.0-8.0
age 55-74:	A1c < 7.5, FBS 5.0-7.0
age 40-54:	A1c < 7.0, FBS 5.0-7.0
age < 40:	A1c < 6.5, FBS 4.0-6.0

Glycemic targets: special

vasculopathy:	A1c < 8.0, FBS 5.0-7.0
diabetes > 20 yr:	A1c < 8.0, FBS 5.0-7.0
significant neuropathy/retinopathy:	A1c < 6.5, FBS 4.0-6.0

First line = metformin

all patients eGFR > 30, A1c > 6.0 or BMI > 25

once daily SR 500 mg preferred ($0.61 vs $0.14)

Start at one & increase Q4 days to max tolerated based on eGFR

> 50	2000 mg/day
40-50	1500 mg/day
30-40	1000 mg/day
20-30	500 mg/day

Second line ?????

GLP-1 agonist (if BMI > 30 & cost not a consideration, $5-9/day)

or

DPP-4 inhibitor (if cost not a consideration, average $2.80 per day)

or

Sulfonylurea - default gliclazide SR 30 mg ($0.15), push to ii daily

or

basal insulin – default glargine ($0.06 per unit vs $0.02 NPH)

GLP-1 agonists

liraglutide start at 0.6 mg acb (increasing to 1.2 & 1.8 mg after one & two weeks respectively, side-effects permitting): $9.00 at full dose

or

exenatide start 5 ug BID (before breakfast & dinner) for one month increasing to 10 ug BID thereafter, side-effects permitting: $5.50 at full dose

or

clinical trial with bcdiabetes.ca (up to 5 years Rx, placebo-controlled 50:50)

Basal insulin

Insulin glargine (or detemir) 6+ units qam (or 0.1 U/kg qam, whichever is greater), increasing by 1-2 units per day until target FBS met. Do not split dose unless > 80 units per day or patient has day-time lows with morning highs.

or

NPH 6+ units HS (or 0.1 U/kg HS, whichever is greater), increasing by 1-2 units per night until target FBS met. Do not split dose unless > 60 units per day or FBS to target but A1c high.

Mealtime rapid insulin

Insulin glulisine is same price as regular insulin (Toronto, Novolin R, Humulin R) but quicker to hit & of shorter duration & doesn't require snack

Insulin glulisine 1+ units immediately before largest meal of day (or meal with highest post-prandial reading), increasing by 1 units per day vs 2hr pc 6-10. Introduce carb-counting early if patient amenable & motivated. Starting carb-ratio 10:1 (20:1 in Type 1s).

Management scenario #1 obese, third party insurance

personal diet coach & personal trainer
metformin SR 500→1000→1500→2000 (+ prn)
Liraglutide 0.6→→→1.8 (?→3.0) mg/day (+ prn)
gliclazide MR 30→60 mg/day, (+ prn)
insulin glargine, (+ prn)
insulin glulisine at dinner

Management scenario #2 non-obese, third party insurance

personal trainer
metformin SR 500→1000→1500→2000 (+ prn)
DPP-4 inhibitor i daily (+ prn)
gliclazide MR 30→60 mg/day, (+ prn)
insulin glargine, (+ prn)
insulin glulisine at dinner

Management scenario #3 no third party insurance

lifestyle therapy, gym membership
metformin 500 mg ½ BID→i BID → ii BID (+ prn)
gliclazide MR 30 I daily → ii daily (+ prn)
sitagliptin 100 mg i daily (Special Authority)(+ prn)
insulin glargine, (+ prn)
insulin glulisine

Take home messages

- Diabetes is caused by progressive insulin deficiency
- Lower is not better
- Metformin then insulin +/- GLP-1 rules
- Once is better than twice daily
- To win is better than to lose

BP in primary care
Diagnosis, targets and choices

Robert Rangno
Professor Emeritus, UBC
DTC Director & Hypertension Savant

In abstentia - G. Michael Allan
Director, Evidence & CPD Program, ACFP
Associate Professor, Dept of Family, U of A

Primary Prevention CVD Risk

- BP
  - Monitoring
  - Targets
  - First Line drugs
  - Renal Myths?
  - Ineffective drugs
  - Night-time dosing

1148 NOVEMBER 26, 1966 THE LANCET

- 9 patients
- avg lying BP 199/109 mmHg

EFFECT OF PROPRANOLOL IN MILD HYPERTENSION

J. W. PATERSON
M.B., B.Sc. Lond., M.R.C.P.
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C. T. DOLLERY
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Getting the Diagnosis

- Mrs Betty Press is a 50 year old woman is today for her periodic health exam. Her BP on automated cuff in your office average 152/88 (3 readings, discard the first).
- She says she checks her BP at the drugstore and it is 130 & 75.
- Next Steps,… CHEP - 160/100 diagnosis on 3rd visit, 140/90 on 5 visits - ODD????

A. Seated, resting x5 minutes, no legs crossed, and not talking.
B. Measuring both arms, if one consistently higher, use that reading. JNC7/CHEP

Home in the Range

- European[1], US[2] and Canadian[3] Guidelines all recommend HBPM.
- Compared to Office Blood Pressure (OBP), HBPM,
  - Is equal to or superior in predicting cardiovascular risk,
  - May result in improved medication compliance
    - Perhaps better BP control
  - Is more accurate (closer to 24-hour Ambulatory BP)
  - BPTRU (automated office device) - BP 5/2 lower than manual office BP - BMJ 2011;342:d286
  - BUT Watch out for OCD

1. J Hypertension. 2008; 26:1505–30. 2. Hypertension. 2008;52:1-9. 3. Can J Cardiol. 2009;25(5): 279-86.

BpTru vs 24 hour ambulatory

Measurement method	Mean systolic (mmHg)	Mean diastolic (mmHg)
Average of the blood pressures measured at the last three office visits	151	83
BpTRU initial reading	150	83
BpTRU average	140	80
24 hour daytime average	142	80

BMC Cardiovascular Disorders 2005, 5:18

Robert Rangno

Home in the Range

- Diagnosis: The threshold for hypertension with HBPM is ≥135/85mmHg
  - Thresholds for sub-groups are not yet firmly established
    - US guidelines suggest possibly 130/80 for diabetes, chronic kidney disease & coronary heart disease[2]
- HBP is generally lower than OBP (averaging 7/5 lower).[3]
  - Difference less when treated (OBP responds to Tx better?)
- No randomized controlled trial have compared HBPM and OBP on hard clinical outcomes

1. J Hypertension. 2008; 26:1505–30. 2. Hypertension. 2008;52:1-9. 3. J Am Coll Cardiol 2005;46:743–51

Mrs BP and targets

- Mrs Betty Press is back and after 2 months, her home readings are 144/83
  - Do you do an office BP?
- What will be her target?
  - In office or at home?
- What if her work-up showed she was diabetic?

Work-up: urinalysis, Blood chemistry (potassium, sodium, creatinine), fasting glucose/ A1C, fasting lipid panel, ECG. CHEP
Add Hematocrit and Calcium for JNC7

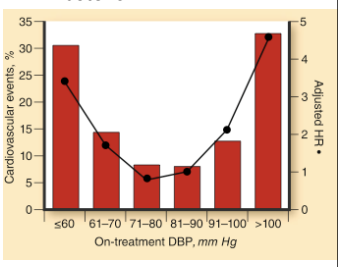
Treatment targets.

- Evidence: Systematic Review[1] of 7 trials (22,089 pts), mean 3.8 yrs. Intensive targets (primarily diastolic) led to
  - BP 139.3/81.7 versus 143.2/85.1
  - No diff total mortality or any CVD outcome.
- 4733 diabetics (ACCORD[2]): Systolic BP was 119.3 versus 133.5
  - No difference except Stroke (NNT 92) but AE up (NNH 50).
- 1111 non-diabetic patients (Cardio-Sys[3]): Baseline 163/90 mmHg - usual (<140) vs tight (<130) control - Systolic BP 3-4 better in tight control
  - Composite CVD outcome down (NNT 22).
- 1094 chronic kidney disease patients (AASK[4]): Systolic BP 11 better at 5 yrs, but 3mmHg after 10 yrs.
  - No diff combined creatinine2x, end-stage renal disease or death
  - Higher urinary protein subgroup reduced (75% vs 85%, NNT 10)

Treatment Targets?

- US[6] and Canadian[7] guidelines recommend
  - <140/90 for most patients
  - <130/80 for diabetics and those with renal disease.
- Europe[8] had <130/80 for diabetics or with CVD but,
  - Now 130-139/80-85 in most patients.

Diastolic BP[1]



1) Curr Hypertens Rep (2010) 12:290–295

Treatment targets.

- COCHRANE - CD004349 - Bottom-line: "Treating hypertension (targeting BP <140/90) lowers risk, but evidence for BP targets of 130/80 is inconsistent, even for patients with diabetes, renal, or CVD disease. Potential benefits and harms of intensive treatment should be weighed for each patient."

Mrs BP: ready to add style to life?

- Mrs Betty Press has come to terms with diagnosis and would like to try lifestyle. Her BMI is 31 and she is inactive.
- What will lifestyle do?
- Minimum 3-6 month (depending on BP, etc)

Lifestyle interventions, best case.

Intervention	BP reduction
More physically active	-5/4 mmHg
Weight reduction	-7/-6 mmHg for every 4.5 kg weight loss
Moderation in alcohol intake (0-2 drinks a day)	-4/-2.5 mmHg
Eating healthier and reducing Na intake DASH/Sodium reduction	-11/-6 mmHg DASH -5/-3 mmHg sodium
Reducing stress	-6/-4 mmHg

CHEP: 2011 Canadian Recommendations for the Management of Hypertension (What's New, What's Old but still important)

Which medication first for Mrs BP?

- 6 months have passed and lifestyle interventions, although started with enthusiasm, faded. BP is still 144 / 83
- What would be your first choice of medications?

HER Framingham CVD Risk - 10 years

- 144/83, 50 years of age, total cholesterol 5 mmol/L, HDL 1, non smoker, no diabetes
- CALCULATED RISKS
- SBP = 164 mmHg - 10 year risk 5.5%
- SBP = 154 mmHg - 10 year risk 4.7%
- SBP = 144 mmHg - 10 year risk 3.9%
- SBP = 134 mmHg - 10 year risk 3.2%

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Who's on First

- Cochrane 2009 review of 24 placebo trials (58,000 pts)
  - RCT # = 19 Thiazides, 3 ACE, 5 Beta-blocker, 1 Ca blocker - BASELINE CVD RISK OVER 5 YEARS WAS approx 10% - HER 10 year risk is 4%
- Authors recommend Low dose Thiazides: Good #'s & robust data
- See below for relative risks (all numbers statistically significant)

Outcome	Diuretic	Low D	ACE	Ca+	Beta
Mortality	0.89	0.89	0.83	NS	NS
CHD	0.84	0.72	0.81	NS	NS
Stroke	0.63	0.68	0.65	0.58	0.83
CVS total	0.70	0.70	0.76	0.71	0.89

Spironolactone - resistant hypertension but NO morbidity/mortality data

Cochrane 2009, Issue 3. Art. No.: CD001841.

Who's on First?

- JAMA 2003 review (42 trials, 192,000 pts)
- Thiazides: As good or better for all outcomes across ACE, ARB, Ca-channel blockers, Beta-blockers, & alpha-blockers.

JAMA. 2003;289:2534-2544

Who's on First

- The First Line Therapy Trial: ALLHAT (33,357 pts)
- Compared to Chlorthalidone = percents are absolute increases over 6 yrs (ns = no statistical difference, and brackets() are Numbers Needed to Harm)

	Ca+ Blocker	ACE Inhibitor
CHD	ns	ns
Mortality	ns	ns
Combined CVD	ns	2.4% (NNH 42)
Stoke	ns	0.7% (NNH 143)
CHF	2.5% (NNH 40)	1% (NNH 100)

JAMA 2002; 288: 2981-97.

Robert Rangno

"The Best of the Best"

- Which Thiazide Diuretic?
  - HCTZ has shorter half-life (3-5 hours) than chlorthalidone (2 days)
  - Meta-analysis finds HCTZ does not reduce 24hr BP = other BP[5]
  - Chlorthalidone (like ALLHAT & SHEP) has good outcomes.
- Older post-hoc analysis found Chlor superior to HCTZ[1]
- Recent RCT[2]: Chlor slight better 24 hour BP vs HCTZ
  - 24 hr mean BP 5 mmHg less, night-time 7 mmHg less
  - One reviewer[3] suggest Chlor should be first line (based on all above)
- A meta-analysis[4] of outcomes found them similar

1. Circulation 1990;82;1616-28. 2. Hypertension. 2006;47:352-358. 3. Hypertension 2006;47;321-322. 4. JAMA. 2004;292(1):43-4. 5. J Am Coll Cardiol 2011;57:590–600

↓BP = ↓CVD ?

- Meta-analysis[2] of all beta-blockers= heterogeneity
- Another Meta-analysis[3] stratified by age: >60 did not do but patients <60 did.
- Note: In patients with a beta-blocker indication (like HF or post MI) they are helpful.

1) Lancet 2004; 364: 1684-9. 2) Lancet. 2005; 366: 1545-53. 3) CMAJ. 2006;174(12):1737-42.

Hypertension Tx & Metabolic Disease

- Beta-blocker (? diuretic) increase 5yr DM risk 1-1.5%
- Beta-blockers not as helpful; don't use?
- Do we stop giving Diuretic? No
  - Good BP reduction[1,2] & best outcomes[2,3]
- Do ACE inhibitors (or others) reduce DM?
  - No (According to the DREAM trial – Ramipril).

1) Am J Cardiol 2007;100:1254 –62. 2) JAMA 2002;288:2981-97. 3) JAMA 2003; 289: 2534-44.

Another med not for first line

- Also Alpha blockers - ALLHAT
- Combined CVD (death, MI, CHF, angina, stroke)
  - Chlorthalidone 14.7%
  - Doxazosin 17.6%
  - Absolute difference = 3.1%, NNH = 35

JAMA 2000; 283: 1967- 1975

ACE or ARB Saving Kidneys

- ACE or ARB in patients kidney disease (for example[1] with proteinuria and impaired GFR <60), various studies[2] show reduced proteinuria and slow doubling of creatinine.
- BUT - 1,408 type 2 diabetics (10 years) - then followed for 10 years - 562 died - 49% due to CVD, 21% cancer - 0.7% went to dialysis - Diabetes Care 2003;26:2353-8

1. Ann Intern Med. 2009;150:731-733. 2. Am J Hypertens. 2008 Aug;21(8):922-9. Cochrane 2006 Oct 18;(4):CD006257. 3 Ann Intern Med. 2008;148:30-48.

ACE or ARB Saving Kidneys

- Other studies have questioned if the "reno-protective effects" of ACE or ARB > it's BP effect.
- A Meta-analysis[1] of 127 trials over 4.2 yrs compared ACE/ ARB vs other BP meds
  - ESRD: 1.7% vs 2%, NNT 385
  - Doubling of creatinine: 8% vs 11.3% (not stat sign)
- Others[2] caution ACE/ARB effect is not to extrapolated to
  - Pt without renal impairment or
  - Healthy Elderly patients with slight reductions in GFR

1. Lancet. 2005;366:2026-33. 2 Ann Intern Med. 2009;150:731-733.

Robert Rangno

Using ACE & ARB Combo vs single

- Renal impairment worse 13.5% vs 10.2% [1]
- Getting 44 increase in Creatinine, NNH =58 [2]
- Doubling of creatinine or dialysis, NNH ≈200 [3]
- (some reduction in Proteinuria)

- Discontinuing due to adverse events, NNH 21-25 [1,2]
- Hyperkalemia (K+≥5.5) NNH= 37-43 [1,2]
- Symptomatic Hypotension, NNH = 32 (17-124) [1,2]

N Engl J Med 2008;358:1547-59. Arch Intern Med. 2007;167:1930-6. Lancet 2008; 372: 547–53

Giving BP Meds at night

- MAPEC[1], 5.6 yr trial, 2156 patients (age 56)
  - BP Med taken a.m. VS ≥1 at bedtime (47% took all qhs)
- BP: Daytime: Awakening 125/75 vs bedtime 125/76
  - Nighttime: Awakening 116/65 vs bedtime 111/63
- Outcomes: Statistically significant reduction in
  - Mortality: Awakening 2.6% vs bedtime 1.1%, NNT 67
  - CVD: Awakening 6.8% vs bedtime 2.8%, NNT 25
  - Diabetic[4] & chronic kidney disease[5] had similar benefits.
- Multiple limitations

Chronobiology International 2100;27: 1652–7

Giving BP Meds at night

- **Bottom-line:** Taking 1 or more BP-lowering drugs at bedtime appears to reduce CVD, based on a single potentially-biased trial. Due to limitations in the evidence, strong recommendations are difficult but taking one or more BP meds before bed may potential help reduce CVD risks.

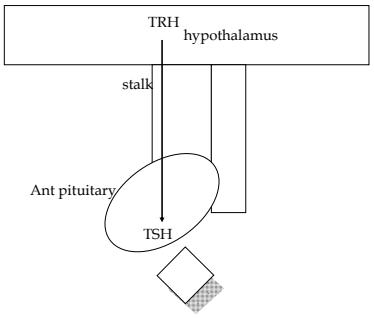
SUBCLINICAL HYPOTHYROIDISM IN THE ELDERLY

Jason Kong MD

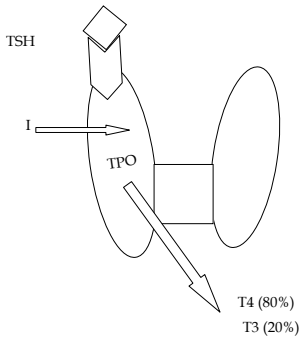
Outline

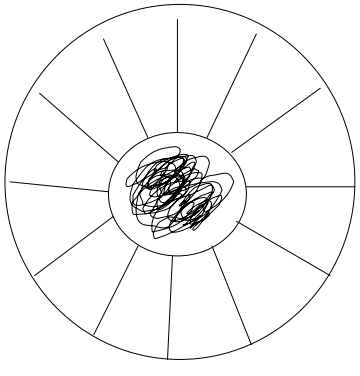
- Physiology Review
- Definition
- Consequences
- Treatment Options

Physiology

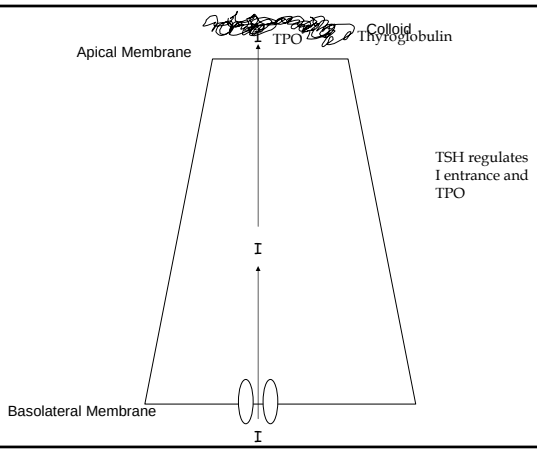


Physiology

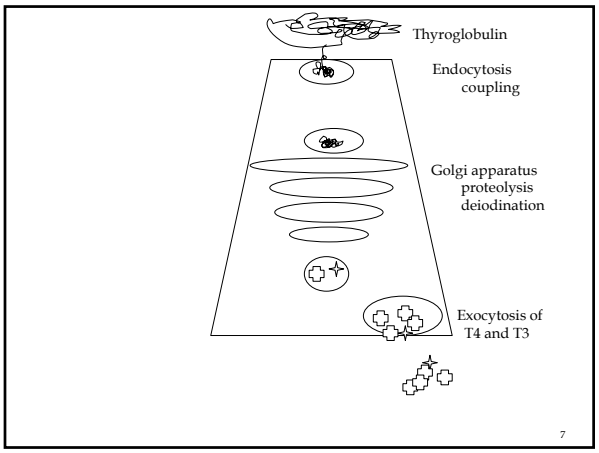




Follicle



Jason Kong



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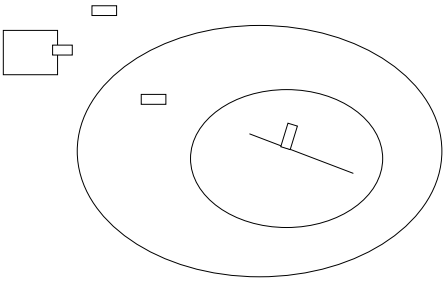
Physiology



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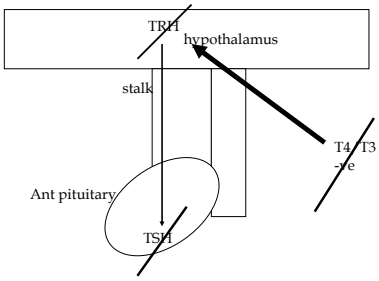
Feedback



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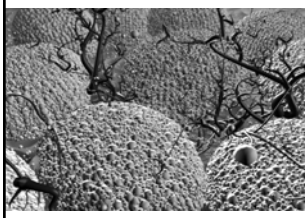
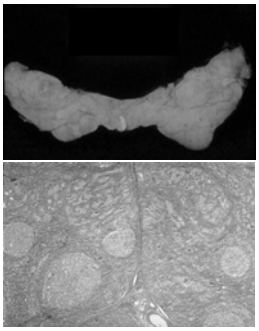
Subclinical Hypothyroidism in the Elderly



- Misnomer
- "mildly" elevated TSH (6-10)
- Normal Free T4 (FT4) and Free T3 (FT3)

Etiology of Primary Hypothyroidism



- Autoimmune
  - Hashimoto's thyroiditis (TPO Ab)
  - Burnt out Grave's Disease
- Iatrogenic
  - Surgical
  - Radioiodine
  - Drugs (lithium, amiodarone)

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Prevalence of Subclinical Hypothyroidism

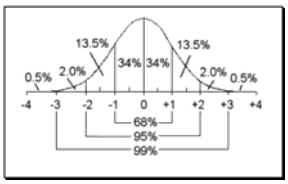
Table 3. Some of the larger epidemiologic studies of hypothyroidism.

Study	No. of subjects	Age (years)	Findings
Bagchi et al[18]	968	>55	7.3 % had TSH >6 mIU/L
Parle et al[15]	1210	>60	11.6 % of women and 2.9% of men had high TSH; antithyroid antibodies were identified in 60% of patients with high TSH concentrations
Bemben et al[17]	370	60–97	14.6% of the women and 15.4% of the men had TSH >5 mIU/L
Tunbridge et al[14]	2779	Mean 47.1 years	7.5% of women and 2.8% of men had serum TSH levels above 6 mIU/L
Canaris et al[19]	25,862	18–74+	9.5% of all subjects had an elevated serum TSH concentration (>5.1 mIU/L) and in the ninth decade of life, the prevalence of elevated TSH was as high as 15–20%
Lindeman et al[16]	825	Mean 74.1 years	16.8% had TSH >4.6 mIU/L; subclinical hypothyroidism did not affect any of the measures of health status until TSH concentrations exceeded 10 mIU/L
Hollowell et al[11]	7353	≥12 years	Hypothyroidism was found in 4.6% of the population (0.3% clinical and 4.3% subclinical) and hyperthyroidism in 1.3% (0.5% clinical and 0.7% subclinical)

Mooradian A. Am J Therapeutics 2011

Jason Kong

What is normal?



- TSH range is a statistical cutoff
- "normal" TSH range rises with age

TSH Rise with Age

- Longitudinal study of 908 subjects without thyroid disease or Ab
- Mean 13 year follow up
- TSH increase 0.08/10y

Bremner A et al. JCEM 2012

TSH Rise with Age

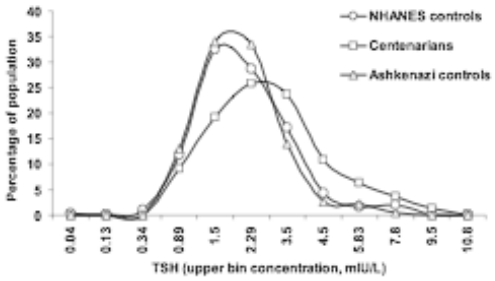
Table 1 Means and reference intervals of serum thyrotropin (TSH) levels according to age group and sex

Age group	All patients (n=1388)				Women (n=1190)				Men (n=198)			
(years)		-2SD	mean	+2SD		-2SD	mean	+2SD		-2SD	mean	+2SD
All ages		0.44	1.48	4.93		0.45	1.48	4.82		0.39	1.48	5.66
	(n)				(n)				(n)			
20-29	477	0.39	1.30	4.29	424	0.38	1.28	4.30	53	0.48	1.42	4.15
30-39	440	0.34	1.53	3.90	386	0.46	1.44	4.46	54	0.24	1.54	4.43
40-49	218	0.56	1.67*	5.02	183	0.57	1.72*	5.25	35	0.54	1.43	3.82
50-59	132	0.51	1.65*	5.30	104	0.54	1.70*	5.31	28	0.42	1.48	5.22
60-69	94	0.60	2.10*	4.85	77	0.71	1.93*	5.25	17	0.22	2.68	5.14
>70	27	0.63	1.96*	6.15	16	0.83	2.39*	6.88	11	0.52	1.48	4.23

Serum TSH values (-2SD, mean, and +2SD) in mIU/L *p<0.05 for the difference from the 20-29-year-old age group

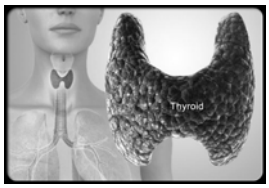
Yoshihara A et al. Endocr J 2011

TSH Range and Longevity



Atzmon G et al. JCEM 2009

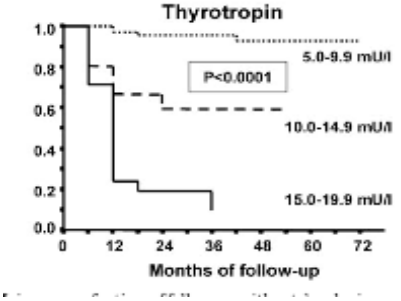
Subclinical Hypothyroidism Natural History



- TSH >10 likely to progress
- TSH 5-10 variable
- TPO Ab likely to progress[1]

Huber G et al. JCEM 2002

Subclinical Hypothyroidism Natural History



Diez J et al JCEM 2004

Consequences of Subclinical Hypothyroidism

- Abnormalities in lipid profile
- Abnormal blood pressure
- Abnormal endothelial function

Consequences Subclinical Hypothyroidism

- Cardiac
  - Cross-sectional study
  - 1149 women
  - Mean age 69
  - Increased CAD (OR 1.7)

Hak E et al Ann Int Med 2000

Cappola A et al. JAMA 2006

Consequences Subclinical Hypothyroidism

- Cardiac
  - Longitudinal study
  - 3200 subjects (1926 women)
  - Mean age 72
  - Mean 12.5 years f/u
  - NO increased CVD
  - NO increased mortality

Cappola A et al. JAMA 2006

Subclinical Hypothyroidism and Longevity

- Subclinical hypothyroidism NOT associated with increased mortality

Haentgens J et al. Eur J Endocr 2008

Treatment Benefit of Surrogate Markers

- Improvements of lipids
- Improvements in carotid intimal thickness
- Improvements in blood pressure
- No benefits on bone density

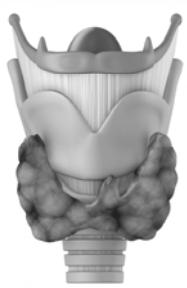
Treatment Benefit for Clinical Outcomes

- NO mortality benefit
- NO cardiovascular disease outcome benefit
- NO neurocognitive benefit

Villar HC et al. Cochrane Database Syst Rev 2007

Jason Kong

Treatment Adverse Effects



- Little if properly dosed.
- Not costly

Treatment Options

- Treat if TSH >10
- Consider treatment if TSH 5.5-10 if
  - TPO Ab positive
  - Patient symptomatic
  - 24-50mcg levothyroxine daily on an empty stomach
- Otherwise simply observe

Conclusions

- Subclinical hypothyroidism common
- Upper limit normal TSH likely 6.5-7
- Harm controversial
- Treatment controversial
- Treat if TSH >10
- TSH 7-10: Consider treatment if symptomatic or TPO positive

Jon Fleming

Insomnia – counting sheep – count the legs and divide by 4

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Disclosures

- No relationship with industry
- Shareowner
  - GlaxoSmithKline
  - Pfizer
- Will be discussing off label use

Objectives

- Primary insomnia
  - What is it?
  - Why it's important
  - Who gets it?
  - What do you do about it?
- The rules for maximizing drug efficacy
- Off label use of sleep promoting medicines

Insomnia – What is it?

- Common symptom
- Syndrome divided into Primary and Secondary Insomnias
- Subjective complaint of unsatisfactory sleep
  - Delayed onset
  - Interrupted
  - Inadequate duration
  - Non-restorative
- Causes distress and impairment

Insomnia – Why it's important

- Quality of life is impaired
- Persistent insomnia increases
  - Nocturnal falls
  - Absenteeism
  - Work related accidents
  - Road accidents
    - Medication effects?
    - Co-morbid disorders?
  - Risk of first episode depression
  - Risk of relapse into depression in those with pre-existing insomnia

Insomnia – Who gets it?

- Prevalence varies (criterion variance)
  - 10-15% chronic and severe
- Prevalence is 1.5 – 2 times higher in females
- Prevalence increases with
  - Age
  - Psychiatric disorders
  - Medical disorders
- Approximately half of all diagnosed insomnia is related to a psychiatric disorder
- The course is chronic (remitting and relapsing)
  - 46% subjects in a population based study who had insomnia at baseline still had it 3 years later

Jon Fleming

Insomnia – What do you do about it?

" There is some disagreement about how long insomnia should be present before it requires intervention but there is general agreement that when insomnia causes significant personal distress or marked impairment then some form of treatment is appropriate."

J Psychopharmacol. 2010 Nov;24(11):1577-601

Insomnia - Treatment

- Goals of treatment
  - To decrease subjective distress
  - To improve daytime functioning
  - To rectify the health risks of insomnia?
- Type of treatment
  - Patient
    - Preference
    - Specific factors
  - Availability
  - Insomnia type
  - Evidence based

Evidence based treatments

- CBT-I
- Short acting benzodiazepines
  - triazolam
  - temazepam
  - (oxazepam)
  - (lorazepam)
- Specific omega-1 receptor agonists – Z drugs
  - zopiclone
  - zolpidem
- Prolonged release melatonin (≥55 yrs)

CBT-I

- An effective treatment for primary and secondary insomnia
  - Individual
  - Group
- As effective as hypnotics in the short-term treatment of chronic insomnia
- Beneficial effects continue past the end of active treatment
- Can be delivered by
  - Phone
  - Internet (*cbtforinsomnia.com*)
  - Non-physicians/non-psychologists
  - Primary Care MDs

The ideal hypnotic …

…doesn't exist

Pharmacokinetics

Drug	**½ life (hrs)**
lorazepam	12-16
oxazepam	7-20
temazepam	7-11
triazolam	2-4
zopiclone	4-8
zolpidem	2–4
(zaleplon)	1-2

Jon Fleming

Zolpidem

- imidazopyridine
  - Only available in 10 mg dose
  - Preferentially binds to the omega-1 receptor
  - No anticonvulsant, muscle relaxation effect
  - Short half life: 2-4 hrs
  - Controversial selling points
    - No withdrawal syndrome
    - Minimal rebound insomnia
    - Conserves sleep architecture
    - Minimal tolerance
    - Minimal daytime impairment
  - Associated with parasomnias

The rules

- Non-emergent treatment begins AFTER a 7 day sleep diary

TWO WEEK SLEEP DIARY

Instructions:
1. Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation.
2. Put the letter "C" in the box when you have coffee, cola, or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise.
3. Put a line [|] to show when you go to bed. Shade in the box that shows when you think you fell asleep.
4. Shade in all the boxes that show when you are asleep at night or when you take a nap during the day.
5. Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

SAMPLE ENTRY BELOW: On a Monday when I worked, I jogged on my lunch break at 1PM, had a glass of wine with dinner at 6PM, fell asleep watching TV from 7 to 8PM, went to bed at 10:30PM, fell asleep around midnight, woke up and couldn't get back to sleep until about 4AM, went back to sleep from 5 to 7AM, and had coffee and medicine at 7 in the morning.

Today's date	Day of the week	Type of day: work, school, off, vacation	Noon	1PM	2PM	3PM	4PM	5PM	6PM	7PM	8PM	9PM	10PM	11PM	midnight	1AM	2AM	3AM	4AM	5AM	6AM	7AM	8AM	9AM	10AM	11AM
Sample	Mon.	Work							A				-									E/C				

http://ow.ly/8ncjO

The rules

- The essential components of the sleep hygiene package are
  - 30 mins of aerobic exercise daily
  - Never take horizontal rests or naps
  - Use the bed and bedroom only for intimacy and sleep
    - No TV, computer or smart-phone use
  - Don't go to bed until you are drowsy tired
  - No visible time cues
  - Never work at getting to sleep; if you feel wide awake after 15-20 minutes (untimed) get out of bed and read, crochet or knit
  - Always get up with an alarm at the same time each day, every day (yes; Sat, Sun and holidays)

The rules

- Discuss the risks
  - Interactions
  - Morning sedation
    - Compensatory sleeping
  - Psycho-motor impairment
  - Cognitive effects
  - Parasomnias (zolpidem > BDZs)
  - Rebound insomnia
  - Dependence
    - Physiological
    - Behavioural
  - Withdrawal syndrome

Dependence

World Health Organization

- Three or more of the following have been present together at some time during the previous year:
  - A strong desire or sense of compulsion to take the substance
  - Difficulties in controlling substance-taking behaviour
  - A physiological withdrawal state when substance use has ceased or has been reduced
  - Evidence of tolerance
  - Progressive neglect of alternative pleasures or interests because of psychoactive substance use
  - Increased amount of time necessary to obtain or take the substance or to recover from its effects
  - Persisting with substance use despite clear evidence of overtly harmful consequences

The rules

- Chart the impairments
- Discuss the course
  - No procedure or clinician can accurately predict the course of treatment for any patient
  - Short courses are the goal but not at the cost of continued distress or impairment
  - Outline the likely withdrawal procedure
    - Low stress time
    - Slow taper
      - Single blind if prominent psychological dependence (pharmacy.ca)
    - Assign (Total Sleep Time – 30 mins) from diary one week prior
    - Add back time; 10 mins each week/sleep disruption worsens

Jon Fleming

The rules

- Start at the lowest available dose
- Chart improvements
  - Sleep diary
  - Change in impairments
- Only renew the prescription when benefits have been documented
  - Should be obvious to any reviewer
- If a patient does not respond to normal doses re-evaluate the diagnosis before increasing the dose or changing the intervention
  - Paradoxical Insomnia (Sleep State Misperception)

The rules

- The two week rule is historical with no evidence to support it
  - Clinical experience indicates that long-term, hypnotic use is effective
  - Studies of 1 year or more have demonstrated subjective and objective efficacy
  - BUT you should still meet the patient every two weeks to assess response and continued need
- Individualize treatment
  - Some may manage well with intermittent use

Off label use

- Using the side-effect of a drug when its main effect is not required is poor medical practice
  - liability
- Off label use does not protect the user from the issues associated with hypnotics
  - Interactions
  - Morning sedation
  - Psycho-motor impairment
  - Cognitive effects
  - Parasomnias
  - Rebound insomnia
  - Dependence
    - Physiological
    - Behavioural
  - Withdrawal syndrome

Off label use

- No antidepressant or antipsychotic has Health Canada or FDA approval for use as a hypnotic
  - Using an antipsychotic for Primary Insomnia risks suit for malpractice
- Done correctly, the use of atypical antipsychotics is substantially more expensive than using BDZ or BDZ-A drugs
  - Done incorrectly use is hazardous to your patient and yourself

Documented iatrogenic illnesses associated with off-label use

- Obesity leading to Metabolic Syndrome and Obstructive Sleep Apnea
- Parasomnias
  - Sleep walking, sleep driving, sexsomnia
  - REM Sleep Behaviour Disorder
- Restless Legs Syndrome
- Periodic Limb Movement Disorder
- Circadian Sleep Disorder

Summary

- Treatment of Primary Insomnia is individualized
- CBT-I is the preferred first intervention but not widely available
- The benzodiazepines and the “Z drugs” are first line interventions
  - Use the lowest dose for the shortest time that continues to provide relief
- Note impairments and response
- Off-label use is risky and rarely indicated in Primary Insomnia

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Antibiotics
Which ones can you count on
& for how long?

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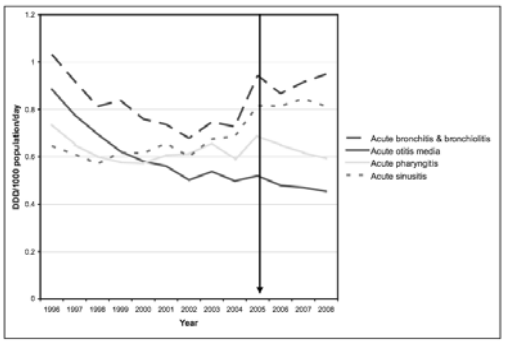

Figure 4) *Overall antibiotic consumption rates in British Columbia according to indication from 1996 to 2008. The arrow indicates the approximate implementation of the Do Bugs Need Drugs? program. DDD Defined daily doses*

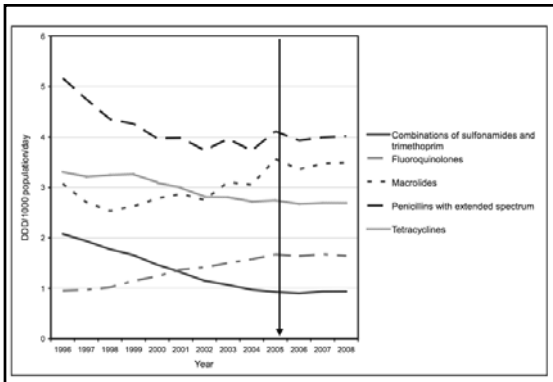

Figure 3) *Consumption of select classes of antibiotics in British Columbia from 1996 to 2008. The arrow indicates the approximate implementation of the Do Bugs Need Drugs? program. DDD Defined daily doses*

The Problem?

- "Antimicrobial resistance is recognized as one of the greatest threats to human health worldwide[1]"

1) Walker B, Barrett S, Polasky S, et al. Environment. Looming global-scale failures and missing institutions. Science 2009;325:1345-6.
Infectious Diseases Society of America (IDSA). Combating antimicrobial resistance: policy recommendations to save lives. Clin Infect Dis 2011;52(suppl 5):S397-428.

Drug Resistant Organisms and their Impact…

- MRSA – 19 000 Americans/year[1]
  - (more than emphysema, HIV/AIDS, Parkinson's and homicide combined)
- HAIs – 99 000 Americans/year[2]
  - (many of which are due to antibiotic resistant pathogens)
- Diabetes – 68 705[3]
- CAD – 599 413

1) Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant Staphylococcus aureus Infections in the United States. JAMA 2007;298:1763-71. 2) Klevens RM, Edwards JR, Richard CI Jr., et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep 2007;122:160-6 3) www.cdc.gov/nchs/fastats/deaths.htm
Infectious Diseases Society of America (IDSA). Combating antimicrobial resistance: policy recommendations to save lives. Clin Infect Dis 2011;52(suppl 5):S397-428.

A Second Problem

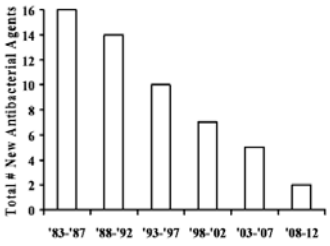

Figure 1. Number of New Molecular Entity (NME) Systemic Antibiotics Approved by the US FDA Per Five-year Period, Through 3/11.

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Estimating Resistance Patterns…

- Very Difficult
- The laboratory designation of antimicrobial resistance may not necessarily correlate with poor patient out- come.
- Tx with TMP-SMX for UTI prophylaxis
  - 90.5% of asymptomatic E coli isolates were resistant at 1 month, despite reduction in UTI up to one year

Arch Intern Med. 2011;171(14):1270-1278

The (somewhat) Current State of Bacterial Resistance in Canada

Antibiotic	S. Pneumoniae Resistant[1,2]	H. influenzae[3]
Penicillin	17% Intermediant Resistance	
Amoxicillin[2]	<2%	19.3%
Amoxicillin-Clavulanate		0.1%
Macrolides	~22%	~2%
Fluoroquinolones	<2%	0
Ceftriaxone	<3% Intermediant Resistance	
TMP/SMX	13%	14.2%
Doxycycline	~10%	1.5%

1) Percentage of penicillin non-susceptible S. pneumoniae in Canada: 1988-2007. [http://microbiology.mtsinai.on.ca/data/sp/sp_2007. shtml#figure1]. 2) J Otolaryngol Head Neck Surg. 2011 May;40 Suppl 2:S99-193 3) Antimicrob Agents Chemother. 2003

Acute (Bacterial) Exacerbation Chronic Bronchitis Guidelines

- '1st-line': aminopenicillins, doxycycline & TMP-SMX recommended for patients without risk factors for treatment failure.
- 2nd generation macrolides, and some 2nd & 3rd generation cephalosporins may be better choices given concerns regarding emerging antimicrobial resistance…

Can Respir J. 2003 Jul-Aug;10 Suppl B:3B-32B

1st-line vs 2nd-line Abx for AECB

- Meta-analysis, 12 RCTs, 1st vs 2nd line antibiotics[1]
  - 2nd line improved clinical outcomes (OR 0.51; CI 0.34 to 0.75).
  - No difference mortality or adverse effects
  - * No information on risk factors for poor outcomes, included out-pts as well as hospitalized patients
- RCT 137 pts, non-significant difference amoxicillin vs amoxicillin/clavulanate (90.9% vs 92.8%) in primary care[2]

1) Chest. 2007 Aug;132(2):447-55 2) Int J Chron Obstruct Pulmon Dis. 2009;4:45-53.

AECB – all the same…

	Treatment Success	# of RCTs
Macrolide vs Quinolone[1]	OR 0.94 (0.73–1.21)	7
Amoxicillin/ clavulanate vs Quinolones[1]	OR 0.86 (0.55–1.34)	4
A/C versus macrolides[1]	OR 1.70 (0.72–4.03)	7
Azithro vs Amoxil/Amox-clav	RR 1.09 (0.64-1.85)	15
Amox/Amp vs Trimethopri	OR 1.68 (0.91-3.09)	5

Considerations: Non-inferiority designs, No discussion of severity of illness, risk factors for poor outcome, ?regional abx resistance profiles…

1) Eur Respir J. 2007 Jun;29(6):1127-37 2) Azithromycin for acute lower respiratory tract infections. Cochrane Oct 2008. CD 001954 3) Can Fam Physician. 2009 Jan;55(1):60-7

Risk of Treatment Failure

- Age <2, or >65, daycare
- Previous hospitalization or abx use (w/in 3mo)
- Co-morbidities
- Degree of pulmonary impairment, frequency of exacerbations
- Immunocompromised

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CAP Guidelines
1st Line for uncomplicated

Canada and the US:[1,2]

- Macrolide (azithro\clarithro\erythro) or Doxycycline

British:[3]

- Amoxicillin preferred 1st agent: 500 mg tid.
- If allergic, Doxycycline or clarithromycin

1) Can Respir J Vol 7 No 5 September/October 2000 2) IDSA/ATS Guidelines for CAP in Adults • CID 2007:44 (Suppl 2) • S000 3) Thorax 2009;64[suppIII]

CAP and Atypical Pathogens
(Chlamydia, Mycoplasma, and Legionella)

- Mild-Mod CAP: Sys Rev 18 RCTs, 6749 pts
  - No advantage of antibiotics active against atypical pathogens over β lactam antibiotics (0.97, CI 0.87 - 1.07).[1]
- In hospital: Sys Rev 25 RCTs, 5244 pts
  - No diff mortality RR 1.15 (CI 0.85-1.56) or clinical efficacy[2,3]

1) BMJ 2005;330:456–60. 2) Cochrane 2008, Issue 1. Art. No.: CD004418. 3) *Arch Intern Med 2005;**165:1992–2000 4)*** Cochrane Database Syst Rev. 2009 Oct 7;(4):CD002109

Known diagnosis of Atypical Pathogens in CAP…

	% failing to reach clinical cure or improvement		
	Mycoplasma	**Chlamydia**	**Legionella**
Macrolide/Quinolone	**7**	**13**	**11**
B-lactam	**13**	**4**	**39**
	NSS	**NSS**	**SS**

1) BMJ 2005;330:456–60

The Rise of Resistant Bacteria
(In Canada)

- While resistance has ↓ or stabilized for most abxs, macrolide resistance continues to ↑:
  - (1993 → 1.9%, 2005 →19%)[1]
- ↑ resistance in those tx in past 3 mo with:
  - TMP-SMX (OR 5.97)
  - Azithromycin (OR 2.78)[2]

1) **Trends in Antimicrobial Prescribing and Pneumococcal Resistance, Canada, 1993-2005**
2) Clinical Infectious Diseases2005;40:1288–97 3) Clin Infect Dis. (2006) 43 (4): 432-438

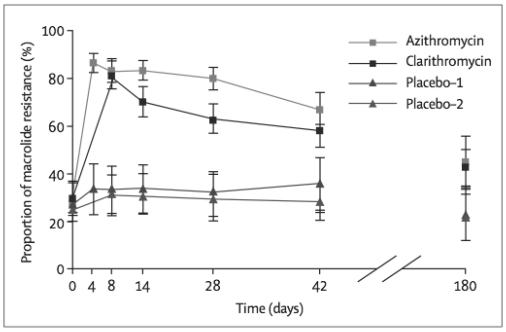

Figure 2: **Temporal changes in the proportion of macrolide-resistant streptococci after azithromycin and clarithromycin use**
Data shown are for all 204 volunteers followed through to day 42, and for 99 volunteers followed through to day 180. Error bars are 95% CI.

Lancet. 2007 Feb 10;369(9560):482-90

Sinusitis Guidelines

- Canada[1]: Amoxil first line. TMP/SMX or Macrolide may be alternative.
- US[2]: Amoxicillin-clavulanate 1st line, Doxy as an alternative
  - ↑ prevalence of H. influenzae among URTIs of children since the introduction of conjugated pneumococcal vaccines
  - Macrolides,TMP-SMX not recommended due to high levels of resistance (30-40%)
  - Tx 5-7d
  - **2 RCTs compared amoxicillin to amoxicillin-clavulanate no benefit with amoxicillin-clavulanate[3,4]**

1) Allery, Asthma & Clinical Immunology 2011, 7:2 2) IDSA Clinical Practice Guidelines for Acute Bacterial Rhinosinusitis in Children and Adults 2012. 3) Pediatrics 2001; 107:619–25.63. 4) Pediatrics 1986; 77:795–800.

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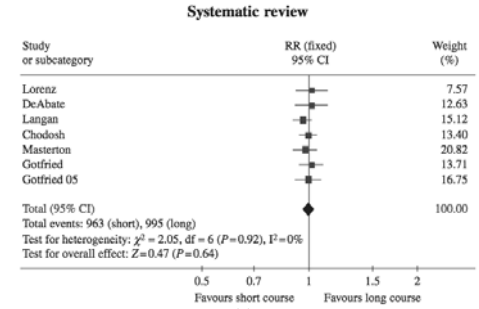
How Long Should We Treat?

- Sinusitis: Sys Rev, 12 RCTs, 4430 patients[1]
  - No difference short-course (3-7d) vs long-course (6-10d)
  - Clinical success (OR 0.95, CI 0.81-1.12) microbiological efficacy; relapses; or adverse events
- CAP:
  1) RCT, 119 pts, 3d IV amoxicillin ± 5d po amoxil[2]
  - 3d tx not inferior to 8 d
  2) Sys Rev: Short (7-8d) vs prolonged (10-15d) abx[3]
  - No diff mortality or overall recurrence of hospital acquired pneumonia

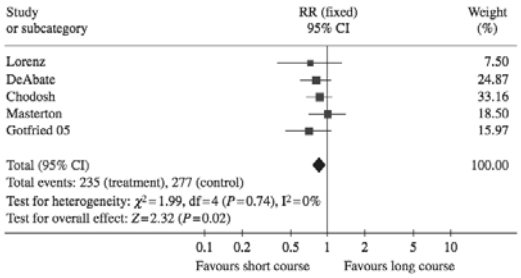
Br J Clin Pharmacol. 2009 Feb;67(2):161-71 2) BMJ 2006; 332 doi: 10.1136/bmj.332.7554.1355 3) **Cochrane Database Syst Rev. 2011;(10):CD007577.**

Short (5d) vs Long (7-10d) Duration Abx Treatment Success AECB



J Antimicrob Chemother. 2008 Sep;62(3):442-50.

Short vs Long Duration Abx Adverse Events AECB



J Antimicrob Chemother. 2008 Sep;62(3):442-50.

OR for Penicillin-Resistant S. pneumoniae According to Daily Dose & Duration of Last Abx Used

Variable	No. of Children	No. of PRSp Carriers	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Last β-lactam						
Daily dose						
No use†	780	10	1.0		1.0	
Low†	84	6	5.9 (2.1-16.7)	.002	7.5 (2.5-22.6)	<.001
High	54	0	NA	.9	NI	
Missing‡	23	0	NA	.9	NI	
Duration of treatment						
No use†	780	10	1.0		1.0	
Long†	139	6	3.5 (1.3-9.8)	.02	3.9 (1.4-11.2)	.01
Short	23	0	NA	.9	NI	

JAMA. 1998 Feb 4;279(5):365-70

Summary

	Pathogens	1st Line	2nd Line	Length of Tx
Chronic Bronchitis	S. Pneumoniae H. Inflluenzae M. catarrhalis	Amoxicillin/Doxycycline	A/C, Macrolide, Quinolone,	5d
CAP	S. Pneumoniae H. Influenzae M. Pneumoniae C. Pneumoniae	Doxycycline/Amoxicillin	Coverage of atypicals	Until afebrile for 72 hrs?[1,2]
Sinusitis	S. Pneumoniae H. Influenzae M. catarrhalis	Amoxicillin/Doxycycline	A/C, Macrolide, Quinolones	5-7d

1) Lancet 2003;362:1991–2001 2)Curr Opin Infect Dis 2007; 20:177–81

Delayed Antibiotic Rx….

- May decrease proportion of pts who receive antibiotics from 93-32%[1] (URTI)
- Facilitates education
- No difference in symptoms on day 1 & day 7[2]

1) Spurling GKP, Del Mar CB, Dooley L, Foxlee R. Delayed antibiotics for respiratory infections. Cochrane Database Syst Rev 2007;3:CD004417. 2) Cochrane Database Syst Rev. 2004 Oct 18;(4):CD004417

Thanks for your questions and discussion.

Thanks for completing your course evaluations.

HAVE A SAFE TRIP HOME

We hope to see you next year!