Hippocrates (460 – 370 BC)

*Medicine Becomes a Science*

*By Robert Thorn*

Hippocrates, the father of medicine, was one of the first to argue that disease was a result of natural processes, rather than a punishment dealt out by supernatural forces.
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A 44 y/o schoolteacher with no significant past medical history presents with a 4 day history of fever and a generalized pustular rash. His current symptoms started with a headache 5 days prior, for which he took ibuprofen. That night he developed a fever and general malaise, and the following day he developed several exquisitely painful “acne-like” lesions around his neckline. Over the next few days, similar lesions arose over his face, chest, back, and limbs. These lesions are shown in the pictures below.

Figure: Scattered pustules on an erythematous base over the patient's face and chest

**What is your diagnosis?**

A) Acute generalized exanthematous pustulosis  
B) MRSA folliculitis  
C) Pustular psoriasis  
D) Drug reaction with eosinophilia and systemic symptoms (DRESS)  
E) Disseminated varicella zoster virus

**What is the appropriate management?**

A) Systemic steroids  
B) Intravenous acyclovir  
C) Stop the offending agent  
D) Systemic antibiotics  
E) Cutaneous decolonization therapy
**Diagnosis**

A) Acute generalized exanthematous pustulosis (AGEP)

**Management**

C) Stop the offending agent

**Discussion**

AGEP is a painful pustular rash that most commonly occurs as a drug eruption (~90% of cases). The medications most commonly linked to this condition are antibiotics (particularly beta-lactams such as penicillins or cephalosporins [1]), proton pump inhibitors and NSAIDs. Cases of AGEP have also been reported as a result of viral infection such as with EBV, CMV and enteroviruses [2].

As in the case described, AGEP is often associated with fever and general malaise. Cutaneous manifestations include the rapid appearance of sterile non-follicular pustules on an erythematous base, often arising in skin folds including on flexural surfaces, palms and back. The lesions can be large and may coalesce. They arise within 1 or 2 days of exposure to the culprit medication. Non-erosive lesions may also arise on mucosal surfaces; in severe cases there may also be systemic organ involvement [3].

Diagnosis is often clinical, but further testing can include patch testing to confirm allergy to the causative agent. A skin biopsy may be warranted for distinction from pustular psoriasis, which can closely mimic this condition. Classic histologic findings include subcorneal or intracorneal pustules and papillary dermal edema containing neutrophils and eosinophils [4]. Additionally, since bacterial folliculitis can present similarly, it is still prudent to perform a full infectious work-up including blood and pustule fluid gram stain and culture.

Treatment involves removing the offending agent; in severe cases, topical and oral steroids may also reduce symptom duration. Prognosis is generally favorable, with most cases reporting resolution within 15 days. However, mortality rate may be as high as 5%, particularly should secondary infections arise [5].

**References**

A 70 y/o male originally from Lebanon with a past medical history notable for CAD s/p POBA in 1994, CEA in 2014 after his PCP auscultated a carotid bruit, tobacco abuse, and hyperlipidemia presented with 2 episodes of chest pressure each lasting 20 minutes. His cardiac history was also significant for a exercise treadmill test approximately a year and a half ago during the patient reports walking almost 15 minutes without developing any chest pain or pressure. He presented to the ED 2 weeks prior to his episode with similar complaints, but had a negative EKG, enzymes and was sent home from the ED with f/u in cardiology clinic.

The evening of his admission, the patient developed a headache that woke him from sleep. The pain progressed down his neck and into his chest with 7-8/10 chest “pressure.” The pain resolved on the way to the ED, then returned while he was in the parking lot. In the ED, he was still having CP. He was hemodynamically stable with negative cardiac enzymes and was given ASA 324 mg. His EKG is shown below:
Cardiology was called to admit the patient. A repeat EKG taken during their initial evaluation is shown below:

He was admitted for observation. Approximately 4 hours after being admitted, the patient again developed chest pain while walking to the bathroom. His EKG is shown below:

**WHAT IS THE DIAGNOSIS?**

(Answer on next page)
Wellens’ Syndrome

**WHAT IS THE NEXT BEST STEP IN MANAGEMENT?**

The patient’s initial troponin was negative, but the second returned positive at 0.05 and he was started on therapeutic enoxaparin. It remained flat before rising slightly to 0.09. He was managed medically for another 24 hours before being taken to the cath lab. As shown in the figure to the right, the patient had a 95% acute thrombotic occlusion of his LAD as well as multiple 50-70% stenosis in his RCA. His LAD was successfully stented, and the patient was discharged on aspirin, clopidogrel, metoprolol, and atorvastatin.

**DISCUSSION**

The patient in this case initially presented with typical chest pain (specifically unstable angina), known CVD, and significant risk factors (age, tobacco abuse, HLD), highly concerning for ACS. His chest pain, however, rapidly resolved, and while there were some concerning EKG changes (small ST depressions in V3, V4 as well as II, III, aVF), he had no laboratory evidence of myocardial necrosis. A repeat EKG taken a few hours later was normal, followed by a third EKG that demonstrated new T wave inversions in V2-V4.

Wellen’s syndrome is defined by deep T wave inversions V2-V3, typical angina chest pain, minimal to no ST segment changes, and normal or minimally elevated cardiac enzymes with a critical stenosis of the left main anterior descending artery (LAD). In their original paper, de Zwaan et al found this pattern in 18% of patients admitted for unstable angina. The authors later published an analysis of patients presenting with unstable angina and new T wave inversions in V2-V3. 180 patients were included in their analysis and all patients had at least a 50% stenosis of their LAD (mean stenosis of 85%). Importantly, the LAD was completely occluded in 18% of these patients.

While acute coronary syndromes are often described in static terms, thrombosis and fibrinolysis are dynamic processes, occurring in tandem. Our patient likely presented after an acute plaque rupture, resulting in chest pain. With at least partial resolution of blood flow, his chest pain resolved. The relatively subtle T wave changes in V2-V4 were signs of critical LAD stenosis, and yet his cardiac enzymes were still negative.

**REFERENCES**


Airway Surfactant Protein D Deficiency in Adults with Severe Asthma


SUMMARY
Asthma treatment has traditionally centered on beta-agonism for the reversal of bronchospasm and inhaled corticosteroid for reduction of inflammation, however, a significant population of asthmatics suffer persistent symptoms despite these efforts often with recurrent hospitalizations. The present study sought to identify a role for the immunomodulatory and innate defense mediator Surfactant-D in the pathogenesis of severe, steroid-resistant asthma through study of a cohort of severe asthmatics in Wessex, UK. Similar to prior reports, these severe asthmatics were identified to not only have airway proliferation and activation of classical inflammatory cells such as mast cells and eosinophils as seen in more mild-asthmatics, but also had an additional expansion in airway neutrophil infiltration and activity unique to steroid-resistant disease. However, the truly novel data presented in this study was that in comparison to healthy controls and mild asthmatics, the severe asthmatic population was found to have significantly decreased levels of surfactant-D in their BAL samples, which inversely correlated with eosinophil and neutrophil counts and myeloperoxidase and eosinophil cationic protein levels in BAL. Furthermore, in serum, increased levels of surfactant-D and surfactant D breakdown products were found suggesting the worsening inflammation and permeability in the lung results in both breakdown of surfactant D in the lung and leakage of surfactant-D into the blood stream.

COMMENTARY
Though this study provides some fair initial data to support the use of surfactant-D as a severe asthma biomarker. Much of the data presented in this article regarding altered BAL concentrations of surfactant-D and airway neutrophilia in severe disease has been previously reported elsewhere with the truly novel report in the above study regarding the revelations regarding serum surfactant-D. To that end, the mechanism of airway surfactant depletion and transfer to the serum remains largely unclear with several mechanisms explored by the authors to varying degrees, all seemingly indicating increased airway permeability. Moreover, while it is encouraging that the above observations achieved statistical significance given the very modest study population a fairly wide dispersion pattern was observed in the surfactant levels with standard error bars overlapping throughout suggesting a significant degree of heterogeneity in the study population that remains unaccounted. Furthermore, similar findings were previously shown in patients with COPD, and the severe asthmatic population in the present study was notably older and contained substantially more former smokers than the mild asthmatic and control groups. From the above data an environmental or hereditary insult peculiar to Wessex,
UK cannot be fully excluded as a possible explanation of the observed serum surfactant levels and may ultimately limit the generalizability of the study. Together, the above study provides interesting preliminary data regarding serum surfactant as a biomarker for severe, refractory, neutrophilic asthma, however, considerable additional study will be required to substantiate its use as a biomarker and a possible therapy as asserted by the authors.

UTSW Link
Excessively High Hydration Volume May Not be Associated with Decreased Risk of Contrast-Induced Acute Kidney Injury After Percutaneous Coronary Intervention in Patients with Renal Insufficiency


Summary
This study retrospectively extracted data from the charts of 1406 patients at a single facility who received intravenous hydration before and after percutaneous coronary intervention as prophylaxis against contrast induced nephropathy. Per facility protocol, patients received 1cc/kg/hr normal saline or 0.5cc/kg/hr normal saline (for LVEF<40%) for at least 2 to 12 hours before and 6 to 24 hours after the procedure. The total volume of crystalloid administered was tallied per patient and indexed to calculate a hydration volume/weight ratio (HV/W). Patients were then grouped into quartiles based on their HV/W and the risk of developing AKI post procedure was calculated.

The HV/W quartiles were not balanced for most of the known risk factors for contrast induced nephropathy (Table A). The authors attempted to control for these baseline differences using multivariate analysis. The higher the HV/W, the higher the risk of contrast induced nephropathy with risk of AKI 4.3% for Q1, 6.6% for Q2, 10.9% Q3, and 15.0% for Q4, P<0.001 (Table B). In addition, increasing HV/W quartiles had increased length of stay, hospitalization costs, risk of heart failure exacerbation, risk of dialysis initiation, and mortality, all P<0.05 (Table B).

Commentary
Contrast induced AKI is a common complication of percutaneous coronary intervention and contrasted CT studies. Given how often contrast is administered, a lot of effort has been in made in finding strategies to mitigate this risk. Unfortunately, many of the promising prophylactic treatments such as sodium bicarbonate rich fluids and acetylcysteine have been debunked with more recent evidence. Does this study show that fluids are also a wash or possibly even harmful when it comes to preventing contrast induced nephropathy?

The most important caveat to this study lies in Table A in which every risk factor for contrast induced AKI is over-represented in the higher HV/W quartiles. In this retrospective study, Cardiologists recognized those older patients with diabetes, LVEF<40%, female gender, and lower body mass as being at increased risk of developing AKI after coronary angiography and administered more fluids to these patients. Therefore, it is not surprising that those patients in the higher HV/W quartiles would have higher rates of AKI. The authors did attempt to control for
these differences with multivariate analysis, but confounding bias still clouds the results from this study.

Despite the confounding bias inherent in this study, the results do bring up several interesting points. The increased fluids given to those patients at highest risk did not reduce the risk of AKI and appeared to have increased the risk of contrast induced AKI, assuming the multivariate analysis controls for most of the baseline differences. This goes against the prevailing hypothesis that intravenous crystalloid prevents contrast induced nephropathy by decreasing contrast concentration, intramedullary osmolarity, and contrast dwell time. However, as seen in Table A, the patients given the most fluid had the highest prevalence of heart failure and LVEF<40% and were, therefore, the most sensitive to fluids. By receiving the additional hydration, the higher HV/W patients may have been inadvertently pushed into cardiorenal physiology with increased renal venous pressures, reduced intramedullary contrast dwell time, and increased tubular damage. The higher incidence of heart failure exacerbation in the higher HV/W quartiles lends credence to this hypothesis.

I believe that the main takeaway in this study is that to prevent contrast induced AKI, you must give the right amount of fluid to the right patient. The goal of fluids is to dilute the contrast in order to expedite clearance and reduce the amount of time that the tubules are exposed to the osmotic and free-radical damage imparted by the contrast. Those patients who are at highest risk of contrast induced nephropathy may be the ones least likely to benefit from aggressive fluids if the fluids are going to change their physiology in a way which will augment the damage caused by contrast. The study cites several articles with alternative hydration strategies which based hydration rates on either clinical or objective measures of volume status and which had promising results. If these studies show us anything, it is that hydration rates for contrast induced nephropathy prophylaxis must be tailored to the individual patient.

UTSW Link
### Table A: Baseline characteristics of HV/W quartiles

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HV/W Quartiles</th>
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<tbody>
<tr>
<td></td>
<td>Q1 (n=350)</td>
<td>Q2 (n=351)</td>
<td>Q3 (n=366)</td>
<td>Q4 (n=339)</td>
<td>P&lt;sub&gt;test&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>319 (91.1)</td>
<td>274 (78.1)</td>
<td>297 (81.1)</td>
<td>239 (70.5)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>61±10</td>
<td>64±10</td>
<td>67±10</td>
<td>69±9</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 y, n (%)</td>
<td>31 (8.9)</td>
<td>37 (10.5)</td>
<td>87 (23.8)</td>
<td>90 (26.5)</td>
<td>&lt;0.001</td>
<td></td>
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</tr>
<tr>
<td>Weight, kg</td>
<td>73.67±7.57</td>
<td>61.42±7.82</td>
<td>64.30±10.18</td>
<td>60.75±9.50</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Systolic blood pressure</td>
<td>130±19</td>
<td>129±21</td>
<td>130±22</td>
<td>131±21</td>
<td>0.783</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IABP</td>
<td>6 (1.7%)</td>
<td>10 (2.8%)</td>
<td>19 (5.2%)</td>
<td>27 (8.0%)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>LVEF, %</td>
<td>58.8±11.7</td>
<td>58.8±11.9</td>
<td>56.4±12.1</td>
<td>55.4±12.2</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>LVEF &lt;40%, n (%)</td>
<td>5 (1.1)</td>
<td>9 (1.9)</td>
<td>37 (7.4)</td>
<td>145 (28.3)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>CHF, n (%)</td>
<td>35 (10.0)</td>
<td>62 (17.7)</td>
<td>73 (19.9)</td>
<td>84 (24.8)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>82 (23.4)</td>
<td>67 (19.1)</td>
<td>98 (26.8)</td>
<td>97 (28.6)</td>
<td>0.019</td>
<td></td>
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<tr>
<td>Smoker</td>
<td>168 (46.0)</td>
<td>138 (39.3)</td>
<td>149 (40.7)</td>
<td>127 (37.5)</td>
<td>0.027</td>
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<td>Hypertension</td>
<td>218 (62.3)</td>
<td>214 (61.0)</td>
<td>237 (64.8)</td>
<td>228 (67.3)</td>
<td>0.325</td>
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<td>Dyslipidemia</td>
<td>61 (17.4)</td>
<td>52 (14.6)</td>
<td>53 (14.5)</td>
<td>38 (11.2)</td>
<td>0.144</td>
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<td>Past MI</td>
<td>45 (12.9)</td>
<td>38 (10.6)</td>
<td>37 (10.1)</td>
<td>37 (10.9)</td>
<td>0.686</td>
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<tr>
<td>History of CABG</td>
<td>5 (1.4)</td>
<td>1 (0.3)</td>
<td>3 (0.8)</td>
<td>1 (0.3)</td>
<td>0.226</td>
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<tr>
<td>Medication, n (%)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>ACE/ARB</td>
<td>323 (92.3)</td>
<td>321 (91.5)</td>
<td>321 (87.7)</td>
<td>299 (88.2)</td>
<td>0.105</td>
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<tr>
<td>ß-blocker</td>
<td>308 (86.0)</td>
<td>299 (85.2)</td>
<td>300 (82.0)</td>
<td>279 (82.3)</td>
<td>0.095</td>
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<tr>
<td>CCB</td>
<td>61 (17.4)</td>
<td>59 (16.8)</td>
<td>65 (17.8)</td>
<td>80 (23.6)</td>
<td>0.082</td>
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<tr>
<td>Diuretics</td>
<td>35 (10.0)</td>
<td>51 (14.5)</td>
<td>80 (21.9)</td>
<td>84 (24.8)</td>
<td>&lt;0.001</td>
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<td>Laboratory measurements</td>
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<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.1±0.2</td>
<td>1.1±0.4</td>
<td>1.2±0.4</td>
<td>1.4±0.6</td>
<td>&lt;0.001</td>
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<tr>
<td>uCr, ml/min per 1.73 m²</td>
<td>73.28±12.51</td>
<td>71.24±14.82</td>
<td>67.06±16.54</td>
<td>58.81±18.80</td>
<td>&lt;0.001</td>
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<td>CrCl, ml/min</td>
<td>72.08±19.04</td>
<td>60.80±17.59</td>
<td>53.90±16.68</td>
<td>47.69±18.21</td>
<td>&lt;0.001</td>
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<td>Total cholesterol, mmol/L</td>
<td>4.17±1.12</td>
<td>4.36±1.16</td>
<td>4.31±1.02</td>
<td>4.40±1.19</td>
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<td>Hba1c, %</td>
<td>6.44±1.14</td>
<td>6.40±1.27</td>
<td>6.42±1.28</td>
<td>6.68±2.07</td>
<td>0.005</td>
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<td>hs-CRP, mg/L</td>
<td>3.74±6.20</td>
<td>5.89±11.00</td>
<td>9.88±19.40</td>
<td>21.54±31.95</td>
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<td>Anemia, n (%)</td>
<td>94 (26.9)</td>
<td>108 (30.8)</td>
<td>117 (32.0)</td>
<td>145 (42.8)</td>
<td>&lt;0.001</td>
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<td>Hematocrit, %</td>
<td>0.40±0.04</td>
<td>0.39±0.05</td>
<td>0.39±0.05</td>
<td>0.37±0.05</td>
<td>&lt;0.001</td>
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<td>K</td>
<td>3.79±0.39</td>
<td>3.73±0.40</td>
<td>3.73±0.46</td>
<td>3.75±0.47</td>
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<td>Na</td>
<td>139.14±3.23</td>
<td>138.69±3.07</td>
<td>138.58±2.97</td>
<td>138.39±3.03</td>
<td>0.081</td>
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<td>Ca</td>
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<td>2.23±0.12</td>
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<td>pH</td>
<td>5.91±0.65</td>
<td>5.92±0.66</td>
<td>5.86±0.83</td>
<td>5.86±0.70</td>
<td>0.628</td>
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### Table B:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HV/W Quartiles</th>
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<td>Q1 (n=350)</td>
<td>Q2 (n=351)</td>
<td>Q3 (n=366)</td>
<td>Q4 (n=339)</td>
<td>P&lt;sub&gt;test&lt;/sub&gt;</td>
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<tr>
<td>Scr increase ≥0.5 mg/dL, n (%)</td>
<td>5 (1.4)</td>
<td>8 (2.3)</td>
<td>20 (5.5)</td>
<td>29 (8.6)</td>
<td>&lt;0.001</td>
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<tr>
<td>Scr increase ≥0.5 mg/dL or ≥25%, n (%)</td>
<td>15 (4.3)</td>
<td>23 (6.6)</td>
<td>40 (10.9)</td>
<td>51 (15.0)</td>
<td>&lt;0.001</td>
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<tr>
<td>Scr increase ≥0.3 mg/dL, n (%)</td>
<td>10 (2.9)</td>
<td>16 (4.7)</td>
<td>31 (8.7)</td>
<td>49 (14.7)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scr increase ≥0.3 mg/dL or ≥50%, n (%)</td>
<td>10 (2.9)</td>
<td>16 (4.7)</td>
<td>31 (8.7)</td>
<td>49 (14.7)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stay, days, median (P25-P75)</td>
<td>4 (2–6)</td>
<td>5 (3–7)</td>
<td>5 (3–8)</td>
<td>6 (4–9)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost, USD, median (P25-P75)</td>
<td>8314 (39.7–67.7)</td>
<td>8634 (40.8–73.9)</td>
<td>9274 (44.6–80.8)</td>
<td>10 073 (45.2–88.3)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute heart failure, n (%)</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
<td>8 (2.2)</td>
<td>15 (4.4)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
<td>10 (2.9)</td>
<td>14 (4.1)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aliskirin, Enalapril, or Aliskiren and Enalapril in Heart Failure


Summary

The ATMOSPHERE trial compared the efficacy of the ACE inhibitor enalapril with the renin inhibitor aliskiren and with the combination of the two drugs in patients with heart failure and reduced ejection fraction. Patients with chronic heart failure, NYHA class II-IV symptoms, EF ≤35%, BNP ≥150 pg/ml or NT-proBNP ≥600 pg/ml, and on a stable beta-blocker and ACE-inhibitor dose (equivalent to 10 mg enalapril daily) were eligible for enrollment. The trial had a two part run-in phase prior to randomization. 8,835 patients entered the first part, during which they received enalapril 5 mg twice daily for 1 to 4 weeks, in a single-blind fashion, followed by 2 to 4 weeks of enalapril 10 mg twice daily. 7,784 patients entered the second part of the run-in phase, during which they received aliskiren 150 mg once daily, again in a single-blind fashion, in addition to enalapril. 7,064 patients who could tolerate both treatments were randomly assigned, in a 1:1:1 ratio, to a double blind, double-dummy treatment in three groups: enalapril 5 or 10 mg twice daily (n=2,336), aliskiren 150 mg once daily (n=2340), or both enalapril 5 or 10 mg twice daily and aliskiren at 150 mg once daily (n=2340). Two weeks after randomization, the dose of aliskiren was increased to 300 mg once daily. Of note, in April 2013 (while the trial was ongoing), patients with diabetes at baseline and those who developed diabetes during the trial were asked to discontinue treatment and were switched to conventional therapy because of reports of worse outcomes in patients with diabetes taking aliskiren in the ALTITUDE and ASTRONAUT trials. The number of patients who had data censored because of diabetes was 665 (28.4%) in the combination-therapy group, 627 (26.8%) in the aliskiren group, and 652 (27.9%) in the enalapril group. The median follow-up time period was 36.6 months (IQR 22.4 to 52.2): 46.0 months (IQR, 28.0 to 56.1) in patients without diabetes and 24.1 months (IQR 15.1 to 33.2) in patients with diabetes.

The primary outcome of interest was a composite of death from cardiovascular causes or a first hospitalization for heart failure. The primary outcome occurred in 770 patients (32.9%) in the combination-therapy group (11.7 events per 100 person-years), in 791 patients (33.8%) in the aliskiren group (12.1 events per 100 person-years), and in 808 patients (34.6%) in the enalapril group (12.4 events per 100 person-years). The hazard ratio in the combination-therapy group, as compared with the enalapril group, was 0.93 (95% CI 0.85 to 1.03; P=0.17) and the hazard ratio in the aliskiren group, as compared with the enalapril group, was 0.99 (95% CI 0.90 to 1.10; P=0.91 for superiority). When comparing aliskiren with enalapril, the non-inferiority margin of 1.104 was met with the use of the 95% CI; but the one-sided P value of 0.0184 did not fulfill the prespecified requirement of a P value ≤0.0123. These results were similar in patients with and without diabetes. Hypotension, renal dysfunction, and hyperkalemia occurred more commonly with combination therapy than with enalapril. Hypotension and cough were more common with enalapril than aliskiren.
**Commentary**

ACE inhibitors are effective in lowering the risks of death and hospitalization among patients with chronic heart failure and reduced ejection fraction. Thus, there has been interest in other approaches to interrupt of the renin–angiotensin system. ARBs have been shown to reduce risk of death from cardiovascular causes and hospitalization for heart failure among patients who could not take ACE inhibitors. The combination of an ARB and an ACE inhibitor has also been examined in two heart failure trials. In both trials, the addition of an ARB to an ACE inhibitor was associated with a lower risk of hospitalization for heart failure and, in one trial, with a lower risk of death from cardiovascular causes. Interestingly, neither trial mandated an evidence-based dose of ACE inhibitor. The AMTOSPHERE trial used an evidence-based dose of enalapril and tested whether the combination of aliskiren and enalapril was superior to enalapril alone and whether aliskiren was at least noninferior to enalapril. The results of the trial show that the addition of aliskiren to enalapril did not result in a lower risk of death from cardiovascular causes or hospitalization due to heart failure, as compared with enalapril alone. Moreover, the combination caused more hypotension, renal dysfunction, and hyperkalemia. The authors suggest that there is a therapeutic ceiling for blockade of the renin–angiotensin system beyond which there is little or no additional efficacy and only more adverse effects. Also, aliskiren did not meet the criteria for noninferiority as compared with enalapril.

**Figure A:**

- **Primary Composite End Point**

  - **Combination vs. enalapril**
    - Hazard ratio, 0.93 (95% CI, 0.85–1.03)
    - P=0.17
  - **Aliskiren vs. enalapril**
    - Hazard ratio, 0.99 (95% CI, 0.90–1.10)
    - P=0.91

**No. at Risk**

- Combination: 2340 2137 1959 1809 1562 1307 1085 895 689 456 273
- Aliskiren: 2340 2127 1934 1761 1510 1288 1064 888 681 474 282
- Enalapril: 2336 2128 1947 1766 1513 1268 1044 866 679 452 281

**USTW Link**
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes


**Summary**

Similar to the EMPA-REG OUTCOME trial that showed Empagliflozin decreases the risk of cardiovascular events in type 2 diabetics, this study looks at the effects of Empagliflozin on renal outcomes. A total of 7020 patients with type 2 diabetes and a eGFR > 30 ml/min/1.73m²BSA received either Empagliflozin (10mg or 25mg) or placebo (similar baseline patient characteristics and patients were already receiving standard care). The treatment duration was 3.1 years (median). The study results included: creatinine doubled in 1.5% Empagliflozin group vs. 2.6% placebo group (p<0.001); development of macroalbuminuria 11.2% Empagliflozin group vs. 16.2% placebo group (p<0.001); start of RRT in 0.3% Empagliflozin group vs. 0.6% placebo group (p 0.04); overall worsening nephropathy in 12.7% Empagliflozin group vs. 18.8% placebo group (p<0.001).

**Commentary**

This study is important because it shows Empagliflozin provides an additional renal protective benefit for patients already receiving the traditional RAAS blockers. The study however is limited by the fact that only type 2 diabetics with high risk of cardiovascular events were included and patients with a eGFR <30 ml/min/1.73m²BSA were excluded. Additionally some of the down sides to this medication includes increased risk of UTIs with candidiasis, hypotension from osmotic diuresis, bone fracture risk and the inability to recognize DKA as it causes euglycemia in the serum.

[UTSW Link](#)
Gastroenterology

Association of Acute Gastroesophageal Reflux Disease with Esophageal Histologic Changes


The “acid” in “acid reflux” may not be the direct cause of damage to the esophagus in GERD as previously suspected.

Summary
For decades, it has been thought that GERD develops due to the direct chemical effect of gastric acid on esophageal epithelium. However, this elegant study by the UTSW/Dallas VA group calls into question this previously accepted dogma. Twelve participants with high-grade reflux esophagitis who had been successfully treated with PPI underwent 24-hour esophageal pH monitoring and EGD with biopsies of the distal esophagus at baseline, while treated with PPI. Subsequently, PPIs were discontinued and pH monitoring and EGD with esophageal biopsies were repeated at 1 and 2 weeks. Importantly, all biopsies were taken from areas without visible erosions. Across all time points, the superficial layers of esophageal epithelium showed no damage. In contrast, there was significant intraepithelial lymphocytic infiltration, basal cell/papillary hyperplasia and basal spongiosis seen in biopsies taken at week 1 and 2, compared to baseline. These changes developed in areas without surface erosions, and there were no neutrophils among the inflammatory cells. These findings were not consistent with the teaching that the histological changes were secondary to physical damage caused by acid.

Commentary
These results suggest that in the pathogenesis of GERD, early histologic events may not take place at the luminal side, but deeper within the epithelium. This contradicts the dogma that reflux esophagitis develops as an acid-peptic burn progressing from luminal surface through to submucosa. Findings reported in this study indicate the possibility that acid reflux stimulates inflammation of the esophagus by a cytokine-mediated process. This notion is supported by previous data from humans and rats showing increased expression of inflammatory cytokines (interleukin [IL]-8 and IL-1β) in esophageal epithelial cells damaged by acid. In esophageal mucosa, these cytokines have not only pro-inflammatory but also proliferative effects, which might have contributed to basal cell and papillary hyperplasia observed in the absence of surface erosions. Taken together, this study suggests that the pathogenesis of reflux esophagitis may be cytokine-mediated rather than the result of chemical injury.

UTSW Link
Rectal Indomethacin Reduces Pancreatitis in High- and Low-Risk Patients Undergoing Endoscopic Retrograde Cholangiopancreatography


Use of rectal indomethacin may be beneficial in preventing post-ERCP pancreatitis across the entire spectrum of patients undergoing ERCP

**Summary**

It is known that in some patients, rectal indomethacin decreases the risk of post-ERCP pancreatitis. As previously published studies have focused mostly on high-risk patients (young females with sphincter of Oddi dysfunction or patients undergoing biliary stenting of benign strictures), it is not known which patients benefit from prophylaxis with indomethacin in real-world scenario. In this study from the University of Pennsylvania, Thiruvengadam et al. retrospectively analyzed data from 4017 patients undergoing ERCP between 2009-2015. Half of the patients received 100 milligrams of indomethacin per rectum at the conclusion of ERCP. Overall, indomethacin reduced the odds of post-ERCP pancreatitis by 65% (OR 0.35; 95% CI 0.24-0.51), with greatest protective effect from moderate or severe post-ERCP pancreatitis (OR 0.17; 95% CI 0.09-0.32). Similar protective effect was observed not only in high-risk patients, but also in...
patients considered low-risk for post-ERCP pancreatitis, including patients with malignant biliary obstruction due to pancreatic adenocarcinoma, or patients with gallstones, primary sclerosing cholangitis or post-operative bile leak. The results indicate that prophylaxis with indomethacin is associated with decreased risk of post-ERCP pancreatitis in most patients undergoing ERCP in real-world scenario.

**COMMENTARY**

Acute pancreatitis is well-recognized complication in about 5% patients undergoing ERCP. The risk of post-ERCP pancreatitis is not stochastic as it is known that young age, female sex, sphincter of Oddi dysfunction or biliary stenting represent independent predictors of post-ERCP pancreatitis (so called high-risk patients). On the other hand, factors associated with decreased risk of post-ERCP pancreatitis include chronic pancreatitis, older age and malignant biliary obstruction (so called low-risk patients). Historically, the use of rectal indomethacin has been advocated for high risk patients, reducing the risk of post-ERCP pancreatitis by approximately 50%. Less attention has been paid to indomethacin in low-risk patients, which, however, comprise the majority of patients undergoing ERCP in the real-world practice. The study of Thiruvengadam et al., confirmed the utility of rectal indomethacin in decreasing the risk of post-ERCP pancreatitis in high-risk patients. However, it is a unique study as it shows a significant reduction in the rate of post-ERCP pancreatitis in a primarily low-risk population. More specifically, in this group of patients, indomethacin reduced the incidence of moderate-to-severe pancreatitis, which contributes to the majority of morbidity/mortality associated with post-ERCP pancreatitis. The surprising finding of this study is that indomethacin reduces the risk of post-ERCP pancreatitis in patients with malignant biliary obstruction, which has traditionally been considered to be low-risk for post-ERCP pancreatitis as it was thought that it causes pancreatic ductal and parenchymal atrophy, decreasing pancreatic enzyme production. If replicated in prospective trial, this data suggests a potential role for increased routine use of rectal indomethacin in prophylaxis of post-ERCP pancreatitis.

**UTSW Link**
Figure 1: (A) PEP in exposed vs unexposed groups overall, in patients with native papilla, and in patients post-sphincterectomy. (B) Moderate-severe PEP in exposed vs unexposed groups overall, in patients with native papilla, and in patients post-sphincterectomy.
Figure 2: (A) patients with malignant biliary obstruction: PEP in exposed vs unexposed groups overall, in patients with native papilla, and in patients post-sphincterectomy. (B) patients with malignant biliary obstruction: moderate-severe PEP in exposed vs unexposed groups overall, in patients with native papilla, and in patients post-sphincterectomy.
**Sodium Excretion and the Risk of Cardiovascular Disease in Patients with Chronic Kidney Disease**


**SUMMARY**

Increased sodium excretion, as a stand-in for dietary sodium intake, has known effects in blood-pressure control and in the development of cardiovascular events. These effects are somewhat controversial in the latter (see JAMA’s 2011 observational study by O’Donnell, et al that showed increased CV events in the highest and lowest sodium intake groups), but point to a relationship between high sodium intake and increased cardiovascular risk. The authors of this prospective cohort study, however, note a paucity of data examining this relationship among patients with chronic kidney disease who are known to have increased risk of cardiovascular events compared to the general population and who are often more sensitive to sodium intake due to impaired renal excretion.

The study group consists of more than 3,000 adult patients with mild to moderate CKD enrolled in the larger Chronic Renal Insufficiency Cohort Study (CRIC). Sodium excretion was measured as a mean over three 24-hour urine collection measurements. Patients were stratified into quartiles by level of sodium excretion and followed for the development of composite cardiovascular events, congestive heart failure, myocardial infarction, and stroke over a 10-year follow-up period (median follow-up was 6.8 years). Participants in the highest excretion quartile (>4.5 grams) had a significantly increased risk of composite CVD events (HR 1.35), CHF (HR 1.25) and stroke (HR 1.91), though significance in the MI group fell out when adjusted for traditional CVD risk factors. No significant effect was seen in the other three quartiles, and the authors interpret this to suggest a benefit in moderate reduction in sodium intake for patients with CKD. Notably, the lowest-excretion group (< 2.9 grams) demonstrated a non-significant trend toward increased events relative to the moderate-excretion groups.

**COMMENTARY**

Overall, the data suggest that high levels of sodium excretion are independently associated with worse cardiovascular outcomes. That these results are independent of blood pressure effects in sensitivity analyses suggests an important physiological relationship not previously explored. The trend toward increased events in the lowest-excretion group, meanwhile, raises important questions about the physiology of sodium intake at lower levels and warrants further investigation.

However, the applicability of these findings to standard clinical practice, particularly in the setting of Kidney Disease: Improving Global Outcomes (KDIGO) guidelines that have for years
recommended two gram salt-restricted diets for blood pressure control in patients with CKD, is less convincing for two reasons. First, sodium excretion is only a means of approximating sodium intake, and a variety of yet unknown factors may confound this relationship. Second, the mean sodium excretion among the CRIC cohort was 3.7 grams, and strict interpretation of their results would suggest no cardiovascular benefit at this level of excretion. What role these findings have to play among individuals with moderate and low sodium excretion remains to be seen.

**UTSW Link**

**Table A**: Kaplan-Meier curves demonstrating development of composite cardiovascular events, congestive heart failure, myocardial infarction and stroke by sodium-excretion quartile.
Comparison of Posthospitalization Function and Community Mobility in Hospital Mobility Program and Usual Care Patients: A Randomized Clinical Trial


SUMMARY

The authors randomized 100 patients age 65 and above admitted to the Birmingham VA from January of 2010 to June of 2011 for a non-surgical reason to either be enrolled in a hospital based mobility program or to receive usual care. The effects on post-hospitalization function and community mobility were then evaluated. To be included in the study, patients had to be ambulatory with or without an assistive device in the two weeks prior to admission. Additionally, they had to screen negative for both cognitive impairment and delirium, and they could not have a significant language barrier requiring use of a translator. Patients rated their independence in the 7 activities of daily living (ADL) on a scale from 1 (independent) to 3 (total assistance) to provide a total score between 7 and 21, both prior to admission and at 1 month post-discharge. Community mobility was measured using the UAB Life-Space Assessment tool (LSA), again both prior to admission and at 1 month post-discharge. The LSA provides a composite score between 0 and 120 which reflects the distance through which a person moves (i.e. within their bedroom or into town), and their independence in doing so over the preceding 4 weeks. A higher score reflects greater community mobility, which has previously been validated as a predictor of death, nursing home admission, and hospitalization.

50 patients were randomized to an in-hospital mobility program that consisted of 15-20 minute visits twice daily with a standardized protocol of assisted sitting, standing, weight shifting, stepping in place, and progression to ambulation as tolerated. There was also a behavioral intervention which encouraged patients to spend time out of bed in addition to the scheduled sessions. Patients were provided a diary to record the time they spent out of bed. 50 patients were randomized to the usual care group, and received 15-20 minute social visits twice daily by research assistants and were provided a diary to document the frequency of visitors. Patients could receive physical therapy as ordered by their physician.

8 patients did not complete the study. Of these, 6 were in the mobility program arm. In the mobility program group, 3 patients were transferred to the ICU, 1 became delirious, 1 died during hospitalization, and 1 died prior to follow up. In the usual care group, 1 patient withdrew and 1 died prior to follow up. 1 patient from each group was lost to follow up. Because more patients in the mobility program did not complete the study than in the usual care group, missing values were replaced with imputed values derived from a Markov Chain Monte Carlo method with 25
imputations. Reportedly, the results of the complete case analysis are similar to the results using the imputed values, though only the analysis using the imputed values is reported. There was no difference in the ADL score between the mobility program and usual care groups at baseline or post-discharge, and the score also did not change significantly over time for either group. The LSA scores were similar at baseline for both groups, but the LSA score decreased by approximately 10 points in the usual care group at one month post-discharge, while it was preserved in the mobility program group.

Commentary

The loss of community mobility experienced by the usual care group in this study is similar in magnitude (approximately 10 point decrease in LSA score) to that seen in other studies of community dwelling older adults after hospitalization. An example of the clinical relevance of a 10 point decline in LSA score would be a patient who went to town 1-3 times per week independently prior to hospitalization and then only went to town 1 time per week or less and required a cane after hospitalization. This study shows how a relatively simple intervention could potentially preserve community mobility in older patients, which is a worthwhile pursuit as declining community mobility has previously been demonstrated to be a predictor of death, nursing home placement, and hospitalization. The merits of the intervention are that it does not require a physical therapist and rather could be done by a trained volunteer or mobility aide. One can imagine how such an intervention could be incorporated into vital signs checks or trips to the bathroom. The foremost limitation of this study is the higher drop-out rate observed in the mobility program arm. The 3 ICU transfers, 1 death, and 1 delirium diagnosis that occurred in the intervention group did not occur in the control group. This raises the question of whether the intervention could have somehow precipitated these events. One reassuring fact is that there were no falls in the mobility program group compared to 3 falls in the usual care group, which would be an anticipated risk of a mobility program. Further, the Markov Chain Monte Carlo method used to derive values for the missing patients is less ideal than using actual values for all patients. This intervention shows promise as a way to preserve community mobility in hospitalized older adults, but future studies with a larger group of patients may be helpful to confirm the results.

UTSW Link
Tables:

Table 2. Analysis of Mean ADL and Life-Space Assessment Scores by Intervention Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) MP</th>
<th>Mean (SD) UC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Weeks prior</td>
<td>8.0 (0.21)</td>
<td>8.0 (0.26)</td>
<td>.83</td>
</tr>
<tr>
<td>Admission</td>
<td>8.4 (0.27)</td>
<td>8.7 (0.33)</td>
<td>.47</td>
</tr>
<tr>
<td>Discharge</td>
<td>8.1 (0.29)</td>
<td>8.0 (0.25)</td>
<td>.96</td>
</tr>
<tr>
<td>After hospitalization</td>
<td>8.2 (0.30)</td>
<td>8.2 (0.32)</td>
<td>.99</td>
</tr>
<tr>
<td>Life-Space Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>53.9 (4.15)</td>
<td>51.5 (2.99)</td>
<td>.46</td>
</tr>
<tr>
<td>After hospitalization</td>
<td>52.6 (4.39)</td>
<td>41.8 (3.15)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; MP, mobility program; UC, usual care.

Table 3. Group Differences in ADL and Life-Space Assessment Scores Between the MP and UC Groups, Adjusting for Admission Values, Age, Sex, and Race

<table>
<thead>
<tr>
<th>Variable</th>
<th>Imputation⁹</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL⁹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>−0.21</td>
<td>.67</td>
</tr>
<tr>
<td>After hospitalization</td>
<td>0.05</td>
<td>.76</td>
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<tr>
<td>Life-Space Assessment⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After hospitalization</td>
<td>10.0</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; MP, mobility program; UC, usual care.

⁹ Multiple imputation methods were used to substitute missing values with imputed values.

On the basis of mixed-model analysis of multiple imputations (n = 25) adjusted for age, sex, and race.

Analysis of covariance of 25 multiple imputations (n = 25) adjusted for baseline admission values; model also includes age, sex, and race.
Summary

In this non-randomized, open-label dose escalation study, Dr. Shima and colleagues enrolled 18 Japanese patients with severe hemophilia A into three cohorts to receive doses of emicizumab (an antibody that binds to and bridges Factor IX and Factor X) at 0.3, 1.0, or 3.0 mg/kg once weekly for 12 weeks to assess the safety, pharmacokinetics, and pharmacodynamics of emicizumab and to assess the annualized bleeding rate of patients on this drug. Their bleeding rates were subsequently compared to the six months prior to administration of the study drug. Emicizumab was well tolerated without any serious adverse events or derangements in coagulation parameters. Plasma levels increased in a dose-dependent manner. Eight of 11 patients with Factor VIII inhibitors experienced no bleeding during the study. None of the patients in the cohorts receiving 1.0 or 3.0 mg/kg experienced a bleeding event. Overall, emicizumab was shown to be safe and effective at reducing bleeding events without producing coagulation abnormalities or causing inhibitor formation.

Commentary

The management of hemophilia A is often complicated by clinically significant bleeding events and inhibitor formation to clotting products, as well as a life-long reliance on both prophylactic and therapeutic factor preparations. This article demonstrates that emicizumab, a humanized monoclonal antibody that is a Factor VIII mimetic by binding to Factor IX and Factor X, can potentially be used as prophylactic therapy for patients with severe hemophilia. Thirteen of eighteen patients had no bleeding episodes while on the trial (compared to seventeen of eighteen patients in the six months preceding the study). Importantly, emicizumab was not associated with thrombotic events or anti-emicizumab formation. This study is limited by its design however the results are promising for the treatment of Factor VIII deficiency with or without inhibitor formation. Another interesting drug, fitusiran, is an RNAi that can decrease the expression of antithrombin and can be used to treat factor VIII and factor IX deficiency with or without inhibitors. Future, definitive studies should be larger, randomized, and blinded appropriately.
Table A: Annualized bleeding rate by cohort dose (cohort 1 = 0.3 mg/kg, cohort 2 = 1.0, cohort 3 = 3.0 mg/kg) separated by the six months prior to the study and separated further by factor VII inhibitor status. A clear decrease in annualized bleeding rates is seen in all cohorts with emicizumab prophylaxis, regardless of factor VIII inhibitor status.
Reducing the hospital burden of heparin-induced thrombocytopenia: impact of an avoid-heparin program


SUMMARY
In this quality improvement study, McGowan and colleagues sought to determine if switching unfractionated heparin (UFH) for low molecular weight heparins (LMWH) for DVT prophylaxis would result in reduced incidences of heparin-induced thrombocytopenia (HIT) and HIT with thrombosis (HITT). The hospital where this study was completed replaced all heparin used for therapeutic or prophylactic purposes with LMWH. Physicians in the study hospital were not aware of the substitution. Cases were defined as suspected HIT (clinical suspicion + HIT ELISA performed), positive HIT ELISA, adjudicated HIT (positive serotonin release assay or positive HIT ELISA without SRA but diagnosed by the thromboembolism service after review) and HITT (Positive HIT ELISA with proven venous or arterial thrombosis less than 7 days before or 30 days after first clinical suspicion for HIT). Cases were compared pre-intervention (2003-2005) and post intervention (2007-2012). There were 453 cases of suspected HIT in the pre-intervention phase and 576 in the post-intervention phase. Overall results showed an annualized reduction of 63% positive HIT assays, 79% reduction in adjudicated HIT, and 91% reduction in HITT. These reductions came at an associated cost savings of $266938 per year (from $322,321 to $55,383/year).

COMMENTARY
This article is most notable not for the reduction in HIT seen with exchanging UFH for LMWH (this fact has been known for some time that LMWH is less HIT-ogenic than UFH), but rather the striking cost savings that have been noted with fewer HIT cases. It is also impressive that the study authors were able to achieve an almost-universal exchange of UFH for LMWH in a tertiary care hospital.

There are several issues with this study, however. LMWH is approximately 8-fold more expensive than UFH. This is an important consideration given that DVT prophylaxis is required in almost all hospitalized patients now. It is currently unknown if LMWH is superior to UFH for DVT prophylaxis. Therefore, all of the cost savings driven by an exchange of UFH for LMWH would be driven by the decreased incidence of HIT and the decreased price of HIT care as well as the decreased clinical consequences of HIT demonstrated in this study. It is important to remember that overall, HIT is a rare occurrence while DVT prophylaxis is not. Furthermore, this study makes no mention of their strategy for DVT prophylaxis in patients with kidney disease, utilization of the newer oral anticoagulants, or any mention of rates of major bleeding requiring transfusion or reversal (heparin is reversible while LMWH reversal with protamine is not as effective).
This study was very elegantly designed to answer the question of cost savings with HIT in UFH vs LMWH, however the debate regarding superiority of LMWH over UFH continues. LMWH would be a good standard choice in the hospitalized patient without kidney disease who also has funding.

**UTSW Link**

![Figure 1: Reduction in cases of HIT/10,000 admissions/year pre and post-intervention. Clearly, exchanging UFH for LMWH results in a statistically significant decrease in the rates of HIT.](image)

*Figure 1:* Reduction in cases of HIT/10,000 admissions/year pre and post-intervention. Clearly, exchanging UFH for LMWH results in a statistically significant decrease in the rates of HIT.
**Treatment of Hepatitis C Virus-Associated Mixed Cryoglobulinemia (HCV-MCS) with Direct-Acting Antiviral Antigens**


**Summary**

HCV accounts for up to 90% of all cases of mixed cryoglobulinemia syndrome. HCV-MCS causes small to medium vessel vasculitis. It has been treated in the past with 48 weeks of interferon and ribavirin. This retrospective case series aimed to look at the effects of treating Hepatitis C Virus-Associated Mixed Cryoglobulinemia (HCV-MCS) with the newer protease inhibitors: direct-acting antiviral agents (DAA). Patients were treated with sofosbuvir-based regimens and compared with historical controls who received interferon and ribavirin. 12 patients received DAA therapy and 4 received rituximab with DAA therapy for a total of 16 patients. Renal function was recorded in these patients before and after treatment as HCV-MCS patients have impaired renal function and glomerulonephritis. SVR12 (sustained virological response at 12 weeks, a measurement of cure of HCV infection) was achieved in 10/12 of those treated with sofosbuvir-based DAA regimens. 9/12 patients had cryoglobulin levels checked and showed decrease in median cryoglobulin levels from a median of 1.5% to 0.5%. 4/9 cases had disappearance of cryoglobulin levels after treatment (Figure 1). 7/12 HCV-MCS patients had renal involvement w/ glomerulonephritis 6/7 had improvement in renal function after treatment. Of the 10 patients who received historical treatment of interferon and ribavirin, only 1/10 achieved SVR. 9/10 patients did not experience SVR or improvement in HCV-MCS symptoms. They did not have a decline in cryoglobulin levels. Only the patient who achieved SVR had a decrease in cryoglobulin level. Overall for this group, pre-treatment cryoglobulin levels had a median of 2.5% and post-treatment median of 4%.

**Commentary**

Patients who were treated with DAA therapies achieved, expectedly, much higher rates of SVR12 (83%) compared to the historical treatment group. This is comparable to the noncryoglobulinemic real-world cohorts. We can conclude that cryoglobunemia is not a barrier to the treatment of HCV. Not only that, but there was decreased proteinuria in patients with glomerulonephritis that were treated with DAA. They conclude that SVR is achieved and maintained without relapse, then the MCS will be well-controlled and in some cases, even cured. It is important to know that it may take months for the cryocrit and symptoms to improve after achievement of virological response to antiviral treatment. Treatment with DAA also led to decreased use of immunosuppression (typically rituximab) versus historical treatment with ribavirin and interferon. Rituximab was added to control MCS symptoms. We will need larger studies or a meta-analysis of all previously done smaller studies to determine the significance of these findings. What can be concluded is that
use of DAA is preferable to ribavirin + interferon in HCV-MCS patients as it achieves higher rates of remission, symptom control and decreased doses of immunosuppression therapy. Results of treatment may not be clinically evident for months after achievement of virological response to antiviral treatment.

**UTSW Link**

![Graph](image)

**Figure 1**: Change in cryoglobulin levels over time in patients treated with sofosbuvir-based DAA therapy. Solid lines represent patients who achieved SVR12. Dashed lines represent relapsed patients.

**Thrombelastography-Guided Blood product Use before invasive procedures in Cirrhosis with Severe Coagulopathy: A randomized, Controlled Trial**


**Summary**

Cirrhotic patients are traditionally thought to be in a pro-hemorrhagic state. As a result, these patients often receive FFP and platelets prior to complex procedures. However, emerging evidence suggests that INR, PT, and PTT are not suitable lab markers to investigate the acquired deficiency of both pro and anticoagulants that occurs in cirrhosis. The purpose of this study was to determine the amount of blood products transfused to cirrhotic patients undergoing low risk and high risk procedures, as well as the rates of bleeding complications. Patients were given blood products either according to the standard of care (SOC) goals of INR > 1.8 or platelet count below 50 or thromboelastography (TEG)-guided transfusion goals.

60 patients were randomized to SOC goals versus TEG goals. TEG is a point of care, global hemostasis assessment device that measures the blood pro- and anti-coagulant properties in real-time. Figure 1 below provides a breakdown of TEG. Two measurements were used: the r time (or CT time), which is the time from start of the TEG tracing until the TEG tracing amplitude reaches 2 mm, which represents the rate of initial fibrin formation and is related to plasma clotting factors and circulatory inhibitor factors. A prolongation of r time represents coagulation factor
deficiencies or severe hypofibrinogenemia. The second measurement is the maximum amplitude (MA) value, which reflects the strength of the clot and is a direct result of platelet function and plasma factors and their interaction. In this study, 100% of SOC patients received blood products, compared to 16.7% in the TEG group (p < 0.0001). Post-procedure bleeding occurred in only 1 patient.

**Commentary**

The conclusion was that TEG-guided transfusion strategy lead to significantly lower use of blood products compared to SOC without an increase in bleeding complications. Even in patients with significant coagulopathy, post-procedure bleeding was rare. Only one case of post-procedure bleeding occurred, and it was in a low-risk procedure (large volume paracentesis) in a patient who was transfused according to the standard of care, which included FFP prior to procedure. This data supports that traditional testing of INR and platelet count is inadequate in assessing a cirrhotic patient’s true coagulopathic state and perhaps other methods such as TEG should be used, as it provides dynamic and comprehensive information on hemostasis as this is already being used during liver transplantation in the OR.

**UTSW Link**

**Figure 1:** Standard clotting assays detect starting time of clotting. ROTEM or TEM provides information on kinetics of haemostasis. This includes clotting time, clot formation, clot stability and lysis. TEM is affected by the activity of the plasmatic coagulation system, platelet function, fibrolysis and by certain drugs.

Source: A Review of Thromboelastography, Thakur M, et al
High Value Care

Overdiagnosis of *Clostridium difficile* Infection in the Molecular Test Era


**SUMMARY**

The aim of this study was to evaluate the natural history of *Clostridium difficile* PCR positive, toxin negative patients. Patients were recruited at the University of California Davis Medical Center if they were hospitalized and had a diarrheal stool sample submitted for *C difficile* infection (CDI) within the first 72 hours of their hospitalization. Diarrhea was defined as 3 unformed bowel movements over 24 hours and/or 600 cc or rectal/colostomy output in 24 hours. Stool samples were tested for *C difficile* DNA PCR as well as *C difficile* toxin A/B. Three separate cohorts were then developed based on the results of this testing.

The primary outcome of this study was duration of diarrhea over a period encompassing the day of sample collection to up to 14 days of treatment for suspected CDI treatment. Secondary outcomes included rate of CDI-related complications (including megacolon, colectomy, and ICU care). In total, 1,416 patients were included in the analysis, 293 of which were *C difficile* positive and 1,123 (79.3%) of which were *C difficile* negative (Tox-/PCR-). Of the 293 patients included who were *C difficile* positive, 131 (9.3%) were toxin and PCR positive (Tox+/PCR+) and 162 (11.4%) were toxin negative and PCR positive (Tox-/PCR+). 100% of Tox+/PCR+ patients received metronidazole or oral vancomycin for a median length of treatment of 14 days. 40.7% of Tox-/PCR+ patients received the same antibiotic regimen for a median duration of 6 days, while 32.1% of Tox-/PCR- patients also received antibiotics for a median duration of 5 days. Age, sex, number of comorbidities, and proportion of leukopenia, renal insufficiency, and hypoalbuminemia were all similar between the three groups, except for toxin negative, PCR negative patients, who had fewer comorbidities.

Duration of diarrhea was significantly longer in the Tox+/PCR+ group, and notably similar in the Tox-/PCR+ and Tox-/PCR- groups (as shown in the figure to the right). With regard to CDI complications, Tox+/PCR+ patients had a significantly higher complication rate (7.6%) compared to Tox-/PCR+ patients (0%) and Tox-/PCR- patients (0.3%). Similarly, the rate of death was significantly higher in the Tox+/PCR+ cohort (8.4%) vs. the Tox-/PCR+ (0.6%) and Tox-/PCR- patients (0%).
Outcome differences between Tox+/PCR+ and Tox-/PCR+ patients remained significant when accounting for the two subgroups of Tox-/PCR+ patients who did and did not receive antibiotics.

**Commentary**

This study adds to the growing body of evidence that the natural history of Tox-/PCR+ is similar to that of Tox-/PCR- patients, reinforcing the notion that CDI is a toxin mediated disease. For much of the 2000s, hospitals around the country relied on toxin based assays to support a clinical diagnosis of CDI. While these assays are highly specific for CDI, up to one quarter of cases may be missed, owing to their imperfect sensitivity. More recently, however, hospitals have begun relying on PCR tests that detect C difficile DNA, but importantly, these tests do not differentiate between colonization and CDI. While this has resulted in increased sensitivity for detecting CDI, some hospitals have reported a 50%-100% increase in the rate of CDI since adopting PCR based detection. This increase in sensitivity has come at the cost of the positive predictive value of the test, with recent assessments of commercial assays being measured at less than 50%.

Patients with CDI in this study were more likely to have more antibiotic exposure in the past, to have been admitted from a health care facility, to present with a WBC >15k, and to have laboratory evidence of colonic inflammation as measured by lactoferrin. No CDI-related complications were seen in the Tox-/PCR+ patients, which is consistent with previous published data. The authors did report one death in which CDI was “a contributing factor” in this group, although it should be noted this patient’s diarrheal illness had resolved prior to death and care was ultimately withdrawn because of “severe underlying illness.” This was not a randomized trial, and 40% of patients in the tox-/PCR+ did receive antibiotics for some duration to treat suspected CDI. Although the authors analyzed the subgroups of tox-/PCR+ that did and did not receive antibiotics and found no differences in outcomes, it remains unclear what patient factors may have lead the treating physician to prescribe antibiotics.

Overall, this data strongly supports the authors’ hypothesis that the natural histories of tox+/PCR+ and tox-/PCR- patients are distinctly different. These differences (shorter duration of diarrhea, extremely low rate of CDI complications) have substantial clinical relevance.
Differentiating between these two very different disease states could, in theory, result in significant cost savings to the healthcare system (e.g., less contact isolation, less frequent prescribing of costly oral vancomycin or fidaxomicin for suspected recurrent CDI). While no single test to date is able to accurately distinguish between the two groups, we as clinicians should be mindful of these differences going forward when evaluating patients with known Clostridium difficile positivity who develop diarrhea.

**REFERENCES**


Should Asymptomatic Bacteriuria Be Systematically Treated in Kidney Transplant Recipients? Results From a Randomized Controlled Trial


**Summary**

- Open-label, parallel-group, single center randomized trial
- Inclusion criteria: ≥ 18 years and AB after the second month post kidney transplant (KT)
- Exclusion criteria: Pregnancy, kidney-pancreas transplant, ureteral stent or urethral catheter, ≥ 1 AB episode prior randomization.
- Intervention: Episodes of AB within the first 2 months were treated in both groups. Then, the experimental arm received systematic susceptibility-guided antibiotics and the control arm did not receive antimicrobials.
- Primary outcome: Cumulative incidence of acute pyelonephritis
- Secondary outcomes included long-term graft function, all-cause mortality, and cumulative incidences of lower urinary tract infections (UTI), acute graft rejection, *Clostridium difficile* infection (CDI), presence of multidrug resistant (MDR) bacteria, and graft loss.
- Follow up: 24 months post KT.

The study randomized 112 patients, 53 to the treatment group and 59 to the control group. The 12-month follow-up was completed for 98 (86.6%) patients and the 24-month follow up was accomplished for 61 (54.4%) individuals. Of the 296 episodes left untreated, 175 (59.1%) exhibited persistence of the same pathogen, 24 (8.1%) grew a new pathogen and 97 (32.7%) showed spontaneous clearance. The cumulative incidence of pyelonephritis and UTI were 8% (9 of 112) and 15.2% (17 of 112), respectively. No differences were found in the incidence of acute pyelonephritis in the ITT population (7.5% [4 of 53] in the treatment group vs. 8.4% [5 of 59] in the control group, p=1.00). Lastly, there were no significant differences in any of the secondary outcomes regardless of the type of population examined.

The study concluded that -in the absence of ureteral stents or urinary catheters- the presence of AB is a weak predictor of progression to a symptomatic infection, and that systematically screening and treating AB episodes after the second month post KT does not provide clear benefit.

**Commentary**

This study provides evidence against systematic screening and treatment of AB in KT recipients without urinary tract instrumentation two months after transplantation.

They reported a low rate of urine sterilization after antibiotic therapy (51.1%) suggesting that even if we can detect and treat AB in a timely manner, urine sterilization will be achieved only in half of the cases. The major limitation was the poor compliance with the protocol study. Only half
of the patients in the treatment group strictly completed the therapy protocol (Figure 1). The two main reasons were limited oral alternatives in case of an MDR bacteria and concomitant treatment of other infectious syndrome with antibiotics active against uropathogens. Interestingly, this poor compliance was considered a relevant study result as it demonstrated the low feasibility of the systematic screening and treatment strategy, even in the optimal settings of a clinical trial.

**UTSW Link**

**Table 1: Occurrence of study outcomes (modified per-protocol population).**

<table>
<thead>
<tr>
<th>Primary study outcome</th>
<th>Treatment group (n = 36)</th>
<th>Control group (n = 50)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pyelonephritis, n (%)</td>
<td>2 (5.5)</td>
<td>4 (8.0)</td>
<td>0.67 (0.11-3.91)</td>
<td>1.00</td>
</tr>
<tr>
<td>Lower UTI, n (%)</td>
<td>3 (8.3)</td>
<td>6 (12.0)</td>
<td>0.66 (0.15-2.88)</td>
<td>0.73</td>
</tr>
<tr>
<td>Overall UTI, n (%)</td>
<td>5 (13.9)</td>
<td>9 (16.0)</td>
<td>0.64 (0.25-2.84)</td>
<td>0.76</td>
</tr>
<tr>
<td>Hospital admission for UTI, n (%)</td>
<td>1 (2.7)</td>
<td>2 (4.0)</td>
<td>0.68 (0.05-7.88)</td>
<td>1.00</td>
</tr>
<tr>
<td>Clostridium difficile infection, n (%)</td>
<td>2 (5.6)</td>
<td>3 (6.0)</td>
<td>0.92 (0.14-6.62)</td>
<td>1.00</td>
</tr>
<tr>
<td>Infection or colonization caused by MDR bacteria, n (%)</td>
<td>8 (22.2)</td>
<td>9 (18.0)</td>
<td>1.30 (0.45-3.75)</td>
<td>0.78</td>
</tr>
<tr>
<td>Acute graft rejection, n (%)</td>
<td>8 (22.2)</td>
<td>9 (18.0)</td>
<td>1.30 (0.45-3.78)</td>
<td>0.78</td>
</tr>
<tr>
<td>Graft loss, n (%)</td>
<td>1 (2.7)</td>
<td>1 (2.0)</td>
<td>1.40 (0.08-23.15)</td>
<td>1.00</td>
</tr>
<tr>
<td>All-cause mortality, n (%)</td>
<td>1 (2.7)</td>
<td>1 (2.0)</td>
<td>1.40 (0.08-23.15)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**eGFR, mL/min/1.73 m², mean ± SD**

- At month 12: 46.36 ± 16.4 vs. 47.34 ± 15.3, p = 0.79
- At month 24: 46.3 ± 15.2 vs. 47.1 ± 15.2, p = 0.85

**Number of UCs performed after enrollment, mean ± SD**

- 17.7 ± 6.7 vs. 18.4 ± 5.9, p = 0.64

**Number of episodes of AB, Isolated microorganisms, n (%)**

- *Escherichia coli: 62 (55.4) vs. 60 (39.2), p = 0.01*
- *Klebsiella pneumoniae: 11 (9.9) vs. 12 (7.8), p = 0.66*
- *Enterococcus faecalis: 20 (17.9) vs. 19 (12.4), p = 0.22*
- *Pseudomonas aeruginosa: 6 (5.4) vs. 23 (15.0), p = 0.02*
- *Klebsiella oxytoca: 2 (1.8) vs. 0 (0.0), p = 0.17*
- *Enterobacter cloacae: 0 (0.0) vs. 10 (6.5), p = 0.06*
- *Others: 11 (9.8) vs. 29 (18.9), p = 0.05*

AB, asymptomatic bacteriuria; CI, confidence interval; eGFR, estimated GFR; MDR, multidrug-resistant; OR, odds ratio; SD, standard deviation; UC, urine culture; UTI, urinary tract infection.
Figure 1: Patient flow diagram.
**Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit**


**Summary**

The AKIKI trial was a multicenter randomized trial designed to guide decision-making around renal replacement therapy in critically ill patients with acute kidney injury but no indication for emergent dialysis (N=620). Patients with stage 3 acute kidney injury by KDIGO classification (see Table), who required mechanical ventilation, vasopressors or both, were randomized to early renal-replacement therapy versus a delayed strategy, in which RRT was started once there was an emergent indication (severe hyperkalemia, metabolic acidosis, pulmonary edema, BUN higher than 112, or oliguria for more than 72 hours). The authors found that there was no significant difference in mortality at day 60 (the primary outcome) between the early and delayed strategies. Among those in the delayed strategy, 49% of patients avoided RRT. However, those who did ultimately receive RRT progressed to worse clinical statuses, as measured by worse Sepsis-related Organ Failure Assessment (SOFA) scores, more vasopressor use, and worse metabolic measures. Among the early strategy group, CLABSI rates were higher (10% vs. 5%, P = 0.03).

**Commentary**

The results suggest that universally initiating RRT in all critically ill patients with stage 3 AKI is not beneficial. Therefore, RRT initiation remains a case-by-case decision that is challenging, as it can be difficult to predict which patients will have renal recovery and be spared RRT versus those who will further decline.

**UTSW Link**

**Table A**: AKI staging by 2012 KDIGO practice guidelines for AKI

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5-1.9 times baseline OR ≥0.3 mg/dl (≥26.5 μmol/l) increase</td>
<td>&lt;0.5 ml/kg/h for 6-12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0-2.9 times baseline</td>
<td>&lt;0.5 ml/kg/h for ≥12 hours</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients &lt;18 years, decrease in eGFR to &lt;35 ml/min per 1.73 m²</td>
<td>&lt;0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours</td>
</tr>
</tbody>
</table>
Palliative Care

Gap Between Recommendations and Practice of Palliative Care and Hospice in Cancer Patients


Summary

This article is a retrospective analysis of administrative data for veterans aged 65 years or older who died from cancer in 2012. The study observed the last 180 days of patients’ lives to evaluate the use of palliative and hospice care (HPC) among patients receiving Medicare compared to VA or VA-purchased care. The major goals of the study were to assess the use of hospice and palliative care in these patient populations but also the timing in which the referral or care began. In particular, they reviewed whether or not a patient was receiving hospice services in the last three days of life. Furthermore, the study compared the use of HPC services for patients with several types of cancers to see if there was a difference in utilization. Roughly 12,000 veterans, age 65 and older met study criteria with a predominance of lung (33%), prostate (11.7%) and hematological cancers (10.1%). Analysis showed that 85.6% of veterans had some exposure to hospice care or palliative care before death with a higher percentage receiving hospice (71%) than palliative care (51.9%). Notably, a large number of patients (71.8%) who received palliative care ultimately received hospice towards the end of life. With regards to initiation of hospice care, patients with VA-Purchased hospice care were exposed earliest, with services starting a median of 28 days before death. Patients who received hospice through the VA and those whose care was paid for by Medicare had services initiated 14 and 16 days before death respectively. Adjusted analysis of hospice care utilization was done using lung cancer as the reference cancer type given its predominance in this study population. The results showed patients with hematological malignancies and prostate cancer were less likely to receive hospice care compared to veterans with melanoma, pancreatic cancer, and brain cancer. With regards to age, patients 80 or older were more likely to receive hospice compared to younger veterans aged 65 to 69. In terms of timing, the study noted veterans covered by the VA (80.1%) and Medicare (83.2%) were more likely to receive hospice care for the last three days of life compared to VA-purchased care (69.4%). Overall, among all cancer types patients started palliative care a median of 38 days prior to death and hospice 20 days prior to death irrespective of payer type.

Commentary

Various societies including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network and the Institute of Medicine have endorsed palliative care for patients shortly after diagnosis of advanced cancer. With regards to hospice the ASCO recommends that patients have hospice care for at least three days prior to death. Despite the large number of veterans receiving some form of palliative care and/or hospice before death it often occurred very late in their disease course. This is evidenced by the majority of patients
having a median of 2 visits with palliative care before death. Earlier studies have shown that early exposure to palliative care has a positive impact on one-year survival due to its ability to address pain and other symptoms tied to quality of life. Difficulties with prognostication of indolent cancers may have contributed to the lower likelihood of patients with some cancer types receiving timely referrals. Many patients did not receive palliative care referral until chemotherapy or radiation treatments were concluded which can be very late in the disease process. This can be remedied with more prompt referrals once a palliative treatment option has been decided upon to improve chances of connecting with a palliative care provider sooner than 1 month before death. Overall, many veterans did receive palliative care and/or hospice before death but there is still room for improvement to meet societal guidelines irrespective of payer type.

**UTSW Link**

**Table A:** Palliative Care, Hospice, and Curative Treatment Use Among Decedent Veterans Aged 66 years and Older, by Cancer Type

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>n</th>
<th>Received cancer treatment (%)</th>
<th>Received hospice (%)</th>
<th>Received palliative care (%)</th>
<th>Median No. of days between first palliative care and death (IQR)</th>
<th>Median No. of days between first hospice and death (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>585</td>
<td>32.0</td>
<td>71.3</td>
<td>50.9</td>
<td>38 (14–93)</td>
<td>19 (7–42)</td>
</tr>
<tr>
<td>Brain</td>
<td>178</td>
<td>47.2</td>
<td>79.8</td>
<td>60.7</td>
<td>40 (15–93.5)</td>
<td>28 (7–57)</td>
</tr>
<tr>
<td>Colon</td>
<td>827</td>
<td>35.9</td>
<td>72.0</td>
<td>51.5</td>
<td>47 (16–111)</td>
<td>21 (8–48)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>778</td>
<td>52.2</td>
<td>70.4</td>
<td>53.2</td>
<td>44 (18–103)</td>
<td>23 (9–54)</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>1216</td>
<td>45.4</td>
<td>59.5</td>
<td>49.7</td>
<td>27 (9–86)</td>
<td>14 (5–36)</td>
</tr>
<tr>
<td>Kidney</td>
<td>304</td>
<td>41.1</td>
<td>73.0</td>
<td>44.7</td>
<td>48 (18–120)</td>
<td>23 (8–53)</td>
</tr>
<tr>
<td>Liver</td>
<td>589</td>
<td>22.2</td>
<td>71.8</td>
<td>54.5</td>
<td>29 (10–73)</td>
<td>15 (5–36)</td>
</tr>
<tr>
<td>Lung</td>
<td>3982</td>
<td>49.2</td>
<td>72.5</td>
<td>52.2</td>
<td>39 (14–93)</td>
<td>20 (7–48)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>147</td>
<td>45.6</td>
<td>83.7</td>
<td>46.3</td>
<td>42.5 (20–86)</td>
<td>19 (8–46)</td>
</tr>
<tr>
<td>Other</td>
<td>896</td>
<td>41.0</td>
<td>73.7</td>
<td>52.6</td>
<td>36 (15–81)</td>
<td>19 (7–44)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>567</td>
<td>36.9</td>
<td>78.7</td>
<td>55.0</td>
<td>35.5 (13–74)</td>
<td>19 (6–45)</td>
</tr>
<tr>
<td>Prostate</td>
<td>1389</td>
<td>47.2</td>
<td>69.5</td>
<td>50.6</td>
<td>54 (19–121)</td>
<td>25 (9–54)</td>
</tr>
<tr>
<td>Stomach</td>
<td>195</td>
<td>38.0</td>
<td>70.3</td>
<td>54.9</td>
<td>35 (15–86)</td>
<td>23 (9–50)</td>
</tr>
<tr>
<td>Unknown</td>
<td>243</td>
<td>10.7</td>
<td>62.5</td>
<td>49.8</td>
<td>12 (6–27)</td>
<td>11 (5–28.5)</td>
</tr>
<tr>
<td>Total</td>
<td>11,896</td>
<td>43.1</td>
<td>70.9</td>
<td>51.7</td>
<td>38 (13–94)</td>
<td>20 (7–46)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.
Patient Navigation for Comprehensive Cancer Screening in High-Risk Patients Using a Population-Based Health Information Technology System: A Randomized Clinical Trial


Summary

The authors conducted a randomized clinical trial to evaluate the benefits of patient navigation for breast, cervical, and colorectal cancer screening in high risk patients over an 8 month period using a population-based health information technology (IT) system in an academic primary care network. Using a pre-existing health IT application, they prospectively identified all patients eligible and overdue for breast, cervical, and/or colorectal cancer screening. They then created an algorithm to identify those patients at high risk for not completing screening based on a history of “no-shows” to visits, non-English speaking status, and number of overdue screening tests. Of this group of high risk patients, 792 were randomized to patient navigation and 820 were randomized to usual care.

The intervention utilized four patient navigators who were college graduates. Each was fluent in 2-5 languages and trained in motivational interviewing, problem solving, goal setting, use of the IT system, EMR documentation, and basic information about breast, cervical, and colorectal cancer screening. Patient navigation occurred predominantly over telephone and included exploring individual barriers to screening, motivational interviewing, reminder calls, arranging transportation, assisting with visit preparation, and accompanying patients to visits if needed.

“Usual care” in this primary care network consisted of the typical visit-based screening reminders embedded in the EMR, non-visit-based outreach by clinicians and staff using the IT application to send reminder letters about overdue screenings, and telephone calls to schedule overdue exams or document deferral or exclusion from screening.

Among the 792 patients randomized to the patient navigation intervention, 19% were unable to be contacted, 38% deferred screening for all overdue cancers (because patient declined, screening was completed elsewhere, patient left the practice, patient had competing co-morbidity, etc.), and 32% successfully completed at least one overdue screening test during the 8 month study period. The primary outcome measure was mean cancer screening test completion rate per patient, which was calculated daily as the number of tests completed divided by the number of eligible tests, and then averaged over the 8 month study period. Generalized estimating equations were used to account for cluster effects associated with a particular primary care physician or primary care practice. The intervention group had a mean cancer screening completion rate that was 3.4% higher for all cancer screenings combined than the control group in intention to treat analyses, and 5.9% higher in as treated analyses. The intervention group also had a higher screening
completion rate for each individual cancer, again with a greater difference seen in the as treated analyses than the intention to treat analyses. The percentage of patients who completed any type of cancer screening was 25.5% in the intervention group and 17% in the control group in intention to treat analyses, and 32.9% in the intervention group and 18.1% in the control group in as treated analyses. The biggest differences in screening completion rates between the intervention and control groups were in white patients, English speaking patients, and patients seen in community health centers.

**Commentary**

This trial demonstrates a statistically significant increase in completion of cancer screenings in high risk patients with the use of patient navigation, which could help to address disparities in healthcare access and outcomes experienced by these high risk groups. However, it is unclear whether or not the increase in screening completion translates into a clinically significant increase in cancer detection and improvement in outcomes. Also, the authors did not evaluate the efficacy of their initial risk stratification algorithm to choose the “high risk” patients for non-completion of cancer screening. Future studies could compare screening completion rates from the patients with overdue cancer screenings who were deemed to be lower risk to see if the algorithm correctly risk stratified the patients.

One limitation of the study is generalizability, as it took place in a single academic primary care network with a pre-existing health IT system used for population management where patient navigation was already an established practice in some of the health centers (though patients from these centers were excluded from the study). Another limitation is that the study did not include fecal immunoassay testing as an acceptable means of colorectal cancer screening. Additionally, the 8 month study period may have been too short to detect all of the patients who would have eventually completed their cancer screening. It is unclear why the 8 month study period was selected, as the benefits from cancer screening are typically realized over a longer time period and there is no urgency for overdue screening to become up to date over a period of months.

Additionally, the cost of the initial training, supervision, and navigator activities was $80,000 for the 8 month study period. The ongoing cost of patient navigation was $100,000 per year, which primarily involves personnel costs, and translates into approximately an additional $125 per year per patient who receives navigation. These figures do not account for costs related to the pre-existing health IT system.

Despite the limitations discussed above, if cancer screening remains cost effective with the additional cost associated with patient navigation, this trial suggests that patient navigation may be an effective way to improve cancer screening compliance, and thereby health outcomes, for some of our most challenging patients.

[UTSW Link](#)
### Table 2. Mean Cancer Screening Test Completion Rate Over 8 Months of Follow-Up Among 1626 Patients Eligible and Overdue for Cancer Screening at Baseline (Intention-to-Treat and As-Treated Analyses)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test Completion Rate, Mean, %</th>
<th>Difference, % (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>All cancers combined</td>
<td>10.2</td>
<td>6.8</td>
<td>3.4 (1.5-5.2)</td>
</tr>
<tr>
<td>Breast</td>
<td>14.7</td>
<td>11.0</td>
<td>3.7 (0.2-7.3)</td>
</tr>
<tr>
<td>Cervical</td>
<td>11.1</td>
<td>5.7</td>
<td>5.4 (2.1-9.2)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>7.6</td>
<td>4.6</td>
<td>3.0 (0.7-5.2)</td>
</tr>
</tbody>
</table>

As-treated<sup>a</sup>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test Completion Rate, Mean, %</th>
<th>Difference, % (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
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<tr>
<td>All cancers combined</td>
<td>13.1</td>
<td>7.2</td>
<td>5.9 (3.6-7.9)</td>
</tr>
<tr>
<td>Breast</td>
<td>18.8</td>
<td>11.7</td>
<td>7.1 (3.1-11.2)</td>
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<tr>
<td>Cervical</td>
<td>14.1</td>
<td>6.2</td>
<td>7.9 (3.6-12.1)</td>
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<tr>
<td>Colorectal</td>
<td>9.9</td>
<td>4.9</td>
<td>5.0 (2.4-7.2)</td>
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</tbody>
</table>

<sup>a</sup> Excluded 56 patients from control and 54 patients from intervention groups who left network or died during follow-up. An additional 133 patients were excluded from the intervention group because they had no contact with patient navigators.

---

### Source Rate Difference % (95% CI) Does Not Favor Does Favor

<table>
<thead>
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<th>Intention to treat</th>
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<td>1.80 (-1.60 to 5.30)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>4.29 (1.90 to 6.60)</td>
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<tr>
<td>Language</td>
<td>Non-English</td>
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<tr>
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<td>English</td>
<td>4.30 (2.00 to 6.60)</td>
</tr>
<tr>
<td>Insurance</td>
<td>Medicaid, self-pay</td>
<td>2.40 (-1.50 to 6.30)</td>
</tr>
<tr>
<td></td>
<td>Commercial, Medicare</td>
<td>3.80 (1.50 to 6.00)</td>
</tr>
<tr>
<td>Practice type</td>
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<td>4.30 (1.20 to 7.40)</td>
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<tr>
<td></td>
<td>Male (CRC only)</td>
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<tr>
<td></td>
<td>Female, &lt;50 y</td>
<td>5.40 (-1.80 to 12.70)</td>
</tr>
<tr>
<td></td>
<td>Female, ≥50 y</td>
<td>3.10 (1.10 to 5.00)</td>
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</table>

<table>
<thead>
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<th>All eligible patients</th>
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<td>White</td>
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</tr>
<tr>
<td></td>
<td>Female, ≥50 y</td>
<td>5.50 (3.20 to 7.80)</td>
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Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996-2013


SUMMARY

The objective of this study was to explain the trends in benzodiazepines (BZD) prescription and overdose mortality related to these medications among US adults. Data on filled BZD was obtained from the Medical Expenditure Panel Survey and numbers on overdose death involving BZD were gathered from multiple-cause-of-death data from the Centers for Disease Control and Prevention (CDC) from 1999 to 2013.

From 1996 – 2013, the number of patients filling a BZD prescription increased 67%, from 8.1 million (95% confidence interval [CI] = 7.3 – 8.9 million) to 13.5 million (95% CI = 12.2 – 14.7 million), please see Figure 1.

The total quantity of BZD filled increased more than threefold from 1.1 (95% CI = 0.9 – 1.2) to 3.6 (95% CI = 3.0 – 4.2) kg lorazepam equivalents per 1000,000 adults (annual percentage change = 9.0%, 95% CI = 7.6 – 10.3%). The most frequent indications for BZD prescription were anxiety (56.1% [95% CI = 52.2 – 60.1%]), mood disorders (12.1% [95% CI = 9.4 – 14.6%]), and others including insomnia (12.0% [95% CI = 9.4 – 14.6%]). The rate of deaths related to BZD overdose increased more than fourfold from 0.58 (95% CI = 0.55 – 0.62%) to 3.07 (95% CI = 2.99 – 3.14) per 100,000 patients. Trends in prescription and overdose mortality changed among demographic groups and although a global plateau in the rate of deaths was observed after 2010, it continued to grow during 2010 – 2013 in patients > 65 years, as well as in Blacks and Hispanics.

This study revealed that overdose mortality increased at a faster rate than did the percentage of adults filling prescriptions and the quantity filled. The authors suggested some explanations for this: 1) the rise in the total quantity filled is a reflection of both a higher number of patients filling BZD prescriptions and a bigger amount of medication received by each individual; 2) individuals at high risk of fatal overdose may be acquiring diverted BZDs however this data is unknown; 3) combining BZDs with alcohol or other medications such as opioids could also increase the risk of fatal overdose.

COMMENTARY

In 2013 approximately 22,767 people expired due to prescription drugs overdose in the US, and BZDs were responsible for about 31% of these deaths. It is unclear what is driving this trend. The study found that anxiety accounted for 56.1% of prescriptions, however we do not know if more anxiety is being diagnosed or if BZDs are being prescribed earlier and/or for longer periods. Additionally, the results suggest dangerous behaviors associated with BZD use; patients are either
taking higher doses or combining them with alcohol, illegal drugs, or other sedating medications such as opioids. In 2015, Jones CM et al analyzed the trends in nonmedical use-related emergency department (ED) visits and overdose deaths due to concurrent use of BZDs and opioids. They reported that the rate of ED visits increased from 11 to 34.2 per 100,000 individuals (p<0.0001), and that overdose deaths increased from 0.6 to 1.7 per 100,000 individuals (p<0.001).

The opioid overdose epidemic caused a strong reaction in the Public Health community, which resulted in appropriate interventions such as the recently published CDC guideline. Much less attention has been paid to BZDs. Additional studies are imperative to examine the causes of the increasing BZD prescription trend in order to design successful interventions and improve BZD safety.

**UTSW Link**

**Figure 1**: Number of Adults Filling a BZD Prescription, Quantity Filled, and Overdose Deaths Involving BZDs: United States, 1996-2013
Serious Asthma Events with Fluticasone Plus Salmeterol Versus Fluticasone Alone


SUMMARY

This large, multicenter, double blinded randomized control trial that enrolled about 11600 participants from 33 countries was conducted to assess the safety and efficacy of the Long Acting Beta Agonist (LABA), Salmeterol, in fixed dose combination with inhaled glucocorticoid, Fluticasone, as compared with Fluticasone alone. The trial was conducted and funded by pharmaceutical company GlaxoSmithKline the manufacturer of Salmeterol. Adolescents and adults with moderate to severe asthma as defined by 1 exacerbation within the year prior to enrollment were included in this trial. Participants with unstable asthma, history of life threatening asthma and smoking for greater than 10 pack years were excluded. The study population was divided into two groups that were treated with either Salmeterol-Fluticasone or Fluticasone alone in 3 different Fluticasone concentrations. The groups were further divided into subgroups based on asthma control on their previous regimen. The study participants were treated and followed for 26 weeks. The primary end point was determined by the rate of asthma related major events including death, endotracheal intubation and hospitalization. The secondary end point was determined by asthma related exacerbations by assessing the use of rescue short-acting beta-agonist inhaler. An adjudication committee was set up to review the data to determine the severity of the events and if events were truly asthma related. Both participants and the adjudication committee were aware of the dose of the inhaled glucocorticoid, but were blinded to the presence or absence of Salmeterol in the formulation. Non-inferiority of Salmeterol-Fluticasone to Fluticasone was defined as an upper boundary of the 95% confidence interval for the risk of the primary safety end point of less than 2.0. The efficacy end point was the first asthma exacerbation. The hazard ratio for a serious asthma related event in the Salmeterol-Fluticasone group was 1.03 (95% Confidence Interval, 0.64 to 1.66) and the upper boundary of the confidence interval did not exceed 2.0, thus the researchers concluded that Salmeterol-Fluticasone combination was non-inferior to Fluticasone alone. The incidence of asthma exacerbation was significantly lower in the Salmeterol-Fluticasone group; however this was only true for the subgroup that had well controlled asthma on LABA + glucocorticoid at baseline. No racial predilection for greater adverse events related to LABA therapy was noted.

COMMENTARY

Prior studies have shown that LABA use in the treatment of moderate to severe asthma is associated with increased incidence of adverse outcomes including death. Two major studies demonstrating this effect were the Severent Nationwide Surveillance (SNS) trial[1] and the Salmeterol MultiCenter Asthma Research trial (SMART)[2], which due to their large sample size,
have heavily influenced subsequent meta-analyses. It has also been shown that the incidence of adverse outcomes with the use of LABA is particularly greater in the black patient population. Supporters of LABA use for the treatment of asthma have debated that both the studies did not assess the concurrent use of LABA and inhaled glucocorticoids when combined in a single metered dose device. To assess the hypothesis that a fixed dose combination of LABA + glucocorticoid is non inferior to inhaled glucocorticoid alone, in 2008, the FDA requested the manufacturers of LABA to analyze all their data to assess the rates of asthma related adverse events in the patient population treated with the LABA + glucocorticoid formulation. This trial was conducted by GlaxoSmithKline, the manufacturer of the LABA, Salmeterol, as a response to the FDA request.

There are several features of this trial that limit the general applicability of the results. First, the participants were not included based on a definition of asthma as reflected by their pulmonary function tests and bronchodilator response; instead, they were enrolled based on a labeled ‘history of asthma’ with at least one asthma exacerbation within the past year. Second, the patients with an asthma exacerbation within the month prior to enrollment were excluded. Why this exclusion was made remains unclear. Also, the definition of severity of this ‘exacerbation’ was not elucidated. Third, patients with unstable asthma were excluded from the trial. Again, the criteria used to define the unstable nature of the asthma remains unclear. In short, based on this inclusion and exclusion criteria, a significant subset of the patients most adversely affected by asthma was excluded. Compliance to medical therapy seen in this study was 95.1%, significantly higher than previously known compliance of 45-50%[3]. Furthermore, the infrequent occurrence of asthma related adverse events noted in this study also reflects the skewed selection of the patient population in favor of healthier subjects.

Though the trial demonstrates the non-inferiority of Salmeterol-Fluticasone to Fluticasone alone, it is difficult to extrapolate these results onto the general patient population, especially those with frequent asthma exacerbations and more severe disease that have the greatest need for better control and have been shown (as per the SNS and SMART trials) to be at the highest risk of adverse events related to the use of LABA. However, based on this study it can be concluded that Salmeterol-Fluticasone formulation in comparison to inhaled Fluticasone alone may have an additional benefit for prevention of asthma exacerbations in the subset of population that has better compliance and improved asthma control at baseline. Further trials, including the patient population with moderate to severe asthma, particularly those with frequent exacerbations and poorly controlled disease will have to be conducted to better assess the efficacy of the LABA+ glucocorticoid fixed dose combination in the treatment of asthma as compared to inhaled glucocorticoid alone.

UTSW Link
Table A: Primary Safety End Point (Intention-to-Treat Population)

References:

Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients with Acute Respiratory Distress Syndrome


SUMMARY

This is a single center RCT from the University of Chicago evaluating the efficacy of a Non Invasive Ventilation (NIV) via helmet vs facemask for the management of Acute Respiratory Distress Syndrome (ARDS). The helmet is a transparent device with a rubber collar neck for that allows titration of positive airways pressures and oxygen delivery with minimal air leak.

206 patients with ARDS diagnosed by the Berlin’s definition who required 8 hours of NIV were randomly assigned to the treatment (helmet), vs control (face mask) arm. The mean Apache II score of the patient's enrolled to both arms was 26. Primary outcome assessed was the rate of endotracheal intubation. Secondary outcomes were 28 day ventilator-free days, duration of ICU and hospital stay, hospital and 90 day mortality.

The trial was stopped early (44 patients in the helmet group and 39 in the facemask group) after reaching pre-defined criteria of efficacy. Intubation rate was 61.5% (n=24) in the facemask group and 18.2% (n=8) in the helmet group (absolute difference, -43.3%; 95% CI, -62.4% to -24.3%; P < .001). Patient within the helmet group also had a significantly higher rate of ventilator free survival and lower 90-day mortality. Adverse events in both arms were related to skin ulcers due to device positioning and were not statistically or clinically different.

COMMENTARY

Standard of care in ARDS:

It is important for us to have a brief overview of the standard of care for ARDS before we comment on this interesting trial. Invasive mechanical ventilation, despite associated risks, has most robust data to support itself as the most effective ventilation strategy for ARDS. Although NIV ventilation via facemask has well documented role in the treatment of cardiogenic pulmonary edema and to some degree COPD exacerbations, initial studies documenting potential benefit in immunocompromised patients with acute hypoxemic respiratory failure (AHRF) have not been replicated. On the contrary, most recently it has been shown, by Frat et. al., that NIV via facemask has an increased mortality compared to high flow nasal cannula in the AHRF. This raises our first concern about the design of this study, where helmet: an experimental treatment strategy, is compared to NIV facemask which is not recommended for ARDS.
The Helmet:
Basically a transparent shell with a rubber seal at the neck, the helmet provides the advantage of an easily titratable possible airway pressure with higher tolerability and lesser air leak. It also carries the benefit of higher ventilator fresh gas flow 100-200L/min that limits CO2 rebreathing. These characteristics in addition to the advantages of greater tolerability and less sedation make the concept of NIV via helmet a theoretically promising strategy.

The Trial:
This was a single center non-blinded randomized controlled trial. Enrolled overall sicker patients based on Apache II scores as compared to similar previous trails. Assessed outcomes associated with use of the helmet (which appears to be an interesting and possibly promising NIV delivery device) to the face mask for the management of ARDS. Notably, the most common indication for intubation was neurologic failure in the helmet group and respiratory failure in the facemask group. The study was stopped early, not only due to end point (significantly less intubation and ventilator free survival) being achieved, but also due to concern raised by the safety monitoring committee about exposing the control (NIV via facemask) to potential harm based on the results from Frat et al.

Conclusion:
Based on this trial, it is not possible to draw any conclusions on the efficacy of NIV via helmet for the management of ARDS because the safety and efficacy of the helmet was compared to that of NIV via facemask, which is known to have detrimental outcomes in the management of AHRF. Finally, a multicenter randomized trial will need to be completed before this can become standard of care comparing noninvasive ventilation via helmet to a high flow oxygen system.

UTSW Link

Table A: Primary and Secondary Outcomes and Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Face Mask (n = 39)</th>
<th>Helmet (n = 44)</th>
<th>Absolute Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome, No. (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Endotracheal intubation</td>
<td>24 (61.5)</td>
<td>8 (18.2)</td>
<td>-43.3 (-62.4 to -24.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Reason for intubation</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Respiratory failure</td>
<td>20 (83.3)</td>
<td>3 (37.5)</td>
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<td>.01</td>
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<tr>
<td>Circulatory failure</td>
<td>3 (12.5)</td>
<td>0 (0)</td>
<td>-12.5 (-25.7 to 0.7)</td>
<td>.55</td>
</tr>
<tr>
<td>Neurologic failure</td>
<td>1 (4.2)</td>
<td>5 (62.5)</td>
<td>58.3 (24.8 to 92.8)</td>
<td>.001</td>
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<tr>
<td>Secondary outcomes, median (IQR), d</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>12.5 (6.49-28)</td>
<td>28 (13.7-28)</td>
<td>8.4 (3.4 to 13.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ICU length of stay</td>
<td>7.8 (3.9-13.8)</td>
<td>4.7 (2.5-8.7)</td>
<td>-2.76 (-6.07 to 0.54)</td>
<td>.04</td>
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<tr>
<td>Hospital length of stay</td>
<td>15.2 (7.8-19.7)</td>
<td>10.1 (6.5-15.9)</td>
<td>-2.92 (-8.47 to 2.63)</td>
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<td>Mortality, No. (%)</td>
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<tr>
<td>Hospital</td>
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<td>-21.4 (-41.9 to -1.0)</td>
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<tr>
<td>90 d†</td>
<td>22 (56.4)</td>
<td>15 (34.1)</td>
<td>-22.3 (-43.3 to -1.4)</td>
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<td>Adverse events</td>
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<td>Mask deflation</td>
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<tr>
<td>Skin ulceration</td>
<td>3 (7.6)</td>
<td>3 (6.8)</td>
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</table>

Abbreviations: ICU, intensive care unit; IQR, interquartile range.
† 90 d Mortality includes hospital mortality.
A Program to Prevent Catheter-Associated Urinary Tract Infection in Acute Care


Summary

Catheter-associated urinary tract infections (CAUTIs) represent a major source of healthcare-associated morbidity and are a source of lost revenue for hospitals, who since 2008 have been denied payment for their treatment by the Centers for Medicare and Medicaid. Given successes of some local interventions, this study presents prospective data on the nationalized On the Cusp: Stop CAUTI program, implemented in more than 600 hospitals in 32 U.S states over an 18-month follow-up period.

The intervention itself provides both technical guidelines and recommendations intended to promote awareness and behavioral change among hospital staff. Few aspects of the program are stated explicitly, as participating hospitals were permitted to interpret the guidelines and implement according to their own practices. The pillars of the technical intervention emphasized daily assessments of catheters, routine consideration of non-catheter options and emphasis on aseptic technique. The behavioral change goals, meanwhile, were met by providing performance feedback to units and encouraging dialogue and education on the unique knowledge gaps of individual units.

Overall, the intervention produced a 22.3% decrease in CAUTIs driven by non-intensive care units (average decrease from 2.28 to 1.54 infections per 1000 catheter-days), with a corresponding statistically significant decrease in catheter use of 1.3%. ICUs had no net reduction in infection rates, and a non-significant reduction in catheter use. Notably these improvements in CAUTI rates exceeded the measured reduction of catheter use in the study, suggesting an effect driven by other aspects of the intervention (including the educational and behavioral change components). Finally, while the analysis includes teaching, rural and critical-access hospitals, the effects of CAUTI reduction appear to be driven by rural hospitals, while rates at teaching and critical-access hospitals rose during the intervention (see Table 3 in the original paper).

Commentary

CUSP’s major contribution is to promote behavioral change and a multidisciplinary investment in CAUTI reduction in a field where strictly technical guidelines have fallen short previously. As is often the case in quality improvement research, however, this study has a number of technical shortcomings and ultimately raises as many questions as it answers. For starters, CUSP provides no true control group for comparison and relies on volunteer institutions (23% of whom dropped out mid-study). The intervention itself is vague and we are ultimately left to wonder what
component—if any—is driving the overall CAUTI reduction. Some of this is unavoidable and necessary given the nature of the intervention: blinding of participating centers may not be feasible, for example, and it is difficult to assess the role here of a placebo or Hawthorne effect in driving more dramatic behavior change than would be observed otherwise.

The finding of CAUTI reductions in non-ICU settings, meanwhile, is contrasted by a puzzling lack of effect in ICUs. Several hypotheses for this discrepancy are posited by the investigators and focus on a shifted risk-benefit ratio in intensive care patients who are typically more ill, have longer hospital stays, and are unable to report catheter presence. Dr. Susan Huang, in her NEJM editorial review of the CUSP data, suggests additional possibilities, including more frequent reflexive culturing and fevers of unknown source that result in possible over-reporting of asymptomatic bacteriuria in these settings. Baseline discrepancies in nursing education and training around CAUTIs in ICU versus non-ICU settings where staff may stand to gain more from a behavioral and educational intervention, may further exacerbate these differences.

The increased rate of CAUTIs reported in teaching and critical-access hospitals raises a second crucial concern. This effect is not explained by the authors of this paper, but is of financial relevance to low-resource hospitals that may be outperformed by wealthier health systems with more revenue to invest in intensive interventions like these. Low-resource hospitals will in turn be victims of reimbursement penalties from CMS, feeding into a vicious cycle of low revenue and poor performance in markers of quality care. Further investigation into the drivers of these disparities as well as cost-effective strategies for preventing CAUTIs will be needed to adequately address this risk.

UTSW Link
Effect of Vitamin D Supplementation on Tibial Cartilage Volume and Knee Pain Among Patients with Symptomatic Knee Osteoarthritis


SUMMARY

The objective of the Vitamin D Effect on Osteoarthritis (VIDEO) study was to compare the effects of Vitamin D supplementation versus placebo on subjective knee pain and tibial cartilage volume. This was a randomized, double-blind, placebo-controlled study that enrolled 413 patients between June 2010 and December 2013. The patients were between the age of 50 and 79 years of age, with an average age of 63.2 years and 50% were women. Subjects were required to have had symptomatic osteoarthritis (OA) (based on American College of Rheumatology Criteria) for at least 6 months. Inclusion criteria included subjects with low serum 25-hydroxyvitamin D levels between 12.5 and 60 nmol/L.

Two hundred and nine patients were randomized to the treatment arm and 204 to the placebo arm. Subjects in the treatment arm were given 50,000 IU (1.25mg) of Vitamin D3 (cholecalciferol) once a month for 24 months. Subjects in the placebo group were given an inert placebo pill once a month for 24 months. WOMAC and visual analog scale knee pain scores were used to assess the subject’s subjective pain. The independent t test was used to evaluate the changes in tibial cartilage volume. Both intention-to-treat and per-protocol analyses (defined as achieving a 25-hydroxyvitamin D level > 60 nmol/L at 3 months) were used. A 2-sided P value of .05 was considered statistically significant.

At the end of this two-year study, the 25-hydroxyvitamin D levels had increased by 40.6 nmol/L in the treatment arm and 6.7 nmol/L in the placebo arm. Seventy nine percent of subjects in the Vitamin D supplementation group reached the goal of a 25-hydroxyvitamin D level of greater than 60 nmol/L compared to 43% from the placebo group. Total WOMAC pain scores decreased at 24 months in both of the groups, 87.0 in the Vitamin D group and 97.2 in the placebo group. They found no significant difference in change in the WOMAC pain between the groups. At the end of the 24 months, the change of tibial cartilage volume was -242.6mm³ in the treatment arm versus -301.4mm³ in the placebo arm. The change was not considered statistically significant.

COMMENTARY

OA is common -- one out of ten individuals are affected by symptomatic OA. Unfortunately, there are few therapeutic options to improve OA symptoms or slow its progression. Vitamin D is known to reduce the breakdown of cartilage, facilitate bone mineralization, and slow bone turnover. This supplement has been thought to slow the progression of OA. Older studies have seen an
association between low 25-hydroxyvitamin D levels and increased knee pain and more severe radiographic disease. The purpose of this trial was to study the effects of Vitamin D supplementation on osteoarthritic pain and tibial cartilage volume in patients with symptomatic OA and low serum 25-hydroxyvitamin D. Ultimately, at the end of 2 years, there were no significant differences in WOMAC pain scores and MRI-measured tibial cartilage volume between the group that received Vitamin D supplementation and the placebo group. While vitamin D supplementation is encouraged in vitamin D deficient patients, this study does not support its use for improving WOMAC pain scores or preventing tibial cartilage degradation.

UTSW Link

Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults with Chronic Low Back Pain


SUMMARY

The objective of the Mind-Body Approaches to Pain (MAP) study was to compare mindfulness-based stress reduction (MBSR) with cognitive behavioral therapy (CBT) and with usual care in patients with chronic low back pain. This was a randomized, interviewer-blind, clinical trial that enrolled 342 subjects between September 2012 and April 204. Individuals were between 20 and 70 years of age with low back pain for at least 3 months in duration. Subjects were randomized to MBSR, CBT, or usual care. The patients that were randomized to the usual care group received no MBSR training or CBT, but were able to seek any type of care they wished. Subjects randomized MBSR and CBT attended group sessions for 2 hours per week for 8 weeks. The patients were given workbooks, CDs, and directions to practice at home. The MBSR sessions were lead by instructors experienced in MBSR. These sessions included lectures as well as mindfulness practice (meditation, body scanning, and yoga). CBT was conducted by psychologists trained in CBT for chronic pain. Sessions focused on education about chronic pain, the relationship between negative thoughts and actions, coping strategies, and ways to change negative thoughts. There were similarities between the groups with mindfulness and meditation in CBT and strategies to challenge destructive thoughts in MBSR.

One hundred and thirteen subjects were randomized to receive usual care, 116 to receive MBSR, and 113 to receive CBT. Functional limitation related to chronic back pain was assessed using a modified Roland Disability Questionnaire (RDQ) scoring system at intervals of 4, 8, 26, and 52 weeks. The statistical analysis followed an intention-to-treat approach and subjects were analyzed despite session attendance. As expected with behavioral interventions, participation in sessions
fell with only 59 (50.9%) in the MBSR group and 64 (56.6%) in CBT group attending at least 6 sessions.

At 26 weeks, there was a significant difference between the treatment groups. Subjects in the MBSR group were more likely to have significant improvement on the RDQ than those randomized to usual care (RR, 1.64 [95% CI, 1.15–2.34]). This difference continued at 52 weeks. They found no significant difference between CBT and MBSR groups at 26 or 52 weeks.

**COMMENTARY**

Chronic low back pain is a leading cause of disability in the United States. While we have numerous treatment options, patients are too often left frustrated and disable. Chronic pain is typically multifactorial with psychosocial factors playing an important role. CBT has been found to improve outcomes in many chronic pain conditions. This study set out to evaluate the effectiveness of MBSR, CBT, and usual care in patients with chronic low back pain. After 26 weeks, treatment with MBSR or CBT, compared with usual care, resulted in greater improvement in back pain and disability. While patient compliance with these alternative therapies may be a challenge, they offer an effective modality option in patients with chronic low back pain. Further research is warranted to identify/evaluate what are the specific effective ingredients of the active intervention and what “dose” is acceptable to provide pain and functional relief.

[UTSW Link]
Faculty and Fellow Mentors

We would like to acknowledge and thank UTSW's Internal Medicine Journal Watch faculty and fellow mentors for their time and effort in assisting with this endeavor:

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