Update in General Medicine

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Objectives

• At the end of this session you should be able to:
  • Describe the main results of several important reports from the past year
  • Decide how you want to change your practice in the context of these findings
Disclosure

• I have no direct financial relationships with any commercial firm having any interest in any of the reports or topics I am about to discuss

• There is some discussion of non-FDA approved medications or indications
Method

• Examined the title of every original research article published from 10/1/2012 through 10/1/2013 in
  • Annals of Internal Medicine
  • JAMA
  • New England Journal of Medicine
  • BMJ
  • The Lancet
• Surveyed articles reviewed in ACP Journal Club, various updates, and other sources
• Selected ~100 for review of abstracts
• Chose ~50 abstracts, ranked according to potential for practice change
• Reviewed the most interesting few for this presentation
Notes and Cautions

- Highly idiosyncratic selection process
  - Substantial risk of “confirmation bias” or splash factor
- Limited subset of huge research database
- Risk of publication bias
- A single study should be handled carefully – it may bite
  - Unlike wolves, studies are easier to manage in packs
- I may lack depth of contextual knowledge for understanding a study properly
- My interpretation is not handed to me by angels
Audience Response

• I currently transfuse patients with upper GI bleeding when:
  A. Their hemoglobin falls below 9, or below 10 for someone with vascular disease
  B. Their hemoglobin falls below 7, unless they are massively exsanguinating
  C. Their hemoglobin drops more than two grams from admission
  D. None of these. Measured hemoglobin is not an important part of the transfusion decision
When to transfuse in Upper GI hemorrhage

• Transfusion Strategies for Acute Upper Gastrointestinal bleeding
  • C Villanueva et al.
  • NEJM
  • January 2013

• Funding appears to be public
Transfusion in UGI bleeding

• Study Question
  • For UGI bleeding, is a transfusion trigger of 7 better than a transfusion trigger of 9?

• Background
  • In critically ill patients, 7 is better than 9
  • Trials excluded acute GI bleeding
Design – Non-blinded RCT

• 900 subjects in Barcelona
  • Age>18
  • Hematemesis or melena but not exsanguinating
  • No symptomatic vascular disease
  • Not considered very low risk

• Randomized to
  • Restrictive (threshold 7, target 7-9)
  • OR
  • Liberal (threshold 9, target 9-11)
  • Transfused 1 unit at a time and rechecked

• All had EGD within 6 hours

• Followed 45 days for death
  • Sought reduction from 10% to 5%
## Results – Baseline

<table>
<thead>
<tr>
<th></th>
<th>Restrictive</th>
<th>Liberal</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUD Bleed</td>
<td>51%</td>
<td>47%</td>
</tr>
<tr>
<td>Variceal Bleed</td>
<td>23%</td>
<td>24%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>Admission Hgb</td>
<td>9.6</td>
<td>9.4</td>
</tr>
</tbody>
</table>
Cautions

• Single Barcelona hospital
• All had early EGD to treat and guide therapy
• Excluded massively exsanguinating patients
  • Also excluded patients with vascular disease
Conclusions

• In non-exsanguinating UGI bleed, a threshold hemoglobin of 7 is superior to a threshold of 9 for RBC transfusion
  • I will generalize this to US
  • I will not require emergent EGD in order to apply it
Audience Response

• I have used vasopressin in the setting of managing a cardiac arrest
  A. Never, though I do manage arrests
  B. Occasionally but not regularly
  C. Usually
  D. Doesn’t apply – I never manage an arrest
Improving Cardiac Arrest Outcome

• Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest
  • S Mentzelopoulos et al.
  • JAMA
  • July 17, 2013

• Funded by Greek government and medical society
Vasopressin and Steroids in Cardiac Arrest

• Study Question
  • Does systematically adding vasopressin and steroids during and after a cardiac arrest improve neurologically favorable outcomes?

• Background
  • Severe neurological dysfunction is common after arrest
  • Single small prior study (same authors) indicated improved overall survival
  • Vasopressin is currently an option in arrest, used variably
Design – Blinded RCT

• 300 patients suffering in-hospital arrest in 1 of 3 Greek hospitals
  • Age 18+, no terminal illness, no pre-hospital arrest, requiring pressors

• Randomized **without consent** to
  • Vasopressin plus epinephrine plus methylprednisolone during CPR, plus hydrocortisone after resuscitation
  • OR
  • Epinephrine plus placebos

• Followed until discharge for survival and favorable neurological status (no or moderate neurological disability)
  • Sought improvement from 4% to 15%
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>VSE</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Male</td>
<td>73%</td>
<td>64%</td>
</tr>
<tr>
<td>Pre-arrest hospital days</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>CAD</td>
<td>32%</td>
<td>34%</td>
</tr>
</tbody>
</table>
Results – Outcomes

![Bar chart showing results for Witnessed, Asystole, and Alive/favorable categories.
- Witnessed: VSE > Control
- Asystole: VSE > Control
- Alive/favorable: VSE > Control with an asterisk (*)]
Cautions

• Three Greek hospitals
• Some baseline differences
• Relative roles of steroids and vasopressin unclear
• Difficult to retrieve actual survival from the data provided
Conclusions

• Despite overall poor outcomes, addition of vasopressin and steroids appears to improve favorable neurological survival after in-hospital arrest

• Complicated issue
  • Will require revision of protocols
  • Regional protocols already use vasopressin as option
  • Immediate practice change impractical
    • Watch for further protocol changes

• Unconsented human subjects research is uncommon, and should stay that way
Audience Response

• For my patients with recurrent leg cellulitis, I have been:
  A. Treating each episode as a separate issue
  B. Trying to prevent episodes by treating their fungal nails
  C. Trying to prevent episodes with prolonged antibacterial antibiotics
  D. Trying to prevent episodes with topical treatments
Recurrent Cellulitis

• Penicillin to prevent recurrent leg cellulitis
  • K Thomas et al
  • NEJM
  • May 2013

• Funded by a British charitable organization
Penicillin and Cellulitis

• Study Question
  • Does prolonged oral penicillin reduce recurrent cellulitis?

• Background
  • Leg cellulitis is common and often recurrent
  • Role of prophylactic antibiotics is unclear
Design – Blinded RCT

• 274 patients in 28 UK and Irish hospitals/areas with history leg cellulitis
  • At least 2 prior episodes, no recent prophylactic antibiotics, no leg ulcerations

• Randomized to receive 12 months of
  • Oral Penicillin 250 mg bid OR
  • Placebo

• Followed 36 months for recurrent episode of cellulitis
  • Sought a reduction from 35% to 17% over 3 years
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Penicillin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>Male</td>
<td>39%</td>
<td>41%</td>
</tr>
<tr>
<td>BMI</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Prior episodes</td>
<td>3.7</td>
<td>3.8</td>
</tr>
</tbody>
</table>
Cautions

• Less effective in those with more than 3 prior episodes or BMI over 35
• The (non-significant) mortality increase is disturbing
• The effect is not maintained after stopping prophylaxis
Conclusions

• Penicillin appears to prevent recurrent cellulitis, as long as you stay on it
• Whether there is a risk is unclear
• I will hold it as an option
Audience Response

• **Without** other special considerations (e.g. CAD), my usual first choice medication for an older patient with hypertension is
  
  A. Hydrochlorothiazide
  B. Chlorthalidone
  C. A beta blocker
  D. An ACE inhibitor
  E. Something else
  F. Nothing – I’ll do almost anything avoid starting antihypertensives in my older patients
Chlorthalidone? HCTZ?

- Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults
  - I Dhalla et al.
  - Ann Int Med
  - March 19, 2013

- Funded by Ontario government
Chlorthalidone vs HCTZ

• Study Question
  • Is Chlorthalidone superior to HCTZ in older adults?

• Background
  • Thiazide diuretics are important for hypertension
  • Chlorthalidone, though less widely used, has been proposed as more effective than HCTZ
    • Mixed data, no good trials
    • Perhaps because of potency (per milligram) and longer half-life
  • Chlorthalidone has good evidence for long term benefit in older patients
Design – Cohort

• Ontario residents age 66+ who started either chlorthalidone or HCTZ from 1993 – 2010
  • Information derived from government insurance databases
  • Excluded those with recent hospitalization for MI, CVA, CHF
• Followed up to 5 years for composite of death, or hospitalization for MI, CHF, CVA, and safety outcomes
• Anticipated effects not stated
• Used propensity score matching, a tool for trying to deal with confounding
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Chlorthalidone</th>
<th>HCTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>Oral diabetes med</td>
<td>10.8</td>
<td>12.3</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>37.7</td>
<td>21.5</td>
</tr>
<tr>
<td>ACE or ARB</td>
<td>34</td>
<td>46</td>
</tr>
</tbody>
</table>
Cautions

• Cohort studies are very challenging
  • Poorly understood differences may account for findings
  • Propensity matching may be useful, does not solve the problem
  • More beta blockers, fewer ACE/ARB in Chlorthalidone group
    • May reflect important differences in patients or doctors
    • Could account for not seeing an outcome difference
Conclusions

• Chlorthalidone, as used in Canada, is not clearly better than HCTZ and may cause more hypokalemia

• I have trouble with chlorthalidone
  • Hard to get, expensive, often not covered, low dose unavailable
  • Superiority to HCTZ not well-established
  • I am (sort of) shifting back to HCTZ, particularly in older patients
Audience Response

• For tennis elbow, in addition to education, analgesics, and maybe some physical therapy, I am likely to provide:
  A. A steroid injection
  B. A TENS unit
  C. A forearm band
  D. More than one of the above
  E. Something else entirely
Tennis Elbow

• Effect of corticosteroid injection, physiotherapy, or both on clinical outcomes in patients with unilateral lateral epicondylalgia
  • B Coombes, et al
  • JAMA
  • Feb 6, 2013

• Funded by Australian government
Tennis Elbow

• Study Question
  • Is steroid injection or physical therapy useful for tennis elbow?

• Background
  • Tennis elbow is common
  • Standard therapies include injection and physical therapy
  • The effects of these therapies are not well studied
Design – Partially blinded RCT

• 165 Australians recruited through advertising in Brisbane
  • Age 18+, >6 weeks of pain over lateral epicondyle
• Received
  • An injection of 10 mg triamcinolone acetonide plus lidocaine OR
  • Placebo (saline)
• AND
  • 8 weekly, individualized 30 minute physical therapy treatments and training
    OR
  • Nothing
• Followed 1 year for self-reported improvement and symptoms
  • Anticipated 25% worsening with steroids, 25% improvement with therapy
# Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Steroids</th>
<th>Therapy</th>
<th>Both</th>
<th>Neither</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>49</td>
<td>49</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>63</td>
<td>63</td>
<td>62</td>
<td>58</td>
</tr>
<tr>
<td><strong>Duration (Weeks)</strong></td>
<td>16</td>
<td>16</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td><strong>Pain Score</strong></td>
<td>62</td>
<td>63</td>
<td>59</td>
<td>62</td>
</tr>
</tbody>
</table>
Cautions

• Therapy was unblinded
  • Injection too? Lidocaine used.
• One particular approach to therapy and injection
• Rather small study
• But the results are discouraging
Conclusions

• Given costs and other potential problems, I will limit my use of injection, and will
  • Offer analgesics
  • Offer education
  • Maybe therapy
And by the Way...

• Adding a TENS unit to primary care management of tennis elbow in the UK:
  • Was not adhered to very well
  • And did not improve pain scores at any time over a year
  • In an unblinded trial

• LS Chesterton, BMJ, September 14, 2013
Audience Response

• I help my diabetics manage their health by, among other things
  A. Recommending weight loss and exercise
  B. Referring for medical nutrition therapy
  C. Specifying a Mediterranean diet plus extra virgin olive oil
  D. More than one of the above
  E. I’ve given up on all that lifestyle stuff, I just try to meet the D5
Diabetes Outcomes

- Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes
  - R Wing et al for the Look AHEAD research group
  - NEJM
  - July 11, 2013
- Funded by the NIH and other public agencies, foundations, and corporations
Lifestyle/Diabetes

• Study Question
  • Does an intensive weight loss and exercise program improve cardiovascular outcomes in overweight type 2 diabetics?

• Background
  • Obesity is an important component of diabetes
  • Weight loss and exercise are accompanied by notable metabolic improvements
  • Bariatric surgery appears to have a large impact on cardiovascular outcomes for diabetics
Design – non-blinded RCT

• 5000 US adults from 16 sites
  • Age 45-75
  • DM-II, BMI>25, A1C<11, SBP<160

• Received
  • Group + individual counselling
    • Weekly x 6 months, then decreasing
    • Goal intake 1200-1800 cal/day
    • Goal exercise 175 min/wk
    • Goal weight loss >7%
    • OR
  • 3 “support” sessions each year

• Planned follow-up 13+ years for
  • Combination CV death, MI, Stroke, Hospitalization or angina

• Anticipated reducing from 2% (control) to about 1.6% (active) per year

• Stopped early (10 y) for futility
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>41%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>A1C</strong></td>
<td>7.2</td>
<td>7.3</td>
</tr>
</tbody>
</table>
Results – Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss Y1</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>A1C Y1</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Main Outcome MI</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Indicates significant difference.
Cautions

• Favorable effects could be long-delayed
  • But weight differences were narrowing over time
• Intervention group got less meds, including statins
  • Presumably due to better metabolic parameters
  • But LDL was lower in controls
• There were other benefits
  • Increased fitness, partial remission of DM
• The control group was already pretty well controlled
Conclusions

• Intensive counselling for weight loss and exercise is at least not a powerful strategy to improve major diabetes outcomes

• Other specific diet strategies might be useful
  • Recent small trial of Mediterranean diet

• I will limit my time spent counselling
  • Focus on what I believe works
  • Metformin, Statins, BP control
Audience Response

• Regarding ARDS:
  A. I never manage it
  B. I manage it together with (or I am) an intensivist
  C. I manage it without a specifically trained intensivist
Upside-Down in the ICU

- Prone positioning in severe acute respiratory distress syndrome
  - C Guerin et al
  - NEJM
  - June 6, 2013

- Funding not clearly stated
  - “No commercial support”
  - Authors acknowledge various industry connections
Prone Positioning in ARDS

• Study Question
  • Does putting patients prone early in course of ARDS improve outcomes?

• Background
  • In ARDS, prone positioning improves oxygenation
  • Controversy whether this improves outcomes
  • Sometimes used as late “salvage” approach
Design – non-binded RCT

• 500 adults in (mostly) French ICU’s
  • ARDS < 36 hours, on mechanical ventilation, PEEP 5+

• Received
  • Prone positioning 16+ hours daily
  • OR
  • Usual semi-recumbent supine positioning
    • With “rescue” prone position in extremis

• Followed 28 days for death, 90 days for multiple outcomes
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Prone</th>
<th>Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Male</td>
<td>70%</td>
<td>66%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>82%</td>
<td>85%</td>
</tr>
<tr>
<td>BMI</td>
<td>28</td>
<td>29</td>
</tr>
</tbody>
</table>
Results – Outcomes

- **28 Day Death**: Prone (10) - Supine (30) *
- **90 Day Death**: Prone (20) - Supine (40) *
- **Off Vent at 90 D**: Prone (50) - Supine (40) *
Cautions

• Unblinded
  • Opportunity for differential treatment?
• Prone positioning is not simple
• Other care in France may be different
• Lacks a strong biological explanation
Conclusions

• Early “Prone-ing” may offer large survival benefit in selected ARDS
  • NNT about 6 to save a life

• **Not** an individual physician-patient decision
  • Will likely require ICU or hospital policy decision
  • Will certainly require team training

• I would advocate formally addressing this at appropriate committee level
Audience Response

• In my setting, Clostridium difficile infection:
  • Is a big and growing problem
  • Is a modest problem
  • Is just not an issue
A Clostridium Triptych

• Prevention
  • BC Johnston, Annals of Internal Medicine, December 18, 2012

• Treatment
  • Els van Nood, NEJM, January 31 2013

• Detection
  • MK Bomers, BMJ, December 22, 2012
Prevention of C Diff

• Systematic review and meta-analysis
• 20 RCT’s with about 4,000 total antibiotic-treated patients
• Received various probiotics or placebo (mostly)
  • Probiotics typically one or more lactobacillus, saccharomyces, streptococcus or bifidobacterium species
• Overall 66% reduction in C diff diarrhea
  • With no identifiable adverse effects
  • Better with higher doses (>10 billion CFU) and multiple strains
• **LATE NOTICE**
  • Conflicting report in Lancet, too late to include
Treatment of C Diff

• Randomized trial of 42 Dutch patients with recurrent C diff diarrhea
• Received oral vancomycin plus
  • Donor feces via nasoduodenal tube (OR not)
• Trial stopped early
  • 81% resolution with first feces infusion
  • About 25% with vancomycin alone
Detection of C Diff

• Study of a rapid (few seconds) diagnostic test for C diff diarrhea
• Based on gold standard of culture positive for toxigenic C difficile
• Among prepared stool samples:
  • Sensitivity 100%
  • Specificity 94-100%
• Among direct patient encounters:
  • Sensitivity 93%
  • Specificity 97%
Test Equipment - Cliff
Also Noted

• CABG is probably superior to stenting multivessel CAD in diabetics
  • But benefit is late, modest, and partially offset by increased stroke with CABG
  • NEJM, 12/20/2012

• Ultrafiltration is less effective than pharmacologic therapy in decompensated CHF with worsened renal function
  • NEJM 12/13/2012

• For prevention of stroke after TIA, clopidogrel plus aspirin is better than aspirin alone (in China)
  • NEJM 7/4/2013
And a Few More

• For primary prevention of cardiovascular disease, a Mediterranean diet plus nuts or extra-virgin olive oil is modestly better than a Spanish diet (?!)
  • NEJM 4/4/2013

• Saxagliptin did not improve cardiovascular outcomes in diabetics, and did slightly increase CHF hospitalizations
  • NEJM 10/3/2013
Summary

- Transfusion at 7 is better than 9 for non-exsanguinating GI bleeding
- Prolonged penicillin can help prevent recurrent leg cellulitis
- Whether chlorthalidone has advantages over HCTZ is unclear, but it has problems
- Tennis elbow probably is not helped much by steroid injection or physical therapy over the long run, and steroids may cause more recurrences
- Diabetes outcomes are not clearly improved with vigorous diet/exercise programs
- Some big policy issues for critical care
  - Vasopressin and steroids may help victims of arrest
  - Early prone positioning probably helps in severe ARDS
- Some non-traditional news for C difficile
Audience Response

• I am committing to
  A. Transfuse UGI bleeders at 7
  B. Use prolonged antibiotics for my patients with recurrent cellulitis
  C. Avoid steroid injections for tennis elbow
  D. Bring prone positioning to my ICU leadership for discussion
  E. Something else
  F. Nothing, until I read this stuff a bit closer and discuss it with colleagues
Remember:

• Before acting on anything you heard here, you may wish to study the original research, and discuss with colleagues or domain experts