Endocrinology

American Diabetes Association’s Standards of Medical Care in Diabetes – 2015

Dr. Jeremy Warshauer reviewing Grant RW, et al. Diabetes Care 2015 Jan;38 Supplement 1

Commentary: The American Diabetes Association released updated Standard’s of Medical Care in Diabetes for the year. Included are some useful algorithms and revisions to guidelines for quick review. Highlights include the following:

Screening: Screening for type 2 diabetes in overweight and obese Asian Americans was changed from a BMI of 25kg/m$^2$ to 23kg/m$^2$ to reflect data showing that the risk of type 2 diabetes develops at lower BMI’s in this population than the general population.

Diabetes and Hypertension: Diastolic blood pressure goal was changed from 80 mmHg to 90 mmHg, although in certain individuals lower targets may be needed. Goal systolic blood pressure is <140 mmHg.

Glycemic Targets: Goal pre-meal blood glucose target is now 80-130mg/dL instead of 70-130mg/dL.

Approach to glycemic treatment in type 2 diabetes: An easy to use algorithm (Below) for glycemic control, updated to include newer investigational medications such as sodium-glucose contrasporter 2 inhibitors (SGLT2):

Strategy for Insulin Dosing: This article gives a useful strategy (Page 3) for insulin dosing by factoring in complexity of the regimen, number of injections and type of insulin, highlighting the need for individualization in diabetes management.
Link: UTSW Link
Metformin in Patients With Type 2 Diabetes and Kidney Disease: A Systematic Review


Commentary: Metformin was first FDA approved for management of type 2 diabetes in 1994. The previous biguanide, phenformin, was withdrawn in 1977 owing to its risk of lactic acidosis. Despite the low risk of developing Metformin Associated Lactic Acidosis (MALA) the US FDA stipulated stringent prescribing criteria based on kidney function:

1. Metformin is contraindicated in “renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels 1.5 mg/dL [males], 1.4 mg/dL [females]) or abnormal creatinine clearance (CrCl).”

2. Metformin “should not be initiated in patients 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.”

In the present study (led by Dr Darren McGuire) assessed the risk of developing MALA in individuals with impaired kidney function. The incidence of MALA ranged from 3 to 10 per 100,000 person-years and was indistinguishable from the background rate in general diabetic population. Overall, data regarding MALA in patients with impaired renal function are limited and lactate levels are not elevated with the use of metformin in patients with mild to moderate chronic kidney disease i.e. eGFR 30-60 ml/min per 1.73 m². Infact, observational studies suggest a potential benefit from metformin on macrovascular outcomes, even in patients with prevalent renal contraindications for its use

Thus, summarizing all the existing literature, the authors propose a novel approach (see below) cautiously expanding the use of metformin in patients with chronic kidney disease

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR, ml/min per 1.73 m²</th>
<th>Maximal Total Daily Dose, mg</th>
<th>Other Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>2550</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60-&lt;90</td>
<td>2550</td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>45-&lt;60</td>
<td>2000</td>
<td>Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function</td>
</tr>
<tr>
<td>3B</td>
<td>30-&lt;45</td>
<td>1000</td>
<td>Do not initiate therapy at this stage but drug may be continued Avoid if kidney function is or expected to become unstable Consider more cautious follow-up of kidney function</td>
</tr>
<tr>
<td>4</td>
<td>15-&lt;30</td>
<td>Do not use</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Do not use</td>
<td></td>
</tr>
</tbody>
</table>

Link: UTSW Link
Rheumatology

Preliminary analysis of the Very Early Diagnosis of Systemic Sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis


Commentary: This article by EULAR (European League Against Rheumatism) Scleroderma Trials and Research Group (EUSTAR) is part of an ongoing effort to improve early detection of systemic sclerosis (SSc). EUSTAR previously identified Raynaud’s phenomenon (RP), puffy fingers (previous history or current), and positive anti-nuclear antibodies (ANA) as “red flags” that should raise suspicion for very early SSc. In this study they assessed the prevalence of ANA positivity and puffy fingers (Figure 1) in patients with RP (Figure 2) and determined how many met the criteria for very early SSc (confirmed by characteristic nail capillaroscopy findings and/or SSc-specific antibodies).

A history of or current puffy fingers, especially in ANA-positive patients, raised the likelihood that patients had more specific signs of SSc including sclerodactyly, telangiectases, and characteristic nailfold capillaroscopy findings. These results suggest a simple, cost-effective way to risk stratify patients with Raynaud’s phenomenon. Puffy fingers in these patients should raise suspicion for early SSc and lower one’s threshold to test patients for autoantibodies and refer for expert evaluation.

Figure 1: Characteristic puffy fingers

Figure 2: Raynaud’s phenomenon

Link: UT SW Link
Health Care Improvement

Using drugs to discriminate - adverse selection in the insurance marketplace.


Commentary: Although eliminating discrimination by health insurers on the basis of pre-existing conditions is one of the central features of the Affordable Care Act (ACA), insurers are resorting to other tactics, such as ‘adverse tiering’ to dissuade high-cost patients from enrolling in their plans. Adverse tiering is the practice of placing all drugs for a particular condition – such as HIV – in the highest cost-sharing tier. Unlike the use of tiered formularies to encourage enrollees to select generic or preferred brand-name drugs instead of higher cost alternatives, the purpose of adverse tiering is to explicitly discourage individuals with high-cost chronic conditions, including HIV, cancer, mental illness, rheumatoid arthritis, or diabetes, from enrolling in an insurer’s plan altogether. This study assessed 48 plans in 12 states using the federal marketplace for health insurance and found that one-quarter – 12 of 48 plans – placed all HIV drugs into the highest-cost sharing category and required patients to pay at least 30% of drug costs. Consequently, annual drug costs were more than triple the costs incurred other plans ($4,892 vs. $1,615) with a cost difference of almost $2,000 even for generic drugs. These findings are consistent with a recent analysis of insurance coverage, which found a high prevalence of adverse tiering in other high-cost chronic conditions.

Taken together, these finding suggests that insurance companies may be using drug costs to discriminate against the sickest Americans. Adverse tiering poses significant potential harms to patients. First, adverse tiering puts patients under substantial and unexpected financial strain; further, this practice endangers patients’ health as many may forego needed but unaffordable medications. Second, this process may cause sicker patients to increasingly enroll in plans that do not use adverse tiering. An influx of sicker patients would reduce profits for these plans and create an incentive for them to reduce prescription drug benefits, creating a downward spiral that would ultimately result in patients being unable to obtain needed medications. Additional policies are needed to end adverse tiering, including establishing “protected classes” of drugs for high cost conditions to maintain patients’ access to these medications; and establishing “protected conditions” with limits on out-of-pocket spending.

Link: NEJM Link
**General Internal Medicine**

**Disorders of Plasma Sodium — Causes, Consequences, and Correction**


**Commentary:** This article is designed for every house-staff who has struggled with understanding sodium disturbances. It explains how disorders of plasma sodium concentration expose cells to hypotonic or hypertonic stress. In addition, it pinpoints the causes and consequences of an abnormal plasma sodium concentration and offers a framework for correcting it.

**Link:** [NEJM Link](#)

**Acid–Base Problems in Diabetic Ketoacidosis**


**Commentary:** This review focuses on three issues facing clinicians who care for patients with diabetic ketoacidosis; all of the issues are related to acid–base disorders. The first issue is the use of the plasma anion gap and the calculation of the ratio of the change in this gap to the change in the concentration of plasma bicarbonate in these patients; the second concerns the administration of sodium bicarbonate; and, the third is the possible contribution of intracellular acidosis to the development of cerebral edema, particularly in children with diabetic ketoacidosis.

**Link:** [NEJM Link](#)

**Platelet Transfusion: A Clinical Practice Guideline From the AABB**


**Commentary:** Due to their low life span and difficult storage ability, platelets are a precious blood product at every blood bank. This has led to strict recommendations on when to transfuse them. For this reason, every house-staff must receive at least one phone call from pathology (with several articles) inquiring about the absolute need for a platelet transfusion. This article reports the new guidelines developed by the American Association of Blood Banks (AABB) on appropriate use of platelet transfusion in adult patients.

**Recommendation 1:** The AABB recommends that platelets should be transfused prophylactically to reduce the risk for spontaneous bleeding in hospitalized adult patients with therapy-induced hypoproliferative thrombocytopenia. The AABB recommends transfusing hospitalized adult patients with a platelet count of $10 \times 10^9$ cells/L or less to reduce the risk for spontaneous bleeding. The AABB recommends transfusing up to a single apheresis unit or equivalent. Greater doses are not more effective, and lower doses equal to one half of a standard apheresis unit are equally effective. (Grade: strong recommendation; moderate-quality evidence)

**Recommendation 2:** The AABB suggests prophylactic platelet transfusion for patients having elective central venous catheter placement with a platelet count less than
Recommendation 3: The AABB suggests prophylactic platelet transfusion for patients having elective diagnostic lumbar puncture with a platelet count less than 50 × 10^9 cells/L. (Grade: weak recommendation; low-quality evidence)

Recommendation 4: The AABB suggests prophylactic platelet transfusion for patients having major elective non-neuraxial surgery with a platelet count less than 50 × 10^9 cells/L. (Grade: weak recommendation; very-low-quality evidence)

Recommendation 5: The AABB recommends against routine prophylactic platelet transfusion for patients who are non-thrombocytopenic and have cardiac surgery with cardiopulmonary bypass. The AABB suggests platelet transfusion for patients having bypass who exhibit perioperative bleeding with thrombocytopenia and/or evidence of platelet dysfunction. (Grade: weak recommendation; very-low-quality evidence)

Recommendation 6: The AABB cannot recommend for or against platelet transfusion for patients receiving antiplatelet therapy who have intracranial hemorrhage (traumatic or spontaneous). (Grade: uncertain recommendation; very-low-quality evidence)

Nephrology

Association of Albumin-Creatinine Ratio and Cystatin C With Change in Ankle-Brachial Index: The Multi-Ethnic Study of Atherosclerosis (MESA)


Commentary: This prospective longitudinal cohort study enrolled 6,814 patients between the ages of 45-84 who were initially free of cardiovascular disease to have baseline albumin-creatinine ratio and cystatin C levels drawn followed by ankle-brachial index (ABI) monitoring over a median time period of 9.8 years. This study found that 221 and 89 subjects, respectively, progressed to low (<0.90) and high (>1.40) ABIs over that time course, with albuminuria being a strong independent risk factor for both high and low ABI progression. While albumin-creatinine ratios are often obtained to monitor for diabetic nephropathy, elevated levels should alert clinicians of the future risk of progressive peripheral vascular disease in the selective population with baseline elevated levels.

Link: UTSW Link
Infectious Diseases

**Diagnosis and Treatment of C. difficile in Adults: Systematic Review**

Dr. Brad Cutrell and Dr. Nicolas Barros reviewing Bagdasarian N, et al. JAMA 2015; 313(4):398-408

**Commentary:** This recent high-level systematic review summarizes recent guidelines and literature on the diagnosis and treatment of C. difficile infection. Key findings include 1) a review of the test performance characteristics of the different testing modalities, including the data to support a possible multi-step approach to improve diagnostic accuracy; 2) a review of the comparison data on metronidazole and vancomycin as first-line therapies as well as potential roles for newer treatments such as fidaxomicin and fecal microbiota transplantation, which is still evolving. Several of the tables and algorithms provide a quick guide to the common clinical scenarios encountered with this disease.

**Link:** [UTSW Link](#)

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**Tenofovir-Based Preexposure Prophylaxis for HIV Infection Among African Women**

Dr. Brad Cutrell and Dr. Nicolas Barros reviewing Marrazzo J, et al. 2015; 372:509-518

**Commentary:** The long-awaited (and already publicized) results of the VOICE trial have been published, providing important guidance in terms of the future of preexposure prophylaxis (PrEP) for HIV prevention especially in sub-Saharan Africa. This placebo-controlled RCT of over 5,000 HIV-negative women in 3 African countries compared daily oral tenofovir, daily oral tenofovir-emtricitabine, and topical tenofovir vaginal gel. The principal results were that none of the regimens tested were effective in reducing rates of HIV acquisition in an intention-to-treat analysis. These results predictably were driven by low rates of adherence to the medication, demonstrated by low levels of detectable drug in the plasma at random sampling intervals. These results are similar to previous negative studies of PrEP in heterosexual African women (such as FEM-PrEP study) but contrast with positive studies showing a benefit to PrEP in an MSM population with much higher rates of adherence.

However, as pointed out in the editorial by Michael Saag, the issue of adherence is more complex than individuals simply choosing not to take their medications. Discrepancies between reported adherence and plasma drug levels as well as detailed interviews of select women to explore reasons for non-adherence exposed the significant impact that stigma plays with regards to individual behavior and willingness to take PrEP in this environment. Similar concerns related to stigma also affect certain high-risk groups within the US (such as young, African American MSM), and these issues must be addressed to enhance the effectiveness of prevention strategies and to make progress in curbing the HIV epidemic.

**Link:** [NEJM Link](#)
Hepatology

An interferon-free antiviral regimen for HCV after liver transplantation

Dr. Jan Petrasek reviewing Kwo et al., NEJM. 2014; Dec 18;371(25):2375-82

Commentary: Cirrhosis due to chronic HCV infection remains the commonest indication for liver transplant (LTx) in the United States. In the era of lack of curative antiviral therapy prior to LTx, nearly all grafts became reinfected immediately after transplant. This was due to universal post-transplant recurrence of hepatitis C in patients who had detectable HCV RNA at the time of transplantation, resulting in an accelerated tempo of HCV infection post-transplant, with high rates of graft dysfunction and progression to cirrhosis and graft failure within 5-10 years of LTx. Successful clearance of HCV after liver transplantation can reduce the risk of subsequent HCV-related complications. Unfortunately, the standard therapy consisting of interferon and ribavirin resulted in clearance of HCV in less than one third of patients post-transplant. In addition, interferon-based therapies in LTx recipients can induce immune graft injury, reducing patient and graft survival.

In a study published in NEJM, Kwo et al. present a compelling dataset from a phase 2, open-label trial involving an all-oral antiviral regimen in 34 patients with recurrence of HCV after liver transplant. All patients underwent antiviral treatment at least one year after liver transplantation. At that time, recurrence of HCV was clearly established and all patients were on a stable immunosuppression regimen. Patients with advanced fibrosis were excluded. All 34 patients received the oral regimen consisting of ombitasvir, ritonavir-boosted ABT-450, dasabuvir and ribavirin, for six months. All 34 patients (100%) cleared the virus by week 4 of treatment. Only one patient relapsed after completion of therapy and the remaining 33 (97%) achieved a sustained clearance of the virus.

This study represents a substantial advance in management of post-transplant recurrence of hepatitis C, and has already been implemented in the AASLD/IDSA guidelines. It is likely that post-transplant recurrence of HCV will become a curable condition and long-term outcomes of liver transplantation for HCV will improve to the level of those that we see in patients who underwent LTx for other indications.

Link: NEJM Link AASLD/IDSA guidelines

Decreasing Mortality Among Patients Hospitalized with Cirrhosis in the United States From 2002 through 2010

Dr. Jan Petrasek reviewing Schmidt et al., Gastroenterology. 2015 Jan 23.

Commentary: In the past 15 years, numerous guidelines have been implemented by the AASLD and other societies offering evidence-based recommendations for the treatment of patients with liver diseases. However, it has not been clear whether evidence-based recommendations for inpatient care of cirrhosis patients are effective in the community. In a study published in Gastroenterology, Schmidt et al. present data from the Nationwide Inpatient Sample/Healthcare Cost and Utilization Project, on more than 750,000
hospitalizations of patients with cirrhosis from 2002 through 2010. The data on patients with liver cirrhosis were compared with data on patients with CHF, matched for age, gender and year of discharge.

Mortality in patients with liver cirrhosis, as in patients with CHF, decreased over time. Specifically, there has been a significant relative decrease in mortality for patients with variceal bleeding, hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP) and HCC, possibly owing to improved therapeutic standards including increased use of albumin, vasoactive medications and antibiotics. An important exception to this trend was sepsis in patients with liver cirrhosis, which was associated with one of the highest risks of mortality, and the risk increased over time, in spite of wide implementation of the Surviving Sepsis Campaign guidelines.

It is remarkable that in spite of therapeutic advances in liver disease, patients admitted for liver cirrhosis still have about 3-fold increased relative risk of in-hospital mortality, compared to patients with CHF. Nonetheless, this data demonstrates that improving inpatient survival despite aging and more medically complex cirrhotic patients is consistent across several cirrhosis complications and suggests improving liver cirrhosis care that may extend beyond general improvement in inpatient care.

**Figure 1.** (A) Inpatient mortality from 2002 to 2010 for cirrhotic patients and patients with CHF. The decline in mortality for patients with cirrhosis was significantly more than that on the CHF cohort. (B) Relative risk of inpatient mortality due to complications of cirrhosis, between 2002 and 2010.

**Link:** Gastroenterology website
Cardiology

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents (DAPT trial)


Summary: This study randomized 9,961 patients who had received a drug-eluting stent to either continue receiving dual antiplatelet therapy with aspirin and clopidogrel or prasugrel (n=5,020), or narrow to aspirin only (n=4,941) after having received 12 months of dual therapy (the current standard of care). Patients were monitored for the next 18 months for three outcomes: stent thrombosis, major adverse cardiovascular and cerebrovascular events (MACCE) and moderate to severe bleeding. The study found that stent thrombosis and MACCE were decreased in the extended dual-therapy group at the expense of an increased risk of bleeding. Death rate was slightly higher in the dual-therapy group, which was attributed to an imbalance in the randomization of patients with malignancy and bleeding-related deaths.

Commentary: Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is the current standard of care following coronary stent placement to help mitigate the risk of thrombotic complications during the stent epithelialization process. The duration of dual antiplatelet therapy has traditionally been 12 months for a drug-eluting stent, but thrombotic complications have been observed after this 12-month mark. Dr. Dharam Kumbhani, a UT-Southwestern interventional cardiologist, offers his insight on the results of this trial. Following concerns regarding late and very late stent thrombosis with first generation DES, ACC/AHA guidelines recommended a minimum duration of 12 months of DAPT following DES PCI. However, the optimal duration remains unknown and trials have sought to study both sides of the duration spectrum. On the one hand, trials such as PRODIGY, RESET, and OPTIMIZE sought to assess shorter durations (3-6 months) of DAPT with second generation DES use in mostly stable patients. On the other hand, trials such as DES-LATE and EXCELLENT have sought to assess if prolonged DAPT treatment would be superior to 12 months.

The DAPT trial is by far the largest trial on this topic to date, and suggests that although there may be an ischemic benefit with prolonged DAPT therapy, there is a price to pay in terms of bleeding risk. The excess in mortality is also concerning, and appears to be a combination of cancer-related and bleeding-related mortality. It should be noted that the DAPT trial results only apply to patients who have not had an ischemic or bleeding event within the first year, and were also fully compliant with DAPT therapy, thus somewhat limiting the generalizability of this trial. Patients in this trial received contemporary stents, although nearly a quarter received paclitaxel-eluting stents (PES), which are inferior to currently utilized second generation DES. The magnitude of benefit appeared to be highest in the PES patients, and lower in patients receiving second generation EES. For these reasons, it does not appear that these results will immediately impact clinical practice.

Link: UTSW Link
EKG Challenge
Dr. Ben Jennings

Summary: A 65 year-old male with a history of tobacco abuse and diabetes presented to the emergency department reporting substernal chest pain that has been continuously present for the past three hours. An EKG was obtained (Figure 1) with the following interpretation: Junctional bradycardia, ST segment elevation and Q waves in leads II, III, AVF and ST segment depression with R waves in V1, V2, V3. The ST segment elevation in the inferior leads combined with the ST segment depression in the precordial leads is consistent with an acute infero-posterior myocardial infarction, likely due to acute thrombotic occlusion of the right coronary artery (RCA). This finding is further supported by the presence of junctional bradycardia, as the RCA supplies branches to the SA node, AV node and posterior descending artery in 55%, 90% and 85% of the population. A common presentation of acute RCA occlusion is bradycardia due to nodal ischemia.

Figure 1: EKG of patient

A right-sided EKG (Figure 2) was obtained, as inferior STEMIIs are often associated with right ventricular (RV) infarctions. While the EKG tracing is not labeled as “right sided,” the poor R wave progression in the lateral precordial leads is a clue to the reverse lead placement. The most sensitive lead for detecting RV infarctions is V4, which in this patient’s EKG is without ST segment elevation. A posterior EKG (Figure 3) was also obtained, which was notable for ST segment elevation confirming the involvement of the posterior wall.
Management of RCA infarctions depends upon the presence or absence of bradycardia and RV involvement. Bradycardia due to RCA infarctions responds well to atropine acutely (hours) but with waning efficacy as time passes. While the bradycardia is initially triggered by ischemia, the acute and sub-acute mechanisms differ: adenosine (acute) and myocardial edema (sub-acute). If the RV is involved and accompanied by hypotension, blood pressure often improves with fluid boluses, which augments venous return via the Starling Curve.

**Key Concepts**

- RCA vascular territory
- Interpretation of right sided and posterior EKGs
- Management of RV infarcts