# "When Faith Becomes Blind, It Dies…"

Aaron M Tejani, BSc(Pharm), PharmD, ACPR

April.19.2007

Fraser Valley Chapter CSHP-BC

## Declaration

- Have not accepted honorariums/gifts directly or indirectly from the pharmaceutical industry in the last 4 years
- No direct or indirect financial associations with the pharmaceutical industry in the last 4 years

## What is the Plan?

- Look at 5 Recent Systematic Reviews
- Call into question…
  - What we have historically been taught to do
  - What we see happening in practice

## Objectives

- Describe the importance of:
  - Systematic Reviews (SR) and Meta-analyses (MA)
- "An Overflow of good converts to bad"
  - Long-acting beta-agonists for asthma
- "To Pee or Not to Pee…"
  - Furosemide for acute renal failure
- "It is best to win without fighting"
  - Atypical coverage for CAP
- "Double, double, toil and trouble"
  - Combination therapy for sepsis
- "If you treat us with warfarin and ASA do we not bleed?"
  - Adding ASA to warfarin

## Importance of Systematic Reviews

- An systematic, rigorous, reproducible, defendable process
- Attempt to find all the best evidence to answer a clinical question
- Provides assessment of the "big picture"
  - "All the evidence" as opposed "some of the evidence" (e.g. narrative review)

## What is a Meta-Analysis?

- Pooling of similar data together
  - Quantitative
  - Allows data from many small trials to come together
    - More power to see differences
- Always ask…
  - Does it make sense to combine these trials?
  - Was heterogeneity assessed and explored (if found)?
    - Heterogeneity= different effects of a drug seen across similar trials
- Be careful!
  - Not all MAs combine data from a SR
  - E.g. there maybe 5 trials out there but you only meta-analyze the 2 trials that you choose

## Summary of the SRs that I will Show you…

- Screened for Quality
  - All follow the QUOROM Statement
- Methods are sound
- Likely to have found most relevant trials
- My summary is not a substitute for your appraisal
  - Limited time so I only will summarize findings
  - Encourage you to read them carefully
- NOTE: This is not meant to be a comprehensive review of literature on each of the 5 subjects

## Effect of Long-Acting Beta-Agonists on Severe Asthma
## Exacerbations and Asthma-Related Deaths

- Salpeter et al. *Ann Intern Med.* 2006;144:904-912.
- Question:
  - What is the effect of long-acting beta-agonists on severe, life-threatening, or fatal asthma exacerbations?
- Background:
  - LABA improves lung function and symptoms in asthma and COPD patients
  - Bigger question: What is the net effect?

## Effect of Long-Acting Beta-Agonists on Severe Asthma
## Exacerbations and Asthma-Related Deaths

- Health Canada Warning October 2005
  - "…advising Canadians of the possible increased risks of asthma-related deaths associated with the use of a class of asthma drugs known as long-acting beta-2 agonists."
  - http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_107_e.html
  - This was based on the SMART trial
- Why would LABA do this?
  - Desensitization and down regulation of beta receptors

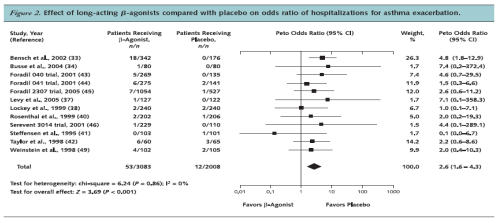
## Effect of Long-Acting Beta-Agonists on Severe Asthma
## Exacerbations and Asthma-Related Deaths

- Search
  - Up to December 2005
- Trials
  - RCT, placebo controlled, >3 months
- Search results
  - 19 RCTs
    - Excluded
      - 51 trials < 3 months duration
      - 1 trial with asthma and COPD patients
      - 28 trials did not report on asthma-related death

## Effect of Long-Acting Beta-Agonists on Severe Asthma
## Exacerbations and Asthma-Related Deaths

- Results
  - All studies allowed prn beta agonists
  - 54% of patients used inhaled steroids (ICS)
  - n=33, 826, mean duration 6 months (3 to 9)
  - All were double-blind and used intention-to-treat analyses

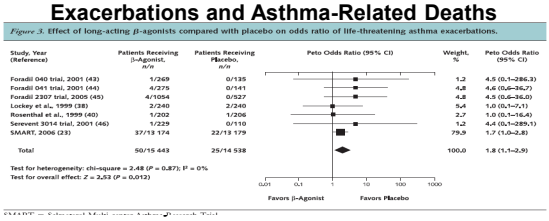
## Effect of Long-Acting Beta-Agonists on Severe Asthma
## Exacerbations and Asthma-Related Deaths




**Hospitalizations for Asthma: Worse with LABA**

Absolute risk increase = 1.12%, NNH=100, p<0.001

## Effect of Long-Acting Beta-Agonists on Severe Asthma
## Exacerbations and Asthma-Related Deaths




**Life-threatening exacerbations: Worse with LABA**

Absolute risk increase = 0.15%, NNH=667, p=0.012

## Effect of Long-Acting Beta-Agonists on Severe Asthma
## Exacerbations and Asthma-Related Deaths

- Asthma-related deaths: ***Worse with LABA***

14 trials reported this outcome

- Absolute risk increase over 6 months
  - 0.07% (95%CI 0.01% to 0.1%), NNH=1430
- Include 28 trials that did not report this outcome
  - Assume no deaths occurred
  - Absolute risk increase over six months
    - 0.06%, NNT=1667

## Effect of Long-Acting Beta-Agonists on Severe Asthma
## Exacerbations and Asthma-Related Deaths

- Was the result the same in patients on inhaled steroids?
  - Risk of hospitalizations
    - OR 2.1 (95% CI 1.2 to 3.4)
    - ***A 2-fold increase in hospitalizations with LABA use***
- What is the possible explanation?
  - Desensitization and down-regulation of beta-receptors due to persistent stimulation

## Meta-analysis of frusemide to prevent or treat acute renal failure

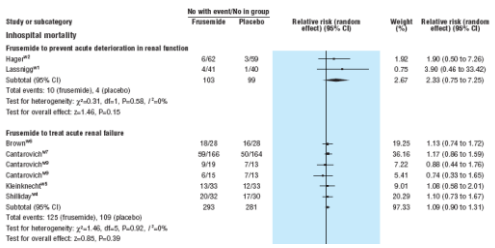
- Kwok et al. BMJ 2006;333:420-25.
- Background:
  - Non-oliguric renal failure has a better outcome than oliguric renal failure
    - (*Clin Exp Dial Apheresis* 1983;7:145-67.)
  - Loop diuretics are used to make patients oliguric and prevent dialysis
- Question:
  - What are the effects of furosemide when preventing or treating renal failure?

## Meta-analysis of frusemide to prevent or treat acute renal failure

- Search
  - Up to February 2006
- Trials
  - RCT, adults, furosemide vs placebo
- Results
  - 9 RCTS, n=849
    - 3 RCTS for prevention (doses 1-2mg/hr infusion, or 80 mg IV bolus)
    - 6 for treatment (doses 600-3400 mg/day)
      - 1 study, acute on chronic RF
      - 5 had acute RF

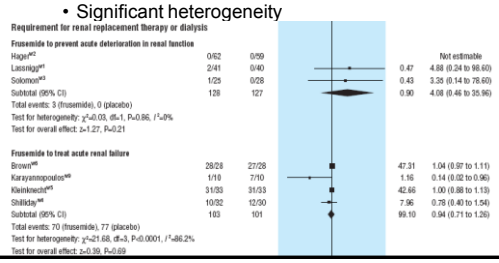
## Meta-analysis of frusemide to prevent or treat acute renal failure

- In-hospital mortality: ***No difference vs placebo***
  - RR 1.11 (95% CI 0.92 to 1.33, P = 0.28)



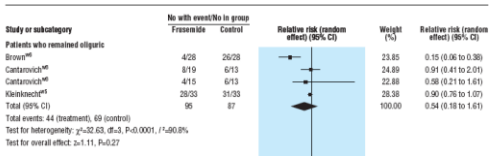
## Meta-analysis of frusemide to prevent or treat acute renal failure

- Need for Dialysis: ***No difference vs placebo***
  - RR 0.99 (95% CI 0.80 to 1.22, P = 0.91)
    - Significant heterogeneity



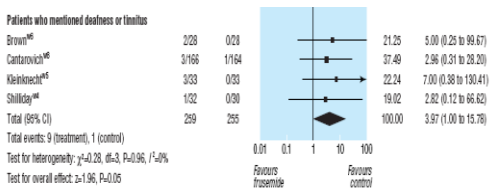

## Meta-analysis of frusemide to prevent or treat acute renal failure

- Persistence of oliguria: ***No difference vs placebo***
  - RR 0.54 (95% CI 0.18 to 1.61, p=0.27)
    - Significant heterogeneity




## Meta-analysis of frusemide to prevent or treat acute renal failure

- Patients reporting tinnitus or deafness
  - ***Worse with furosemide***
  - RR 3.97 (95% CI 1.0 to 15.8, p=0.05)




## Meta-analysis of frusemide to prevent or treat acute renal failure

- Limitations
  - Significant heterogeneity
    - Why are "similar" trials showing different effects?
      - Definitions, patient severity, small numbers…
  - Small numbers
- Possible explanation for findings
  - Furosemide induces diuresis in milder RF only
  - Hence, diuretic response to fursoemide is due to mild RF in patients

## Atypical Coverage in Hospitalized CAP Patients

- Shefet D et al.
  - *Arch Intern Med. 2005;165:1992-2000*
- Question:
  - Do you need to cover for atypical organisms in the empiric treatment of CAP?
- Search:
  - Up to August 2004
- Trials:
  - RCTs typically beta-lactam versus monotherapy (i.e. fluoroquinolones)
  - Atypical coverage vs no atypical coverage

## Atypical Coverage in Hospitalized CAP Patients

- Background
  - Canadian Cap Guidelines 2000

cases. Thus, "atypical" agents are probably a more frequent cause of CAP than is currently recognized, and the use of a macrolide or a fluoroquinolone for the empirical initial treatment of patients presenting with CAP appears warranted.

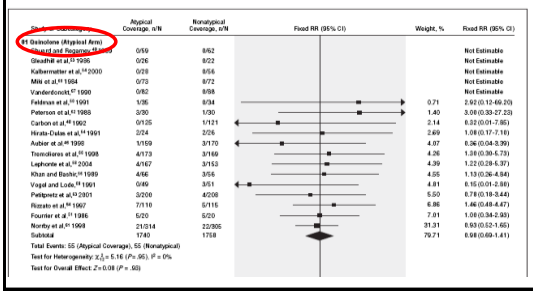
CID 2000;31 (August)

## Atypical Coverage in Hospitalized CAP Patients

- Search results:
  - 24 RCTs
  - Patients=5015
  - Treatment duration=10 days
  - 18 of the 24 studies sponsored by the drug industry
  - Comparators: Amoxicillin (the most), Cefaclor, Amox-clav, Ceftriaxone

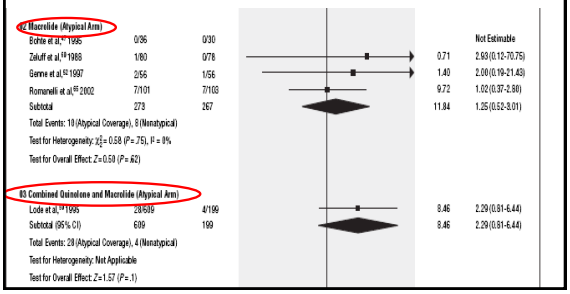
## Atypical Coverage in Hospitalized CAP Patients

- Results: Total Mortality NO ADVANTAGE




## Atypical Coverage in Hospitalized CAP Patients

- Results: Total Mortality NO ADVANTAGE (n=4846)




## Atypical Coverage in Hospitalized CAP Patients

- Results:
  - Clinical failure (n=4682)
  - Overall = NO ADVANTAGE
    - All Trials RR 0.92 (95% CI 0.82-1.03)
    - Trials with adequate allocation generation
      - i.e. appropriately randomized patients
      - RR 0.99 [95% CI, 0.82-1.19]
    - Trials with adequate allocation concealment
      - i.e. minimal selection bias
      - RR 0.98 [95% CI, 0.81-1.19]

## Atypical Coverage in Hospitalized CAP Patients

- Results:
  - Bacteriological failure (n=1968)
    - All trials
      - RR 0.73(95% CI 0.59-0.91)
        - » ADVANTAGE with atypical coverage
    - Only the best quality trials
      - There was NO ADVANTAGE SEEN
        - » Adequate allocation generation and concealment
        - » RR 0.96 (95% CI 0.61-1.52)

## Atypical Coverage in Hospitalized CAP Patients

- Results:
  - Adverse events (n=4261)
    - Total ADR = NO ADVANTAGE
    - Requiring discontinuation =NO ADVANTAGE
    - GI ADRs
      - RR 0.73 (95% CI 0.54-0.99)
      - ATYPICAL COVERAGE BETTER

## Atypical Coverage in Hospitalized CAP Patients

- If Legionella was isolated?
  - Atypical coverage patients did better only for bacterial eradication
  - Benefit lost when you look at higher quality studies

## Atypical Coverage in Hospitalized CAP Patients

- Bottom Line
  - No advantage in empirically covering for atypical organisms in hospitalized CAP patients
    - Especially using fluorquinolones or macrolides as initial therapy

## Beta-lactam (BL) Monotherapy vs Combination with Aminoglycosides (BL-AG) for Sepsis

- Silbiger P et al. Cochrane Library November 2005
- Question:
  - Is there a difference in efficacy and safety of BL versus BL-AG for patients with sepsis?
- Search:
  - Up to July 2004
- Trials:
  - RCTs of hospitalized with sepsis (hospital or community acquired)

## (BL-AG) vs (BL) Monotherapy for Sepsis

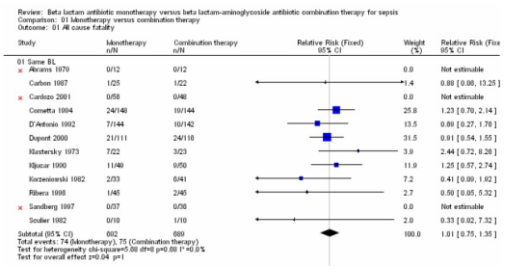
- Silbiger P et al. Cochrane Library November 2005
- Search results:
  - 145 citations
  - 64 RCTs met inclusion criteria
  - Patients=7586
  - Abdominal, UTI, Pneumonia, suspected gram-negative sepsis

## (BL-AG) vs (BL) Monotherapy for Sepsis

- Background:
  - Reasons for double-coverage
    - Synergy
    - Enhanced spectrum
    - Lower resistance pressure
  - Likely most beneficial in patients with suspected gram negative sepsis

## (BL-AG) vs (BL) Monotherapy for Sepsis

- Results: Total Mortality NO ADVANTAGE

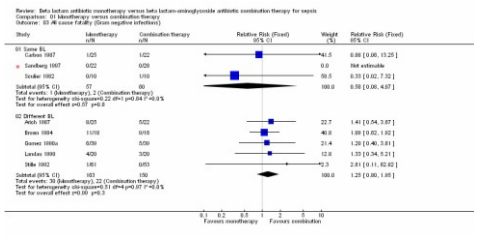


## (BL-AG) vs (BL) Monotherapy for Sepsis

- Results: Total Death for studies with a different BL in both groups
  - MONOTHERAPY BETTER
  - RR 0.83 (95% CI 0.69-0.99)
- Total Death for studies with the same BL in both groups
  - NO ADVANTAGE FOR (BL-AG)

## (BL-AG) vs (BL) Monotherapy for Sepsis

- Results: Gram negative infections NO ADVANTAGE



## (BL-AG) vs (BL) Monotherapy for Sepsis

- Note: Sepsis studies with different BL
  COMBINATION BETTER
  clinical failure RR 0.77 (95% CI 0.69-0.86).
  - Keep in mind that for Total Death with different BL
    - NO DIFFERENCE
    - Arguably the more "objective" outcome would be more reliable
      - i.e. Clinical failure is subject to more bias and hence is less reliable

## (BL-AG) vs (BL) Monotherapy for Sepsis

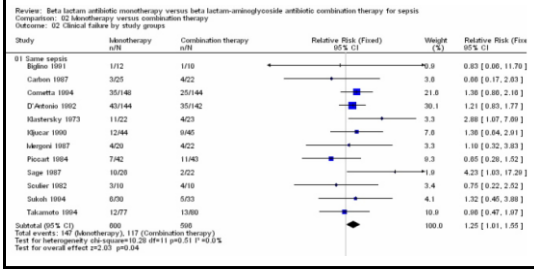
- Adverse events
  - Any ADR NO ADVANTAGE
  - Nephrotoxicity RR 0.30 (95% CI 0.23-0.39)
    - MONOTHERAPY BETTER
- Gram positive infections
  - NO ADVANTAGE
- Resistance (superinfection or colonization)
  - NO ADVANTAGE

## (BL-AG) vs (BL) Monotherapy for Sepsis

- Results: Clinical Failure and Subgroups
  - NO ADVANTAGE FOR
    - Most subtypes of infection
    - Gram negative or Pseudomonas infections
  - Benefit for combination therapy in the subgroup of "sepsis patients"

## (BL-AG) vs (BL) Monotherapy for Sepsis

- Results: Clinical Failure in "Sepsis" studies with same BL



## (BL-AG) vs (BL) Monotherapy for Sepsis

- Results: Clinical Failure in Overall "Same BL" trials
  - NO ADVANTAGE

## (BL-AG) vs (BL) Monotherapy for Sepsis

- Bottom Line (from authors)
  - "We have not identified a specific pathogen, or pathogen group, where combination therapy is advantageous."
  - "We have not identified a specific site of infection, or disease severity, where combination treatment has an advantage."
- A good guideline…

Monotherapy with third- or fourth-generation cephalosporins is as effective as combination therapy with a beta-lactam and an aminoglycoside for the empirical treatment of nonneutropenic patients with severe sepsis.

Intensive Care Med (2001) 27: S128–S134

## Who gets Warfarin Plus ASA?

- Larson RJ et al.
  - J GEN INTERN MED 2004;19:879–886.
- Question:
  - Which patients who are on warfarin need ASA as well?
- Search:
  - Up to October 2003
- Trials:
  - RCT of Warfarin alone OR Warfarin plus ASA

## Who gets Warfarin Plus ASA?

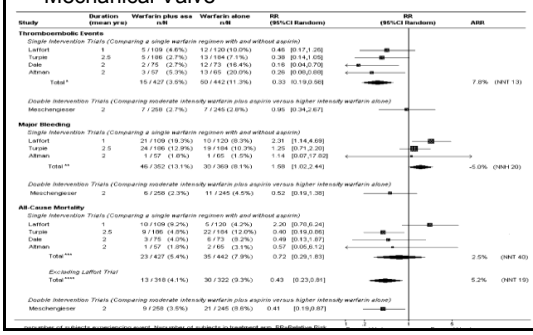
- Background
  - Anecdotal experience tells me that ASA is added to warfarin for:
    - Mechanical heart valve patients
    - "High" risk cardiac patients with and without Atrial fibrillation
    - Post myocardial infarction patients

## Who gets Warfarin Plus ASA?

- Search results:
  - 5 RCTs in Mechanical valve patients
  - 3 RCTs in post-MI patients
  - 1 in Afibr patients at "high risk" for thromboembolism

## Who gets Warfarin Plus ASA?

- Mechanical Valve



## Who gets Warfarin Plus ASA?

- Mechanical Valve Trials
  - Thromboembolic events
    - COMBINATION BETTER ARR=7.8%, NNT=13
  - Major bleeding
    - COMBINATION WORSE ARI=5%, NNT=20
  - Total Death
    - COMBINATION BETTER ARR=5.2%, NNT=19

## Who gets Warfarin Plus ASA?

- Post MI trials (3)
  - NO ADVANTAGE FOR ALL 3 ENDPOINTS
- Afibr Trial
  - NO ADVANTAGE FOR ANY ENDPOINT

## Who gets Warfarin Plus ASA?

- Bottom line
  - Add ASA to Warfarin only for patients with Mechanical Heart Valves
    - Consider the trade-off between major bleed increase and mortality/thrombo-embolism reduction

## When Should Warfarin be Added to ASA?

- *Ann Intern Med.* 2005;143:241-250. Systematic review to see which post-acute coronary syndrome ASA patients need warfarin added
  - Death = NO ADVANTAGE
  - MI = ARR 1.9% (Comb better) NNT~50
  - Ischemic stroke = ARR 0.4% (Comb better) NNT~200
  - Major bleeds = ARI 0.9%, NNH~100

## Questions?

Fill your bowl to the brim
and it will spill.
Keep sharpening your knife
and it will blunt.
Chase after money and security
and your heart will never unclench.
Care about people's approval
and you will be their prisoner."

Do your work, then step back.
The only path to serenity.

Tao Te Ching
Lao-tzu (abt.551-479 BCE)