UTSW Internal Medicine Journal Watch (May 2014)

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1. Aortic Dilatation in Patients with Bicuspid Aortic Valve

**Commentary:** Bicuspid aortic valve is a common congenital heart defect that often leads to stenosis, insufficiency and/or aortic dilation. Aortic dilation begins early, and is attributed to both abnormal valve flow patterns and genetics. Aortic dissection is a potentially fatal complication of aortic dilation, but as a whole has decreased in frequency with the advent of thorough surveillance imaging algorithms for patients with known bicuspid aortic valves. It is important for housestaff to recognize aortic dilation and dissection as significant complications of bicuspid aortic valve, and to initiate yearly surveillance with echo or MRI/CT when the aortic root or ascending aorta is greater than 4.0cm.

Link: [Journal Website](#) [Full article via UTSW](#)

2. Effect of Evolocumab or Ezetimibe Added to Moderate or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia. The LAPLACE-2 Randomized Clinical Trial

**Commentary:**
The LAPLACE-2 clinical trial was a randomized, double-blind, placebo controlled study that evaluated the LDL lowering efficacy of the addition of the monoclonal antibody evolocumab to background statin therapy with a variety of statins. Evolocumab was given subcutaneously every 2 or 4 weeks and binds PCSK9 which, when uninhibited, degrades LDL receptors. At the conclusion of this 12-week study, patients in the evolocumab treatment arm had 59-65% lower LDL levels on top of statin therapy. Several PCSK9 inhibitors are now in development, with much of the science and major studies behind this class of drugs originating at UTSW. These agents are now being evaluated in large Phase III randomized trials with >10,000 subjects to determine their efficacy for clinical endpoints. The results of these studies will inform the potential use of these agents which are among the most exciting novel therapies in cardiovascular medicine.

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Endocrinology

1. Overnight Closed-Loop Insulin Delivery in Young People With Type 1 Diabetes: A Free-Living, Randomized Clinical Trial.

2. Feasibility of Closed-Loop Insulin Delivery in Type 2 Diabetes: A Randomized Controlled Study.

Commentary: The artificial pancreas, a device that automatizes insulin (and glucagon) delivery and "takes the patient out of the equation," has been referred to as the Holy Grail of diabetes research. We're not there yet, but there has been very impressive progress over the past few years towards the production of a commercially-available artificial pancreas. In this month's Diabetes Care, two small, randomized-control trials were published which used the closed-loop insulin delivery system in patients with diabetes. The closed-loop system involves a continuous glucose monitor (CGM), which measures interstitial glucose, and automatically "talks to" an insulin pump in order to increase or decrease insulin delivery based on sensor glucose levels (using an algorithm).

The first article evaluated the home use of a closed-loop system in 16 adolescents (aged 12-18 years) with T1DM. Patients were randomized to a crossover design (3 weeks of sensor-augmented therapy, meaning that they had a CGM and insulin pump but had to manage the pump manually; and 3 weeks of a closed-loop system with automatized CGM and insulin pump). The patients using the closed-loop system had better overnight BGs (the primary outcome), lower total-daily insulin doses, and less hypoglycemia than the "conventional" group.

The second article was the first study with a closed-loop system in patients with T2DM. It evaluated 12 subjects with T2DM not requiring insulin (mean age 57, BMI 30.5, A1C 8.4%) by use of a randomized, crossover design (usual oral diabetes regimen vs closed-loop system) during two 24-hr visits. It found that patients on the closed-loop system spent more time in the target BG range (~70-144 mg/dL); no hypoglycemia was noted in either group.

We are moving closer and closer to the development of a commercially-available, artificial pancreas for our DM patients. While small, these studies help us to see the promise of a technology that will improve outcomes in our patients with diabetes while actually making it easier for them to manage the disease.

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1. Changes in Mortality After Massachusetts Health Care Reform: A Quasi-Experimental Study

**Commentary:** This article doesn't address day-to-day clinical care, but speaks to important shifts in the provision of healthcare in our country. Using a ‘quasi-experimental’ design, the authors analyzed all-cause mortality and deaths from causes amenable to healthcare before and after the implementation of healthcare reform in Massachusetts. The implementation of reform was associated with statistically significant reductions in both. Clearly, this study cannot conclude that healthcare reform was the cause of these reductions in outcomes. However, it certainly adds weight to the argument that access to healthcare is important to health.

**Link:** Full Article via UTSW

2. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis

**Commentary:** Red blood cell transfusion represents a common procedure in hospitalized anemic patients. Multiple trials have addressed the question of what would be an appropriate hemoglobin target when RBC transfusions are indicated. Previous studies have shown that restrictive red blood cell transfusion (Hgb<7 mg/dl) are associated reduced in-hospital mortality (number needed to prevent 1 death was 33). This is also true for patients with acute upper GI bleed as noted in a meta-analysis by Wang et al.

In the present article Rhodes JM, et al show that among hospitalized patients, a restrictive RBC transfusion strategy (Hgb<7 mg/dl) was associated with a reduced risk of health care-associated infection compared with a liberal transfusion strategy (8-9 mg/dl). Risk ratio (RR): 0.82 (95% CI, 0.72-0.95). Number needed to treat (NNT) with restrictive strategies to prevent serious infection was 38 (95% CI, 24-122). The risk of infection remained reduced with a restrictive strategy, even with leukocyte reduction (RR, 0.80 [95% CI, 0.67-0.95]). For trials with a restrictive hemoglobin threshold of <7.0 g/dL, the RR was 0.82 (95% CI, 0.70-0.97) with NNT of 20 (95% CI, 12-133).

Although an explanation for the given findings is not given in the study, a recent report showed increased levels of regulatory cytokines in liberal transfusion strategies and they correlated with the numbers of RBCs transfused.

RBC transfusions should be indicated with caution and avoided in patients without a clear indication.

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Geriatrics

1. The CAM-S: Development and Validation of a New Scoring System for Delirium Severity in 2 Cohorts

Commentary: Delirium is a strong predictor of poor patient outcomes but despite efforts, it remains grossly under diagnosed and undertreated. This may be in part due to lack of diagnostic tools and our preconceived notion of delirium as an "agitated" state when in fact, the hypoactive form is more common and perhaps more dangerous due to lack of recognition. CAM (Confusion Assessment Method) is a standardized, validated measure that has gained widespread use in screening for delirium but does not measure severity which would greatly enhance its clinical value. By quantifying the severity we can advance clinical care by improving our understanding of delirium effect, prognosis, pathophysiology and response to treatment. As described in this article, the authors created CAM-S to measure and track delirium severity to follow response to delirium treatment and management interventions. The short 4 item (vs. long 10 item questionnaire) is an easy tool which would not increase rounding burden but may provide benefits given the strong association of delirium with poor outcomes. The availability of this measure will hopefully serve to facilitate critically needed studies of delirium and its outcomes and lead to improved quality of life for older persons and their families.

Link: Full article via UTSW

Palliative Care

1. Oncologists' Palliative-Care Referrals: Oncologist factors that influence referrals to outpatient palliative care

Commentary: As many of us know there has been much discussion on the benefits of initiating early palliative care for oncology patients. However, we can also agree that there are many barriers that continue to exist in coordinating this care. This multisite, qualitative study identified 3 major and specific barriers to palliative care referrals for oncology patients in the United States:

1) persistent impressions of palliative care as an alternate therapy as opposed to a complimentary therapy to standard cancer care
2) belief that the oncologist should be able to treat the full spectrum of the disease
3) a lack of knowledge of existing palliative care resources in the community.

The trial demonstrates that although barriers exist, they are surmountable and represent potential educational opportunities both amongst the community and fellow physicians.

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1. Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E$_2$

Commentary: The function of the innate immune system is suppressed in patients with acutely decompensated cirrhosis and predisposes these patients to severe bacterial infections. A study published in this month’s *Nature Medicine* shows that increased synthesis of the immunosuppressive prostaglandin PGE$_2$ by monocytes/macrophages and impaired hepatic synthesis of albumin, resulting in increased levels of free PGE$_2$, are major contributors to immune suppression in cirrhosis. Intravenous administration of albumin to patients with acutely decompensated cirrhosis increased the amount of albumin-bound PGE$_2$, decreased free PGE$_2$ and restored immune competence. To this end, it is not known whether this data translates into decreased rate of severe bacterial infections and improved mortality but randomized clinical trials are under way to test this hypothesis ([NCT00839358](https://clinicaltrials.gov/ct2/show/NCT00839358), [NCT01288794](https://clinicaltrials.gov/ct2/show/NCT01288794)).

Link: [Full article via UTSW](https://utsouthwesternmedicine.org/patient-care/news-and-publications/)

2. Spectrum of statin hepatotoxicity: Experience of the drug-induced liver injury (DILI) network

Commentary: Statins were originally thought to have a high potential for causing DILI and routine monitoring of LFTs was recommended when first approved for use in the United States. In this large prospective study only 22/1188 (2%) cases of DILI reported between 2004 and 2012 were attributable to statins. Liver injury from the statins was mild-to-moderate in severity, and developed months to years after initiation; no patient developed DILI within 4 weeks of starting the statin. Clinical presentation included cholestatic (40%), hepatocellular (30%) and autoimmune hepatitis-like manifestations (30%). Liver injury from statins rapidly reversed upon stopping, although cases with an autoimmune phenotype of liver injury had evidence of active disease more than 6 months after onset requiring treatment with prednisone. Based on this report, prospective monitoring for DILI from statins is not indicated, but patients who develop a liver injury with an autoimmune phenotype should be evaluated for immunosuppressive therapy if liver tests fail to improve.

Link: [Full article via UTSW](https://utsouthwesternmedicine.org/patient-care/news-and-publications/)
Infectious Disease

1. Acute Infectious Diarrhea in Immunocompetent Adults

Commentary: This excellent and comprehensive review article covers the major infectious causes of acute diarrhea in adults without immunocompromise and key salient aspects of epidemiologic risk factors, diagnosis and management. In particular, the table of important pathogens with diagnostic and treatment recommendations is high yield for board review and clinical reference. This review article, by an international expert in the field, establishes the bar for introduction to this topic in the literature and would also be a great starting point for a didactic session with students or residents on the wards or in the clinic.

Link: Full article via UTSW

2. Vital Signs: improving antibiotic use among hospitalized patients

Commentary: This summary report from the CDC highlights the widespread use of antimicrobials in US hospitals and discusses opportunities to reduce overuse and complications such as C. difficile infection. Key findings include:
1) Over 50% of patients received at least one antibiotic during their hospital stay in 2010
2) Antibiotic misuse was high, with opportunities to improve over 1/3 of antibiotics prescribed
3) Exposure to broad-spectrum abx significantly increases a patient's risk for C. difficile infection and represents a key target for curbing the tide of the C. difficile epidemic.

3. First Confirmed Cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection in the United States, Updated Information on the Epidemiology of MERS-CoV Infection and Guidance for the Public, Clinicians, and Public Health Authorities

Commentary: This report from the CDC reports on the first two imported cases of the new Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in the United States. Both cases were in healthcare workers from the Arabian Peninsula who were visiting family or friends in Indiana (first case) or Florida (second case). There have been a total of 536 lab-confirmed cases with 145 deaths worldwide since its discovery in September 2012. This report provides a review of the epidemiology of this viral respiratory pathogen as well as practical guidance regarding laboratory testing, infection control, and travel guidance. The CDC website also has a dedicated webpage with useful information. While it is too early to know how widespread cases will be in the United States, recognition of cases in a major travel hub such as the Dallas-Ft Worth area is certainly possible and requires vigilance on the part of healthcare workers. Healthcare providers should evaluate, as well as notify infection control and infectious diseases at their respective hospital, for any patients who meet the following criteria:
Fever + pneumonia or ARDS + either of the following:
1) travel from countries in or near the Arabian Peninsula w/in 14 days of symptoms
2) close contact with a symptomatic traveler with fever and acute respiratory illness within 14 days of travel in or near the Arabian Peninsula
3) member of a cluster of patients with severe acute respiratory illness of uncertain etiology in which MERS is being considered. Close contacts of confirmed or probable MERS cases during the affected person’s illness should also be evaluated.

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Nephrology

1. Utility of renal biopsy in the clinical management of renal disease

**Commentary:** Renal biopsy is an important clinical tool in diagnosing the etiology of kidney disease in patients. While there are certain indications for renal biopsy that many nephrologists would agree upon (significant proteinuria or systemic disease with accompanying renal impairment), this paper argues for the more liberal use of this procedure. Of particular interest are patients with diabetes and concurrent renal impairment, where several studies have reported non-diabetic renal disease in up to 60% of patients biopsied. Interval biopsy in patients with lupus nephritis and renal transplant can also provide illuminating information regarding treatment response and disease progression in patients with continued renal disease. This should be an especially relevant consideration, as immunosuppressive medications are not without their own risks.

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