Currently, Baylor Scott & White Research Institute is conducting more than 2,000 research projects. Studies open to enrollment are listed in the Table. To learn more about a study or to enroll patients, please call or e-mail the contact person listed.

<table>
<thead>
<tr>
<th>Research area</th>
<th>Specific disease/condition</th>
<th>Contact information (name, phone number, and e-mail address)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesiology</td>
<td>Various device trials, measuring oxygenation levels; EEG algorithms of sedation; SpO2 and fluid volume levels; delivery of various anesthesia medications</td>
<td>Zhang Zhang 214-865-3128 <a href="mailto:Zhang.Zhang@BSWHealth.org">Zhang.Zhang@BSWHealth.org</a></td>
</tr>
<tr>
<td>Asthma and pulmonary disease</td>
<td>Chronic obstructive pulmonary disease, asthma (adult), lung transplant, pulmonary hypertension, diaphragm impairment, nebulizer, inhalation</td>
<td>Franci Crockett, RRT 214-820-5829 <a href="mailto:Franci.Crockett@BSWHealth.org">Franci.Crockett@BSWHealth.org</a></td>
</tr>
<tr>
<td>Cancer</td>
<td>Breast, ovarian, endometrial, prostate, brain, lung, bladder, colorectal, pancreatic, and head and neck cancer; hematological malignancies, leukemia, multiple myeloma, non-Hodgkin's lymphoma; bone marrow transplant</td>
<td>Grace Townsend 214-818-8472 <a href="mailto:cancer.trials@BaylorHealth.edu">cancer.trials@BaylorHealth.edu</a></td>
</tr>
<tr>
<td>Central Texas</td>
<td>Cancer, cardiology, family medicine, gynecology, infectious disease, kidney, neurology, obstetric, ophthalmology, orthopedics, pathology, pediatrics, plastic surgery, pediatrics, psychiatry, pulmonary, radiology, rheumatology, surgery, transplant, urology</td>
<td>Vanessa Hoischen 1-888-863-3675 <a href="mailto:vanessa.hoischen@bswhealth.org">vanessa.hoischen@bswhealth.org</a> Johnn Nichols 1-888-863-3675 <a href="mailto:joann.nichols@bswhealth.org">joann.nichols@bswhealth.org</a></td>
</tr>
<tr>
<td>Diabetes (Dallas)</td>
<td>Type 1 and type 2 diabetes, cardiovascular events</td>
<td>Lisa Mamo, RN 214-818-7974 <a href="mailto:Lisa.Mamo@BSWHealth.org">Lisa.Mamo@BSWHealth.org</a></td>
</tr>
<tr>
<td>Diabetes (Dallas)</td>
<td>Pancreatic islet cell transplantation for type I diabetics, who either have or have not had a kidney transplant</td>
<td>Annie Marie Jones 214-818-7823 <a href="mailto:Annie.Jones@BSWHealth.org">Annie.Jones@BSWHealth.org</a></td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>Traumatic brain injury</td>
<td>Jon Thammavong 214-818-9687 <a href="mailto:Jon.Thammavong@BSWHealth.org">Jon.Thammavong@BSWHealth.org</a></td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Inflammatory bowel disease</td>
<td>Sandra Kirby, RN 214-818-9792 <a href="mailto:Sandra.Kirby@BSWHealth.org">Sandra.Kirby@BSWHealth.org</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Dallas)</td>
<td>Aortic aneurysms; coronary artery disease; hypertension; poor leg circulation; heart attack; heart disease; congestive heart failure; angina, cardiomyopathy disease, familial hypercholesterolemia, renal denervation for hypertension, diabetes in heart disease, cholesterol disorders; heart valves; thoracic aneurysm, stem cells, critical limb ischemia, cardiac surgery associated with kidney injury; pulmonary hypertension</td>
<td>Meriele Boatman 214-820-2273 <a href="mailto:Meriele.Boatman@BSWHealth.org">Meriele.Boatman@BSWHealth.org</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Fort Worth)</td>
<td>Atrial fibrillation, atrial fibrillation post PCI</td>
<td>Ava Wallace 817-922-2586 <a href="mailto:ava.wallace@bswhealth.org">ava.wallace@bswhealth.org</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Legacy Heart)</td>
<td>All risk for heart attack/stroke; previous heart attack/stroke/PAD; cholesterol disorders; atrial fibrillation; overweight/obese; other heart-related conditions</td>
<td>Kathy Rodney, BS, RCS, COAC 469-800-6470 <a href="mailto:Kathie.Rodney@BSWHealth.org">Kathie.Rodney@BSWHealth.org</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Plano)</td>
<td>Aortic aneurysms; coronary artery disease; renal failure for uncontrolled hypertension; poor leg circulation; heart attack; heart disease; heart valve repair and replacement; critical limb ischemia; repair of arterial dissections with endografts; surgical link repair; atrial fibrillation; heart rhythm disorders; cardiac artery disease; congestive heart failure; gene profiling</td>
<td>Tina Worley, RN, BSN 469-814-4712 <a href="mailto:Christina.Worley@BSWHealth.org">Christina.Worley@BSWHealth.org</a></td>
</tr>
<tr>
<td>Hepatology</td>
<td>Liver disease</td>
<td>Niechelle Lloyd Theresa Cheyne 214-820-1710 817-922-2579 <a href="mailto:Niechelle.Lloyd@bswhealth.org">Niechelle.Lloyd@bswhealth.org</a> <a href="mailto:Theresa.Cheyne@bswhealth.org">Theresa.Cheyne@bswhealth.org</a></td>
</tr>
<tr>
<td>Infectious disease</td>
<td>HIV/AIDS</td>
<td>Bryan King, LVN 214-823-2533 <a href="mailto:bryan.king@tidel.org">bryan.king@tidel.org</a></td>
</tr>
<tr>
<td>Nephrology</td>
<td>HIV/AIDS</td>
<td>Niechelle Lloyd Theresa Cheyne 214-820-1710 817-922-2579 <a href="mailto:Niechelle.Lloyd@bswhealth.org">Niechelle.Lloyd@bswhealth.org</a> <a href="mailto:Theresa.Cheyne@bswhealth.org">Theresa.Cheyne@bswhealth.org</a></td>
</tr>
<tr>
<td>Neurology</td>
<td>Nephrology</td>
<td>Verle Sliemak 214-820-4628 <a href="mailto:Verle.Sliemak@BSWHealth.org">Verle.Sliemak@BSWHealth.org</a></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Stroke, migraine</td>
<td>Quynh Lan Doan 214-818-2522 <a href="mailto:Quynh.LanDoan@BSWHealth.org">Quynh.LanDoan@BSWHealth.org</a></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Multiple sclerosis, stroke</td>
<td>Vicki Stokes, RN 214-818-2529 <a href="mailto:victoria.stokes@BSWHealth.org">victoria.stokes@BSWHealth.org</a></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Fabry disease, Gaucher disease types 1 &amp; 3, and mucopolisaccharide type IV (or ML IV)</td>
<td>Mary Wallace 214-820-4752 <a href="mailto:Mary.Wallace@BSWHealth.org">Mary.Wallace@BSWHealth.org</a></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Cerebral aneurysms</td>
<td>Kenneth Layton, MD 214-827-1600 <a href="mailto:Kenneth.Layton@BSWHealth.org">Kenneth.Layton@BSWHealth.org</a></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Interventional stroke therapy</td>
<td>Tomica Harrison 214-820-2615 <a href="mailto:tomica.harrison@BSWHealth.org">tomica.harrison@BSWHealth.org</a></td>
</tr>
<tr>
<td>NICU</td>
<td>Neurosurgery</td>
<td>Jon Thammavong 214-818-9687 <a href="mailto:Jon.Thammavong@BSWHealth.org">Jon.Thammavong@BSWHealth.org</a></td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>Rehabilitation</td>
<td>Individuals with mobility impairment, stroke, traumatic brain injury, and spinal cord injury</td>
</tr>
<tr>
<td>Rheumatology (800 N. Central Expressway)</td>
<td>Rheumatology</td>
<td>Rhenium salts, psoriatic arthritis, lupus, gout, ankifying spondylitis</td>
</tr>
<tr>
<td>Surgery</td>
<td>Rheumatology (800 N. Central Expressway)</td>
<td>Chronic limb ischemia, pain management with chest tubes, colon polyps, diaphragm stimulators, and surgery as it pertains to GERD, breast cancer, esophageal cancer, colon cancer, pancreas, lung, hernias, dallas access, per-endoscopic musculoscopy (PECM), thoracic outlet syndrome</td>
</tr>
<tr>
<td>Transplantation</td>
<td>Bone marrow, blood stem cells</td>
<td>Grace Townsend 214-818-6472 <a href="mailto:Grace.Townsend@BSWHealth.org">Grace.Townsend@BSWHealth.org</a></td>
</tr>
<tr>
<td>Transplantation</td>
<td>Abdominal, solid organs, liver/kidney</td>
<td>Niechelle Lloyd Theresa Cheyne 214-820-1710 817-922-2579 <a href="mailto:Niechelle.Lloyd@bswhealth.org">Niechelle.Lloyd@bswhealth.org</a> <a href="mailto:Theresa.Cheyne@bswhealth.org">Theresa.Cheyne@bswhealth.org</a></td>
</tr>
<tr>
<td>Transplantation</td>
<td>Heart and lung transplant, mechanical assist device such as LVAD</td>
<td>Jessica Propps 214-820-1821 <a href="mailto:jessica.propps@bswhealth.org">jessica.propps@bswhealth.org</a></td>
</tr>
<tr>
<td>Trauma and critical care</td>
<td>Trauma and critical care</td>
<td>Jennifer Rainey 214-865-2410 <a href="mailto:Jennifer.Rainey@BSWHealth.org">Jennifer.Rainey@BSWHealth.org</a></td>
</tr>
<tr>
<td>Trauma and critical care</td>
<td>Trauma and critical care</td>
<td>Jennifer Rainey 214-865-2410 <a href="mailto:Jennifer.Rainey@BSWHealth.org">Jennifer.Rainey@BSWHealth.org</a></td>
</tr>
<tr>
<td>Wisco</td>
<td>Trauma and critical care</td>
<td>Jennifer Rainey 214-865-2410 <a href="mailto:Jennifer.Rainey@BSWHealth.org">Jennifer.Rainey@BSWHealth.org</a></td>
</tr>
<tr>
<td>Weight management</td>
<td>Weight management</td>
<td>Lisa Mamo, RN 214-818-7974 <a href="mailto:Lisa.Mamo@BSWHealth.org">Lisa.Mamo@BSWHealth.org</a></td>
</tr>
<tr>
<td>Women's Health (Fort Worth)</td>
<td>Weight management</td>
<td>Lisa Mamo, RN 214-818-7974 <a href="mailto:Lisa.Mamo@BSWHealth.org">Lisa.Mamo@BSWHealth.org</a></td>
</tr>
</tbody>
</table>

Baylor Scott & White Research Institute is dedicated to providing the support and tools needed for successful clinical research. For more information, please contact Kristine Hughes at 214-820-7556 or Kristine.Hughes@BSWHealth.org.
We propose a novel Myocardial Injury Summary Score (MISS) integrating the 4 biomarkers suggested by the 2013 American College of Cardiology/American Heart Association guidelines for management of heart failure. In this case series, we examined 4 heart failure patients who received treatment guided by the biomarker results and 4 patients who received routine clinical management with no information about the biomarkers. Most of the patients receiving biomarker-guided management had medications adjusted based on the biomarker values, while no changes were recommended for patients in the biomarker-blinded category. This case series suggests that biomarker-guided therapy with serial biomarker values leads to timely therapeutic adjustment and that biomarker values as a composite score can be used effectively to measure the severity of heart failure.

About 5.7 million Americans suffer from heart failure (HF) (1), and the mortality rate is approximately 50% over 5 years for a patient newly diagnosed with HF (2). The prevalence of HF has been documented to be increasing, given prolonged survival due to better treatment modalities (3). Cardiac biomarkers have been recommended as prognostic and diagnostic tools in the clinical management of HF, and American College of Cardiology/American Heart Association guidelines have suggested the use of 4 biomarkers—B-type natriuretic peptide (BNP), troponin, galectin-3, and suppression of tumorigenicity 2 (ST2)—to guide the prognosis of patients with HF (4). Management of HF with routine biomarkers as part of the follow-up was shown to increase the survival benefit for these patients (5). We incorporated the 4 recommended biomarkers into the Myocardial Injury Summary Score (MISS) (6), a novel score to measure the severity of HF. In this case series, we examined 8 HF patients who received either treatment guided by the biomarker results or routine clinical management, where the clinicians were blinded to the results of the biomarkers. The advocated therapeutic management for the biomarker-guided therapy is detailed in Table 1.

For each patient, the 4 biomarker values were integrated into a novel score to measure the severity of HF. The basic metric is the ratio of the biomarker value at the current office visit to the baseline value obtained during the previous office visit:

\[
MISS = \frac{\sum_{i}^{n} \log_{10} \text{Biomarker}(i)_{\text{current visit}}}{\text{Biomarker}(i)_{\text{prior visit}}}\]

where \(n\) denotes the number of total available biomarkers and \(i\) denotes BNP, troponin, galectin-3, or ST2. The logarithmic

### Table 1. Drug titration chart for biomarker-guided therapy

<table>
<thead>
<tr>
<th>Marker result</th>
<th>Protocol-directed drug titration step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin I &gt;99% detection limit</td>
<td>Add or up-titrated isosorbide mono- or dinitrate every month to maximally tolerated</td>
</tr>
<tr>
<td>B-type natriuretic peptide &gt;100 pg/mL</td>
<td>Add or up-titrated furosemide every month to maximally tolerated</td>
</tr>
<tr>
<td>Galectin-3 &gt;25.9 ng/mL</td>
<td>Add or up-titrated enalapril or valsartan or spironolactone every month to maximally tolerated</td>
</tr>
<tr>
<td>Suppression of tumorigenicity 2 &gt;35 ng/mL</td>
<td>Add or up-titrated carvedilol or long-acting metoprolol every month to maximally tolerated</td>
</tr>
</tbody>
</table>

### METHODS

HF patients who were ambulatory with an ejection fraction <40% and an estimated glomerular filtration rate ≥30 mL/min/1.73 m² were included in this study. The patients were randomized to either management based on the biomarkers obtained at each visit or by standard clinical management, where the clinicians were blinded to the results of the biomarkers. The advocated therapeutic management for the biomarker-guided therapy is detailed in Table 1.

From Baylor Heart and Vascular Institute, Dallas, Texas (Vasudevan, Won); Texas A&M Health Science Center College of Medicine, Dallas Campus, Dallas, Texas (Vasudevan, Won, McCullough); Baylor Research Institute, Dallas, Texas (Vasudevan, Won); Baylor University Medical Center, Dallas, Texas (Jazi, Ball, Patankar, Sarmast, McCullough); Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, Texas (Ball, Won, Patankar, Sarmast, McCullough); Division of Aging, Department of Medicine, Brigham and Women’s Hospital/Harvard Medical School, Boston, Massachusetts (Shin); Division of Cardiology, Department of Medicine, VA Boston Health Care System, Boston, Massachusetts (Shin); and The Heart Hospital Baylor Plano, Plano, Texas (McCullough).

**Corresponding author:** Anupama Vasudevan, BDS, MPH, PhD, Baylor Heart and Vascular Institute, 621 N. Hall Street, Suite H030, Dallas, TX 75226 (e-mail: Anupama.Vasudevan@BSWHealth.org).
Based on the pharmacologic regimen of the HF drugs, a therapeutic intensity index was formulated for each patient after every visit. The index was based on HF drug classes and their corresponding doses, which ranged in intensity from 1 to 3. The summed therapeutic intensity index ranges from 0 to 24, with 24 being the highest intensity of medical management. Table 2 provides the details of the drugs and their corresponding intensity scores.

RESULTS

Four of the 8 patients were randomized to the biomarker-guided management (B) arm, and the remaining 4 were randomized to the usual clinical management (UC) arm. The median age of patients was 57.5 years (range 52–71) in the B arm and 56 years (range 43–65) in the UC arm. There were 5 men (3 in B and 2 in UC) and 3 women (1 in B and 2 in UC). The etiology of HF was considered ischemic in 6 of the patients included in this study (3 each in the B and UC arms). Three of the 4 patients randomized to the B arm had diabetes, while only one patient in the UC arm had diabetes. All patients included in this case series had hypertension, and 2 and 3 patients in the B and UC arms had dyslipidemia, respectively. The demographic details and comorbidities are shown in Table 3.

Table 4 shows the therapeutic management and MISS for each of the 8 patients. Figure 1 shows the baseline MISS segregated by age, and Figures 2 and 3 show the changes in the MISS and therapeutic intensity index for each patient. For patients on biomarker-guided management, the pharmacologic transformation corrects the observed right-skew of the MISS distribution, which is constructed from biomarkers bounded by zero, but potentially having relatively large values. A biomarker having the same value after a patient receives treatment as before the patient receives treatment has a ratio of 1 and a log score of 0. Further, biomarkers changing by a scaled factor of 10 have $\log_{10}$ values between –1 and +1, which is appealing. For the baseline visit, the MISS score was calculated using the upper limit of normal of the corresponding biomarker as the denominator.

---

**Table 2. Drug classes and dosage used to calculate therapeutic intensity index**

<table>
<thead>
<tr>
<th>Drug or equivalent</th>
<th>Low = 1</th>
<th>Moderate = 2</th>
<th>High = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril (mg bid)</td>
<td>&lt;10</td>
<td>10–19</td>
<td>≥20</td>
</tr>
<tr>
<td>Valsartan (mg bid)</td>
<td>&lt;80</td>
<td>180–159</td>
<td>≥160</td>
</tr>
<tr>
<td>Carvedilol (mg bid)</td>
<td>&lt;12.5</td>
<td>12.5–24.9</td>
<td>≥25</td>
</tr>
<tr>
<td>Spironolactone (mg qd)</td>
<td>&lt;12.5</td>
<td>12.5–24.9</td>
<td>≥25</td>
</tr>
<tr>
<td>Isosorbide mononitrate (mg qd)</td>
<td>&lt;30</td>
<td>30–59</td>
<td>≥60</td>
</tr>
<tr>
<td>Hydralazine (mg qd)</td>
<td>&lt;25</td>
<td>25–49</td>
<td>≥50</td>
</tr>
<tr>
<td>Digoxin (mg qd)</td>
<td>&lt;0.125</td>
<td>0.125–0.24</td>
<td>≥0.25</td>
</tr>
<tr>
<td>Furosemide (mg bid)</td>
<td>&lt;20</td>
<td>20–79</td>
<td>≥80</td>
</tr>
</tbody>
</table>

*bid indicates 2 times/day; qd, daily; qid, 4 times a day.*

**Table 3. Patient demographics and clinical characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Biomarker-guided management (B)</th>
<th>Biomarker-blinded management (usual clinical management, UC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B1</td>
<td>B2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61</td>
<td>54</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.5</td>
<td>30.8</td>
</tr>
<tr>
<td>Cause of heart failure</td>
<td>Nonischemic</td>
<td>Ischemic</td>
</tr>
<tr>
<td>New York Heart Association functional class</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
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<td>+</td>
</tr>
<tr>
<td>Smoker</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prior percutaneous intervention</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Prior coronary bypass</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Implantable cardioverter defibrillator</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

0 indicates No; +, Yes.
regimen was adjusted based on the values of the biomarkers, leading to improved MISS. For patients in the biomarker-blinded category, the therapeutic intensity index, as reflected by the intensity and frequency of drugs prescribed, in general remained unchanged compared to those guided by biomarkers. A lower aggregated MISS score suggested that the values of the individual biomarkers were lower than the values obtained at the previous clinical visit, signaling a better prognosis in a patient with HF.

**DISCUSSION**

We found in this case series that it was feasible to randomize patients to either a biomarker-informed or -blinded approach for ambulatory management of HF patients. Additionally, we found that it was feasible to calculate and monitor a novel multimarker score reflecting HF disease severity. Lastly, we were able to calculate an integrated measure of therapeutic intensity, which changed modestly in the patients with biomarker-guided management. The results showed that biomarker-guided therapy led to timely therapeutic adjustment that might be beneficial to the patient with HF and might help with systematic therapeutic management.

Several randomized controlled trials have shown that targeting the biomarkers resulted in better prognostics and diagnostics for HF patients. The Barcelona Bio-Heart Failure Risk Calculator incorporating ST2, N-terminal pro BNP, and troponin T biomarkers allowed better prediction of death among HF patients (7). Compared to the Seattle Heart Failure Model, the Penn Heart Failure Study found that a multimarker score incorporating biomarkers increased
the ability to predict adverse outcomes in ambulatory patients with chronic HF (8). A post hoc analysis including 151 patients with chronic HF showed that baseline measurement of 3 biomarkers (ST2, growth/differentiation factor 15, and highly sensitive assay for troponin T) increased the overall prognostic ability, while serial ST2 measurement helped predict change in left ventricular function (9). In older patients with stable HF, soluble isoform of ST2 was found to be an independent predictor of worsening HF, suggesting an association between increasing values of soluble isoform of ST2 and progressive myocardial failure (10). Titration therapy based on the serial values of natriuretic peptides was proven to be associated with a significant reduction in mortality in a meta-analysis, including 6 randomized clinical trials with HF patients (11), and targeting these biomarkers has been shown to benefit HF patients. In our case series, we assimilated the 4 biomarkers into a composite score to guide the prognosis of these patients while managing the therapeutic therapeutic intensity index from baseline to final visit for each patient in the biomarker-guided management (B) arm and usual clinical management (UC) arm. Figure 3. Myocardial Injury Summary Score and corresponding changes in the therapeutic intensity index from baseline to final visit for each patient in the biomarker-guided management (B) arm and usual clinical management (UC) arm.

Our study has all the limitations of small pilot studies testing the feasibility of a new randomized approach with novel assessments of both exposures and endpoints. As we did not order renal function tests during each study visit, we were unable to make inferences regarding kidney function over time. We recognize that these measures will be positioned with clinical judgment and cannot predict many individual scenarios. For example, we observed several integrated MISS scores in the stable range despite having several cases of decompensation that were not signaled by a meaningful change in the score.


Emergency department discharge prescription errors in an academic medical center

Kelly A. Murray, PharmD, April Belanger, PharmD, Lauren T. Devine, PharmD, Aaron Lane, DO, and Michelle E. Condren, PharmD

This study described discharge prescription medication errors written for emergency department patients. This study used content analysis in a cross-sectional design to systematically categorize prescription errors found in a report of 1000 discharge prescriptions submitted in the electronic medical record in February 2015. Two pharmacy team members reviewed the discharge prescription list for errors. Open-ended data were coded by an additional rater for agreement on coding categories. Coding was based upon majority rule. Descriptive statistics were used to address the study objective. Categories evaluated were patient age, provider type, drug class, and type and time of error. The discharge prescription error rate out of 1000 prescriptions was 13.4%, with “incomplete or inadequate prescription” being the most commonly detected error (58.2%). The adult and pediatric error rates were 11.7% and 22.7%, respectively. The antibiotics reviewed had the highest number of errors. The highest within-class error rates were with antianginal medications, antiparasitic medications, antacids, appetite stimulants, and probiotics. Emergency medicine residents wrote the highest percentage of prescriptions (46.7%) and had an error rate of 9.2%. Residents of other specialties wrote 340 prescriptions and had an error rate of 20.9%. Errors occurred most often between 10:00 AM and 6:00 PM.

According to the Food and Drug Administration, there have been over 95,000 reports of medication errors to MedWatch since 2000, with the number of actual errors estimated as even higher (1). The National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project showed that nearly 17% of 700,000 US patients treated annually for adverse drug events in the emergency department (ED) require hospitalization (2, 3). The ED’s increasing patient volumes, pressure to see more patients in shorter amounts of time, lack of continuity of care, and unfamiliar patients all play a role in the development of medication errors (4, 5). Despite computerized provider order entry and decision support tools in place to prevent prescribing errors in the ED, high error rates of 10% to 21% persist (5–9). Cesarz et al found that out of 674 ED discharge prescriptions reviewed, 68 prescriptions required intervention to prevent errors and optimize therapy (54% and 46%, respectively) (6). This study provided evidence to support pharmacist prescription review in the ED, but it lacked the description of what prescriptions required interventions most often and for what reason, the time of day the interventions occurred most frequently, and what providers were most likely to need intervention. The current study aimed to describe those specifics regarding discharge prescription errors in an academic medical center ED.

METHODS

This study was approved by the study site’s institutional review board. This study was a retrospective chart review that used content analysis in a cross-sectional design to systematically categorize prescription errors found in a report capturing a convenience sample of the first 1000 discharge prescriptions written and submitted in the electronic medical record (Meditech 6.8) in February 2015. Providers for these visits included emergency medicine (EM) attending physicians, EM residents, attending physicians from other specialties, and resident physicians from other specialties. All prescriptions written during this timeframe were included in the analysis.

The study site is an urban academic medical center with an annual ED volume of approximately 48,000 patients. The ED has 48 hours of EM faculty physician coverage daily (four 12-hour shifts: 7:00 AM–7:00 PM, 9:00 AM–9:00 PM, 1:00 PM–1:00 AM, and 7:00 PM–7:00 AM). An EM clinical pharmacist is available on site from 8:00 AM to 4:30 PM and is physically present in the ED from 11:00 AM to 4:30 PM focusing on drug information questions, drug dosing, and medication reconciliation. Numerous EM, off-service, and pharmacy residents also are present in the department.

The primary objective of this study was to identify the percentage of prescription errors in a sample of discharge prescriptions from an academic medical ED. The secondary objectives were to describe errors based on 1) patient age, 2) type of error...
that occurred, 3) medication class, 4) prescriber type, and 5) time of day the prescription was written.

Data collected from the electronic medical record included a list of discharge prescriptions (drug name, strength, dose, route, frequency, dispense quantity, number of refills), sex of the patient, patient age, weight (in kg), time of day the prescription was printed, and provider type. Prescribing errors were categorized into three broad categories (with subcategories also listed): incomplete/inadequate prescription (directions missing/“as directed,” directions unclear, quantity calculated in error, quantity missing, quantity sufficient with number of days’ supply not indicated), dosing outside recommended range (below recommended dose, duration outside recommended range, over recommended dose, frequency outside recommended range), and drug selection error (direction/dosage mismatch, dosage form not available, not recommended for age, wrong dosage form).

One pharmacy intern and one clinical pharmacist reviewed the discharge prescription list for errors following training in error identification. Open-ended data were viewed by an additional clinical pharmacist for agreement on categories. The final prescription data set evaluated was compiled based on the majority’s decision of whether a prescription error occurred. The errors were then evaluated based on the primary and secondary outcomes listed above. Excel was used to evaluate data and formulate results.

RESULTS

Out of 1000 discharge prescriptions, prescribing errors were present in 134 (13.4%). The number of prescriptions written for adults and pediatric patients were 846 and 154, respectively. Of the 134 total prescription errors, 35 (26.1%) were for pediatric patients, which is an age group error rate of 22.7%. The adult prescription error rate was 11.7% (99 prescriptions with errors out of 846). The most common prescription error type was “incomplete/inadequate prescription,” with “directions missing/as directed” the most common subcategory error. The most frequently prescribed medications that fell into this category of error were prednisone, albuterol, and azithromycin. Table 1 shows the subtypes of errors detected, including frequencies.

Fifty-two classes of medications were prescribed. The drug class with the highest number of prescription errors was antibiotics, resulting in a within-class error rate of 14.9%. Within this category, errors were found most frequently in prescriptions written for azithromycin and amoxicillin. Azithromycin errors found were “directions missing/as directed,” “quantity calculated in error,” “directions unclear,” or “duration outside recommended range.” Amoxicillin errors found were either “quantity missing” or “quantity sufficient but with number of days’ supply not indicated.” Eleven of the 23 antibiotic prescription errors were for pediatric patients. The medication classes with 50% or higher within-class error rates included antianginal medications, antiparasitic medications, antacids, appetite stimulants, probiotics, nebulized medications, and insulin. Table 2 lists the frequencies of error rates by drug class.

Forty-four individual physicians wrote ED discharge prescriptions. EM attending physicians and residents were responsible for 40.3% of the total errors that were identified. The error rate was 6.1% for EM attending physicians, 9.2% for EM residents, 69.2% for non-EM attending physicians, and 20.9% for non-EM residents (Table 3). The average rate of prescriptions written per hour over the study period was 6.9, with rates increasing around 10:00 AM, peaking at 2:00 PM, and decreasing around 8:00 PM (Figure 1a). Most prescription errors occurred between 10:00 AM and 6:00 PM (104 errors, 77.6%), and particularly between 2:00 PM and 3:00 PM (22 errors, or 19% of all prescriptions written) (Figure 1b).

DISCUSSION

This study shows that nearly 14% of discharge prescriptions written in the ED contain medication errors. The finding that nearly half of the errors in antibiotic prescriptions were for children is concerning. The potential for underdose or overdose is present and can impact the patient response and recovery for the condition for which the antibiotics were prescribed. Reasons for incorrect dosing of an antibiotic may be due to incorrect weight-based dosing or simply not being able to visualize the label comments or handwritten edits on “take as directed” antibiotics.

The type of error that occurred most frequently was missing directions or simply noting “take as directed”—which was also found in a study conducted by the Institute for Safe Medication Practices (10). Many patients may be unable to remember specific administration directions given by a practitioner without written instruction as a backup. Similar to the study by Bizovi et al (11), medication prescriptions with fill-in prepopulated

<table>
<thead>
<tr>
<th>Table 1. Types of prescription errors detected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>Incomplete/inadequate prescription</td>
</tr>
<tr>
<td>Directions missing/noting only “take as directed”</td>
</tr>
<tr>
<td>Directions unclear</td>
</tr>
<tr>
<td>Quantity calculated in error</td>
</tr>
<tr>
<td>Quantity missing</td>
</tr>
<tr>
<td>Quantity sufficient but no indication of number of days</td>
</tr>
<tr>
<td>Dosing outside recommended range</td>
</tr>
<tr>
<td>Below recommended dose</td>
</tr>
<tr>
<td>Duration outside recommended range</td>
</tr>
<tr>
<td>Higher than recommended dose</td>
</tr>
<tr>
<td>Frequency outside recommended range</td>
</tr>
<tr>
<td>Other (unable to find indication for nonprocedural use)</td>
</tr>
<tr>
<td>Drug selection errors</td>
</tr>
<tr>
<td>Direction/dosage mismatch</td>
</tr>
<tr>
<td>Dosage form not available</td>
</tr>
<tr>
<td>Not recommended for age</td>
</tr>
<tr>
<td>Wrong dosage form</td>
</tr>
</tbody>
</table>
information were prone to errors. If a specific medication regimen was incorrect in a prepopulated “favorite prescriptions” list, then it may have been incorrect for all of the prescriptions printed for that medication by that physician. Also, the lack of directly available dosage calculators and decision support aids may have contributed to a greater chance for inaccurate dosing, especially for weight-based medications. Errors were also observed when the dose and frequency of liquid solutions or suspensions were included but the quantity to be dispensed was “1 bottle” instead of the specific bottle size needed. Also seen were prescriptions where the package size was left in the dose category, such as a 30 g tube of hydrocortisone 1% cream printed as “Hydrocortisone 1% cream 30 g, 30 applications TP daily #1 tube.” Dose and package size interchange may lead to patient confusion, supratherapeutic doses, and adverse events.

In the ED, analgesics, muscle relaxers, antiepileptics, and inhalers are often prescribed in acute care patient visits, supporting the low within-class error rate seen in this study. Seventeen percent of all prescription errors were written for antibiotics, paralleling other medication error identification studies (8, 12). Other classes of drugs that demonstrated high levels of prescription errors were nebulized, topical, and steroid medications. These are all medications that require special instructions, and counseling should be given both verbally and via the prescription label to maximize patient understanding. Medications less frequently prescribed, such as antiparasitics, antianginals, nebulized medications, and appetite stimulants, may be less familiar to physicians, and therefore may be more prone to errors. Knowing the classes of medications that have high within-class error rates as well as high total error rates may help determine appropriate educational and quality improvement interventions.

The error rate for EM residents was higher than that for EM attending physicians. The prescription error rates were highest for off-service resident and attending physicians. Medication regimens used by off-service disciplines can be significantly different from those prescribed in the ED setting. This suggests a potential need for better orientation of these residents to the types of prescriptions written in the ED and potentially more oversight and input from attending physicians, pharmacists, and nurses.

Unsurprisingly, the greatest amount of prescription errors occurred during the busiest time of day for an ED, from 10:00 AM to 6:00 PM. There were 641 prescriptions written during this time frame, 104 of which contained an error. This result is proportional to the number of patients roomed in the ED at the time of prescription printing, increasing the demand on providers and expectedly dividing their focus.

Dedicating more ED pharmacist, pharmacy resident, or student time to prescription review during peak hours of patient care could help minimize errors. EM pharmacists have the advanced knowledge and skill set to help reduce patient harm through minimization of prescription medication errors. The data showing that pharmacists improve the error rates for medications is robust, showing a positive impact on medication errors (12), decreasing unintended medications being continued from

<table>
<thead>
<tr>
<th>Class</th>
<th>Prescriptions</th>
<th>Errors</th>
<th>Errors in class (%)</th>
<th>Class’s % of total errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td>154</td>
<td>23</td>
<td>14.9%</td>
<td>17.2%</td>
</tr>
<tr>
<td>Analgesic</td>
<td>141</td>
<td>5</td>
<td>3.5%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>106</td>
<td>9</td>
<td>8.5%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Inhaler</td>
<td>77</td>
<td>5</td>
<td>6.5%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>54</td>
<td>16</td>
<td>29.6%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>42</td>
<td>7</td>
<td>16.7%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Topical</td>
<td>30</td>
<td>13</td>
<td>43.3%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>26</td>
<td>11</td>
<td>42.3%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Muscle relaxer</td>
<td>24</td>
<td>1</td>
<td>4.2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Nebulized medication</td>
<td>22</td>
<td>14</td>
<td>63.6%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>19</td>
<td>1</td>
<td>5.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Anti epileptic</td>
<td>18</td>
<td>1</td>
<td>5.6%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Supplement</td>
<td>15</td>
<td>4</td>
<td>26.7%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Diuretic</td>
<td>15</td>
<td>1</td>
<td>6.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>12</td>
<td>3</td>
<td>25.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Antiviral</td>
<td>10</td>
<td>2</td>
<td>20.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>10</td>
<td>1</td>
<td>10.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Laxative</td>
<td>7</td>
<td>1</td>
<td>14.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Insulin</td>
<td>5</td>
<td>3</td>
<td>60.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>5</td>
<td>2</td>
<td>40.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>5</td>
<td>1</td>
<td>20.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Nasal</td>
<td>5</td>
<td>1</td>
<td>20.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>3</td>
<td>1</td>
<td>33.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Otic</td>
<td>3</td>
<td>1</td>
<td>33.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Antianginal</td>
<td>2</td>
<td>2</td>
<td>100.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Antiparasitic</td>
<td>2</td>
<td>1</td>
<td>100.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Antacid</td>
<td>1</td>
<td>1</td>
<td>100.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Appetite stimulant</td>
<td>1</td>
<td>1</td>
<td>100.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Probiotic</td>
<td>1</td>
<td>1</td>
<td>100.0%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physician type</th>
<th>Rx written</th>
<th>Percentage of total Rx written</th>
<th>Errors</th>
<th>Percentage of total errors</th>
<th>Percentage of Rx with errors</th>
<th>Rx written</th>
<th>Percentage of total Rx written</th>
<th>Errors</th>
<th>Percentage of total errors</th>
<th>Percentage of Rx with errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM attending</td>
<td>180</td>
<td>18%</td>
<td>11</td>
<td>8.2%</td>
<td>6.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM resident</td>
<td>467</td>
<td>46.7%</td>
<td>43</td>
<td>32.1%</td>
<td>9.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-EM attending</td>
<td>13</td>
<td>1.3%</td>
<td>9</td>
<td>6.7%</td>
<td>69.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-EM resident</td>
<td>340</td>
<td>34%</td>
<td>71</td>
<td>53.0%</td>
<td>20.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EM indicates emergency medicine; Rx, prescriptions.
medication reconciliation (13), reducing pediatric adverse drug events (14, 15), reducing pediatric prescription errors (16), and reducing ED prescription errors (6). A dedicated discharge prescription reviewing policy may be prudent; however, implementation could have an impact on ED metrics such as total length of stay in the ED for those being discharged. Pharmacists could also conduct in-service training regarding the importance of electronically correcting prescriptions in lieu of hand-correcting the already printed version.

This study is not without its limitations. The prescriptions reviewed spanned a 6-day period and represented a small subset of physicians. Also, any handwritten prescription corrections or handwritten prescriptions that may have been distributed during these 6 days were not included in the analysis. Additionally, the potential for harm or delay of patient receipt was not assessable. Finally, interobserver variability was not formally assessed, and classification bias cannot be ruled out.

This pilot study can help researchers springboard into more robust research, including confirmation of error rate with a larger sample size, design of interventions to help reduce error rates, improvement of error rates after the educational intervention in this particular academic medical center ED, and further solidification of the positive impact an ED pharmacist can have on discharge prescription error rates.

Pre and post hoc analysis of electronic health record implementation on emergency department metrics

Kyle J. Rupp, DO, MBA, Nathan J. Ham, DO, Dennis E. Blankenship, DO, Mark E. Payton, PhD, and Kelly A. Murray, PharmD

Longitudinal time-based emergency department (ED) performance measures were quantified 12 months before and 12 months after (March 2012–February 2014) implementation of a Meditech 6.0® electronic health record (EHR) at a single urban academic ED. Data assessed were length of stay from door to door, door to admission, door to bed, bed to provider, provider to disposition, and disposition to admission, as well as number of patients leaving against medical advice and number of patients leaving without being seen. Analysis of variance was used to compare levels before and after EHR implementation for each variable, with adjustments made for the number of admissions, transfers, and month. No difference was seen in monthly volume, admissions, or transfers. Implementation of an EHR resulted in a sustained increase in ED time metrics for mean length of stay and times from door to door, door to admission, door to bed, and provider to disposition. Decreased ED time metrics were seen in bed-to-provider and disposition-to-admit times. The number of patients who left against medical advice increased after implementation, but the number of patients who left without being seen was not significantly different. Thus, EHR implementation was associated with an increase in time with most performance metrics. Although general times trended back to near preimplementation baselines, most ED time metrics remained elevated beyond the study length of 12 months. Understanding the impact of EHR system implementation on the overall performance of an ED can help departments prepare for potential adverse effects of such systems on overall efficiency.

A n increasing number of hospitals and health care centers are adopting electronic health record (EHR) systems with the goal of improving health care quality while potentially decreasing costs (1). However, there are concerns regarding how efficiency and physician productivity are affected secondary to EHR implementation. Unlike ambulatory and inpatient settings, where patient volume can be adjusted to help with this transition, EDs are unable to alter volume and must maximize efficiency during this process. Currently, limited data exist in the ED literature showing the effects on productivity and the length of those effects, and research has shown that errors and unanticipated problems will arise from implementation (2). In addition, while computer physician order entry (CPOE) can provide many benefits when orders need to be placed and processed quickly (3), its implementation has unanticipated adverse effects, such as workflow issues, difficulties in the transition away from paper records, increased system demands, overdependence on technology, and loss of professional autonomy (4), which may affect overall department efficiency, resulting in ED crowding (5–7) and patient elopement (8). Several crowding measures have been endorsed by the National Quality Forum and Joint Commission, such as ED length of stay (LOS), waiting times, disposition to admission times, and rates of patients leaving without being seen (9, 10), and soon hospitals will report ED crowding measures to the Centers for Medicare and Medicaid Services to receive full Medicare payment (11). To date, little to no data exist showing results for an extended period of time surrounding the implementation of an EHR system. The objectives of this study were 1) to describe the effects of EHR implementation on various ED-specific metrics over the course of 12 months and 2) to compare those metrics to the 12 months prior to EHR implementation.

METHODS

This retrospective analysis of ED metrics was performed at a single urban, university-affiliated, public, 25-bed ED in Tulsa, Oklahoma, with an emergency medicine residency program and an annual ED census of roughly 46,000. The ED was staffed with board-certified emergency physicians, emergency medicine residents, and other rotating residents from various services (i.e., internal medicine, family medicine, surgery, etc.).

Prior to implementation, the ED utilized paper documentation sheets, dictation, and written physician order entry via a clerical tech. Meditech 6.0® was implemented in the ED in a stepwise manner on March 1, 2013, with implementation completed on May 7, 2013. The first step involved implementation for registration, medical records review, laboratory, radiograph results, and electronic ED tracker board. Physician

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orders continued on paper until May 7, 2013, when CPOE was implemented. A simultaneous project was implemented on March 3, 2013, as a bedding initiative in an effort to reduce the door-to-admission time for newly admitted patients. Resident physicians utilized paper documentation with hand-off to supervising attending physicians. Board-certified emergency medicine attending physicians utilized dictation for formal, electronic patient encounter documentation.

ED metrics were analyzed during the timeframe of March 1, 2012, to February 28, 2014, with the break in pre- and post-implementation occurring on March 1, 2013. This information was compiled on a data information sheet for each 24-hour day. Individual data points were collected through standardized reporting from the ED operations committee. The ED metrics were collected for each day and grouped as dependent variables; they included LOS for admitted patients and non-admitted patients, door-to-door time for discharged patients, door-to-admission time, door-to-bed time, bed-to-provider time, provider-to-disposition time, and disposition-to-admit time. In addition to the service time metrics above, the data for total ED visits, admission rates, and transfer rates were collected. Outcome measures for patient flow that may correlate with prolonged ED service times were also measured and included leaving against medical advice and leaving without being seen. Each of these grouped dependent variables was used in analysis of variance and compared to the ED metric timeframes before and after EHR implementation for each metric. The three covariates used to adjust for month-to-month variation and patient acuity differences within the groups were month, admission rate, and transfer rate.

Excel was used to calculate time metrics. Considering that the data set contained errors, patient data were only excluded if the data resulted in the integer of “0.” When standard errors and means were calculated with and without these data points, there was no significant difference. To determine standard error between the two groups, the dependent variable time stamps were determined for each patient encounter. These were averaged each day, then for the month, and then adjusted as above for each of the three covariates. The time metrics were grouped into pre- and post-implementation. Means and standard errors of the two major groups for each dependent variable were obtained for the 12 months before and the 12 months after EHR implementation. P values were obtained by comparing pre vs. post and adjusting for number of admits, transfers, and month. Any P value <0.05 was considered statistically significant.

RESULTS
A total of 100,198 ED visits were reviewed and included in this analysis, including 701,323 unique ED metric data points. Of these metric data points, 378,560, or 54%, were from after EHR implementation. During the course of the study, 13,174 patients were admitted, with the remaining number of patients either being discharged from the ED, transferred to another facility, leaving against medical advice, or leaving without being seen. The average monthly volume did not significantly change after implementation (P=0.11) (Figure). Similarly, the monthly admission and transfer rates were also not significantly different from pre- to post-implementation, each with a P value of 0.06 (Table).

The mean LOS increased from 92.4 to 95.4 minutes (P = 0.01), with a change that persisted for more than 12 months after implementation. This trend persisted through many of the service intervals. The mean door-to-door time for total throughput time of ambulatory patients remained prolonged by increasing from 76.8 minutes to 81.6 minutes (P = 0.01). The mean door-to-bed time showed a statistically significant increase

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (standard error)</th>
<th>Mean difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly volume (n)</td>
<td>Pre-EHR</td>
<td>Post-EHR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4023 (84)</td>
<td>3863 (75)</td>
<td>160</td>
</tr>
<tr>
<td>Monthly admissions (n)</td>
<td>528 (17.1)</td>
<td>489 (13.6)</td>
<td>39</td>
</tr>
<tr>
<td>Monthly transfer (n)</td>
<td>17 (1.3)</td>
<td>13 (0.7)</td>
<td>4</td>
</tr>
<tr>
<td>Length of stay (min)</td>
<td>92.4 (1.6)</td>
<td>95.4 (1.0)</td>
<td>3.0</td>
</tr>
<tr>
<td>Door-to-door time (min)</td>
<td>76.8 (1.2)</td>
<td>81.6 (0.6)</td>
<td>4.8</td>
</tr>
<tr>
<td>Door-to-admission time (min)</td>
<td>192 (4.0)</td>
<td>193.8 (0.2)</td>
<td>1.8</td>
</tr>
<tr>
<td>Door-to-bed time (min)</td>
<td>10.8 (0.5)</td>
<td>13.8 (0.5)</td>
<td>3.0</td>
</tr>
<tr>
<td>Bed-to-provider time (min)</td>
<td>4.2 (0.1)</td>
<td>3.0 (0.1)</td>
<td>–1.2</td>
</tr>
<tr>
<td>Provider-to-disposition time (min)</td>
<td>48.0 (0.7)</td>
<td>49.8 (0.4)</td>
<td>1.8</td>
</tr>
<tr>
<td>Disposition-to-admit time (min)</td>
<td>85.8 (2.7)</td>
<td>78.6 (3.1)</td>
<td>–7.2</td>
</tr>
<tr>
<td>Leaving against medical advice</td>
<td>6.3 (0.85)</td>
<td>11.6 (1.17)</td>
<td>5.3</td>
</tr>
<tr>
<td>Leaving without being seen (n)</td>
<td>19.5 (4.33)</td>
<td>15.5 (2.23)</td>
<td>4.0</td>
</tr>
</tbody>
</table>
from 10.8 to 13.8 minutes. The mean provider-to-disposition time increased from 48.0 to 49.8 minutes ($P = 0.01$). Door-to-admission time was not significantly different between pre- and postimplementation (Table).

Even though many of the service intervals were prolonged, there were improvements after implementation for two separate timeframes. The first of these was for bed-to-provider time. This service interval was shortened by nearly 1.5 minutes, from 4.2 minutes to 3 minutes ($P < 0.01$). The second service interval that improved in average time was the disposition-to-admit, which improved from 85.8 to 78.6 minutes, a mean difference of 7.2 minutes. It should be noted, however, that the $P$ value of 0.8 implied that this was not a statistically significant difference (Table).

The two clinical outcome measures of leaving without being seen and leaving against medical advice had surprisingly different significance between the two groups. The number leaving against medical advice nearly doubled from 6.3 (SE 0.85) patients per month to 11.6 (SE 1.17) per month ($P < 0.01$), yet the number leaving without being seen remained similar at 19.5 patients per month before implementation and 15.5 patients per month after implementation ($P = 0.24$) (Table).

**DISCUSSION**

Many facilities struggle to manage the same volume and acuity of patients in the same timely manner as they had prior to EHR implementation. This study has added an additional purview of similar results, with the addition of a longer data collection timeframe. Overall, patient visit metrics appeared to be mostly negatively impacted during the EHR implementation. LOS and door-to-door, door-to-bed, and provider-to-disposition times were all found to be longer after implementation, yet improvements in bed-to-provider and disposition-to-admit times after EHR implementation were surprising.

The first service time noted to have a trend toward improvement was disposition to admit. Soon after EHR implementation, this metric was noted to be a large component of the overall LOS. The ED had challenges with moving patients who have a disposition for admission to an inpatient hospital bed in a timely manner. A departmental goal was implemented in March 2013 to decrease disposition-to-admit times to a target of <45 minutes once disposition for admission was determined by the provider. This effort to improve performance likely resulted in a shortened disposition-to-admit time. Therefore, it remains unclear what effect EHR had in improving this metric.

The second improved timeframe was bed to provider, which decreased by nearly 1.5 minutes. It is likely, however, that this finding was a result of a change in procedure. Prior to EHR implementation, bed-to-provider service times were taken from providers’ documentation of their start time on a paper documentation sheet in the room with the paper medical chart. However, once EHR was implemented, the bed-to-provider time was initiated when the provider signed up for the patient on the computer screen. Additionally, it has been observed that providers frequently initiate patient encounters prior to their registration in the computer. This could result in the provider completing a history, physical, and perhaps early electrocardiogram or I-Stat evaluation prior to initiating the mouse click in the computer, which registers the bed-to-provider time. These elements are likely the cause for the differences in service time and may have resulted in an artificially lowered time metric. The inconsistencies in documenting bed-to-provider time present unreliable data analysis. More research is needed on this metric to make a more definitive conclusion regarding EHR’s effect on it.

The negative impact from EHR implementation was seen in most of the metrics when comparing year-to-year data. With significant and trended increases in LOS, as well as door-to-door, door-to-admission, door-to-bed, and provider-to-disposition times, implementation of EHR had a primarily negative impact on the ED throughput metrics and service times over a 12-month period. Similarly to the study of Ward et al (5), ED physicians described themselves wading through patient encounters with cumbersome, disjointed movements. Once user and operations knowledge improved, this began to ease.

Many EHR implementations are all or nothing—i.e., they are all-encompassing and include medical records/chart reviewing, CPOE, documentation, and disposition paperwork (discharge instructions and prescriptions). At the study institution, a staged approach was employed. The EHR hospital system went live on March 1, 2013. The CPOE implementation was delayed for the ED until May 7, 2013. The hospital-wide CPOE went live on April 14, 2014. This was also a time when admission rates increased. Furthermore, the ED’s documentation methodology had little to no change between paper documentation of a chart to dictation pre- and postimplementation. In many EHR implementations, a change in the documentation process also occurs. This may include documentation using point-and-click, computer dictation, or direct provider entry into the EHR. Because the department maintained dictation for the entire study period, the confounders of learning this new system and comfort with the new system of dictation were absent, also limiting generalizability.

This study was conducted at a single academic urban ED with an average ED discharge time well below the national average (12). Also, this study did not analyze many aspects of a complex emergency care system such as patient safety, quality, user satisfaction, patient satisfaction, and differences in system selection. A baseline period of 12 months and comparison period of 12 months were selected to attempt to incorporate the full impact over a 1-year reporting period. Patient volume dropped 3% over the 12 months prior, admission rates dropped 7%, and transfers dropped 29%. It is uncertain what effect this change in volume had on the overall ED metrics. Had volume and acuity level not dropped after EHR implementation, the increase in time metrics could have been even more significant due to ED crowding.

Other confounders included the disposition-to-admit departmental initiative as well as the method of time documentation pre- and post-EHR implementation. Times prior to EHR implementation were based on handwritten times on paper documentation sheets, whereas times in the EHR were obtained...
from a mouse click in the system. There is a certain amount of unknown variability between the two different methods of collection for the ED time metrics. More studies on these metrics are needed for full understanding of the impact of implementation.

Overall, the study hypothesis was confirmed that an EHR system would have a negative impact on ED metrics at a single institution using a stepwise approach to EHR implementation. Further study is required to find other impacts of mandated EHR implementation and what potential improvements can be made.

Perineal body length and perineal lacerations during delivery in primigravid patients

T. Lance Lane, MD, Christopher P. Chung, MD, Paul M. Yandell, MD, Thomas J. Kuehl, PhD, and Wilma I. Larsen, MD

This study assessed the relation between perineal body length and the risk of perineal laceration extending into the anal sphincter during vaginal delivery in primigravid patients at an institution with a low utilization of episiotomy. This was a prospective study of primigravid patients in active labor. Primigravid women with singleton pregnancies who were in the first stage of labor at 37 weeks gestation or greater were recruited, and the admitting physician measured the length of the perineal body. The degree of perineal laceration and other delivery characteristics were recorded. Data were analyzed using univariate analyses, receiver-operator curve analyses, and multiple logistic regression for factors associated with increased severity of vaginal lacerations. The perineal body length, duration of second stage of labor, type of delivery, and patient age were associated (P < 0.1) with third- and fourth-degree (severe) perineal lacerations in primigravid women using receiver-operator curve analysis. Using logistic regression, only the duration of second stage of labor and length of the perineal body were significant (P < 0.04) predictors of third- and fourth-degree lacerations, with odds ratios of 32 (1.3 to 807) and 24 (1.3 to 456), respectively. Both a perineal body length of ≤3.5 cm and a duration of second stage of labor >99 minutes were associated with an increased risk of third- and fourth-degree lacerations in primigravid patients.

Anal sphincter lacerations place patients at increased risk for pelvic organ prolapse, genuine stress urinary incontinence, sexual dysfunction, and fecal incontinence (1–5).

Operative vaginal delivery, persistent occiput posterior, and fetal macrosomia are known risk factors for anal sphincter injury (6–9); however, there is some evidence that a shortened perineal body may also be a risk factor for severe lacerations (10–13). Prior studies have been confounded by high rates of episiotomy, multiparous patients, and a retrospective design. The aim of our study was to assess the relation of perineal body length and other characteristics to the risk of perineal laceration extending into the anal sphincter during delivery in primigravid patients in an institution with a low episiotomy rate.

METHODS

Prior to the initiation of the study, approval was obtained from the institutional review board at Scott and White, Temple, Texas. All primigravid women with singleton pregnancies who were in the first stage of labor with a gestational age of 37 and 0/7 weeks or greater were eligible for our prospective study. Primigravids were defined as women who had not carried a pregnancy past 20 weeks gestational age prior to the current gestation. The first stage of labor was defined as the interval between the start of regular contractions combined with any cervical dilatation and/or effacement until a cervical dilation of 10 cm was reached. Women with a fetal station greater than zero were excluded. Primigravid women delivered by cesarean and multigravid women were also excluded.

The resident physician measured the length of the perineal body upon presentation using a form for data collection that did not include any patient-identifying information. The perineal body length was defined as the distance from the posterior vaginal fourchette to the center of the anal orifice. This measurement was taken at rest while the patient was in the dorsal lithotomy position, using a sterile Q-tip. The measurement was recorded to the nearest tenth of a centimeter. A diagram of the distances measured was also included on the preprinted form. These measurements were transcribed on the same form along with other patient characteristics, including maternal age, race, maternal height, maternal weight, and gestational age. After delivery, data on the degree of vaginal laceration, oxytocin use, length of second stage of labor, fetal presentation, fetal birth weight, use of episiotomy, and delivery type used were recorded. The delivering physicians, which included both residents and attending physicians, graded perineal lacerations clinically as none or first through fourth degree. First-degree lacerations involve only the epithelial layer. Second-degree lacerations can extend into the perineal body but not into the external anal sphincter. Third-degree lacerations extend into the anal sphincter. Fourth-degree lacerations extend through the rectal mucosa.

From the Department of Obstetrics and Gynecology, Scott and White Memorial Hospital and Clinic and Texas A&M Health Science Center College of Medicine, Temple, Texas.

This work was presented as an oral poster at the combined national meeting of the American Urogynecologic Society and the International Urogynecological Association in Washington, DC, in July 2014.

Corresponding author: Wilma I. Larsen, MD, Department of Obstetrics and Gynecology, Scott & White Health, 2401 South 31st Street, Temple, TX 76508 (e-mail: wilarsen@hot.rr.com).
Cases were partitioned into two categories of lacerations—1) none to second degree and 2) third or fourth degree—with variables presented as means with standard deviations or percentages. The data were analyzed using univariate analyses (Student’s t test or chi-square test) for differences. Receiver-operator curve analyses were performed on parametric variables to identify thresholds and statistical differences associated with third- and fourth-degree lacerations. Variables with trends ($P < 0.1$) were formatted as logistical for evaluation using a multiple logistic regression model to identify those with significant associations with increased severity of vaginal lacerations. The final model included variables with $P < 0.05$.

**RESULTS**

Data were collected on 127 women from December 2011 through March 2013. Eighty-nine percent of the measurements were obtained by two physicians. Tables 1 and 2 list the parametric and nonparametric variables. The mean perineal body length among these primigravid women averaged 3.7 cm, with a range of 2.3 to 5.0. Among this group of women, the rate of third- and fourth-degree lacerations was 3.9% (5/127).

The relation of patient characteristics to the two subgroups of lacerations is shown in Table 3 with results of univariate analyses. A tendency was seen with patient age and perineal body length ($P \leq 0.1$) being related to variation in laceration degree. The duration of second stage of labor and operative vaginal delivery were significant in relation to variation in laceration degree ($P \leq 0.05$). Receiver-operator curve analysis was used to set thresholds for age, perineal body length, and duration of second stage of labor, and a logistic regression model was used to identify independent associations from among these four variables, using the threshold values (Table 4). Both the duration of second stage of labor and perineal body length were found to have significant ($P < 0.04$) independent associations with third- and fourth-degree lacerations. The odds ratio for the duration of second stage >99 minutes was 32 (1.3 to 807, 95% CI). The odds ratio for perineal body length ≤3.5 cm was 24 (1.3 to 456).

**DISCUSSION**

This is the first prospective trial to address the association of perineal body length with the risk of third- and fourth-degree lacerations in primigravid women in an institution with a low episiotomy rate. Our finding in univariate analysis that the length of the second stage of labor and having had an operative delivery were risk factors for third- or fourth-degree laceration corroborated many prior studies. However, using logistic regression analysis, we found that a perineal body length of ≤3.5 cm and a second stage of labor >99 minutes were the most predictive for risk of third- and fourth-degree lacerations.

Several studies have addressed perineal body length as a possible risk factor for severe perineal body lacerations during vaginal delivery (10–14). These studies differ from ours. They all had episiotomy rates much greater than our rate of <2%. The study by Deering, which more closely matched our patient population, was retrospective in nature and included both multiparous and primiparous patients. In another American study, most patients were of Asian descent (14). However, our average perineal body length of 3.7 cm was consistent with the average perineal body reported in other Western studies (12–15). A recent study by Tsai et al failed to show a relationship between perineal body length and severe lacerations; however, this study had a larger operative vaginal delivery rate, a higher episiotomy rate, and a higher number of occiput posterior deliveries, which may have made reasons for severe lacerations less clear (14).

---

**Table 1. Noncategorical characteristics of the 127 primigravid study participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perineal body measurement (cm)</td>
<td>3.7 (0.5)</td>
<td>2.3–5.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>23.7 (4.7)</td>
<td>15–38</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.6 (1.1)</td>
<td>37.1–41.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>31.2 (5.9)</td>
<td>20.8–50.3</td>
</tr>
<tr>
<td>Baby weight (g)</td>
<td>3367 (403)</td>
<td>2156–4460</td>
</tr>
<tr>
<td>Length of second stage (min)</td>
<td>58 (44)</td>
<td>5–232</td>
</tr>
</tbody>
</table>

*Data were missing for three patients.

**Table 2. Categorical characteristics of the 127 primigravid study participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Categories</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>White</td>
<td>83 (65%)</td>
</tr>
<tr>
<td></td>
<td>African American</td>
<td>19 (15%)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>19 (15%)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>3 (2%)</td>
</tr>
<tr>
<td></td>
<td>Native American</td>
<td>1 (1%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Presentations</td>
<td>Occiput anterior</td>
<td>97 (76%)</td>
</tr>
<tr>
<td></td>
<td>Left occiput anterior</td>
<td>17 (13%)</td>
</tr>
<tr>
<td></td>
<td>Right occiput anterior</td>
<td>11 (8%)</td>
</tr>
<tr>
<td></td>
<td>Occiput transverse</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Lacerations</td>
<td>None</td>
<td>38 (29%)</td>
</tr>
<tr>
<td></td>
<td>First degree</td>
<td>17 (13%)</td>
</tr>
<tr>
<td></td>
<td>Second degree</td>
<td>67 (52%)</td>
</tr>
<tr>
<td></td>
<td>Third degree</td>
<td>3 (2%)</td>
</tr>
<tr>
<td></td>
<td>Fourth degree</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Episiotomy</td>
<td>None</td>
<td>125 (88%)</td>
</tr>
<tr>
<td></td>
<td>Midline</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Delivery type</td>
<td>Spontaneous vaginal</td>
<td>107 (84%)</td>
</tr>
<tr>
<td></td>
<td>Vacuum assisted</td>
<td>10 (8%)</td>
</tr>
<tr>
<td></td>
<td>Forceps</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>Oxytocin used</td>
<td>Yes</td>
<td>106 (83%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>20 (16%)</td>
</tr>
<tr>
<td></td>
<td>Missing data</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>
The long-term morbidity associated with severe perineal lacerations remains significant. We need to continue to better characterize the risk factors that can lead to these unwanted outcomes. Further research in the area of perineal anatomy may help patients avoid severe lacerations.


Table 3. Relation of patient characteristics to two laceration subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>None, first, or second degree (n = 122)</th>
<th>Third or fourth degree (n = 5)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perineal body length (cm)</td>
<td>3.7 (0.5)</td>
<td>3.4 (0.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>23.5 (4.7)</td>
<td>27.0 (3.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.6 (1.1)</td>
<td>39.5 (1.3)</td>
<td>0.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.2 (5.9)</td>
<td>32.6 (5.4)</td>
<td>0.6</td>
</tr>
<tr>
<td>Baby weight (g)</td>
<td>3363 (407)</td>
<td>3441 (285)</td>
<td>0.7</td>
</tr>
<tr>
<td>Length of second stage (min)</td>
<td>56 (43)</td>
<td>99 (32)</td>
<td>0.03</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>65</td>
<td>80</td>
<td>0.5</td>
</tr>
<tr>
<td>Presentation (% occiput anterior)</td>
<td>98</td>
<td>100</td>
<td>0.8</td>
</tr>
<tr>
<td>Episiotomy (% without)</td>
<td>98</td>
<td>100</td>
<td>0.8</td>
</tr>
<tr>
<td>Delivery type (% without operative vaginal delivery)</td>
<td>86</td>
<td>40</td>
<td>0.006</td>
</tr>
<tr>
<td>Oxytocin used (%)</td>
<td>83</td>
<td>100</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*The first six variables were examined using Student’s t test, and the last five variables by chi-square test.

Table 4. Logistic regression model for relation of factors to development of third- or fourth-degree laceration in nulliparous patients*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criterion†</th>
<th>Coefficient</th>
<th>P value</th>
<th>Odds ratio</th>
<th>95% CI for odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of second stage (min)</td>
<td>&gt;99</td>
<td>3.47</td>
<td>0.035</td>
<td>32</td>
<td>1.3 to 807</td>
</tr>
<tr>
<td>Perineal body length (cm)</td>
<td>≤3.5</td>
<td>3.19</td>
<td>0.033</td>
<td>24</td>
<td>1.3 to 456</td>
</tr>
<tr>
<td>Patient age (years)</td>
<td>&gt;26</td>
<td>2.41</td>
<td>0.15</td>
<td>11</td>
<td>0.43 to 293</td>
</tr>
<tr>
<td>Spontaneous vaginal delivery (SVD)</td>
<td>SVD = 1</td>
<td>–0.29</td>
<td>0.86</td>
<td>0.75</td>
<td>0.03 to 17.9</td>
</tr>
<tr>
<td>without use of forceps or vacuum</td>
<td>others = 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Overall model P = 0.0004 with 98% of 127 cases correctly classified.
†Criteria were developed for quantitative variables using receiver-operator curve analyses. Perineal body length: area under the curve (AUC) of 0.71; P = 0.047; sensitivity 80%; specificity 66%. Age: AUC of 0.75; P = 0.005; sensitivity 80%; specificity 75%. Second stage duration: AUC of 0.82; P < 0.0001; sensitivity 80%; specificity 88%.

One strength of our study was its inclusion of only primiparous women. As in the study by Tsai et al, excluding multiparous patients excludes the potential bias of parity on perineal body length (14). Also, primiparous patients have a greater risk of severe lacerations. We also had two physicians performing most measurements, which decreased interobserver bias on perineal body lengths. This was also a weakness in that patient collection was limited to the times when those physicians were working in the labor and delivery unit. Although our study showed significance, having a higher patient volume would likely have increased the number of severe lacerations, strengthening our data. We also had a very low rate of third- and fourth-degree lacerations, at 3.9%.
Anatomic relation between single-incision slings and the obturator vessels

Amy L. O’Boyle, MD, Christopher P. Chung, MD, and Wilma Larsen, MD

The risk of arterial vascular injury within the retropubic space is a potentially life-threatening complication associated with mid-urethral sling placement for the treatment of female stress urinary incontinence. To determine the relationship between the major blood vessels and a single incision sling, these slings were placed in 12 fresh female cadavers. Following the insertion of each sling, the retropubic space was dissected and sling placement was observed relative to the obturator neurovascular bundle bilaterally. The distance between the most distal aspect of each sling arm, or the point of anchoring, was measured from the most medial aspect of the obturator vessels bilaterally. The mean distance between each sling arm and the medial portion of the obturator vessels was an average of 3.4 cm (range 2.0–6.0 cm) in 24 observations. Placement of the single incision sling may have a lower risk of injuring major vessels within the retropubic space compared to full-length mid-urethral slings.

METHODS
Fellows and faculty from the Walter Reed National Military Medical Center in Bethesda, Maryland, and the Scott & White Hospital in Temple, Texas, participated in training involving female cadavers as part of an educational curriculum in the surgical treatment of SUI. Local approval was granted by the Anatomic Material Review Committees at each institution prior to the use of these cadavers for educational purposes. Slings were donated by Caldera Medical (Agoura Hills, CA; Desara™) and Boston Scientific (Natick, MA; Solyx™).

A total of 12 SISs were placed according to manufacturer guidelines by the first author. Initially, an incision of approximately 1.5 cm was made along the anterior vaginal wall at the level of the mid-urethra in each cadaver. Next, a tunnel was created sharply to the interior portion of the inferior pubic ramus at about a 45-degree angle from the midline to place each sling arm bilaterally. After each sling was placed, the retropubic space was inspected by exposing the space of Retzius via a low transverse abdominal incision. Each sling was inspected at the most lateral aspect of each point of fixation into the obturator internus fascia. The distance between this anchoring point of the sling arm and the medial aspect of the obturator neurovascular bundle was measured and recorded bilaterally. A total of 24 measurements were performed with a flexible plastic ruler marked in 1 mm increments. Each measurement was taken by one author and confirmed by a second prior to recording to the nearest 0.5 cm. Dissection, measurement, and interpretation of the observations were shared, discussed, and interpreted by all of the authors.

Stress urinary incontinence (SUI) is a major health problem with a significant health burden affecting 20% to 40% of all women, and surgery remains the most effective treatment option (1). The mid-urethral sling (MUS) is now considered the gold standard of incontinence surgery (2). The long-term efficacy and technical ease in inserting MUSs have resulted in their widespread popularity; however, serious and potentially fatal complications have been reported with these procedures. It is important for any surgeon who treats female SUI to be familiar with the anatomic relationship between their surgical procedure of choice and the vascular anatomy of the retropubic space.

In 2006, the third generation of synthetic slings for SUI emerged with the development of single-incision slings (SIS), or “mini-slings” (3). The TVT-Secur™ (TVT-S; Gynecare, Ethicon, Somerville, NJ) was described first, and subsequently a number of other SISs were reported. This version of sling was described as avoiding the blind passage through the retropubic or obturator spaces via trochars (4). Despite the lack of long-term evidence regarding its efficacy, the SIS offers the least-invasive surgical treatment approach and remains a popular choice among many surgeons who treat SUI (1, 5, 6).

Previous reports have described the vascular anatomy of the retropubic space relative to both retropubic and trans obturator approaches of the MUS (7, 8). This article describes observations during cadaveric dissections following the insertion of SISs and reviews the relevant vasculature in proximity of MUS approaches used to treat female SUI.

From the Division of Urogynecology, Department of Obstetrics and Gynecology, Walter Reed National Military Medical Center, Bethesda, Maryland (O’Boyle); the Division of Urogynecology, City of Hope Duarte, Duarte, California (Chung); and the Division of Urogynecology, Department of Obstetrics and Gynecology, Baylor Scott and White Health and Texas A&M Health Science Center College of Medicine, Temple, Texas (Larsen).

Corresponding author: Wilma Larsen, MD, Department of Obstetrics and Gynecology, Baylor Scott & White Health, 2401 South 31st Street, Temple, TX 76508 (e-mail: Wilma.Larsen@BSWHealth.org).
of the blind upward passage of the TVT trochar through the major vessels in 10 cadavers, highlighting the unique aspects the distance between the lateral margin of the TVT needle to that found in two other reports (8, 9). Muir et al described SUI.

With the rapidly evolving armamentarium of options to treat remains a valuable training tool in pelvic surgery, particularly DISCUSSION

As shown in Table 1, the mean distance in the 24 measurements was 3.4 cm (range 2.0–6.0 cm). Distances for the right side did not differ between the two devices ($P = 0.15$ using unpaired $t$ test). In addition, distances between sides did not differ in 24 observations ($P = 0.54$ using unpaired $t$ test).

RESULTS

As with MUSs, SISs have also been associated with complications, including vaginal mesh exposure, groin pain, persistent urinary incontinence, bladder perforation, urethral obstruction, and significant bleeding complications (7, 15–17). The vessel known as the corona mortis, or “crown of death,” has been reported as a source of significant hemorrhage following the placement of the TVT Secur (10, 11). This anomalous anastomosis between the obturator and epigastric vessels may be at risk when a device closely skims the peristeum of the pubic ramus, a characteristic unique to insertion of the original TVT Secur. Newer devices seem to have evolved to decrease the likelihood of such injuries.

As the need for surgical treatment of SUI continues to grow, so will the demand for more safe and cost-effective treatment options. Although venous bleeding into the retropubic space secondary to blind insertion of the MUSs may be unavoidable, catastrophic arterial hemorrhage should be avoided with proper training and familiarity with the retropubic anatomy. Surgeons should have a clear understanding of the vascular relationships to their MUS sling of choice.

Table 1. Distance between single incision sling and obturator vessels in 12 female cadavers

<table>
<thead>
<tr>
<th>Sling</th>
<th>Insertion</th>
<th>Right (cm)</th>
<th>Left (cm)</th>
<th>Right and left (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Scientific (Solyx)</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
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<td>3</td>
<td>4.5</td>
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<tr>
<td></td>
<td>6</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Mean ± SD</td>
<td>3.6 ± 1.4</td>
<td>3.8 ± 0.7</td>
<td>3.7 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Caldera Medical (Desara)</td>
<td>7</td>
<td>2.5</td>
<td>3</td>
<td></td>
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<td>8</td>
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<td>2.5</td>
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<td>12</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.0 ± 0.8</td>
<td>3.3 ± 0.8</td>
<td>3.1 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Both (n = 24)</td>
<td>Mean ± SD</td>
<td>3.3 ± 1.2</td>
<td>3.5 ± 0.8</td>
<td>3.4 ± 1.0</td>
</tr>
</tbody>
</table>

Table 2. Mean distance between type of mid-urethral sling and the retropubic vascular structure

<table>
<thead>
<tr>
<th>Type of mid-urethral sling</th>
<th>Report</th>
<th>Mean distance (cm) to obturator vessels (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retropubic tension-free vaginal tape</td>
<td>Muir et al (n = 20)</td>
<td>3.2 (1.6–4.3)</td>
</tr>
<tr>
<td>Transobturator tape</td>
<td>Zahn et al (n = 14)</td>
<td>1.8 ± 0.7 (0.8–3.2)</td>
</tr>
<tr>
<td></td>
<td>Inside-out</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>Outside-in</td>
<td>2.3 ± 0.4*</td>
</tr>
<tr>
<td>Single-incision sling</td>
<td>Current report (n = 24)</td>
<td>3.4 ± 1.0 (2.0–6.0)</td>
</tr>
</tbody>
</table>

*P < 0.001 for inside-out vs. outside-in using $t$ test; mean difference = 1.0 ± 0.6 cm.

Practical and ethical considerations in the management of pacemaker and implantable cardiac defibrillator devices in terminally ill patients

Mina M. Benjamin, MBBCh, and Christine A. Sorkness, MD

More than 4.5 million people worldwide live with an implanted pacemaker, including >3 million in the USA alone. Also, >0.8 million people in the USA have an implantable cardioverter defibrillator (ICD). Knowing the principles of managing these devices towards the end of life is important, as the interruption of their function may have serious consequences. This article provides health care providers who are not specialized in cardiac electrophysiology with an introduction to the general principles of management of pacemakers or ICD devices towards the end of life, with a suggested algorithm for approaching this process. Also discussed are pertinent ethical and practical considerations in deciding on and implementing a management strategy for these devices during terminal illnesses.

The nurse called the on-call cardiology fellow at 1:00 am asking him to deactivate the cardiac device of a patient pursuing hospice. The patient was a 78-year-old man, admitted with an acute kidney injury on top of chronic kidney disease. The device identification card carried by the patient indicated that he had an implantable cardioverter defibrillator (ICD) for primary prevention after a myocardial infarction. The patient was deemed in need of urgent hemodialysis during this hospitalization, but he was hesitant because of his short life expectancy of 6 to 12 months due to metastatic prostate cancer. The palliative care service was consulted. The patient decided at night, after consulting with his family, that he would rather pursue hospice. Device interrogation showed periods of heart block of varying length, but no fatal arrhythmias. The patient was not interested in any therapies that would prolong his life and requested device deactivation. The patient's daughter stated that she was worried her father was "not thinking straight" and that deactivating the pacemaker device would make him feel bad. What should be done with the device monitoring, defibrillating, and pacing functions? Unfortunately, these case scenarios are not uncommon.

This article is intended to provide health care providers who are not specialized in cardiology or medical ethics with brief insights into the principles and ethical and practical considerations of pacemakers or ICD device management towards the end of life.

GENERAL CONSIDERATIONS

 Interruption of cardiovascular implanted electronic device (CIED) function, especially in pacemaker-dependent patients, may have immediate and serious consequences. In 2010, the Heart Rhythm Society, in association with the European Heart Rhythm Association, released an expert consensus statement on the management of CIEDs in patients nearing the end of life or requesting withdrawal of therapy (1). This statement includes an outline of the practical, ethical, legal, and religious principles of managing CIEDs towards the end of life. Basically, patients (or their legally designated surrogates) can request discontinuation of any medical or device treatment. Moreover, it is not necessary for patients to be terminally ill to make these requests.

Several factors affect the strategy to recommend to patients towards the end of life. Having clear answers to these questions eases many of the potential practical, ethical, and legal dilemmas for health care providers. First and foremost, the health care provider should determine if the patient is cognitively competent and able to comprehend the consequences of different changes in device settings. Ideally, discussions about device management in the event of terminal illness should start at the time of implantation. Unfortunately, in real life, only a minority of patients are asked about their wishes at the time of implantation. It is of utmost importance to also discuss this issue when patients with CIEDs are admitted with conditions that could lead to rapid deterioration in their health, especially their cognitive status.

Next, the type of device needs to be identified, as devices may vary considerably in their monitoring/therapy capabilities. Each patient is provided with an identification card, with information about the device and company contact information, at the time of implantation. If the patient does not carry an identification card and the medical records are unavailable, other methods can be used. A chest x-ray provides information about the number and position of the intracardiac leads (Figure 1).
These comorbidities also help predict potential arrhythmias as the terminal illness progresses. Thus, all pertinent medical records should be obtained and queried for such documentation. Communication between the health care providers themselves, and then between the health care providers and the patient and his or her surrogate(s) or family, is essential to provide information and set expectations. Concise documentation of these communications and detailed consent forms are very important from a legal standpoint (4).

ETHICAL CONSIDERATIONS

Pacemaker-dependent patients may request deactivation of their device towards the end of life. Ethical analyses of withdrawal of CIEDs have compared them to other life-sustaining treatments that physicians readily withdraw near the end of life, such as hemodialysis or mechanical ventilators. Physicians are often concerned that deactivation of pacemaker function towards the end of life could be interpreted as assisted dying, analogous to voluntary euthanasia. Most medical ethicists agree that when death follows withdrawal of treatment, the person’s underlying condition is deemed the actual cause of death (4). It is unethical, on the other hand, to “withdraw or discontinue” a treatment that becomes a part of the patient’s “self,” like a heart transplant. Most ethicists, though, do not consider a pacemaker a part of the patient’s self and thus it can be withdrawn, like a ventilator (5).

Such withdrawal is lawful, provided that it follows from the person’s competent refusal of treatment. Currently in the US, ethically and legally, there are no differences between refusing CIED therapy and requesting withdrawal of CIED therapy. Laws governing the management of CIEDs towards the end of life vary by country, and physicians should acquaint themselves with the rules of their jurisdiction (5–7).

Although patients have the right to request withdrawal of therapy, it is possible that the personal and professional values of the care provider and the patient may differ. Heart Rhythm Society guidelines (1) stipulate that clinicians in this position...
have an obligation to arrange for alternative provision of care in cases of conscientious objection that cannot be resolved by ethical or clerical consultation.

It is important to explain to pacemaker-dependent patients that deactivating the pacemaker function might not result in eminent death but rather in inadequate cardiac output symptoms like dizziness and even syncopal episodes.

Disagreements may ensue between family members about the management of a CIED when a patient’s decision-making capacity is compromised. Surrogates should usually advocate for the patient’s expressed wishes, if known, or otherwise should use their best judgment in determining the patient’s most probable choice. Determining early on who has the health care power of attorney and who is the next of kin can help obviate unnecessary friction. Family meetings are necessary to address concerns and misconceptions and often facilitate consensus, but the hospital ethics committee may also need to be involved.

PRACTICAL CONSIDERATIONS

The effect of magnet placement differs by the nature of CIED. Pacemakers respond by switching to an asynchronous pacing mode at a fixed rate depending on the manufacturer, device model, and battery status. If magnet application on a pacemaker site does not produce any response on the pacing rate or mode, the reason might be a depleted pacemaker battery. Alternatively, the device might not be within the magnetic field, as in the case of those with deep (abdominal or submuscular) implants. In almost all pacemakers, removal of the magnet causes the device to revert to pacing at the normal preprogrammed rate. In ICDs, magnet application suspends antitachycardia therapy without any effect on the pacing mode (8).

In patients with a do not resuscitate (DNR) order in force, ICD deactivation should be seriously considered. However, patients with an ICD who have a DNR directive may still benefit from ongoing ICD therapy if the arrhythmias being treated reflect the primary cardiac condition and not an irreversible secondary medical illness or if prompt ICD therapy confers the likelihood of added survival with meaningful quality of life and the patient concurs with this approach. The deactivation of a CIED does not necessarily mean shutting off its diagnostic capabilities. The patient, or his or her surrogate, needs to decide whether to keep these features on. Some patients might prefer not to know, or not to let their families know, what happens to their heart rhythm. In this case, the consequences of turning off the CIED monitoring features should be explained in detail to the patient, noting that cardiac rhythm data will not be available to guide the treatment of any medical condition.

There is often a misconception among patients and families that a pacemaker will keep the patient alive when he or she would have otherwise died from the underlying disease. Pacemakers are not resuscitative devices, and they will not keep a dying patient alive. Most dying patients become acidic before cardiac arrest, which effectively renders a pacemaker nonfunctional, as under such conditions, the myocardium does not respond to the pacemaker’s discharges. Thus, for most patients, an active pacemaker will not affect the timing or circumstances of death (9).

When a person with an ICD has cardiac arrest from a shockable rhythm, the device delivers a sequence of shocks to terminate the arrhythmia. If the device does not deliver such shocks or if the shockable rhythm persists, external defibrillation should be attempted. External defibrillator electrodes should not be placed close to the CIED site. If a person with a pacemaker or ICD has return of spontaneous circulation after receiving cardiopulmonary resuscitation, the device should be interrogated at the earliest opportunity (10).

In conclusion, the management of CIEDs in terminally ill patients can be complicated; the algorithm in Figure 2 summarizes appropriate steps for data gathering and decision making in this situation. The concept of patient autonomy underlies both the ethical and legal principles surrounding CIED deactivation, and these principles have been well established. Awareness of the practical and ethical considerations outlined above is essential for the optimal and timely management of CIEDs in terminally ill patients and for optimal communication between health care providers, patients, and their families.

Figure 2. Suggested algorithm for data gathering, decision making, and implementation of changes to device therapy in terminally ill patients.


This minireview describes 6 previously reported patients with left ventricular free wall rupture and/or aneurysm complicating acute myocardial infarction (AMI) in patients with aortic stenosis. The findings suggest that left ventricular rupture and/or aneurysm is more frequent in patients with AMI associated with aortic stenosis than in patients with AMI unassociated with aortic stenosis, presumably because of retained elevation of the left ventricular peak systolic pressure after the appearance of the AMI.

In 1983, one of us (WCR) reported a patient with severe aortic stenosis (AS) and a healed left ventricular (LV) apical aneurysm (1). The authors speculated that LV aneurysm and LV free wall rupture would be more frequent in patients with acute myocardial infarction (AMI) associated with severe AS than in patients with AMI without AS. Herein, we summarize findings in 5 subsequently reported patients with LV rupture and/or aneurysm with AMI associated with severe AS.

METHODS
An initial PubMed search was conducted to locate publications of “cardiac rupture or aneurysm in patients with acute myocardial infarction complicated by aortic stenosis.” A second search was made for publications of “myocardial infarction in patients with aortic stenosis”.

RESULTS
Since the report by Roberts and colleagues (1) in 1983, we found 5 additional case reports of patients with AMI complicated by LV free wall rupture and/or aneurysm in patients with AS (2–6). The findings in them are summarized in the Table 1, which also includes the initial report by Roberts et al (1). No reported cases were found in the search for AMI associated with AS irrespective of whether an LV free wall rupture and/or aneurysm was present. At the time of AMI, the 6 patients ranged in age from 57 to 74 years (mean 64); 4 were women and 2 were men. The rupture site in all patients was the LV free wall, leading to hemopericardium. The interval from onset of AMI to rupture ranged from 1 to possibly 30 days. The AS appeared to be severe in all patients: the peak LV systolic gradients (reported in 4 patients) ranged from 50 to 177 mm Hg.

DISCUSSION
When AMI occurs in patients with systemic hypertension, the systemic arterial and LV pressures generally return to or toward normal if the AMI is fairly large. Several reports have demonstrated that systemic hypertension unassociated with

Table 1. Reported cases of acute myocardial infarction in patients with aortic valve stenosis with left ventricular free wall rupture or aneurysm

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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</thead>
<tbody>
<tr>
<td>1. Age (years) at AMI</td>
<td>62</td>
<td>57</td>
<td>62</td>
<td>58</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>2. Sex</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>3. LV free wall rupture</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4. LV aneurysm</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>5. Days from AMI onset to rupture</td>
<td>–</td>
<td>6</td>
<td>?30</td>
<td>10</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>6. Previous hypertension (history)</td>
<td>+</td>
<td>0</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>7. ECG location of the infarct</td>
<td>–</td>
<td>Ant</td>
<td>Ant</td>
<td>Ant</td>
<td>–</td>
<td>Ant</td>
</tr>
<tr>
<td>8. Apical location of the infarct</td>
<td>+</td>
<td>+</td>
<td>0*</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>9. LV-SA psg (mm Hg)</td>
<td>–</td>
<td>–</td>
<td>50</td>
<td>105</td>
<td>70†</td>
<td>177†</td>
</tr>
<tr>
<td>10. Aortic valve area (cm²)</td>
<td>–</td>
<td>–</td>
<td>0.4</td>
<td>–</td>
<td>0.7†</td>
<td>0.3†</td>
</tr>
<tr>
<td>11. Systemic artery (s/d) (mm Hg)</td>
<td>–</td>
<td>110/70</td>
<td>100/60</td>
<td>150/90</td>
<td>–</td>
<td>116/85</td>
</tr>
<tr>
<td>12. Heart weight (g)</td>
<td>630</td>
<td>610</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
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</table>

*False left ventricular aneurysm.
†By echocardiogram.
AMI indicates acute myocardial infarction; Ant, anterior; ECG, electrocardiographic; LV, left ventricular; psg, peak systolic gradient; SA, systemic artery; s/d, peak systole/end diastole.

From the Baylor Heart and Vascular Institute and the Departments of Internal Medicine and Pathology, Baylor University Medical Center at Dallas (Roberts); and Texas College of Osteopathic Medicine, Fort Worth, Texas (Sheikh).

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AS in patients with AMI is not a risk factor for LV free wall rupture and/or aneurysm formation (2, 3). When AMI occurs in patients with significant AS, however, the LV systolic pressure remains elevated and the continuation of this elevation appears to increase the likelihood of LV rupture and/or aneurysmal formation, particularly when the AMI involves the LV apical wall, which normally is several times thinner than the LV basal wall.

There is some data on the frequency of AS in older populations and on the frequency of AMI and sudden cardiac death among patients with AS. In an autopsy study, Roberts and Shirani (7) found severe AS to be present in 43 (11%) of 391 patients aged 80 to 89 years, in 8 (9%) of 93 patients aged 90 to 99 years, and in 0 of 6 patients aged ≥100 years, or in 51 (10%) of the total 490 patients aged 80 years or over. Of the 490 autopsied patients, 229 (47%) had acute and/or healed myocardial infarcts. Aronow and colleagues (8) studied by echocardiogram 1797 older patients (mean age 82 years) and found AS in 301 (17%)—severe in 40, moderate in 96, and mild in 165. Among their 301 patients with AS, 158 (52%) had had an earlier AMI that healed, and 217 (72%) had a new AMI or died suddenly. There was no mention of LV free wall rupture or LV aneurysm. There have been at least 2 case reports of AMI in patients with AS and normal epicardial coronary arteries (9, 10). Neither had LV free wall rupture or aneurysm.

The major limitation of this minireview is that the number of patients with AMI associated with AS without LV free wall rupture or LV aneurysm is entirely unknown. Conversely, the reported cases of LV free wall rupture and/or aneurysm complicating AMI in patients with AS may represent, of course, the tip of the iceberg.

Heterogeneity of systematic reviews in oncology

Jonathan Holmes, BS, David Herrmann, BS, Chelsea Koller, BS, Sarah Khan, BS, Blake Umberham, BS, Jody A. Worley, PhD, and Matt Vassar, PhD

Systematic reviews synthesize data across multiple studies to answer a research question, and an important component of the review process is to evaluate the heterogeneity of primary studies considered for inclusion. Little is known, however, about the ways that systematic reviewers evaluate heterogeneity, especially in clinical specialties like oncology. We examined a sample of systematic reviews from this body of literature to determine how meta-analysts assessed and reported heterogeneity. A PubMed search of 6 oncology journals was conducted to locate systematic reviews and meta-analyses. Two coders then independently evaluated the manuscripts for 10 different elements based on an abstraction manual. The initial PubMed search yielded 337 systematic reviews from 6 journals. Screening for exclusion criteria (nonsystematic reviews, genetic studies, individual patient data, etc.) found 155 articles that did not meet the definition of a systematic review. This left a final sample of 182 systematic reviews across 4 journals. Of these reviews, 50% (91/182) used varying combinations of heterogeneity tests, and of those, 16% (15/91) of review authors noted excessive heterogeneity and opted to not perform a meta-analysis. Of the studies that measured heterogeneity, 51% (46/91) used a random-effects model, 7% (8/91) used a fixed-effects model, and 43% (39/91) used both. We conclude that use of quantitative and qualitative heterogeneity measurement tools are underused in the 4 oncology journals evaluated. Such assessments should be routinely applied in meta-analyses.

S
ystematic reviews bring together all related empirical evidence based on predetermined eligibility criteria to answer a research question (1). This methodology is designed to minimize bias using an explicit, reproducible approach involving a systematic and comprehensive literature search, an assessment of validity of primary studies, and a systematic presentation and synthesis of findings. Oftentimes, systematic reviews also contain one or more meta-analyses that make use of statistical procedures to summarize the results of primary studies. It is evident that when multiple studies are combined for data synthesis, there will be differences, such as location of testing, drug doses, dosing schedules, follow-up, or ethnicity of participants, to name a few. If statistically significant heterogeneity is present, then researchers must decide if the primary studies are too diverse to synthesize or if follow-up analyses should be used to explore the effects of these differences on study outcomes.

Exploring heterogeneity between primary studies in systematic reviews can be done with multiple statistical tests such as I², Cochran’s Q (chi-squared), and Tau². All of these tests have their own strengths and weaknesses, and so it is best to use multiple tests to fully inform clinicians on the dependability of a systematic reviews analysis (1–9). While much advice has been offered on evaluating heterogeneity, little is known about the ways that systematic reviewers actually address heterogeneity. Questions remain regarding the practices of systematic reviewers outside of Cochrane review groups, such as researchers in clinical specialties like oncology.

METHODS

Using the h5-Index from Google Scholar Metrics, we selected the 6 oncology journals with the highest index scores from the oncology subcategory. We searched PubMed using the following search string: (((((((“Journal of clinical oncology: official journal of the American Society of Clinical Oncology” [Journal] OR “Nature reviews. Cancer” [Journal]) OR “Cancer research” [Journal]) OR “The Lancet. Oncology” [Journal]) OR “Clinical cancer research: an official journal of the American Association for Cancer Research” [Journal] OR “Cancer cell” [Journal]) AND (“2007/01/01” [PDAT]: “2015/12/31” [PDAT]) AND “humans” [MeSH Terms]) AND (meta-analysis [Title/Abstract] OR systematic review [Title/Abstract]). This search strategy was adapted from a previously established method that is sensitive to identifying systematic reviews and meta-analyses (10). Searches were conducted on May 18 and May 26, 2015.

We used Covidence (covidence.org) to initially screen articles based on title and abstract. To qualify as a systematic review, studies had to summarize evidence across multiple studies and provide information on the search strategy, such as search terms, databases, or inclusion/exclusion criteria. Meta-analyses were classified as quantitative syntheses of results across multiple studies. From the Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma (Holmes, Herrmann, Koller, Khan, Umberham, Vassar) and the University of Oklahoma, Norman, Oklahoma (Worley).

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studies (11). Two screeners independently reviewed the titles and abstracts of each citation and made a decision regarding its suitability for inclusion based on the definitions previously described. To standardize the coding process, an abstraction manual was developed and pilot tested. After completing this process, a training session was conducted to familiarize coders with abstracting the data elements. A subset of studies was jointly coded. After the training exercise, each coder was provided with 3 new articles to code independently. Inter-rater agreement of these data was calculated using Cohen’s kappa. Since inter-rater agreement was high (k = 0.86; agreement = 91%), each coder was assigned an equal subset of articles for data abstraction. We coded the following elements: a) statistical test used to evaluate heterogeneity; b) a priori threshold for statistical significance; c) type of model (random, fixed, mixed, or both); d) whether authors selected a random-effects model based on significance of the heterogeneity test; e) whether authors used a random-effects model without explanation; f) what type of plot was used to evaluate heterogeneity, if any; g) whether the plot was published as a figure in the manuscript; h) whether a follow-up analysis was conducted and, if so, the type of analysis (subgroup, meta-regression, and/or sensitivity analysis); i) whether heterogeneity was mentioned in writing only; and j) whether authors concluded there was too much heterogeneity to perform a meta-analysis. After the initial coding process, validation checks were conducted such that each coded element was verified by the other coder. Next, the screeners held a meeting to discuss the differences in decisions for inclusion/exclusion and reconcile any discrepancies by reaching consensus. Following the screening process, full-text versions of included articles were obtained via EndNote. Analysis of the final data was conducted using STATA 13.1. Data from this study are publicly available on Figshare (http://dx.doi.org/10.6084/m9.figshare.1496574).

RESULTS

The PubMed search resulted in 337 articles from 6 journals. After screening titles and abstracts via Covidence, 79 articles were excluded that did not meet the definition of a systematic review and/or meta-analysis. Full-text article screening for exclusion criteria resulted in the removal of an additional 74 articles. Additionally, 2 studies could not be retrieved. Two of the 6 journals were not heavily represented in the original sample of 337 articles, and with the exclusion of 155 articles 2 journals were excluded from the final sample. In total, 182 manuscripts representing 4 journals were analyzed for heterogeneity (Figure)

Half (91/182) of all meta-analyses used at least 1 heterogeneity test. The most widely reported statistic was $I^2$ (41.2%; 75/182) followed by $X^2$ (24.2%; 44/182). In combination, $X^2$ and $I^2$ (13.2%; 24/182) were reported with greatest use followed by $Q$ and $I^2$ (12.6%; 23/182). Other combinations were utilized by the manuscripts but were not used to a great extent ($I^2$ and Tau$^2$ [0.55%; 1/182]; $Q$ and $X^2$ [0.55%; 1/182]; $Q$, $X^2$, $P$ [3.3%; 6/182]; and $X^2$, $P$, Tau$^2$ [0.55%; 1/182]). As shown in the Table, authors selected a random-effects model most frequently (25%) followed by both fixed- and random-effects models (21%). Fixed-effects models were reported in 4% of studies, and a mixed-effects model was used in only 1 study. The remaining 48% did not report the type of model used for analysis. Twenty-four percent (43/182) used the random-effects model without considering the results of a heterogeneity test to confirm the need for such an analysis, and 15% (27/182) changed from the fixed- to random-effects model based on the results of a heterogeneity test.

The level of statistical significance for heterogeneity tests was reported in 45 systematic reviews. Among those reporting predefined thresholds for statistical significance, the most frequently reported $P$ value was $< 0.05$ (64.4%; 29/45) followed by $P < 0.10$ (31.1%; 14/45). ($P < 0.01$ and $P < 0.001$ were both reported in 1 study.) Forty-three percent (78/182) of systematic reviews contained heterogeneity plots published as figures in the article (Table). A forest plot was the most common heterogeneity plot (42%). Only 2% used an L’Abbé to graphically represent heterogeneity.

Of the 3 tests designed to investigate heterogeneity (subgroup, meta-regression, and sensitivity analyses), subgroup analysis was used the most (21%), sensitivity analysis was second (18%), and meta-regression was used the least (9%) (Table 1). It was found that 20% (36/182) of the available manuscripts wrote about heterogeneity, but never actually evaluated it. Fifty-eight percent (105/182) of manuscripts did not find significant heterogeneity, 3% (5/182) found enough evidence of heterogeneity to disregard “some” of the meta-analysis, 4% (8/182) found significant heterogeneity, and 35% (64/182) never attempted to assess heterogeneity.
DISCUSSION

Systematic reviews operate based on methods designed to assist researchers in minimizing bias, performing literature searches, and evaluating data in a manner that hopefully limits biased results. One important aspect of this systematic process is the analysis of heterogeneity at its origin and the subsequent effect on meta-analysis. Although some studies assessed heterogeneity, it was not a common practice in the studies included in this systematic review. Only half of the available studies applied one or more of the common heterogeneity tests evaluated in this study, with 20% of available studies mentioning heterogeneity without further assessment. With interstudy variance always present on some level, heterogeneity evaluation in systematic reviews becomes necessary in many cases. The paltry use of meta-regression and/or subgroup analysis (9% and 21%, respectively) limits studies assessing the effect of heterogeneity on meta-analysis. The random-effects model was underused, with 25% using this model and 21% using both random- and fixed-effects models. The random-effects model assumes that parameters underlying studies follow a distribution, while fixed-effects models assume a single parameter value common to all studies (12). The random-effects model is a more likely event and may be used in cases of heterogeneous study outcomes. It is recognized that all systematic reviews will have some level of heterogeneity, and this study recommends the use of random-effects modeling for meta-analysis of heterogeneous intervention effects. The Institute of Medicine’s Standards for Systematic Reviews state that “although the committee does not believe that any single statistical technique should be a methodological standard, it is essential that the SR [systematic review] team clearly explain and justify the reasons why it chose the technique actually used” (13). From this review, only 15% of available studies used the random-effects model with justification. This finding highlights the need for greater explanation during the decision-making process.

There have been recent developments for exploring and interpreting heterogeneity both before and after the review process. Evidence mapping is a process developed for systematic reviewers to explore sources of heterogeneity among primary studies prior to pooling (14). This qualitative approach may be a useful mechanism to identify sources of heterogeneity and could be a mechanism to inform subgroup analyses. A second means for interpreting heterogeneity is to calculate and report prediction intervals. Prediction intervals may be used to present an expected range of true effects and can assist in the clinical interpretation of heterogeneity by estimating an expected true treatment effect in future settings (15). We recommend that these areas be explored in future research.

This study has many positive attributes, including its adequate sample size and the careful application of coding procedures. Additionally, our findings shed light on current practices of heterogeneity assessment, which is greatly lacking in oncology reviews. Given that little research on heterogeneity practices has been conducted to date, especially in clinical specialties such as oncology, comparison of our results with other studies is difficult. To our knowledge, this is the first study of its kind in oncology. This study also has some limitations. We examined systematic reviews published in high-impact-factor oncology journals, and our results may not represent oncology systematic reviews as a whole. It is possible that higher-impact-factor journals have more rigorous reporting and methodological standards, and systematic reviews published in these journals may reflect these standards. Our search was also date limited, and our results should not be generalized outside of our search dates.

Hemodialysis failure secondary to hydroxocobalamin exposure

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Hydroxocobalamin is a recently approved antidote for the treatment of cyanide poisoning. The case presented involves a young patient administered empiric hydroxocobalamin due to suspected cyanide overdose. Due to the development of acute kidney injury and severe metabolic derangement, emergent hemodialysis was initiated. Unfortunately, hemodialysis was confounded by a recurrent “blood leak” alarm. This unforeseen effect was secondary to interference from hydroxocobalamin. Hydroxocobalamin causes orange/red discoloration of bodily fluids and permeates the dialysate. This leads to defraction of light in the effluent path of the blood leak detector from discolored dialysate, which can result in activation of the blood leak alarm and an inability to continue hemodialysis treatment. This case highlights several new and emerging critical concerns with this medication, including the potential consequence of delayed initiation of emergent renal replacement therapy with empiric administration, the need for increased awareness among clinicians of various disciplines, and the need for multidisciplinary communication.

Hydroxocobalamin was approved by the Food and Drug Administration in December 2006 for the treatment of cyanide poisoning. For decades, cyanide poisoning has been treated using the cyanide antidote kit (1, 2). This kit contains amyl nitrite, sodium nitrite, and sodium thiosulfate, which can cause hypotension and reduced oxygen-carrying capacity of hemoglobin (3–5). In contrast, hydroxocobalamin does not cause these complications. This property makes it advantageous for patients with already decreased oxygenation, those who have been exposed to carbon monoxide, and pregnant patients. Hydroxocobalamin can therefore be safely used in cases where combined carbon monoxide and cyanide toxicity is suspected. The side-effect profile of hydroxocobalamin is considered minimal compared to its predecessor cyanide antidote kit (6). It can, however, cause orange/red discoloration of skin, blood, urine, and secretions, and this can lead to statistically significant alterations in certain colorimetric tests and co-oximetry measurements (7–9). A newly recognized problem associated with the increasing usage of hydroxocobalamin is the interference of hemodialysis. This is particularly concerning due to the potential ramifications of limiting the provision of life-saving treatment in critically ill intoxicated patients. Here we describe a case of a young patient administered empiric hydroxocobalamin with failure of emergent hemodialysis secondary to interference from hydroxocobalamin.

CASE REPORT

A 24-year-old man with asthma was found unresponsive and profoundly hypotensive by emergency medical services. No eyewitnesses were available. On arrival to the emergency room, he was found in extremis with significant agonal breathing, a Glasgow coma scale score of 3, temperature of 35.3°C, blood pressure of 60/45 mm Hg, heart rate of 74 beats/min, respiratory rate of 24 breaths/min, and cool extremities. His serum creatinine was 1.3 mg/dL; sodium, 145 mmol/L; potassium, 4.6 mmol/L; bicarbonate, 10 mmol/L; anion gap, 39; phosphate, 4.9 mmol/L; lactate, 21.3 mmol/L; and white blood cell count, 27.3 K/uL. A bedside arterial blood gas was significant for a pH of 6.99, a partial pressure of carbon dioxide of 47, and a partial pressure of oxygen of 76. A blood and urine toxicology screen were negative.

Sonography was negative for blunt abdominal trauma. Echocardiogram showed a severely diminished ejection fraction. Radiographs showed mildly increased interstitial markings bilaterally. Despite emergent intubation and intravenous fluid resuscitation, he required rapid escalation to multiple vasopressors. He was administered hydroxocobalamin empirically in the emergency room due to concern for cyanide intoxication. Due to profound acid-base disturbance and concern for intentional overdose, emergent dialysis was initiated using the Fresenius 2008K machine. This was confounded by a recurrent “blood leak alarm” that repeatedly shut down the machine despite a change to a new dialyzer. Emergent salvage extracorporeal membrane oxygenation was commenced, but the patient died. It was later revealed that instead of cyanide, the patient was most likely intoxicated with sodium azide.

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Blood leak detector. Substances that deflect or scatter light, such as hemoglobin or medications causing discoloration of fluids, will result in a loss of transparency at the base of the column, triggering the blood leak detector.

DISCUSSION

There is a severe paucity of data available today to guide the management of hydroxocobalamin use in critically ill patients requiring renal replacement therapy. The case presented here highlights several new and emerging critical concerns with this medication that can impede the delivery of life-saving treatment.

First, while the use of hydroxocobalamin remains an advantage compared to the cyanide antidote kit due to its low toxicity profile, universal discoloration of bodily fluids can impede the delivery of hemodialysis by inducing a “pseudo-blood leak” (10). The hemodialysis machine operates on the principle that blood passes on one side of a semipermeable membrane. An aqueous solution, the dialysate is pumped on the opposite side, typically in the opposite direction of the blood flow, to maximize the diffusion gradient across the membrane. All hemodialysis machines contain a blood leak detector that alarmed if red blood cells penetrate into the dialysate (Figure). This is a vital safety feature of hemodialysis machines. The blood leak alarm system consists of a photodetector at the bottom of the dialysate column with a light source at the top. Substances that deflect or scatter light such as hemoglobin or medications causing discoloration of fluids will result in a loss of transparency at the base of the column, triggering the blood leak detector (11). Hydroxocobalamin administration results in discoloration of the dialysate and triggers this alarm. Activation of the blood leak detector in the Fresenius 2008K machine causes the blood pump to stop, the venous clamp on the level detector to occlude, the ultrafiltration pump to stop, and the remaining time on dialysis clock to halt (12).

Very limited data are available on the types of dialysis machines that may be affected by hydroxocobalamin. While the Fresenius 2008K hemodialysis machine used in our case can be interfered by hydroxocobalamin, not all types of hemodialysis machines share this property. There is evidence that the Gambro Phoenix X36 and the NxStage machine are unaffected (10, 13). It has been postulated that hemodialysis machines that utilize a photodetector consisting of a single optical emitter designed to detect light scatter and signal drop off are unlikely to be affected by hydroxocobalamin (10). However, photodetectors that use a dual LED array that depends on light absorption, such as those on the Fresenius 2008K, are susceptible to the “pseudo-blood leak” phenomenon.

Another critical concern this case raises is the empiric administration of hydroxocobalamin. An increased awareness of the adverse effects of hydroxocobalamin in patients potentially requiring emergent renal replacement therapy is needed among emergency room physicians, critical care physicians, and nephrologists alike. This will help increase multidisciplinary communication, better inform management decisions and therapeutic options for the critically ill, and help steward dialysis resources. In the case presented, empiric hydroxocobalamin was administered and the patient was eventually found to have not overdosed on cyanide. In another recent case at our institution, a potential kidney donor had received hydroxocobalamin prior to being considered a donor. The transplant team decided to decline the kidney for transplantation in part due to the possibility that intermittent hemodialysis to treat delayed graft function could not be performed due to interference from hydroxocobalamin. While the outcomes of similar scenarios involving transplant donors have not previously been reported, this scenario and the case presented here highlight the critical need for more data to help guide management decisions in patients exposed to hydroxocobalamin requiring renal replacement therapy.

Acquired 5-oxoprolinemia is increasingly recognized as a cause of anion gap metabolic acidosis. It predominantly occurs in chronically ill, malnourished women with impaired renal function and chronic acetaminophen ingestion. Depletion of glutathione and cysteine stores leads to elevated 5-oxoproline levels. N-acetylcysteine, given its effect in repleting glutathione and cysteine stores, has been proposed as a potential treatment for 5-oxoprolinemia, though reports of its successful use are lacking. We present a case of 5-oxoproline metabolic acidosis that persisted despite discontinuation of acetaminophen. However, the acidosis rapidly resolved with N-acetylcysteine administration.

We report a case of an anion gap metabolic acidosis due to 5-oxoprolinemia that rapidly resolved with administration of N-acetylcysteine (NAC).

CASE REPORT

A 38-year-old woman who had bilateral lung transplantation 4 months earlier for restrictive lung disease was transferred from a rehabilitation facility to the hospital because of acidemia. Her posttransplant course was complicated by an episode of acute rejection, several episodes of pneumonia, malnutrition requiring gastric feeding tube placement with nutrition primarily through tube feedings, and several episodes of acute kidney injury (AKI) requiring renal replacement therapy (RRT). Her immunosuppression regimen included tacrolimus, mycophenolate mofetil, and prednisone. She had been discharged from this same hospital 2 weeks prior when she was admitted for pneumonia with oliguric AKI in the setting of sepsis that required a prolonged course of RRT. During the final 2 weeks of this prior hospitalization, she had renal recovery with adequate urine output and a serum creatinine of 0.91 mg/dL at the time of discharge. Over this same time period, she experienced abdominal pain around the site of her feeding tube that was treated with 650 mg to 1300 mg of acetaminophen daily. On the day of discharge, her anion gap had risen to 29 mEq/L.

After 2 weeks in a rehabilitation facility, she was transferred back to the hospital for persistent acidemia. A blood gas on admission revealed a pH of 7.29 with serum bicarbonate of 12 mg/dL, partial pressure of carbon dioxide of 27 mm Hg, anion gap of 28 mEq/L, and albumin of 1.8 g/dL. These results suggested an anion gap metabolic acidosis with appropriate respiratory compensation. Based on the delta-delta calculation, she had a simultaneous metabolic alkalosis likely related to oral bicarbonate administered at the rehabilitation facility. Evaluation into the etiology of her anion gap metabolic acidosis included serum creatinine 0.91 mg/dL, L-lactate 0.8 mmol/L, undetectable D-lactate, undetectable urine ketones and serum salicylates, calculated serum osmolality of 295 mosm/kg, and a measured serum osmolality of 304 mosm/kg. Urine pH was 5.0 with a calculated urine anion gap of +25. A serum acetaminophen level was <2.0 μg/mL. Ultimately, a urine organic acid screen was performed and revealed a markedly elevated 5-oxoproline level of 17,455 mmol/mol creatinine (reference range <62) with no other unusual organic acids detected. Given a high degree of suspicion for 5-oxoprolinemia, acetaminophen was discontinued at the time of readmission. However, the anion gap remained elevated in the 25 to 31 mEq/L range for the next 7 days while the urine organic acid screen was pending. Once the results of the urine organic acid screen returned, NAC was administered intravenously at a dose of 150 mg/kg over 60 minutes followed by 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours. Subsequently, the anion gap declined rapidly and her acidemia resolved (Figure 1).

DISCUSSION

5-oxoprolinemia is increasingly recognized as a cause of anion gap metabolic acidosis. Many cases likely go undiagnosed due to lack of a universally available assay for 5-oxoproline. The patient described above fits the classic profile for a patient with 5-oxoproline metabolic acidosis: a chronically ill, malnourished woman with chronic kidney disease (1–4). She had multiple serious complications after lung transplantation. She suffered from malnutrition due to recurrent infections and deconditioning, which left her reliant on tube feedings. Though her serum values were within normal limits, her anion gap increased to 29 mEq/L.

We present a case of 5-oxoproline metabolic acidosis that persisted despite discontinuation of acetaminophen. However, the acidosis rapidly resolved with N-acetylcysteine administration.
creatinine was in the “normal” range, that value was likely deceptive due to her low muscle mass and her recurrent episodes of AKI requiring RRT suggestive of chronic kidney disease.

5-oxoproline is an organic acid intermediate of the \( \gamma \)-glutamyl cycle (Figure 2), which produces the antioxidant glutathione. 5-oxoprolinemia and its resultant anion gap metabolic acidosis can occur from both hereditary and acquired mechanisms. Hereditary causes include rare deficiencies in two essential enzymes in the \( \gamma \)-glutamyl cycle: glutathione synthetase and 5-oxoprolinase (5). Acquired 5-oxoprolinemia results from longstanding depletion of glutathione and cysteine stores that occurs due to malnutrition, sepsis, and chronic acetaminophen use (6). The acetaminophen is typically not in the toxic range and is more often due to chronic use within the accepted therapeutic range. Reduced glutathione levels eliminate the feedback inhibition of \( \gamma \)-glutamyl cysteine synthetase (Figure 2), causing accumulation of \( \gamma \)-glutamyl cysteine that is subsequently metabolized to 5-oxoproline. Reduced cysteine levels prevent conversion of \( \gamma \)-glutamyl phosphate to \( \gamma \)-glutamyl cysteine despite the increased activity of \( \gamma \)-glutamyl cysteine synthetase, as cysteine is required for this reaction. Instead, \( \gamma \)-glutamyl phosphate is converted to 5-oxoproline as part of a futile ATP-depleting cycle (4).

The utility of NAC for acute acetaminophen toxicity is well known (7). It has also been postulated that NAC may be of benefit in cases of acquired 5-oxoprolinemia, as it has been shown to increase glutathione and cysteine levels in patients with hereditary glutathione synthetase deficiency (8). Theoretically, repletion of glutathione stores should reestablish the feedback inhibition of \( \gamma \)-glutamyl cysteine synthetase, thereby reducing the conversion of \( \gamma \)-glutamyl cysteine to 5-oxoproline. Repletion of cysteine stores should reestablish conversion of \( \gamma \)-glutamyl phosphate to \( \gamma \)-glutamyl cysteine, thereby preventing conversion of \( \gamma \)-glutamyl phosphate to 5-oxoproline and breaking the futile ATP-depleting cycle. Reported evidence in the literature supporting NAC administration for 5-oxoprolinemia is limited (9, 10). Although the profound anion gap metabolic acidosis persisted for a week in our patient despite discontinuation of acetaminophen, the anion gap metabolic acidosis rapidly resolved after NAC administration. We suggest that NAC, along with discontinuation of acetaminophen, is the preferred treatment for 5-oxoproline metabolic acidosis.

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Nitrous oxide is a gas that is odorless, colorless, and has a sweet taste at room temperature. Nitrous oxide has several uses, including in surgery and dentistry (referred to as “laughing gas”), in automotive racing, and in aerosol spray propellants. The aerosol spray propellants that typically use nitrous oxide are whipped cream canisters and cooking sprays. Unfortunately, these over-the-counter household items are a source of nitrous oxide that can be used for recreational use. The most popular is the use of industrial-grade canisters having the slang term “whippets.” The nitrous oxide can be extracted by pushing the nozzle down slightly to the side and catching the released gas with a balloon. The contents of the balloon can then be directly inhaled, giving an instant feeling of euphoria. This is not a benign means to achieve a euphoric state but can cause severe nitrous oxide–induced B12 deficiency, which is presented in this case report.

An estimated 800,000 young adults abuse inhalants every year (1), and almost 11% of high school seniors report using inhalants at least once in their lifetime (2). Heavy inhalant abuse can result in a variety of side effects, including cardiac arrhythmias, hypoxia, metabolic acidosis, and neurologic deficits. Of all inhalants, nitrous oxide is particularly toxic due to its conversion of the active monovalent form of vitamin B12 to its inactive bivalent form (3). We present a case of subacute combined degeneration of the spinal cord due to nitrous oxide–induced vitamin B12 deficiency.

CASE DESCRIPTION

A 22-year-old man with a history of polysubstance abuse and asthma presented with a 1-month history of worsening hand numbness and difficulty with fine motor movements, followed by intermittent numbness in both feet and significant gait ataxia. He admitted to daily nitrous oxide abuse for months prior, reportedly inhaling over 30 whipped cream chargers every day. Neurologic exam was remarkable for decreased vibratory sensation in bilateral lower extremities, absence of distal proprioception, hyperreflexia, impaired coordination, rapid alternating movements, truncal ataxia, and a positive Romberg test. Serologic workup illustrated a mild anemia with a hemoglobin of 11.7 g/dL and mean corpuscular volume of 98 fL. His vitamin B12 level was at the low end of normal at 222 pg/mL; however, his homocysteine and methylmalonic acid levels were elevated at 16.3 μmol/L and 1.56 μmol/L, respectively. Magnetic resonance imaging (MRI) of the spine illustrated abnormal T2 hyperintensity of the dorsal columns of C1 to T5, consistent with extensive subacute combined degeneration (Figure). B12 supplementation was started along with cessation of nitrous oxide use, resulting in significant clinical improvement. The patient was not tested...
for other causes of B12 deficiency, such as atrophic gastritis, given his excessive use of nitrous oxide and improvement after discontinuation of nitrous oxide.

DISCUSSION

Although our patient’s vitamin B12 level was at the low end of normal, his clinical presentation, elevated levels of homocysteine and methylmalonic acid, and MRI findings are consistent with a diagnosis of nitrous oxide–induced vitamin B12 deficiency. Unfortunately, the accessibility and low cost of whipped cream chargers have made nitrous oxide inhalation, or “whippets,” increasingly popular among teenagers and adults alike. While significant toxicities rarely occur with occasional inhalation, heavy nitrous oxide abuse can result in significant polyneuropathy and ataxia (5), as seen in our patient. Provider recognition and early identification of nitrous oxide–induced vitamin B12 deficiency is essential, as neurologic deficits are often reversible with aggressive vitamin B12 supplementation and nitrous oxide cessation (4).

Systemic infection and splenic abscess

Aaron R. Belknap, MD, and Joseph Guileyardo, MD

Splenic abscess is a rare complication of systemic infection, sometimes associated with infective endocarditis. Due to its rarity and nonspecific symptoms, diagnosis is difficult. Antibiotic therapy alone is usually unsuccessful, and definitive treatment requires splenectomy, although percutaneous ultrasound-guided drainage has been successful in some patients. Abdominal computed tomography scans and ultrasound evaluation are usually diagnostic. We present two patients with treatment-resistant sepsis who were found at autopsy to have splenic abscess.

CASE REPORTS

Case 1

A 57-year-old woman with chronic lower back pain presented to an outside hospital with a 1-month history of nausea, vomiting, and fatigue. Three to four days prior to admission, she had been bitten by her dog. The outside hospital diagnosed septic shock, and she was transferred to Baylor University Medical Center at Dallas. Blood cultures were positive for *Streptococcus anginosus*.

Autopsy found a puncture wound consistent with a dog bite on the left index finger. Ischemic necrosis of the distal extremities and acute lung injury were also confirmed. An unexpected finding was a subcapsular splenic abscess measuring 3.5 cm in greatest dimension with associated organizing splenic vein thrombosis. She died from multisystem organ failure due to a systemic inflammatory response syndrome associated with septic shock, likely due to *Streptococcus anginosus*.

Case 2

A 52-year-old man with severe obesity, sleep apnea, and atrial fibrillation presented to an outside hospital for atrial ablation therapy. Following this procedure, he developed a bloody pericardial effusion, pericarditis, and multiorganism bacteremia including *Gemella sp.*, *Prevotella sp.*, *Fusobacterium nucleatum*, anaerobic gram-positive cocci, and anaerobic gram-negative coccobacilli. Culture of the pericardial effusion was positive for *Propionibacterium acnes*. Cranial imaging demonstrated multifocal acute and subacute hemorrhagic infarcts in addition to multiple cerebral abscesses. Following deterioration of his condition, the patient was transferred to Baylor University Medical Center at Dallas for a higher level of care.

Upon arrival, intensive antibiotic therapy including central nervous system doses of vancomycin, ceftriaxone, metronidazole, and ceftazidime were given, but the source of the continuing bacteremia could not be identified, and the patient remained febrile. A few days following transfer, the patient suffered myocardial infarction with troponin levels peaking >200 ng/mL, but due to the cerebral hemorrhage, he was not a candidate for anticoagulation. He was transitioned to comfort measures and died.

An autopsy confirmed multifocal organizing cerebral hemorrhages and abscesses, pericarditis, and an acute myocardial infarction. The autopsy also demonstrated multifocal splenic abscesses, with the largest measuring 6.0 cm in greatest dimension. The patient died from complications of morbid obesity.

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resulting in massive cardiomegaly and atrial fibrillation requiring atrial ablation with subsequent infectious complications.

**DISCUSSION**

These patients both died from bacterial sepsis associated with unrecognized splenic abscesses, and abdominal imaging, such as computed tomography or ultrasound, was not performed on either patient. The rarity of this complication, along with the difficulty in diagnosis, requires a high index of suspicion in patients with sepsis that is refractory to antibiotic therapy. However, the classic triad of fever, leukocytosis, and left upper quadrant abdominal pain is not present in many cases. The most sensitive signs are fever (90%) and leukocytosis (88%); however, these are obviously nonspecific (4). Furthermore, both patients had multiple negative blood cultures after the initial positive culture, but despite aggressive antibiotic therapy, neither improved. In general, patients with infective endocarditis or other forms of severe bacterial sepsis with abdominal pain or swelling or with prolonged fever despite appropriate antibiotic therapy should be considered for abdominal imaging in search of a splenic abscess (5).

After diagnosis of a splenic abscess, standard therapy has included immediate splenectomy (2). However, recent studies have found some success with percutaneous ultrasound-guided drainage, followed by splenectomy in patients who did not improve, and the reported rates of successful drainage procedures ranged from 17% to 100% (4, 6, 7). Furthermore, some of these patients had multiple splenic abscesses that were successfully treated by multiple separate drainage procedures (6). However, in view of the dire consequences of inadequate therapy for splenic abscess, further studies are needed to clarify which patients may be safely managed without splenectomy.

Tularemia is a zoonotic disease caused by *Francisella tularensis* that can be transmitted to humans when they handle rabbits, receive tick bites, consume contaminated water, or inhale aerosolized particles. We present the case of a 51-year-old white man with rheumatoid arthritis who was taking immunosuppressive medications and presented with tularemia. Our patient acquired the typhoidal form of tularemia, which is a severe systemic illness that manifests with fevers, headaches, myalgias, vomiting, diarrhea, and neurological symptoms, due to his immunocompromised state. The diagnosis was made through biopsy of a pulmonary nodule found incidentally on computed tomography scan.

**CASE PRESENTATION**

A 51-year-old white man with rheumatoid arthritis and Addison’s disease came in to the emergency department complaining of generalized weakness, watery diarrhea, fever, and chest pain for 3 days. On the day of admission, he was confused and lethargic. His medications included a monthly infliximab infusion, leflunomide 5 mg orally two times daily for rheumatoid arthritis, and fludrocortisone 0.1 mg orally once daily for Addison’s disease. He lived with his wife, children, and a dog on a ranch in Wichita Falls, Texas. At admission, his blood pressure was 130/70 mm Hg; heart rate, 103 beats per minute; and temperature, 101.9°F. Physical examination was unremarkable. His white blood cell count was 6100/µL and platelet count, 80,000/µL. Computed tomography (CT) showed multiple pulmonary parenchymal nodules bilaterally with mediastinal adenopathy and a right pleural effusion (Figure).

He was started on intravenous vancomycin, cefepime, and metronidazole. On day 3, one of the pulmonary nodules was biopsied. Bactrim 80 to 160 mg/day was added on day 4, and he was discharged. One week later, he was informed by the state health department that the lung biopsy culture grew *Francisella tularensis*. He was then readmitted for intravenous infusion of gentamicin and oral ciprofloxacin. Further history revealed that he had found dead cottontail rabbits in his backyard several weeks earlier and had picked them up with his bare hands. Thereafter, he may have inhaled the aerosolized organism from mowing the lawn. His dog became sick after this and developed supraclavicular lymphadenitis that required incision and drainage along with intravenous antibiotics. He was treated with 3 weeks of intravenous gentamicin and oral ciprofloxacin. A repeat CT of the chest showed that the pulmonary nodules had decreased in size.

**DISCUSSION**

Tularemia is a zoonotic infection that is endemic in North America, continental Europe, Russia, Japan, and China. In 1911, McCoy and Chapin first isolated a gram-negative bacterium from ground squirrels suffering from a plague-like disease in Tulare County, California, and named it *Bacterium tularense* (1). The first documented case of human infection was in 1914, when this bacterium was isolated from a meat cutter who developed conjunctivitis and lymphadenopathy (2). Edward Francis reviewed about 800 cases of infections with this bacterium and published a paper describing the clinical characteristics of the disease in 1928 (3); the bacterium was renamed *Francisella tularensis* after him.

*F. tularensis* is gram-negative coccobacilli that can be contracted through an arthropod bite, the handling of an infected animal carcass, or the consumption of contaminated water and meat. Small rodents and lagomorphs (hares and rabbits) are the most common animal reservoirs. From 2005 to 2014, 95 to 203 cases of tularemia were reported per year in the United States (4). This condition is most prevalent in the Southwest region of the United States, including Arkansas, Kansas, Louisiana, Missouri, Oklahoma, and Texas. Men have contracted more than 70% of cases of tularemia, possibly due to exposure from hunting and landscaping (4).

Of the six described forms of tularemia, ulceroglandular tularemia is most common and is acquired through an infected skin lesion that leads to lymphadenopathy (5). This patient was diagnosed with the typhoidal form of tularemia, which usually presents with acute-onset fevers, headaches, myalgias, vomiting, diarrhea, and neurological symptoms including...
confusion. Pulmonary tularemia is a subacute or chronic infection that presents with fever, cough, weight loss, and mediastinal lymphadenopathy that mimics tuberculosis, lymphoma, or sarcoidosis (6). A distinctive feature of this case is that the patient was on immunosuppressive therapy for rheumatoid arthritis, which placed him at a higher risk for typhoidal tularemia than an average individual. This is an atypical presentation for tularemia because the patient presented with nonspecific symptoms and was found to have incidental pulmonary nodules on CT scan of the chest.

Blood cultures are usually falsely negative because *F. tularensis* is a fastidious organism that requires cysteine-enriched media, and the laboratory must be made aware of its possibility ahead of time. Serology with agglutination or enzyme-linked immunosorbent assay can be used for diagnosis with titers of 1:128 or 1:160. Antibodies may not be detectable until the second week of illness (7). Streptomycin is usually the drug of choice but is not readily available in most hospitals. Streptomycin and gentamicin have 97% and 86% cure rates, respectively, against *F. tularensis* (6).

Figure. Cross-sectional CT shows pulmonary nodules (arrows) in the (a) left upper lobe measuring 1 cm, (b) right upper lobe measuring 1.3 cm, and (c) left lower lobe measuring 1.6 cm.

Benign pancreatic hyperenzymemia (Gullo syndrome), histamine intolerance, and carbohydrate malabsorption

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Benign pancreatic hyperenzymemia (Gullo syndrome) is characterized by a more than threefold increase of the pancreatic enzymes lipase and amylase in the absence of a pancreatic disease (1). Gastrointestinal malabsorption is caused mainly by carbohydrates (lactose and fructose), proteins (gluten), and biogenic amines (e.g., histamine) and frequently manifests in nonspecific abdominal complaints. We tested a patient with Gullo syndrome for gastrointestinal malabsorption and diagnosed lactose and histamine malabsorption. This patient with nonspecific abdominal complaints due to lactose and histamine malabsorption recovered with an individually tailored diet free of lactose and histamine within a few days (2).

Benign pancreatic hyperenzymemia (Gullo syndrome) is characterized by a more than threefold increase of the pancreatic enzymes lipase and amylase in the absence of a pancreatic disease over a period of more than 1 year, with elevations and significant undulations of pancreatic enzyme serum concentrations occurring on a day-to-day basis for 5 consecutive days. Nonspecific abdominal complaints may be caused by carbohydrate and/or protein malabsorption. We report a patient with benign pancreatic hyperenzymemia with lactose and histamine malabsorption; the symptoms of gastrointestinal malabsorption were treated successfully with an individually tailored lactose- and histamine-free diet.

CASE DISCUSSION

A 71-year-old white man was examined for repeatedly elevated lipase and amylase serum values over a time period of 3 years and presented with sustained nonspecific abdominal complaints. His symptoms were postprandial abdominal discomfort in the right upper quadrant, bloating, diffuse abdominal pain, and semisolid stools. Physical examination showed a bloated abdomen, and anamnesis revealed no weight loss.

During the 3 years before presentation, the elevation of serum lipase and amylase levels reached 450 U/L (normal <60) and 367 U/L (normal 20–100), respectively. Abdominal sonography revealed gallbladder stones, and subsequently a laparoscopic cholecystectomy was performed. Repetitive abdominal computed tomography and magnetic resonance imaging demonstrated no abdominal or pancreatic abnormalities. Gastroscopy ruled out Helicobacter pylori infection or other abnormalities, and colonoscopy disclosed no abnormalities. The serum total cholesterol was 253 mg/dL; low-density lipoprotein cholesterol, 166 mg/dL; glutamate-oxaloacetate-transaminase, 49 U/L (normal <35); and glutamate-pyruvate-transaminase, 52 U/L (normal <45). Using a radio extraction assay, the diamin oxidase in serum (Sciotec Diagnostic Technologies, Tulln, Austria) was 2.6 U/mL (normal >10 U/mL) (3). Triglycerides, calcium, IgG4, carcinoembryonic antigen, carbohydrate antigen 19-9, fecal pancreatic elastase test, and C-reactive protein were normal. The erythrocyte sedimentation rate was <20 mm in 2 hours.

Hydrogen breath tests were performed to detect lactose and fructose malabsorption (Gastrolyzer, Bedfont Scientific Inc., Kent, England). During the breath test with a drink containing 50 g lactose dissolved in 200 mL water, the end-expiratory exhalation of hydrogen was measured every 30 minutes for a period of 150 minutes. The hydrogen value increased from the baseline 10 up to 19 parts per million (ppm) (normal <20). This test demonstrated decreasing blood glucose levels from a fasting value of 105 mg/dL to 88 and 86 mg/dL after 1 and 2 hours, respectively (normal is an increase >20) (4). In the breath test with a drink containing 25 g fructose load dissolved in 200 mL water, the end-expiratory exhalation of hydrogen was <20 ppm. Antibodies against tissue transglutaminase were not found.

A registered dietitian developed an individually tailored diet for this patient, which resulted in the improvement of symptoms within a few days. At 6 months, the patient was still symptom free. Written informed consent was obtained for all procedures, which were in accordance with the Declaration of Helsinki and the recommendations of the local ethics committee.

From Practice for General Internal Medicine, Bruck, Austria (Schnedl); Institute of Pathophysiology, Centre for Molecular Medicine, Medical University of Graz, Graz, Austria (Schnedl, Lackner, Holasek); Institute of Laboratory Medicine, General Hospital Steyr, Steyr, Austria (Enko); Clinical Institute of Medical and Chemical Laboratory Diagnosis, Medical University of Graz, Graz, Austria (Mangge); and Das Kinderwunsch Institut Schenck GmbH, Dobl, Austria (Schenk).

Competing interests: Wolfgang J. Schnedl received speaking honoraria from Sciotec Diagnostic Technologies. The other authors declare no competing interests. The authors have received no funding for this manuscript.

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in symptoms due to bacterial metabolism and fermentation in the colon. Various combinations of malabsorption were reported in patients with gastrointestinal malabsorption syndromes (2).

Lactose malabsorption is related to lactase deficiency and causes nonspecific gastrointestinal complaints with the ingestion of dairy products (9). Histamine intolerance is a disproportionate amount of histamine in the body caused by the consumption of histamine-containing food and/or a reduced ability of diamine oxidase to catalyze histamine within the gastrointestinal tract. In the patient described here, the diagnosis of this condition was based on a diamine oxidase value < 10 U/mL in serum and more than two typical gastrointestinal symptoms allegedly belonging to histamine malabsorption (10). Nonspecific abdominal symptoms in this patient with benign pancreatic hyperenzymemia (Gullo syndrome) were due to lactose and/or histamine malabsorption and were treated effectively with an individually tailored diet.


### DISCUSSION

Guidelines for diagnosis of pancreatitis are based on the presence of two of the three following criteria: typical abdominal pain, characteristic imaging findings, and elevated lipase and/or amylase levels of threefold or higher than the upper limit of normal (5). However, high amylase and/or lipase levels do not automatically confirm the diagnosis because there are numerous differential diagnoses, including renal insufficiency, inflammatory bowel disease, pathologies of the hepatobiliary tract system, neoplastic diseases, diabetes mellitus, drugs, and infections (6). Diagnosis of Gullo syndrome is made if all evaluations for pancreatic diseases are normal during the time period of at least 1 year, and if elevations and significant undulations of pancreatic enzyme serum concentrations occur on a day-to-day basis for 5 consecutive days (Table) (7). It is speculated that a defect in the intracellular transport of pancreatic enzymes in exocrine pancreatic cells may be responsible for the increased passage of enzymes into the blood circulation (8).

However, if certain foods consumed before the tests might influence enzyme levels, it was reported that the ingestion of various meals did not increase pancreatic enzymes (1). Since in our patient lactose- or histamine-rich or -reduced food did not influence enzyme levels, we confirmed this conclusion. The clinical importance in asymptomatic individuals with Gullo syndrome is to differentiate a myriad of differential diagnoses, and multiple complex diagnostic tests and/or hospital admissions may be prevented (7).

Gastrointestinal malabsorption syndromes are caused by carbohydrates (mainly lactose and fructose), proteins (gluten), and biogenic amines (e.g., histamine). Unabsorbed food results in symptoms due to bacterial metabolism and fermentation in the colon. Various combinations of malabsorption were reported in patients with gastrointestinal malabsorption syndromes (2).
Pott puffy tumor

Pranav Sharma, MD, Salil Sharma, MD, Nishant Gupta, MD, Puneet Kochar, MD, and Yogesh Kumar, MD

Pott puffy tumor is osteomyelitis of the frontal bone with associated subperiosteal abscess causing swelling and edema over the forehead and scalp. It is a complication of frontal sinusitis or trauma. We present the case of an 8-year-old girl with frontal swelling. Imaging evaluation showed frontal osteomyelitis as a complication of frontal sinusitis with associated epidural and subperiosteal abscesses. The patient was treated surgically and recovered well. This case highlights the need for high clinical suspicion and early diagnosis and management to prevent life-threatening complications. Unfortunately, in our case the patient had to undergo surgery for this complication, which could have been prevented by earlier diagnosis.

CASE REPORT

An 8-year-old girl was referred for persistent headaches and gradually increasing frontal swelling for 3 days. She had sinusitis 1 month earlier and was treated with azithromycin. She had multiple drug allergies to penicillin, cephalosporin, and cotrimoxazole. A computed tomography (CT) scan revealed frontal sinusitis with cortical erosions and frontal subperiosteal and epidural soft tissue swelling (Figure 1). Magnetic resonance imaging (MRI) revealed frontal sinusitis, frontal bone defect, and frontal epidural collection with peripheral rim enhancement suggestive of epidural abscess (Figure 2). A small subperiosteal abscess was also noted in the frontal soft tissues. The patient was started on intravenous antibiotics and underwent craniotomy with trephination and drainage of the brain abscess. Functional endoscopic sinus surgery with a left ethmoidectomy and frontal and maxillary antrostomy was also performed. Culture of the pus revealed *Streptococcus intermedius*. The follow-up MRI revealed resolution of subperiosteal and epidural abscesses (Figure 3).

DISCUSSION

Pott puffy tumor is a rare clinical entity with the advancement in antibiotic treatment. Initially described with head trauma, now it is known to be associated with untreated or partially treated sinusitis; however, cases due to mastoid surgery, dental infections, wrestling injuries, and insect bites have been reported (2, 3). Pott puffy tumor can be found in all age groups, but occurs predominantly in adolescents (4). Frontal sinuses are often pneumatized by 2 years of age and are approximate adult size by the late teens. Venous drainage occurs through diploic veins that have communication with the dural venous sinuses, which can propagate septic emboli (4). These infections

Figure 1. Sagittal CT of the brain with (a) bone window and (b) soft tissue window images shows erosion of the outer and inner cortices of frontal bone (arrow) with prefrontal soft tissue swelling (arrow).
A CT scan with contrast can be performed if there is a high suspicion of intracranial extension. Intracranial complications with or without direct erosion of the frontal bone have been observed in about 60% to 85% of these patients (5, 7). Tsai et al reported a 100% rate of intracranial complications in their six pediatric patients with Pott puffy tumor (8). Ketenci et al indicated that intracranial complications are often present during a regimen of antibiotics and are often asymptomatic when the abscess is localized in a silent area of the central nervous system (5, 9, 10).

CT scan can demonstrate sinusitis, bone erosion, subperiosteal collection, and extradural abscess. In our case, CT showed frontal sinusitis, bone erosion, subperiosteal collection, and epidural abscess. As with other intracranial pathologies, MRI is the modality of choice (11, 12). MRI can better delineate intracranial pathology, dural sinus thrombosis, and bone edema. Abscesses show restricted diffusion (13, 14) on diffusion-weighted sequences, indicating thick viscous pus. In this case, MRI showed frontal bone edema and extradural abscess, without dural venous sinus or meningeal involvement. MRI is helpful particularly in follow-up after medical or surgical management, reducing overall radiation exposure.

Bone scintigraphy with Tc-mMP may be more sensitive than CT in detection of early osteomyelitis, but its sensitivity is poor in the setting of acute sinusitis (15).

Early diagnosis and treatment of Pott puffy tumor is necessary. Broad-spectrum antibiotics for 4 to 6 weeks, along with surgical drainage, is the standard of care. This patient underwent frontal craniotomy and functional endoscopic sinus surgery in addition to 4 weeks of antibiotics. Follow-up MRI showed complete resolution.

Figure 2. (a) Sagittal T2 fluid-attenuated inversion recovery and (b) axial contrast-enhanced T1-weighted images show frontal sinusitis (smaller arrow), frontal bone defect (curved arrow), and frontal epidural collection (longer arrow) with peripheral rim enhancement (larger double arrows) suggestive of epidural abscess. A small subperiosteal abscess is also noted in the frontal soft tissues (smaller double arrows).

Figure 3. Postoperative postcontrast (a) axial and (b) sagittal MRI images show resolution of the extradural abscess and frontal sinus infection. The burr holes (arrows) are related to surgical evacuation of the abscess.

5. Ketenci I, Unli Y, Tucer B, Vural A. The Pott’s puffy tumor: a dangerous sign for
Acquired thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome successfully treated with eculizumab

Appalanaidu Sasapu, MD, Michele Cottler-Fox, MD, and Pooja Motwani, MD

Acquired idiopathic thrombotic thrombocytopenic purpura is a life-threatening disease with a mortality of up to 90%, if not promptly recognized and treated. We report a 64-year-old woman with this condition who presented with left-sided weakness and seizure-like activity preceded by headache and easy bruising. She did not achieve optimal response to plasma exchange, corticosteroids, rituximab, and vincristine. We initiated treatment with eculizumab, following which she had durable remission that continued for 30 months after discontinuation of the drug. We later found that our patient has homozygous deletion in two closely related genes, complement factor H–related 1 and complement factor H–related 3.

We report an unusual case of thrombotic microangiopathy with ADAMTS13 <5% and an inhibitor that did not respond to conventional treatment for thrombotic thrombocytopenic purpura (TTP), but was treated successfully with eculizumab. The patient later tested positive for a classic mutation in the alternate complement pathway consistent with concurrent atypical hemolytic uremic syndrome.

CASE PRESENTATION

A 64-year-old black woman with diabetes mellitus and hypertension presented with left-sided weakness and seizure-like activity preceded by 2 days of headaches and 2 weeks of easy bruising. On admission, her vital signs and physical exam were unremarkable. Her basic metabolic profile, antinuclear antibody panel, and testing for hepatitis, HIV, and anti-phospholipid antibody were negative. Her hemoglobin was 9.0 g/dL, platelets were 13 K/μL, lactate dehydrogenase was 954 IU/L, haptoglobin was <30 mg/dL, and blood smear showed 4 to 5 schistocytes/high power field. ADAMTS13 activity was <5%, and there was an inhibitor level of 1.1 Bethesda units. Her complement 3 level was 75.3 (normal 90–180 mg/dL), and complement 4 was <10 mg/dL (normal 15–45 mg/dL).

On hospital day 1, she was started on oral prednisone and daily therapeutic plasma exchange. After 6 days of plasma exchange without signs of improvement, the first dose of rituximab 375 mg/m² was given on hospital day 7. During the second week of hospitalization, the patient developed delirium and altered mental status. Magnetic resonance imaging of the brain showed small left frontal and right occipital lobe infarcts. On hospital day 13, vincristine 2 mg intravenous was given, and on hospital day 14 she received a second dose of rituximab. Her renal function was still normal. Due to declining mental status, severe thrombocytopenia, and continued hemolysis, a decision was made on hospital day 17 to stop plasma exchange and administer eculizumab 900 mg. After the second dose of eculizumab on hospital day 24, her platelets improved to 117 K/μL and continued to rise (Figure). Eculizumab 900 mg was given weekly for 4 weeks for a total of 4 doses, after which ADAMTS13 activity was 75% and the inhibitor was undetectable. Eculizumab 1200 mg was then given every 2 weeks, for a total of 4 doses. The last dose of eculizumab was on day 90, at which time her blood work was normal, with ADAMTS13 activity of 73% and a negative inhibitor screen. Eculizumab was stopped after 8 doses at the patient’s request, and after approximately 3 years of close follow-up her labs remained normal.

We sent blood for atypical hemolytic uremic syndrome 12-gene panel testing to Machaon Diagnostics Laboratory 2.5 years after the diagnosis. The testing revealed a large homozygous deletion in complement factor H–related 1 and complement factor H–related 3 genes. Also, the patient had a heterozygous missense variant (c.3019 G>T; V1007L) in exon 19 of complement factor H. She had heterozygous polymorphism (IVS9-78G>A) within an intron in MCP/CD46. Complement factor H autoantibody was not detected.

DISCUSSION

Thrombotic thrombocytopenic purpura is characterized by a congenital or acquired deficiency of the von Willebrand factor cleaving protein ADAMTS13. Anti-ADAMTS13 autoantibodies contribute to the pathogenesis of acquired TTP (1, 2). Idiopathic TTP caused by ADAMTS13 deficiency tends to relapse (3), although rituximab has been reported to decrease the risk of relapse (4). Atypical hemolytic uremic syndrome is caused by alternate complement pathway dysregulation due to mutations in complement factor H, factor I, factor B, or membrane cofactor protein (3). There are reports of patients with atypical hemolytic uremic
alternate complement pathway, we initiated treatment with the anti–complement 5 monoclonal antibody eculizumab, following which the patient had durable remission that continued for 30 months after discontinuation of the drug. We later found out that our patient had a large homozygous deletion in complement factor H–related 1 and complement factor H–related 3 genes in the alternate complement pathway. This could explain the durable remission that she achieved with eculizumab.

This case, along with the other two reported cases with simultaneous occurrence of severe idiopathic TTP and the presence of alternate complement pathway mutations, argues for a common shared pathogenesis in TTP and atypical hemolytic uremic syndrome disease processes. Identifying the underlying complement genetic defects in severe ADAMTS13-deficient patients may help us to predict the poor response of this subset of TTP patients to plasma exchange and to explore different treatment options.

A rare hemoglobin variant, Hb Belliard

Stacey Murthy, MD, and Raul Benavides, MD

There are many documented variants of hemoglobin; however, other than a limited number (such as sickle cell disease), very few are known to have any clinical significance. As advances in detection and identification continue through gel electrophoresis, capillary electrophoresis, and DNA sequencing, more rare variants are identified. Without case reporting, the significance of these variants will remain unknown or continue to be thought of as insignificant. Here we report a rare hemoglobin variant, Hb Belliard, which was detected in a 68-year-old Indian immigrant to the United States. He presented with elevated hemoglobin and was found to have a unique peak on capillary electrophoresis. The specimen was sent for sequencing and was subsequently found to have Hb Belliard. Currently, Hb Belliard is thought to be insignificant.

CASE DESCRIPTION

A 68-year-old Indian man who immigrated from Mumbai, India, to Garland, Texas, in 1980 presented with weakness, fatigue, and morning nausea. His hemoglobin was 17.1 g/dL, and 3 months later it was 17.2 g/dL. A peripheral blood smear revealed significant microcytosis with moderate hypochromasia and a moderate number of target cells. Hemoglobin electrophoresis revealed 83.9% Hb A, 5.6% Hb A2, and 10.5% Hb Bart’s or variant (Figure 1a). To further classify the Hb Bart’s/variant, the specimen was sent to ARUP Laboratories for gene sequencing and identification. The variant, Lys56Asn, was detected on the HbA1 gene, corresponding to the Hb Belliard variant. Additional testing also found that the patient had a JAK2 mutation and β0 thalassemia.

DISCUSSION

Hemoglobin is a tetrameric protein that is predominantly composed of HbA (2 α and 2 β chains) (Figure 1b). Most mutations are caused by a point mutation that substitutes one amino acid for another in one of the globins. The majority of hemoglobin variants occur in the beta globin chains (such as sickle mutation); however, some mutations are known to occur in the alpha chains (such as Hb Belliard). Over 80 diseases have been identified that are due to substitutions that result in changes to the structure of the hemoglobin; some alter function and others are silent (1, 2). As each mutation was discovered, it was assigned a letter as its designation. As more mutations at the same position were identified, nomenclature started to include the name of the city where it was discovered (2, 3). In the modern laboratory, capillary electrophoresis has replaced traditional gel electrophoresis due to its much higher resolution, producing faster, more accurate results. As more mutations are elucidated, it becomes increasingly difficult to identify them, and more sophisticated ways of differentiating the mutations are
required. Thus, high-pressure liquid chromatography, isoelectric focusing, hemoglobin DNA sequencing, mass spectrometry, and matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) are now used to differentiate rare mutations not detected by conventional methods, as in this case (3).

The only other documented case report of Hb Belliard was published in *Hemoglobin* (1989) as part of a study to find hemoglobin disorders within at-risk populations in Brussels (4). An asymptomatic 20-year-old man of Spanish origin involved in the study was found to have an incidental alpha chain that eluted faster than normal and comprised approximately 25% of the total hemolysate. The abnormality detected was Lys56Asn and was named after a street (Belliard) in Brussels. To further investigate the possible inheritance pattern, his father and brother were also tested and found to have the same mutation. Other mutations at this same position include Hb Thialand (Lys56Thr) and Hb Shaare Zedek (Lys56Glu) (4).

Many variants of hemoglobin do not have known clinical significance; however, with future advances in medicine and more sophisticated detection of physiologic derangements, this may not be true. More consistent case reporting may aid in better understanding of these variants and identification of new clinical importance.


### Avocations

Ruby-throated hummingbird with bee at trumpet honeysuckle, taken at Stillhouse Hollow Lake, Belton, Texas, on April 25, 2016, with a Canon EOS 5D Mark II camera and EF70-200 mm lens. Photo by Terry C. Lairmore, MD (Terry.Lairmore@BSWHealth.org), director of surgical oncology at Baylor Scott & White – Temple.
Intravascular large B-cell lymphoma (IVLBCL) is a rare and deadly malignancy involving the growth of lymphoma cells within vessel lumina of all organ types. IVLBCL is further divided into the hemophagocytic Asian variant and a classical Western variant. Both variants are difficult to diagnose by imaging, and although diagnostic criteria have been developed to guide workup, histopathological examination remains imperative. Treatment of IVLBCL remains difficult given the high mortality of the disease, but rituximab has emerged as a promising therapeutic option when combined with various cytotoxic regimens. The two main variants of IVLBCL generally manifest in their respective Asian or Western populations, and crossover between ethnicities is rare. We present the second described case of Asian-variant IVLBCL in an African American individual.

Asian-variant intravascular large B-cell lymphoma

Derrick W. Su, MD, Whitney Pasch, DO, Cristina Costales, MD, Imran Siddiqi, MD, and Ann Mohrbacher, MD

Intravascular large B-cell lymphoma (IVLBCL) is a rare large B-cell lymphoma that often has a poor clinical outcome (1). Despite its propensity to involve all organ types in a diffuse vascular growth pattern, IVLBCL is difficult to diagnose due to the lack of overt lymphadenopathy and peripheral blood involvement (2–5). Asian and Western variants of IVLBCL share similar features, but generally differ in presentation (5). We present a rare case of Asian-variant IVLBCL in a black man.

CASE PRESENTATION

A 69-year-old black man with coronary artery disease and chronic kidney disease presented to an outside facility with 2 weeks of B symptoms. He had no smoking, tobacco, or illicit drug history and was active and functional prior to these symptoms. His pertinent travel history included military service in Vietnam during the Vietnam War. He had no known family history of malignancies and no known Asian family ancestry. After initially leaving against medical advice, he presented to another facility where he developed refractory hypotension and fever, acute-on-chronic kidney disease progressing to end-stage renal disease requiring hemodialysis, and progressive pancytopenia. An extensive workup ruled out many bacterial, fungal, parasitic, viral, and atypical infections, and a bone marrow biopsy revealed no infection, tuberculosis, or evidence of malignancy. Thrombotic thrombocytopenic purpura was ruled out by peripheral blood smear examination and ADAMTS13 testing. Given the patient’s progressive deterioration and lack of etiology for his fevers, he was transferred to our facility for a higher level of care.

On transfer, his temperature was 39.2°C (102.6°F); pulse rate, 122 beats per minute; and systolic blood pressure, 70 mm Hg. He had mild bilateral upper lobe wheezing, epigastrum tenderness, and marked pretibial pitting edema in the lower extremities bilaterally. There was no skin rash or hepatosplenomegaly. Laboratory studies revealed leukocytosis of 11.2 × 10^3/μL (range 3.8–10.8) with a neutrophil predominance, a hemoglobin of 9.2 g/dL (range 13.8–17), and platelets of 21 × 10^3/μL (range 135–400). Blood urea nitrogen and creatinine were 87 mg/dL (range 8–23) and 5.0 mg/dL (range 0.67–1.17), respectively. The aspartate transaminase was 264 U/L (range 0–23) and alanine transaminase, 42 U/L (range 0–41); alkaline phosphatase, 371 U/L (range 40–130); total bilirubin, 7.4 mg/dL (normal high ≤1.0); and direct bilirubin, 5.6 mg/dL (range 0.0–0.3). Lactate dehydrogenase was 2240 U/L (range 135–225), D-dimer was 4375 ng/mL (normal high ≤250.0), and ferritin was 15,219 ng/mL (range 30–400). Fibrinogen was 293 mg/dL (range 201–485). Peripheral blood film revealed one to two schistocytes per high-powered field, anisocytosis, numerous shift cells, large granular lymphocytes, large platelets, and nucleated red blood cells.

The patient was treated with broad-spectrum antibiotics and antifungals, continuous renal replacement therapy for refractory hypotension, and intubation for progressive altered mentation and inability to protect the airway. Computed tomography disclosed hepatomegaly (24 cm), splenomegaly (14 cm), bilateral nephromegaly (right kidney 13 cm, left kidney 15 cm), and bilateral adrenal enlargement without evidence of a focal mass. A serum protein electrophoresis was negative for paraproteins, and a peripheral blood leukemia and lymphoma flow cytometry panel identified predominantly mature T cells with fewer NK cells and polyclonal B cells, but no clonal population. Bone marrow biopsy showed a mildly hypocellular marrow with trilineage...
cardia and vasopressor-refractory shock, worsening acidosis, and shock liver. On hospital day 7, the family opted for comfort-oriented care, and shortly after palliative extubation, the patient died.

Autopsy disclosed the spleen to weigh 500 g (normal 150–200 g) and liver 2750 g (normal ≤1700 g) but found no discrete masses, enlarged lymph nodes, or skin lesions. Microscopic examination revealed widespread, multiorgan capillary infiltration by enlarged, atypical lymphocytes. Organs involved included vessels throughout the brain and brainstem, lungs, vaso vasorum of the aorta, epicardiac and cardiac vessels, kidneys, adrenal glands, gastrointestinal tract, psoas muscle, gallbladder, pancreas, urinary bladder, spleen, liver, and bone marrow (Figures 1 and 2). Immunohistochemical stains showed the atypical intravascular lymphocytes to be immunoreactive for CD5, CD20, Bcl-2 (focally positive), and MUM1 (subset) and negative for Bcl-1, Bcl-6, CD10, and CD30. The bone marrow also revealed extensive CD68+ hemophagocytic histiocytes (Figure 2). The final diagnosis and cause of death was IVLBCL with hemophagocytic syndrome and multiple organ failure.

**DISCUSSION**

IVLBCL is classified by the World Health Organization as a rare type of extranodal large B-cell lymphoma characterized by the selective growth of lymphoma cells within vessel lumina—particularly capillaries—with the exception of large arteries and veins. Historically, 53% of patients are diagnosed on autopsy (1). IVLBCL involves all organ types, including bone

**Figure 1.** Representative hematoxylin and eosin sections of atypical intravascular lymphocytes infiltrating capillaries of (a) lung, (b) thalamus, (c) esophagus, (d) bladder, (e) pancreas, and (f) psoas muscle. CD20 stain of (g) spleen and (h) bladder.
marrow, central nervous system, spleen, liver, gastrointestinal tract, adrenal glands, skin, and others, though lymphadenopathy is usually absent (2–4). Despite its diffuse vasculature growth pattern, peripheral blood involvement is seen in only 5% to 9% of patients (5).

The two distinct variants of IVLBCL—a hemophagocytic Asian variant and a classical Western-variant—were described through examination of patient case series in Japan (4, 7) and Italy (2), respectively (Table 1) (5). Both variants appear to affect men and women equally and present with B symptoms. Central nervous system involvement is manifested by heterogeneous symptoms of sensory and motor deficits, seizures, vertigo, and altered mentation and is more common in the Western variant (2, 7). The Asian variant more frequently involves the liver, spleen, and bone marrow, while skin involvement occurs more often in the Western variant (2, 7). The Asian variant IVLBCL is also strongly associated with HLH (7), whereas HLH is not typically seen in the Western variant (2, 8). Skin lesions vary widely in morphology and distribution and are commonly located in the upper arms and legs, low abdomen, and breast (2). Interestingly, the Asian variant is rarely seen outside of Asian patient populations. To date, there have only been occasional case reports of IVLBCL with hemophagocytic syndrome in Caucasian patients (9, 10) and only one other case report of Asian-variant IVLBCL in a patient of African descent (11).

Diagnostic criteria for Asian-variant IVLBCL have been proposed; these are summarized in Table 2 (4, 12). Workup of IVLBCL should include a search for suspicious cutaneous lesions for biopsy, peripheral blood smear, and routine blood tests. Given anecdotal reports of cerebrospinal fluid involvement, lumbar puncture with cerebrospinal fluid examination is recommended, whereas bone marrow biopsy may reveal lymphomatous or hemophagocytic

### Table 1. Comparison between sites of disease and laboratory findings in Asian and Western variants of intravascular large B-cell lymphoma*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asian variant (n = 96)</th>
<th>Western variant (n = 38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B symptoms</td>
<td>76%</td>
<td>55%</td>
<td>0.018</td>
</tr>
<tr>
<td>Sites of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>75%</td>
<td>32%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spleen</td>
<td>67%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver</td>
<td>55%</td>
<td>26%</td>
<td>0.003</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>24%</td>
<td>5%</td>
<td>0.012</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>27%</td>
<td>39%</td>
<td>0.171</td>
</tr>
<tr>
<td>Skin</td>
<td>15%</td>
<td>39%</td>
<td>0.002</td>
</tr>
<tr>
<td>Lymph node</td>
<td>11%</td>
<td>11%</td>
<td>0.99</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia (hemoglobin &lt; 12 g/dL)</td>
<td>78%</td>
<td>63%</td>
<td>0.075</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet &lt; 150 × 10^9/L)</td>
<td>76%</td>
<td>29%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated serum lactate dehydrogenase</td>
<td>93%</td>
<td>66%</td>
<td>0.278</td>
</tr>
<tr>
<td>Hypoalbuminemia (&lt; 36 g/L)</td>
<td>84%</td>
<td>18%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Reprinted from Ponzoni et al, 2007 (5) with permission from the American Society of Clinical Oncology. Data on the Asian variant are from Murase et al, 2007 (7), and data on the Western variant are from Ferreri et al, 2004 (2).

### Table 2. Criteria for the diagnosis of Asian-variant intravascular lymphoma*

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| 1. Clinical and laboratory criteria (at least 2 of the 3 are required) | • Cytopenia (not caused by hypoplastic or dysplastic marrow), affecting at least one of the two lineages, i.e., erythrocytes and platelets. Leukocytes are not included. It is prescribed by hemoglobin (<11 g/dL) or red blood cells (<3.5 × 10^12/L) and/or platelet count (<100 × 10^9/L).  
• Hepatomegaly and/or splenomegaly, identified by computed tomography, ultrasonography, or physical examination.  
• Absence of overt lymphadenopathy and tumor formation. |
| 2. Histopathological criteria (all 3 terms are required) | • Erythrocyte-hemophagocytosis; usually seen mildly or moderately in hematopoietic system.  
• Immunophenotypical evidence of proliferating neoplastic B cells with large cell morphology.  
• Pathological findings of intravascular proliferation and/or sinusoidal involvement of lymphoma cells. |

*Reprinted from Murase et al, 2000 (4) with permission from John Wiley & Sons.
cells. Contrast whole-body computed tomography as well as contrasted magnetic resonance imaging of the brain are also suggested, though a high level of false-negative results has been reported (5). [18F]fluorodeoxyglucose positron emission tomography also carries a high false-negative rate for IVLCL, with only a 29% detection rate of pathologically confirmed lesions (13), likely due to the diffuse nature of IVLCL and lack of adenosopathy contributing to a lower volume of regional tumor. Random skin biopsies of the abdomen and extremities may also be an option in the workup of IVLCL, with a small series showing a 36% rate of diagnosis (14).

IVLCL cells are large, with increased nuclear-to-cytoplasmatic ratios, irregular nuclear contours, hyperchromatic, condensed chromatin with occasionally prominent nucleoli, and scant cytoplasm. Mitotic figures are markedly increased, and Ki-67 staining is usually above 50%. By immunohistochemistry, IVLCL is virtually always immunoreactive for CD20 and CD79a (7) (Figure 1). Interestingly, the lymphoma cells lack cell surface proteins critical to lymphocyte transvascular migration, which is thought to contribute to a deficiency in the ability to migrate out of the microvasculature (15, 16).

The introduction of rituximab has dramatically improved the outcome of IVLCL. In one of the largest retrospective studies on IVLCL treatment, patients receiving rituximab-based chemotherapy regimens had longer progression-free survivals and overall survivals compared to patients receiving non–rituximab-based therapies (2-year progression-free survival of 56% vs. 27% and 2-year overall survival of 66% vs. 46% for rituximab-based vs. chemotherapy alone groups, respectively) (17), with chemotherapy being predominantly cyclophosphamide, vincristine, doxorubicin, and prednisolone (CHOP) or CHOP-like regimens. Other studies have also demonstrated improved complete remission and survival rates with rituximab-based regimens in the Western variant (18), and there have even been reports of single-agent rituximab inducing long-term remission in disease refractory to anthracycline-based therapy (19). The choice of specific cytotoxic chemotherapeutics in IVLCL is less clear, particularly in the setting of disease associated with HLH. While etoposide-based regimens have been used successfully for HLH (6), there are no studies to date on the use of the HLH-94 protocol in the treatment of IVLCL.

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We present a case of intrabiliary primary B-cell lymphoma masked as a cholangiocarcinoma in an HIV-positive patient. The two entities have similar symptoms, laboratory findings, and imaging findings but require very different treatments. The case highlights the need to confirm the diagnosis by biopsy.

HIV-associated primary non-Hodgkin’s lymphoma of the bile duct is an uncommon presentation of obstructive jaundice, with few published cases (1). With similar symptoms and laboratory and imaging findings, bile duct lymphoma and cholangiocarcinoma can be almost identical (2). Since cholangiocarcinoma is far more prevalent than primary bile duct lymphoma, a presumed diagnosis of cholangiocarcinoma is often made before biopsy confirmation (3)—an approach that raises concern since the two malignancies require radically different treatment.

**CASE REPORT**

A 61-year-old HIV-infected man with a CD4 count of 77 mL presented to the emergency department with nausea, vomiting, epigastric pain, jaundice, and pruritus. He also reported dark urine and light-colored stools. Laboratory workup was consistent with obstructive jaundice. Magnetic resonance imaging of the abdomen showed intrahepatic and extrahepatic biliary dilation and an abnormal enhancement at the bifurcation of the common hepatic duct (arrow). This finding is often correlated with hilar cholangiocarcinoma, also known as Klatskin tumor (Figure 1). Endoscopic retrograde cholangiopancreatography demonstrated nodular, erythematous walls and high-grade bile duct stricture. He underwent sphincterotomy and stenting. Biopsy of the bile duct was positive for CD20, BCL-2, BCL-6, two-paired box protein Pax-5, CD10, and B-cell lymphoma 6 protein, with antigen Ki-67 demonstrating >90% confirmation of high-grade large B-cell lymphoma (Figure 2). Immunoperoxidase stains for c-Myc demonstrated staining in >30% of the cells. Positron emission tomography–computed tomography showed hypermetabolic activity in the

**Figure 1.** Magnetic resonance imaging of the abdomen—(a) a dual-echo image and (b) a T2-weighted image—showing intrahepatic and extrahepatic biliary dilation and an abnormal enhancement at the bifurcation of the common hepatic duct (arrow). This finding is often correlated with hilar cholangiocarcinoma, also known as Klatskin tumor.
advanced disease, only emphasizing the importance of rapid diagnosis and initiation of correct treatment. As lymphoma is an AIDS-defining illness, its diagnosis in an HIV-infected patient is not only important for initiation of appropriate treatment but also serves a prognostic purpose. The diagnosis indicates an immunocompromised state, regardless of CD4 count, and the need for careful oversight of the patient’s overall management.


**DISCUSSION**

Non-Hodgkin’s lymphoma resulting in obstructive jaundice is primarily caused by extrahepatic lymphoma compressing the bile duct, causing a mass effect. Very rarely is obstructive jaundice due to primary bile duct lymphoma, as in this vignette (4). On imaging, intra- and extrahepatic bile duct dilation was noted. Essentially identical radiologic findings may be found in the setting of cholangiocarcinoma.

Adequate biopsy is needed for definitive diagnosis, as the management and prognosis for cholangiocarcinoma and lymphoma are notably different (5). Treatment for cholangiocarcinoma is surgical resection or gemcitabine-based chemotherapy. Lymphoma is more chemoresponsive, and management utilizes the R-CHOP regimen. In addition, a diagnosis of lymphoma carries a better overall prognosis than cholangiocarcinoma.

Biliary obstruction in the setting of lymphoma correlates with advanced disease, only emphasizing the importance of rapid diagnosis and initiation of correct treatment. As lymphoma is an AIDS-defining illness, its diagnosis in an HIV-infected patient is not only important for initiation of appropriate treatment but also serves a prognostic purpose. The diagnosis indicates an immunocompromised state, regardless of CD4 count, and the need for careful oversight of the patient’s overall management.

**Figure 2.** (a) A hematoxylin and eosin stain demonstrates distorted cells, with arrows demarking an entrapped gland. (b) The biopsy demonstrates positive CD20 staining. Overall findings were consistent with B-cell lymphoma.
Plasma cell myeloma with lymphoplasmacytic morphology and cyclin D1 expression, an uncommon variant

Daniel A. Hale, MD, and John R. Krause, MD

The genetic complexity of multiple myeloma is due in part to the accumulation of mutations, with primary and secondary events. One such secondary event is the development of a gene mutation that may result in overexpression of cyclin D1. The pathway involving cyclin D1 is intricately involved in cell cycle regulation from the G1 to S phase, and alterations may contribute to tumorigenesis. We present a case of cyclin D1–positive multiple myeloma with lymphoplasmacytic morphology and discuss potential diagnostic pitfalls and effects on prognosis.

The molecular pathway of tumorigenesis in multiple myeloma (MM) has been extensively studied but remains to be fully elucidated. A common model for clonal evolution of MM begins with a primary event, such as a chromosomal translocation, deletion, or a hyperdiploid state. The accumulation of secondary events occurs next and is believed to result in progression to MM. Secondary events include additional chromosomal translocations, deletions, and mutations involving specific genes such as KRAS, NRAS, MAF, and MAFB. One secondary event that can occur is the development of a mutation in cyclin D1. Up to 75% of plasma cell disorders have at least one mutation of retinoblastoma protein, p16INK4a, cyclin D1, or a related kinase in the G regulatory pathway commonly targeted in tumorigenesis (1). It has also been shown that overexpression of cyclin D1 in MM can present with different plasma cell morphologies (2). Cyclin D1 is involved in the regulation of the cell cycle, and inhibition of cyclin D1 function can reduce the proliferation of many different cell types (3). Several mechanisms exist that may result in overexpression of cyclin D1, including the translocation t(11;14)(q13;q32) involving the immunoglobulin heavy chain promoter and cyclin D1 (4). One recent study showed that overexpression of cyclin D1 in MM is an independent negative prognostic variable for overall survival (5). The potential for shorter overall survival with varied plasma cell morphology leading to diagnostic pitfalls makes this unique entity one to be aware of in the field of hematology.

Case Report

A 51-year-old woman presented with anemia and chronic back pain. A workup revealed a compression fracture of L1 with an abnormal signal. Serum protein electrophoresis was negative at presentation, and the peripheral blood showed no abnormalities. A bone marrow biopsy was performed, and the aspirate smear showed few scattered plasma cells with numerous lymphoplasmacytic cells. The classic plasma cell morphology exhibiting an eccentric nucleus, perinuclear hof, and basophilic cytoplasm was only rarely seen (Figure 1e). A differential diagnosis of lymphoplasmacytic lymphoma (LPL) versus lymphoid-appearing MM was entertained. The biopsy and clot preparation showed a 50% to 55% normocellular marrow with numerous lymphoplasmacytoid cells and only a few plasma cells.

Immunohistochemistry (IHC) was performed on the clot preparation, and CD138 showed 65% to 70% positive plasma cells. Cyclin D1 was diffusely positive in the plasma cells (Figure 1e). A differential diagnosis of lymphoplasmacytic lymphoma (LPL) versus lymphoid-appearing MM was entertained. The biopsy and clot preparation showed a 50% to 55% normocellular marrow with numerous lymphoplasmacytoid cells and only a few plasma cells.

Flow cytometry found 21% variably sized plasma cells expressing CD20, CD56, CD138, and cytoplasmic kappa, but no clonal B-cell population was identified in the specimen. Because of the lymphoplasmacytic morphology, the specimen had been sent for MYD88 L265P mutation testing, and was negative in our case. Chromosome analysis showed no abnormalities. The findings were consistent with a cyclin D1–positive lymphoplasmacytoid MM involving 65% to 70% of marrow cellularity.

The patient received four cycles of Revlimid-Velcade-dexamethasone induction with partial response measured by plasma cell myeloma with lymphoplasmacytic morphology and cyclin D1 expression, an uncommon variant

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be related to MM, but it has been determined to be a separate entity and is now classified as LPL. Greater than 90% of bone marrow–based LPLs are positive for the MYD88 L265P mutation (6). Our case was negative for the MYD88 L265P mutation, and flow cytometry further helped rule out WMG by finding a clonal plasma cell population with no clonal B-cell population. In our case, it was difficult morphologically to distinguish a subset of lymphoplasmacytic cells from lymphocytes or plasma cells; in a setting of limited IHC, molecular, and cytogenetic testing, it is an important diagnostic consideration to include both LPL and MM in the differential diagnosis.

There is conflicting data regarding the clinical significance of cyclin D1 expression in MM. Cyclin D1 overexpression was found to identify a subset of MM patients who are more likely to have prolonged duration of remission and event-free survival following autologous transplantation (7). However, data from the same study found that there was not a statistically significant difference in overall survival between cyclin D1–positive and cyclin D1–negative groups (7). While the aforementioned study related to transplantation, Moreau et al conducted a study to further investigate the prognostic value of specific chromosome rearrangements in MM patients treated with intensive chemotherapy. They found that patients with chromosomal translocation t(11;14) displayed favorable outcomes in the form of longer overall survival as compared to patients with neither t(4;14) or t(11;14) (8). Cook et al also showed that IHC staining for cyclin D1 overexpression is associated with a longer overall survival time (9). Yet another study revealed that cyclin D1 expression in MM treated with novel agents predicts a shorter overall survival as compared to cyclin D1–negative MM cases (5). This study’s participants consisted of a predominantly non–transplant-eligible population.

The wide variability in results for cyclin D1 overexpression suggests there are numerous unaccounted-for variables affecting disease progression relative to cyclin D1 levels. This large number of variables may contribute to the lack of consensus regarding cyclin D1 expression in MM.


### Avocations

Great Sand Dunes National Park outside Alamosa, Colorado. Photo by William L. Rayburn, MD (William.Rayburn@BSWHealth.org), an obstetrician/gynecologist and chief medical officer of the College Station Region for Baylor Scott & White Health. Dr. Rayburn serves as a trustee for Baylor Scott & White Holdings.
Myeloid sarcoma is an extramedullary collection of blasts of the myeloid series that partially or totally effaces the architecture of the tissue in which it is found. These tumors have been described in many sites of the body, but the skin, lymph nodes, gastrointestinal tract, bone, soft tissue, and testes are most common. They can arise in a patient following the diagnosis of acute myeloid leukemia, but they may also be precursors of leukemia and should be considered diagnostic for acute myeloid leukemia. The differential diagnosis of this neoplasm includes malignant lymphoma, with which it is often mistaken, leading to diagnostic and therapeutic delays. We present the case of an 84-year-old African American man with a history of renal disease secondary to hypertension and coronary artery disease without any prior history of malignancies who presented with airway obstruction. He was diagnosed with a myeloid sarcoma of the mediastinum compressing his trachea.

Myeloid sarcoma, also known as granulocytic sarcoma, extramedullary myeloid leukemia, or chloroma, is the soft tissue equivalent of acute myeloid leukemia. It is found in less than 1% of patients with acute myeloid leukemia (1), but can also be found as a precursor lesion in patients who have not been diagnosed with acute myeloid leukemia. In up to 47% of patients, myeloid sarcoma is initially misdiagnosed as malignant lymphoma (2). It is important to properly diagnose this entity because it should be treated as acute myeloid leukemia. We present the case of an 84-year-old man with no prior history of malignancies presenting with airway obstruction, initially believed to be caused by non-Hodgkin lymphoma, that was treated unsuccessfully with steroids while the biopsy was being evaluated. The biopsy of the lesion was diagnosed as a myeloid sarcoma.

CASE REPORT
An 84-year-old man with previous end-stage renal disease, type 2 diabetes mellitus, hypertension, and coronary artery disease presented with dyspnea that had progressively worsened over a 3-week period. The dyspnea was present at rest and worsened in the supine position. He had a mild cough with minimal sputum production. Additionally, the patient had recently noticed that his appetite had decreased and he had been losing weight. He did not have fever or night sweats.

A chest computed tomography scan showed a superior mediastinal mass measuring up to 7.3 cm in greatest dimension.

Myeloid sarcoma causing airway obstruction

Aaron R. Belknap, MD, and John R. Krause, MD

Figure 1. Computed tomography image showing compression of the trachea (arrowhead) by a soft tissue mass (arrows). A calcified left thyroid nodule (star) extended into the mass.

It entirely encased the trachea and narrowed the lumen to 4 mm at one point (Figure 1). The mass also compressed the right brachiocephalic vein and the upper third of the esophagus. The patient’s white blood cell count was 2.2 K/μL; hemoglobin, 10.4 g/dL; hematocrit, 33.3%; and platelets, 81 K/μL.

A biopsy of the mediastinal mass disclosed large atypical discohesive cells percolating through a background of sclerotic tissue. Most cells had prominent nucleoli, and a few cells had small indistinct granules. On initial morphologic assessment, the mass was most likely a lymphocytic neoplasm, and a diffuse large cell lymphoma was considered. A battery of immunostains (CD3, CD20, CD10, BCL-1, BCL-2, BCL-6, Mum-1, cMyc, Ki-67, EBER, CD34, CD79a, CD4, and CD30) was performed, but of these stains only BCL-2 (90%), CD34 (100%), and Ki-67 (40%–45%) were positive. Additional stains (pancytokeratin, TdT, myeloperoxidase, CD15, CD68, and CD33) were performed to

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elucidate the origin of the tumor cells, and myeloperoxidase, TdT, CD15, and CD33 were positive (Figure 2). With this immunostaining profile, the tumor was diagnosed as a myeloid sarcoma.

The patient then had a bone marrow biopsy that showed 25% cellularity with trilineage hematopoiesis and only 1% myeloblasts by morphology, 1% to 2% by CD34 immunohistochemistry, and no evidence of a high-grade hematopoietic neoplasm by flow cytometry. Mild megakaryocytic dyspoiesis was identified. A myelodysplastic syndrome fluorescence in situ hybridization study on the patient's bone marrow came back positive for deletions of chromosomes 5q and 20q in 74% and 22% of the cells examined, respectively, which is sufficient in the context of refractory cytopenia for a presumptive diagnosis of myelodysplastic syndrome, even in the absence of overt morphologic evidence.

The patient remained intubated without any clinical improvement following high-dose corticosteroid therapy. Due to the patient's multiple comorbidities and age, chemotherapy was considered to be detrimental to the patient. By request of the family, he was transferred to the local Veteran's Administration hospital, intubated, and sedated without plans for further treatment.

**DISCUSSION**

This patient developed a myeloid sarcoma likely arising in a lymph node or the soft tissue of the mediastinum leading to immediately life-threatening airway obstruction. Myeloid sarcoma is an extremely aggressive extramedullary manifestation of acute myeloid leukemia. Primary myeloid sarcoma, defined as myeloid sarcoma without evidence of acute myeloid leukemia in the bone marrow, is rare (5). It is generally considered a precursor lesion for acute myeloid leukemia; one series prior to the advent of effective chemotherapy showed 29 of 30 cases progressing to overt acute myeloid leukemia in a median time of 7 months (4). Granulocytic sarcomas have been described in myelodysplastic and myeloproliferative disorders (5).

Previous case reports of myeloid sarcomas described compression-related symptoms as the initial presentation. The symptoms can vary dramatically based on the site of presentation, ranging from back pain and bilateral leg weakness from spinal cord compression to intestinal obstruction and appendicitis from mesenteric involvement to airway obstruction from a mediastinal mass (6, 7). Due to the broad range of symptoms that can be caused by primary myeloid sarcoma, a high index of suspicion is necessary to avoid missing or delaying this diagnosis.

These lesions often are initially diagnosed or worked up and treated as a lymphoma. In our case, the patient initially was treated with high-dose steroids for presumed lymphoma while the tissue was being examined by pathology. The first suspicion that this might be a myeloid sarcoma came when the initial round of immunohistochemical stains, which were designed to identify a high-grade lymphoma, failed to establish that diagnosis. On the day of marrow biopsy, the clinical team visited pathology to discuss the failure of the patient to respond to high-dose steroids. Further immunohistochemical stains for myeloid sarcoma were ordered and the correct diagnosis was established. It is important to distinguish between a large-cell lymphoma and a myeloid sarcoma for treatment purposes.

Acute myeloid sarcomas are generally treated in the same manner as acute myeloid leukemia. Overall prognosis is extremely poor, with a median survival of 9.5 months; this includes both primary and secondary myeloid sarcomas (8). One older series of 90 patients with primary myeloid sarcoma showed a median survival of 22 months (9). Due to the numerous locations in which myeloid sarcoma can present, it is likely that the prognosis is largely dependent on the location and symptoms.

Sarcoidosis is an immunologic disease of unknown etiology that manifests most frequently within the lungs or associated lymph nodes. Sarcoidosis involving the breast is seen in <1% of cases and usually is diagnosed in patients with multisystem disease. The clinical and imaging presentations of sarcoidosis of the breast can be variable. Though uncommon, sarcoidosis should be considered in the differential diagnosis of a breast lesion, and given that imaging characteristics cannot distinguish between sarcoidosis and malignancy, all breast lesions in patients with sarcoidosis should be biopsied. Our case study demonstrates a diagnosis of sarcoidosis in an asymptomatic patient presenting with a single dilated duct and associated filling defect within the right breast.

CASE DESCRIPTION

An asymptomatic 37-year-old black woman with no significant past medical history presented to Baylor University Medical Center at Dallas for a bilateral diagnostic mammogram due to concern for an underlying primary breast malignancy after a recent chest computed tomography exam demonstrated multiple pulmonary nodules and mediastinal and hilar adenopathy. The patient’s physical exam was unremarkable, without a palpable abnormality identified on a clinical breast exam. The patient also denied breast problems such as nipple discharge or skin changes. A single dilated duct was identified within the subareolar tissues of the right breast on the diagnostic mammogram (Figure 1), with an associated asymmetry at the 12 o’clock position of the right breast 4 to 5 cm from the nipple. Targeted ultrasound of the right breast also demonstrated the dilated duct within the subareolar tissues, as well as an associated 1.2 cm ill-defined hypoechoic lesion at the 11 to 12 o’clock position (Figure 2). Percutaneous ultrasound-guided core needle biopsy of the lesion was performed. Sections from the biopsy sample demonstrated small nonnecrotizing epithelioid granulomas in interlobular and intralobular stroma of the mammary parenchyma (Figure 3). Special stains were negative for acid-fast bacilli and fungi. These morphological findings, together with clinical findings, were consistent with a diagnosis of sarcoidosis.

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Sarcoidosis is an immunologic systemic disease of unknown etiology that can involve any organ and is most frequently seen involving the lungs or lymph nodes. Extra-pulmonary manifestations of sarcoidosis are identified in up to 30% of patients, including the spleen, liver, skin, and heart (1). Sarcoidosis of the breast accounts for <1% of cases (2, 3), with a review of the scientific literature showing only 35 histologically proven cases from 1921 to 1997 (3). Breast involvement is seen most commonly in patients with a known diagnosis of sarcoidosis who demonstrate multisystem involvement. A breast lesion can rarely be the initial presentation of sarcoidosis, with 7 of the 35 reviewed patients having a breast mass as the primary presentation without clinical evidence of systemic sarcoidosis (3). The average age of presentation of mammary sarcoidosis is similar to the timeframe of involvement of other anatomic structures, typically in the third to fourth decades of life (4).

The clinical appearance and imaging characteristics of breast sarcoidosis are variable. The clinical presentation can include skin dimpling with a peau d’orange appearance, a mobile nontender mass, or a tender lesion (3–5). Mammographic findings can range from a spiculated mass suspicious for carcinoma to an ill-defined or irregular lesion (3, 4). Microcalcifications are not associated with sarcoidosis (6). The ultrasound appearance can be variable, but typically demonstrates irregular hypoechoic masses (4). Magnetic resonance imaging is also variable and can show a slow delayed persistent postcontrast enhancement typical for a benign lesion or malignant characteristics with rapid postcontrast enhancement with rapid washout (5–7).

It is suggested that sarcoidosis involves breast tissue by epithelioid granulomas forming nodules among ducts and lobules (4). Fat necrosis or caseous necrosis is not typically found on pathology sampling (8, 9). While sarcoidosis of the breast is extremely rare, it should be considered in the differential diagnosis, as it can be seen even in patients without systemic manifestations of sarcoidosis (3). Although there is no relationship between breast sarcoidosis and the risk of breast cancer, as imaging findings and clinical characteristics cannot distinguish between the two, it is recommended that all suspicious breast lesions in patients with sarcoidosis are biopsied to exclude underlying malignancy (10).

Primary small-cell carcinoma of the breast

Benjamin Raber, MD, Tuoc Dao, MD, Evan Howard, MD, and Arthur Bredeweg, DO

Early diagnosis of rare breast cancers is expected to occur more frequently as screening compliance improves and diagnostic modalities become more sensitive. Well-defined treatment algorithms exist for the management of ductal and lobular carcinomas; however, less information is available to guide the treatment of atypical breast cancers. This case report describes a 38-year-old African American woman with primary small cell carcinoma of the breast and her treatment.

Extrapulmonary small cell cancer comprises only 5% of all small cell carcinomas (1), and small cell carcinoma of the breast comprises <1% of all breast cancers (2). For the minority of small cell cancers that are extrapulmonary, treatment guidelines and prognostic risk factors are not well defined. Here we report a case of primary small cell carcinoma of the breast; treatment involved multidisciplinary application of principles learned in the treatment of small cell lung cancer (SCLC) as well as other extrapulmonary small cell carcinomas.

CASE STUDY

A 38-year-old African American woman with no significant past medical history presented to her gynecologist complaining of a new-onset palpable mass in her left breast. An ultrasound demonstrated a $2 \times 1.2 \times 1.7$ cm hypoechoic oval mass with irregular microlobulated margins (Figure 1). Ultrasound-guided core needle biopsy was performed. In the biopsy specimen, normal breast lobular architecture was visible just adjacent to the tumor, which demonstrated a high-grade malignant neoplasm with lymphovascular invasion. The tumor displayed some of the classic features of small cell carcinoma. The immunostains for pancytokeratin, chromogranin, and synaptophysin were positive, consistent with the neuroendocrine nature of small cell carcinoma (Figure 2). Pathologic interpretation supported the diagnosis of an epithelial lesion with at least some neuroendocrine differentiation consistent with small cell carcinoma of the breast.

The patient was referred to breast surgical oncology. On exam, the known breast mass was palpated, as well as a few abnormally large left axillary lymph nodes, concerning for nodal spread. Before definitive operative intervention, given the patient’s young age of diagnosis and aggressive histology of the tumor, genetic testing and a staging positron emission tomography (PET) scan were performed. Genetic testing was negative for BRCA, and no additional cancer gene mutations were tested. PET scan demonstrated 3 hypermetabolic masses in the upper outer quadrant of the left breast, consistent with multifocal malignancy. Additionally, there was hypermetabolic...
left axillary lymphadenopathy, suggestive of axillary nodal metastatic disease. She was also found to be negative for systemic metastatic disease, excluding the existence of a lung primary.

Medical oncology recommended neoadjuvant carboplatin and etoposide, a standard double-agent regimen used in neuroendocrine tumors, including SCLC. Neuroendocrine tumors are highly replicative, as seen in this patient’s proliferative index of 100%. Etoposide inhibits topoisomerase, which prevents DNA replication, therefore halting tumor growth (3). Carboplatin induces cross-linking of DNA strands to further prevent DNA replication and leads to cell death (4). The decision to undergo neoadjuvant, rather than adjuvant, therapy in our patient was twofold. Neoadjuvant therapy can be clinically monitored for effectiveness by examining the size of the mass during treatment. If the tumor demonstrates progression during neoadjuvant therapy, the clinician can change regimens or proceed directly to surgery. Additionally, after resection, the tumor can be evaluated microscopically for the exact degree of response to treatment.

After completing her course of chemotherapy, the patient had almost complete resolution of her palpable breast and axillary masses. She then underwent left skin and nipple-sparing modified radical mastectomy, which included a left axillary lymph node dissection. No sentinel lymph node biopsy was performed, as the patient’s axillary nodes were already known to be involved. Per the patient’s wishes, this surgery was immediately followed by breast reconstruction with a tissue expander.

Since the landmark NSABP B-06 study, published in 1985, treatment of breast cancer with lumpectomy and adjuvant radiation has been known to be oncologically safe, providing the same long-term survival as a mastectomy (5). Therefore, aside for a few contraindications, patients are given the option to undergo either mastectomy or lumpectomy with adjuvant radiation. Reasons for deciding between the two are multiple and diverse. This patient elected to undergo mastectomy.

Final pathology demonstrated a 0.1 mm microscopic focus suspicious for residual tumor, and an additional 1.2 cm area of high-grade ductal carcinoma in situ, negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor. The 7 axillary lymph nodes examined histologically were found to be negative for active invasive disease. Given that the patient had clinically palpable axillary lymph nodes, which were active on PET scan, we believe that her neoadjuvant therapy completely cured her nodal disease. On follow-up CT scans of the chest, abdomen, and pelvis, the patient had no evidence of residual disease. She is now undergoing postoperative care with routine screening right breast mammogram and bilateral breast exam.

DISCUSSION

The early diagnosis of rare breast cancers will continue to increase along with that of typical breast cancers as screening and diagnostic modalities continue to improve. Given the paucity of atypical diagnoses, the treating physician is left with limited consensus data to guide his or her management. Treatment of our patient’s primary breast small cell carcinoma involved multidisciplinary application of principles learned in the treatment of SCLC as well as other extrapulmonary small cell carcinomas.

Pulmonary SCLC constitutes 95% of all small cell cancers (1). Standard management of pulmonary SCLC is complex; however, it essentially entails 4 cycles of cisplatin and etoposide along with thoracic radiotherapy with or without lobectomy. Prophylactic cranial irradiation is also given to patients who have proven response to chemotherapy and radiation (6). The delivery of this multimodal treatment has a proven survival benefit for patients with SCLC. Standard staging for SCLC consists of tumor, node, and metastasis evaluation. For practical treatment, however, a unique staging system, the Veterans Administration Lung Study Group, was developed. Under this system, SCLC patients are categorized as either limited disease or extensive disease (7). Under contemporary multimodal treatment, SCLC patients with limited disease have a 13.3% 5-year survival rate. SCLC patients with extensive disease have a 1.2% 5-year survival rate (8). Although this is a bleak outcome, survival without treatment rarely exceeds more than a few months.

For the remaining 4% to 6% of small cell cancers that are extrapulmonary, treatment algorithms and prognostic risk factors are less defined (1). The question at hand is whether or not the treatment of SCLC can be applied to extrapulmonary small cell cancer with similar results. A study published in 2010 from Peter MacCallum Cancer Centre in East Melbourne, Australia, attempted to answer this question. This retrospective review determined the recurrence rate, 5-year survival rate, and prognostic risk factors of 120 cases of extrapulmonary small cell cancer treated with the same algorithm as SCLC. Patients were staged according to the aforementioned Veterans Administration Lung Study Group staging system. The treatment, in general, consisted of 4 cycles of cisplatin/carboplatin and etoposide, radiation therapy to the primary site and involved lymph nodes to a dose equivalent of at least 50 G in 2 G fractions, and surgical resection if feasible. Prophylactic cranial irradiation was administered to 7 of the 120 patients. Recurrence-free survival at 1 year ranged from 13% (genitourinary) to 64% (head and neck). The overall 5-year survival rate was 25.4% for patients with limited disease and 0% for patients with extensive disease. Improved overall survival was seen in patients with associated weight loss, the use of definitive radiation therapy, higher-dose radiation therapy, higher number of chemotherapy cycles, and the combination of chemotherapy and radiation (8). Interestingly, surgical resection was not associated with an improved outcome. The use of prophylactic cranial irradiation was determined to be a positive prognostic factor for survival; however, given the low incidence of brain metastasis in the nonprophylactic cranial irradiation group, the study concluded that prophylactic cranial irradiation should not be a part of extrapulmonary small cell cancer treatment.

Prior case reports of primary small cell carcinoma of the breast suggest that a breast primary may carry a higher survival rate than other primary sites. A report of 9 cases from 1996 to 1999 at New York Presbyterian Hospital found all 9 patients alive at follow-up 3 to 35 months after treatment. All 9 patients presented with disease limited to either the breast or the axilla.
Three underwent mastectomy, and 6 underwent lumpectomy. Eight of the 9 underwent axillary dissection, and 7 underwent adjuvant chemotherapy. Metastases to the liver and bone developed in 11 and 32 months in 2 patients (9).

Although possibly less fatal than SCLC, extrapulmonary small cell cancer remains a very aggressive cancer. Despite the lack of formal randomized controlled trials, the application of SCLC treatment to primary small cell carcinoma of the breast appears to carry the best chance of survival. Our patient underwent neoadjuvant treatment with the recommended platinum-based carboplatin and etoposide, followed by mastectomy and axillary dissection. At the time of writing, she was 15 months out from her diagnosis and was disease free.

Breast plasmacytomas are extremely rare entities that can be seen as primary malignant neoplasms in the absence of bone involvement or as secondary neoplasms from disseminated multiple myeloma. Clinicians should be aware of this entity, as it may mimic benign and malignant lesions in the breast. Microscopically, immature plasmacytomas may mimic other neoplasms, so caution should be made on histological examination to ensure the correct diagnosis and corresponding therapy. Here we present a case of a plasmablastic plasmacytoma of the breast in a 55-year-old woman that was originally thought to be an angiosarcoma.

**CASE DESCRIPTION**

In August 2016, a 55-year-old woman presented at an outside facility with a chief complaint of an upper outer quadrant left breast mass, measuring 7.5 × 5.5 cm on physical examination. Laboratory values were unremarkable, except for a low white blood cell count (4.5/L) and a low hematocrit level (35.9%). A diagnostic mammogram showed a round mass at the 1 o’clock position, posterior depth of the left breast. The patient had a core biopsy of the lesion. Pertinent immunostains that were positive included CD31, vimentin, and Ki-67, and on this basis, the lesion was favored to be an angiosarcoma.

A right subclavian MediPort was placed shortly thereafter for intravenous access. No protein studies were done at this time.

The patient was referred to our institution in October 2016. Pertinent past medical history included a diagnosis of multiple myeloma with an autologous stem cell transplant in 2011. On physical examination, the mass measured approximately 11 × 8 cm and was mobile over the chest wall. There was no overlying skin fixation or axillary and supraclavicular lymphadenopathy. Our department was consulted for a second opinion on the core biopsy, and we were concerned for a possible plasmablastic plasmacytoma. In the interim, the patient was advised to undergo excision of the lesion, and due to its large size, a total mastectomy was recommended. Adjuvant radiation therapy was considered. A sentinel lymph node biopsy was to be performed at the time of surgery due to the possibility of a sarcoma from the original report. The patient agreed to the aforementioned procedures.

The sentinel lymph nodes and nipple-sparing left total mastectomy were evaluated by our pathology department. Grossly, the left breast lesion was well circumscribed, tan, and firm. It measured 8.8 × 8.5 × 6.0 cm and involved the upper inner and outer quadrants, spanning the 10 to 2 o’clock positions. Microscopic examination of the left breast lesion showed a solid mass of atypical cells with enlarged eccentric nuclei, prominent nucleoli, and faintly basophilic cytoplasm (Figures 1a, 1b). Moderate mitotic figures were identified. Atypical duct hyperplasia and malignancy were not seen. The tumor extended to the anterior margin and measured 0.3 mm from the posterior margin. Because of our concern that the original biopsy might be a plasmablastic plasmacytoma, a CD138 immunostain was performed and was diffusely positive. CD56 was also positive in 50% of the plasma cells (Figures 1c, 1d). CD31 had membranous staining of cells. It has been shown that about 50% of plasmacytomas will express CD31 (6). In situ hybridization showed lambda restriction (Figure 1e, 1f). The lymph nodes showed follicular hyperplasia and the presence of polyclonal plasma cells in the sinusoids. There was no evidence of carcinoma by pancytokeratin immunostain. The patient returned to establish care with her oncologist in December.

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**Plasmablastic plasmacytoma of the breast**

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These neoplasms are usually cured with local radiation therapy and/or chemotherapy; however, regional recurrences can occur in up to 25% of patients (5). Metastasis to distant extramedullary sites is not uncommon, and 30% to 50% of patients may progress to multiple myeloma with a median time of 1.5 to 2.5 years (1). Conversely, plasmacytomas may be secondary to disseminated multiple myeloma. In a study by Surov et al, 8 of 53 patients (15%) presented with a primary breast plasmacytoma, and the remaining 45 patients (85%) had secondary breast plasmacytoma from spread of multiple myeloma (2). It may be prudent, therefore, to perform bone marrow biopsy and laboratory testing, such as serum and urine protein electrophoresis and immunofixation, in patients who are diagnosed with breast plasmacytoma to rule out multiple myeloma. Primary breast plasmacytomas have a better prognosis than secondary involvement of the breast by multiple myeloma (2). After successful treatment of the tumor, 70% of patients remain disease free at 10 years (5).

The reported incidence of plasmablastic breast plasmacytomas is very rare. Given the patient’s history of multiple myeloma, the presence of an extramedullary plasmacytoma could be a manifestation of recurrent multiple myeloma or an independent, primary process. The nature of the original myeloma as to light chain restriction could not be obtained. Clinically and microscopically, plasmacytomas can mimic other processes, both benign and malignant, as in this case. It is important for clinicians and pathologists to be knowledgeable about this entity to ensure correct diagnosis and therapy.

**DISCUSSION**

Primary breast plasmacytomas are not common. Approximately 45 cases of breast plasmacytoma have been published in the literature since 1928 (7). The prevalence of breast plasmacytomas at one institution (out of all identified plasmacytomas) was reported at 1.5% (1). Both primary and secondary plasmacytomas can be misdiagnosed as primary breast carcinoma or even a benign process. Clinically, the majority of cases occur in women with a mean age of 53 years (3). Patients present with a palpable breast mass. Skin thickening and inflammatory signs may occur and suggest a breast abscess or inflammatory carcinoma. Patients have no clinical or imaging features of multiple myeloma. There is an absence of hypercalcemia, renal insufficiency, anemia, and lytic bone lesions. About 20% of patients have a small M-protein, most commonly IgA. Serum or urinary paraprotein levels are <2 g/dL (1).

2016. She underwent a bone marrow biopsy and aspirate that showed no evidence of a plasma cell dyscrasia.

![Figure 1](image-url)

**Figure 1.** (a) Solid mass of atypical plasma cells measuring 8.8 cm in greatest dimension. (b) Atypical cells with enlarged, eccentric nuclei and prominent nucleoli. There is background eosinophilic stroma. (c) CD138 immunostain is diffusely positive for plasma cells. (d) CD36 is positive in 50% of the plasma cells. (e) Kappa in situ hybridization is negative in plasma cells. (f) Lambda in situ hybridization is 100% positive in plasma cells.
Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) rarely occurs as a primary renal tumor. The disease affects young adults and children and has an aggressive course. The clinical presentation and imaging of these tumors are nonspecific, and they often present at an advanced stage. We present the clinical features, imaging, diagnosis, and treatment of 7 cases of renal PNET (4 men, 3 women; median age, 32 years). Common presenting symptoms were flank or abdominal pain and a mass in the abdomen. On imaging, a large heterogenous infiltrating renal mass with areas of calcification, hemorrhage, and necrosis and tumor thrombus can give a clue to the diagnosis of renal PNET. Immunohistochemistry and molecular studies are essential to confirm the diagnosis. The prognosis of renal ES/PNET is generally poor. Radical nephrectomy combined with chemotherapy and radiotherapy is the standard treatment for renal PNET. An early and accurate diagnosis is crucial for the proper management of these aggressive tumors.

Ewing's sarcoma/primitive neuroectodermal tumors (ES/PNET) are a group of small round cell tumors primarily affecting the bone and soft tissues. Very rarely, they can occur as a primary renal tumor (1). The disease commonly affects young adults and children and runs an aggressive course (2). Molecular studies have established that ES and PNET are part of the same tumor family and exhibit similar biologic behavior. Most of the literature on renal PNET consists of isolated case reports. The clinical presentation and imaging of these tumors are nonspecific, and they often present at an advanced stage. We present the clinical features, imaging, diagnosis, and treatment of 7 cases of renal PNET treated in our center.

METHODS
This is a retrospective analysis of 7 patients diagnosed with PNET of the kidney treated in the Department of Medical Oncology at Regional Cancer Center, Trivandrum, during a 15-year period. The case records of the patients were studied with respect to clinical presentation, diagnosis, treatment received, and survival.

RESULTS
The details of the 7 cases are summarized in Table 1. In our series, the median age was 32 years (range 16–73 years), and there were 4 women and 3 men. In all the patients except one, the presenting symptom was abdominal pain and a huge mass in the abdomen. In one case (#1), the renal mass was detected during antenatal checkup when investigating fetal bradycardia. Most of the patients presented at an advanced stage, and 4 out of 7 had metastatic disease at presentation involving the lungs and bone. Computed tomography (CT) imaging details were available in 5 of our cases and showed heterogenous hypodense mass lesions arising from the upper or lower poles of the kidney with areas of hemorrhage and necrosis; 3 cases also had calcifications. Histopathological examination showed a small round blue cell neoplasm in all the cases, and immunohistochemistry, which was available in 5 cases, was positive for CD99.

Only 3 of our cases had localized disease, and all underwent radical nephrectomy; however, only 2 received adjuvant chemotherapy with vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide (VDE/IE), and one received adjuvant irradiation to the primary site. Among our 4 cases with metastatic disease, 3 presented following radical nephrectomy, 3 received chemotherapy, and 3 were given palliative irradiation to the metastatic site. Two patients did not receive any systemic treatment after radical nephrectomy, and their follow-up details were not known. Among the 5 patients who received chemotherapy, 4 were alive beyond 1 year, and one is alive in remission at 15 months. The survival of our patient group ranged from 6 months to 18 months.

DISCUSSION
ES/PNET of the kidney was first reported by Seemayer and colleagues in 1975 (3) and is exceedingly rare. It usually affects young adults at a median age of 28 years and has a male predominance of 3:1 (4, 5). In our series, the median age was 32 years, and the male:female ratio was 4:3. The common presenting symptoms are flank or abdominal pain, mass in the abdomen, and hematuria (6). Patients are usually asymptomatic until the tumor reaches a large size; the maximum diameter of
such tumors is often 10 cm (7, 8). Systemic symptoms such as weight loss and fever may also occur (9). Our patients presented similarly, except in one patient in whom the renal mass was detected during antenatal checkup. Most of the patients presented at an advanced stage with distant metastasis, which is in concordance with the aggressive behavior of this tumor (4, 10).

Common sites of metastasis include the lung, liver, and bone (6). In our series, 4 out of 7 had metastatic disease at presentation involving the lungs and bone.

The imaging characteristics of renal PNET are often non-specific and overlap with those of other renal tumors, such as renal cell carcinoma, Wilms tumor, neuroblastoma, lymphoma, and desmoplastic small round cell tumor (11). Renal PNETs appear hypoechoic, isoechoic, and/or hyperechoic to the adjacent renal parenchyma on ultrasound and show increased vascularity on Doppler imaging. CT scan shows a large heterogeneous mass with areas of hemorrhage or necrosis (12). On magnetic resonance imaging (MRI), the tumor appears as a lobulated isointense and/or hypointense mass on T1-weighted images and as a heterogeneous to hyperintense mass on T2-weighted images, with heterogeneous contrast enhancement (6, 12). MRI and CT also help to evaluate renal vein and inferior vena cava.
Figure 2. (a) Hematoxylin and eosin stain (40×) showing the neoplasm composed of large nests of cells with a moderate amount of cytoplasm, moderately pleomorphic nuclei with granular chromatin, and areas of geographic necrosis, with thin vascular channels in between. Scattered mitosis was seen. (b) MIC-2 (CD99) shows strong membrane positivity.

Figure 3. Contrast-enhanced CT of the abdomen showing a large irregular heterogeneously enhancing mass lesion arising from the upper pole of the right kidney, with multiple specks of calcification within.

Diagnosis of renal PNET is challenging. Although radiological features may be suggestive, biopsy with immunohistochemistry is required to confirm the diagnosis. Renal PNET is characterized by small uniform round cells with dark nuclei, ill-defined cytoplasmic borders, and poorly formed rosette-like structures (9). The histopathologic features overlap with other small round blue cell tumors like neuroblastoma, desmoplastic small round cell tumor, and lymphoma. Immunohistochemistry and molecular studies play a crucial role in differentiating these tumors. PNET shows strong positivity for MIC-2 gene product and CD-99 over the membrane of tumor cells, which is seen in more than 90% of renal PNET cases (7). It is also positive for different neural biomarkers such as S-100, Leu 7, and NSE (13). The immunohistochemistry findings are further supported by the identification of a characteristic EWSR1/FLI1 fusion product that results from a t(11;22) (q24;q22;q12) translocation. This translocation is identified in 90% of cases and unequivocally confirms the diagnosis (7, 14). Among our cases, IHC details were available in 5 patients, and all were positive for CD99.

Renal PNET appears to be a unique clinical entity that behaves more aggressively than PNET arising at other sites. As the tumor is highly aggressive, it is often diagnosed in an advanced stage when it has already involved perinephric fat, hilar lymph nodes, renal veins, and the inferior vena cava. In more advanced stages, the tumor involves the liver, spleen, peritoneum, and lungs. The prognosis for renal ES/PNET is generally poor, with a 5-year disease-free survival of 45% to 55% in localized cases, whereas cases with an advanced stage at presentation have a median relapse-free survival of only 2 years (9, 13, 15).

The treatment for renal ES/PNET is similar to that for ES/PNET elsewhere and includes surgery, chemotherapy, and radiation (6, 10). Surgical options include partial or total nephrectomy with cavotomy in cases of renal vein involvement (6, 14). The diagnosis of renal ES/PNET is often made postoperatively and hence chemotherapy is generally given as an adjuvant. The recommended chemotherapy regimen is vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide given for a period of 1 year (16). The role of radiotherapy is not clear, but it may be given in locally advanced disease and in those with positive margins. Despite aggressive therapy, the overall cure rate of renal PNET is only 20% (17).

Among the 7 cases reported here, 6 underwent radical nephrectomy, 5 received chemotherapy, and 4 received radiation therapy. Four patients were alive beyond 1 year, and one is alive in remission at 15 months. The survival of our patient group ranged from 6 months to 18 months. Since the overall prognosis of this tumor is poor, an early and accurate diagnosis is crucial for the proper management of these aggressive tumors.


True cystic structures within the umbilical cord are rare, and when they persist into the second and third trimester, they are often associated with an abnormal karyotype or other developmental abnormalities. Clinically significant pseudocysts resulting from massive edema of the umbilical cord have been associated with a congenitally patent urachus. We present a case of intrauterine fetal demise at 28 weeks’ gestation in which cystic dilatation of the umbilical cord was diagnosed prenatally by ultrasound imaging. At autopsy, a congenitally patent urachus was contiguous with the massively edematous umbilical cord.

Umbilical cord cysts detected beyond the first trimester have a strong association with congenital anomalies and aneuploidy (1). In a case series by Smith et al, 18 of 23 neonates diagnosed with cystic umbilical cords were found to have an abnormal karyotype or other congenital anomalies (1). Pseudocysts are not true epithelial-lined cysts but result from edema of the umbilical cord and may be associated with a patent urachus (2, 3). Herein we describe a stillbirth of a fetus previously diagnosed, by ultrasound, with a large, cystic umbilical cord in the second trimester.

CASE DESCRIPTION

A 21-year-old gravida 2 para 0 woman presented to her obstetrician at 8 weeks and 1 day gestation for confirmation of pregnancy. Her medical history was unremarkable aside from a previous ectopic pregnancy treated with salpingectomy. Routine ultrasonography, performed at 19 weeks’ gestation, disclosed a large cystic umbilical cord measuring 42 × 34 × 30 mm. A sonogram performed at 24 weeks’ gestation confirmed the large cystic cord (Figure 1) and polyhydramnios. Noninvasive perinatal testing, antiphospholipid antibody screening, and TORCH titers drawn during the pregnancy were normal. Amniocentesis for karyotyping was declined by the patient, who was evaluated again at 26 weeks and had a normal umbilical Doppler exam. A short cervix was noted during this encounter, and the patient was given steroids to promote fetal lung maturity. At 27 weeks there were no changes, but at 28 weeks and 4 days the patient reported excessive fetal movement followed by absence of fetal activity. Fetal demise was documented, induction and vaginal delivery followed, and a massively enlarged and cystic umbilical cord was seen at delivery.

Autopsy findings of the male fetus included a patent urachus extending from the dome of the urinary bladder into the three-vessel umbilical cord. The urachus could be easily probed to the clamped portion of the cord nearest the baby (Figure 2). This patent urachus was contiguous with the massively edematous and cystic portion of the umbilical cord (Figure 3). Additional findings included an atrial septal defect and a large left atrial diverticulum.

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carries a favorable prognosis, but infectious and even neoplastic complications are known to occur. Clinical appreciation of this anomaly can lead to further evaluation and follow-up in order to determine the need for additional therapy such as surgical ligation or excision. Therefore, the finding of a cystic umbilical cord should prompt careful search for a patent urachus, which may be the cause of this condition.

Normal live birth without other developmental abnormalities or aneuploidy may be seen with cystic umbilical cord dilatation, but cystic cords have also been associated with vascular thrombosis and stillbirth (5). No standard exists for evaluation, monitoring, and treatment of cystic umbilical cords, but due to the high occurrence of congenital anomalies and aneuploidy, detailed sonographic imaging and karyotyping have been recommended (3). However, umbilical cord Doppler echograms were performed weekly on this patient with no abnormal findings, and it is unlikely that closer surveillance would have changed the outcome in this case. It has also been proposed that color Doppler may distinguish vascular and nonvascular cord masses and may aid in detecting impaired blood flow (4).

Abnormal findings on routine skin exams are common and can be a source of unnecessary medical workup if a clinician is unfamiliar with the finding. Sebaceous nevi are rare skin lesions that are most often benign but may be associated with a multiorgan syndrome or local skin cancer. Dermatologists and primary care physicians may encounter these on routine exams and thus must be comfortable with diagnosis and management. We present the clinical characteristics of a benign sebaceous nevus to help aid in diagnosis of these lesions and outline suggestions for appropriate management options.

The total body skin examination is one of the most common dermatologic visits and a common component of primary care visits. Examining the skin for potential malignancies can be taxing; therefore, efficient evaluation is a necessity for high-volume clinics. Quick identification of malignant features and confidence in evaluating rare nevi is fundamental to efficiency. We present a case describing the evaluation and management of a rare, unusual-appearing congenital nevus with neoplastic potential.

CASE DESCRIPTION

A 52-year-old white woman presented to the dermatology clinic for a routine annual full-body skin exam and evaluation of a suspicious lesion she noticed on her posterior auricular skinfold. She was unsure how long the lesion had been present but believed it to be growing in size over the past 5 years. She denied pain, pruritus, bleeding, or drainage from the lesion and denied ophthalmologic defects, neurologic symptoms, skeletal deformities, or a personal history of skin cancers.

The postauricular lesion was a linear, waxy, flesh- and yellow-colored plaque that measured approximately 40 mm in length (Figure). No erythema or drainage was noted. On palpation, the lesion was firm and nonmobile, and sebum could not be expressed. No punctum was identified. No other similar lesions were found on the remainder of the skin exam, only benign nevi and seborrheic keratoses.

The lesion was determined to be a single sebaceous nevus based on texture, anatomic distribution, physical characteristics, and presence for more than 5 years. A biopsy was not performed as the lesion was not felt to have any significant characteristics suggesting malignancy. The patient was counseled to observe the lesion for continued growth, change in texture, ulceration, or pruritus. The lesion was photographed to assist with monitoring it over time, with plans for yearly follow-ups.

DISCUSSION

Sebaceous glands are sebum-secreting glands located in the dermis of all hair-bearing skin and are associated with hair follicles and apocrine ducts (1). Hormones strongly affect the activity level of these glands; thus, at the time of puberty, sebum production increases. However, as an individual ages further, sebaceous glands become diffusely hyperplastic, sebum production decreases, and cell turnover and migration slow (2).

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Figure. A 40-mm linear sebaceous nevus in the left posterior auricular region.
A sebaceous nevus, or nevus sebaceus of Jadassohn, is a benign lesion classified as a hamartoma consisting of sebaceous and apocrine glands and epidermal and follicular elements (3). These lesions are most often present at birth, classically appearing on the scalp as an alopecic area of a yellow-orange, linear, crescentic, or round plaque with a waxy sheen (4–6). Histologically, biopsy may reveal immature hair follicles, ectopically located apocrine glands, and abundant sebaceous glands sitting uncharacteristically superficial in the dermis (7). Sebaceous nevi often enlarge near the time of puberty due to sebaceous gland hyperplasia, apocrine gland maturation, and epidermal hyperplasia (8). The verrucous appearance that often develops at this time may incite initial presentation to dermatology or primary care.

Initial workup of these lesions should include a clinical evaluation for nevus sebaceus syndrome, or Schimmelpenning syndrome. Nevus sebaceus syndrome is characterized by diffuse sebaceous nevi on the face or scalp and is associated with central nervous system abnormalities including seizures and mental retardation, ocular impairments, and skeletal defects such as craniofacial abnormalities and hypophosphatemic rickets resistant to vitamin D (9–11). Thus, in pediatric patients especially, the presence of a sebaceous nevus should be documented with a brief neurologic, ocular, and musculoskeletal exam. Any patient suspected of having nevus sebaceus syndrome should undergo a more thorough physical exam with possible laboratory and/or imaging evaluations.

The most frequent complications of a sebaceous nevus are increased size, nodularity, and alopecia, which may result in undesirable cosmesis (6). Serious complications can occur such as the development of a secondary neoplasm and a risk of malignant transformation (6, 12, 13). The rate of malignancy remains unknown due to a lack of prospective studies, but current literature suggests that the most common secondary neoplasms seen within sebaceous nevi are benign syringocystadenoma papilliferum and trichoblastomas (6, 13–16). There is a known association with basal cell carcinomas, which have been reported to occur in <1% of patients with sebaceous nevi (13–15). Many other malignant tumors have been reported to be associated with sebaceous nevi, including squamous cell carcinomas, sebaceous carcinomas, and apocrine carcinomas (6, 13, 17). Despite the overall risk of malignancy increasing with age, Rosen et al showed that basal cell carcinomas can develop within these lesions even prior to puberty and without significant physical change (14). Conversely, Santibanez-Gallerani et al studied 757 cases of sebaceous nevi in children <16 years of age and found no basal cell carcinomas, thereby drawing the conclusion that prophylactic excision is not indicated (16). Determining workup and management of these lesions requires acknowledgment of these risks and consideration of patient goals.

Treatment of a sebaceous nevus is controversial. Historically, it was believed that prophylactic excision was necessary in all cases due to the risk of malignant transformation, but newer studies have shown that the rate of malignancy was grossly overestimated and have drawn conflicting conclusions. Some authors have concluded that observation only is acceptable and excisional biopsy is not necessary, while others still propose prophylactic excision, with disagreements on the timing of treatment (5, 13–15). If treatment is desired, definitive removal of the lesion requires full-thickness surgical excision (14). This may be preferred by some patients or parents for cosmetic outcomes or may be indicated due to clinical signs of malignancy such as rapid growth, ulceration, or bleeding (12). Treatment timing must consider the age of the patient, the need for general versus local anesthesia, the size of the lesion, and overall goals of treatment (14). Due to the inconsistency of treatment recommendations in the literature, management of a sebaceous nevus must be decided upon by the clinician and the patient with consideration of the associated risks accompanying each option.

Leukocytoclastic vasculitis drug reaction to certolizumab pegol

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Tumor necrosis factor (TNF)-alpha antagonists are a common treatment modality for autoimmune disorders, but their use can be associated with many side effects, including various dermatologic conditions. Certolizumab pegol, a newer TNF antagonist that lacks the Fc portion of the IgG antibody, has recently been approved to treat psoriatic arthritis, rheumatoid arthritis, and Crohn’s disease. Though other TNF antagonists have been associated with leukocytoclastic vasculitis, this finding has not yet been reported with certolizumab pegol. We present a case report of leukocytoclastic vasculitis caused by certolizumab pegol.

Certolizumab pegol (CZP) is a pegylated, humanized, tumor necrosis factor (TNF)-alpha inhibitor that differs from other TNF-alpha inhibitors by being solely composed of a Fab fragment and lacking the Fc portion of the IgG antibody (1, 2). By lacking the Fc portion, CZP cannot activate complement nor mediate antibody-dependent cell-mediated cytotoxicity; theoretically, this should reduce the potential for CZP to have Fc-mediated effects. While the other TNF-alpha antagonists have been cited to cause leukocytoclastic vasculitis (LCV), we believe this is the first report of CZP causing LCV.

CASE PRESENTATION

A 28-year-old woman with Crohn’s disease and ankylosing spondylitis presented for evaluation of a rash on her bilateral lower legs, feet, palms of hands, and plantar surface of her feet 6 months after beginning CZP. At age 26, she was diagnosed with severe ankylosing spondylitis; 6 months after diagnosis, she was placed on CZP as sole therapy. She received 400 mg of subcutaneous CZP every 4 weeks for approximately 1 year. She initially developed a rash after being on CZP for 6 months and remained on the CZP for an additional 6 months, due to the effective control of ankylosing spondylitis. Initially, many pruritic inflammatory macules and papules involved the patient’s legs and feet and extensive small vesicles were evident on the plantar surface of the patient’s feet (Figure). Several months after the initial presentation, the eruption extended to the patient’s trunk and scalp, with the scalp lesions appearing as sebopsoriasis. The eruption progressed to include a folliculitis-like rash on the patient’s thighs and arms. The patient additionally reported lower extremity edema with prolonged standing and lower leg muscle soreness.

The patient had documented intolerance for TNF-alpha inhibitors previously. At the initial diagnosis of Crohn’s disease, she was treated with adalimumab but had intolerable side effects including alopecia, scalp psoriasis, severe hidradenitis of the groin and axillae, and vesicular eruption on her palms and soles. Adalimumab was thus discontinued and the patient subsequently underwent subtotal colectomy.

The patient underwent a punch biopsy of her left foot and right leg. Microscopic evaluation of the left foot demonstrated an unremarkable epidermis overlying dermal infiltrates, composed mostly of neutrophils and scattered eosinophils. Chemotaxis of neutrophils leading to vessel wall injury, fibrin deposition, and erythrocyte extravasation along with fragmented neutrophils were also noted. Microscopic evaluation of the right leg...
showed superficial and deep perivascular and dermal infiltrates of neutrophils and eosinophils. Both biopsies were consistent with LCV with significant tissue eosinophilia.

Against the patient’s rheumatologist’s recommendations, the patient stopped taking CZP and began a 3-week prednisone taper, which entailed taking 60 mg by mouth for week 1, 40 mg by mouth for week 2, and 20 mg by mouth for week 3. The patient additionally received 50 mg of dapsone once daily for 1 month. The rash cleared completely approximately 3 months after cessation of CZP.

**DISCUSSION**

LCV may have a multitude of presentations, making it difficult to diagnose. While the initial presentation is often cutaneous, LCV may cause a variety of other problems including myopathy, gastrointestinal bleeding, and renal insufficiency (3, 4). It can also result in permanent scarring (5). Common presentations of LCV include palpable purpura, urticaria, ulcers, or nodules (3, 6). These lesions may be exquisitely painful or pruritic, and lower leg edema and myalgias are frequently present (3). Histopathologically, LCV is described as fibrinoid necrosis of dermal small vessels, hemorrhage, thrombosis, and perivascular polymorphonuclear leukocytes (3, 6). However, the histologic variability of LCV has been reported to morph over the course of 24 to 48 hours from a neutrophilic-predominant infiltrate to a mononuclear-predominant infiltrate (7). Furthermore, drug-induced LCV is often characterized as having an eosinophilic-predominant infiltrate (8).

CZP is approved for treatment of psoriatic arthritis in many countries, including the US (1). With the increasing use of CZP, physicians should be aware of this side effect and consider drug cessation if indicated.

Dementia is a chronic loss of neurocognitive function that is progressive and irreversible. Although rare, dural arteriovenous fistulas (DAVFs) could present with a rapid decline in neurocognitive function with or without Parkinson-like symptoms. DAVFs represent a potentially treatable and reversible cause of dementia. Here, we report the case of an elderly woman diagnosed with a DAVF after presenting with new-onset seizures, deteriorating neurocognitive function, and Parkinson-like symptoms.

In this case, we highlight how familiarity with symptoms of dural arteriovenous fistulas (DAVFs) can reduce the incidence of misdiagnosis of dementia syndromes and lead to early treatment and better outcomes (1).

CASE PRESENTATION
An 82-year-old woman presented with a 1-year history of reduced limb control and difficulty finding words. She had been on carbidopa-levodopa without significant improvement. One month prior, she had a cluster of generalized unprovoked seizures with loss of consciousness with initiation of levetiracetam. Subsequently, she had progressive loss of memory. In the distant past, she had dural sinus thrombosis, recurrent deep venous thrombosis, and pulmonary embolism, for which she was on warfarin. She also complained of a constant loud whooshing sound. She had a nonfocal neurological exam with the following exceptions: speech was fluent, appropriate, but slow; her Mini-Mental State Examination was 21 with poor recall and attention and an inability to draw overlapping pentagons or write words; and her clock drawing test showed marked visuospatial abnormalities (Figure 1a).

Magnetic resonance imaging of the brain revealed a chronic thrombus in the right transverse sinus with enlarged cerebral veins and multiple right-sided leptomeningeal collaterals. There were hyperintense signal changes in the periventricular white matter on the T2-weighted sequence. A fluid-attenuated inversion recovery sequence showed a hyperintense signal over a portion of the right transverse sinus with the loss of normal flow void. Cerebral angiography revealed a hypervascular DAVF predominantly at the left skull base midline parietal calvarium. Vessels from the external carotid, vertebral, and subclavian arteries supplied the DAVF, which drained into the torcular Herophili, superior sagittal sinus, and left and right transverse-sigmoid sinuses. Occlusion or near occlusion of the right transverse sinus was noted. Marked venous hypertension was present in the right cerebral hemisphere, deep basal ganglia, and posterior fossa. Cortical veins were enlarged. There was prolonged drainage bilaterally from the cerebellar hemispheres (Figure 2a).

The patient underwent a right partial DAVF transarterial endovascular embolization (Figure 2b) with marked improvement in her clinical symptoms on repeat evaluation 14 weeks later. Her Mini-Mental State Examination score increased from 21 to 25. On the clock drawing test, she was able to fill in numbers correctly into a predrawn circle. Her ability to draw overlapping pentagons improved, and she could write legible and comprehensible sentences (Figure 1b). Her whooshing sounds nearly resolved.

DISCUSSION
DAVF is an abnormal connection between arteries and veins. It is rare, accounting for about 10% to 15% of vessel malformations in the brain (1). Blood is supplied to DAVFs mainly through branches arising from the external carotid artery. Vessels from the internal carotid and meningeal arteries can also be involved (2).

The exact mechanism of DAVF development is unknown. A percentage of it is believed to develop from acquired causes that result in increased pressure in the dural sinuses. The presence of a transverse sinus thrombus in our patient corroborates previous reports identifying thrombosis in the venous sinuses as a possible trigger for developing DAVF (3–6). DAVF usually presents in the fifth or sixth decades of life (3, 6). It occurs with a female-to-male ratio of 1:1.65 (1). No family history or hereditary pattern predisposes or increases the risk of developing a DAVF (3).

Patients with DAVFs present with a wide array of clinical symptoms. Common symptoms range from the less severe...
presentations of headache, orbital bruit, pulsatile tinnitus, and ophthalmoplegia to more severe presentations of neurological deficits and acute intracranial hemorrhage (1, 3). There are only a few reports of DAVFs presenting with dementia syndrome, a decline in neurocognitive function, and parkinsonism (3, 7). The clinical presentation of DAVFs depends on their location and pattern of cerebral venous drainage (1, 3, 6). DAVFs with isolated dural sinus drainage have a benign clinical course. Most cases present with pulsating tinnitus and visual symptoms, depending on the proximity of the dural venous sinus to adjacent organs.

DAVFs with isolated dural sinus drainage to the cavernous sinus commonly present with ophthalmoplegia, proptosis, chemosis, retroorbital pain, and decrease in visual acuity. Pulsating tinnitus is the most frequent presentation of a DAVF with increased drainage to the transverse and sigmoid dural venous sinuses. Clinical presentation is best explained by the proximity of the sigmoid sinus to the auditory apparatus (3).

In our case, increased drainage was seen in the transverse and sigmoid dural venous sinus, which explains the presence of pulsating tinnitus at the time of her presentation.

Cortical venous hypertension presents with more severe symptoms and carries a higher risk of future neurological events in comparison to a more benign clinical course seen in patients with isolated dural sinus drainage (3). Presentation of severe cortical venous hypertension includes but is not limited to intracranial hemorrhage and nonhemorrhagic congestive neurological deficit such as progressive dementia, parkinsonism, seizures, cerebellar symptoms, and other focal neurological deficits (3).

The exact pathogenesis for developing dementia in patients with DAVFs remains largely unknown. The occurrence of ischemia involving the frontal and temporal lobe is associated with the development of dementia (2, 8). Ischemia occurs from the downstream effect of arterialization of cortical venous drainage from cortical venous hypertension, leading to cerebral venous congestion (3). Some reports have suggested that patients with DAVFs involving the superior sagittal sinus have a higher rate of presenting clinically with dementia (9).

The mechanism by which DAVFs cause parkinsonism is also unclear (8). Hypoperfusion of the frontal lobe due to venous hypertension is thought to be responsible for developing parkinsonism in patients with DAVFs (2, 8). Another possible explanation is from hypoperfusion of the basal ganglia due to impaired drainage of the deep internal veins (8).

Figure 1. Mini-Mental State Examination (a) 12 days prior to partial embolization of the dural arteriovenous fistula, with a score of 21/30, and (b) about 2.5 months after partial embolization, with a score of 25/30.

Figure 2. (a) Digital subtraction angiogram of the direct left occipital artery injection. An extensive rete of arterial pedicles supplying the fistula is densely radiopaque. The ipsilateral transverse sinus exhibits early opacification. Note the retrograde drainage via the straight sinus. (b) Unsubtracted completion of the left occipital angiogram shows hyperdense embolization material throughout feeding vessels, with diminished shunt physiology.
Previous reports on patients presenting with dementia and parkinsonism showed frontal lobe, temporal lobe, and basal ganglia ischemia. Ischemia was a direct result of the connection between the DAVF and superior sagittal sinus. It has been hypothesized that this leads to the development of an arterial steal phenomenon believed to be responsible for the ischemia. Local venous congestion was also involved in the development of hypoxia. Dementia was attributed to frontal lobe ischemia, while damage to the frontal white matter and basal ganglia was hypothesized to be the cause of the parkinsonism (3, 10).

Other symptoms reported in our patient such as decreased speech output may be the result of decreased frontal lobe perfusion. Seizures could be attributed to global venous congestion (8). Hemorrhage in the basal ganglia has been reported to cause seizure-like tonic-clonic movements (5). It appears that the seizures seen in our patient were more from venous congestion than from hemorrhage. Reduced speech, as with dementia, showed significant improvement with postendovascular embolectomy.

Unlike most known causes of dementia syndromes, DAVFs do not have a single constant or defining symptom. The presentations of DAVFs are highly variable and may be reversible. DAVF represents one of the rare but reversible causes of dementia. Early diagnosis and treatment may have the potential of dramatically improving patients’ clinical condition and minimizing long-term residual disability.

Right hemispheric reversible cerebral vasoconstriction syndrome in a patient with left hemispheric partial seizures

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We report a right-handed 19-year-old girl who developed reversible cerebral vasoconstriction syndrome (RCVS) lateralized to the right hemisphere with simultaneous new-onset left hemispheric seizures. RCVS, typically more diffuse, was lateralized to one of the cerebral hemispheres.

Reversible cerebral vasoconstriction syndrome (RCVS) is a self-limited, underrecognized clinicoradiologic syndrome characterized by recurrent thunderclap headaches and reversible, bilateral, and multifocal vasoconstriction of cerebral arteries. Calabrese et al proposed the name of this syndrome in 2007. We report a patient who had lateralized RCVS possibly due to the vasodilatory effects of seizures that were occurring on the contralateral side.

CASE DESCRIPTION

A right-handed 19-year-old girl with severe developmental disability, who could converse, make lunch, and ambulate, presented with nausea, vomiting, confusion, word-finding difficulty, and fever (100.5°F); when found by her mother, she was in the fetal position in pain. She had not had significant headaches in the past. The patient then developed left-sided hemiplegia over the course of 7 days. This was followed by recurrent right arm extension with some facial twitching, later confirmed to be frequent seizures by prolonged electroencephalogram. Her last known seizures occurred at 6 months of age and were attributed to vaccinations. Her blood pressure was not elevated, with an initial blood pressure of 102/68 mm Hg.

Magnetic resonance imaging of the brain revealed scattered foci of diffusion restriction throughout the right hemisphere indicating multifocal small infarctions and right hemispheric cortical edema (Figure 1). Magnetic resonance angiography and subsequent computed tomography angiography revealed severe right supraclinoid internal carotid artery narrowing and mild right M1-middle cerebral artery narrowing (Figure 2). No stenosis was present within the left intracranial arterial vasculature. Transcranial Doppler showed elevated velocities only in the right middle cerebral artery territory. An electroencephalogram showed right brain slowing and left brain interictal and ictal rhythmic sharps with partial seizures (Figure 3).

Cerebrospinal fluid (CSF) collected prior to antibiotic initiation was negative for infections: the red blood cell count was 43 K/µL; white blood cell count, 9 K/µL; protein count,
18 mg/dL; and glucose, 67 mg/dL. CSF cultures did not show bacterial or fungal growth, and the IgG index was normal. The patient was treated aggressively with lorazepam, fosphenytoin, levetiracetam for seizures, and aspirin and verapamil for strokes. Conventional intracranial catheter angiography performed 4 days after computed tomography angiography revealed complete resolution of the stenoses. Initial empiric antibiotics with ceftriaxone and vancomycin were stopped at 5 days since CSF, urine, and blood cultures returned without any growths and the patient had some renal decompensation. It was thought that her fever was neurogenic, and a second CSF sample 11 days after the first also did not exhibit any growths (with red blood cell count of 7 K/µL; white blood cell count, 2 K/µL; proteins, 20 mg/dL; and glucose, 62 mg/dL).

The patient experienced steady clinical improvement prior to discharge to inpatient rehabilitation after being in the hospital for 17 days. After 2 weeks in rehabilitation, she developed a drug rash to an unclear source with eosinophilic leukocytosis and transaminitis leading to cessation of her phenytoin and amoxicillin/clavulanic acid. She ultimately stayed in a long-term acute care facility and went home with minimal left-sided weakness, slight difficulty with word finding, some visual field deficits, and labile emotions.

**DISCUSSION**

RCVS is characterized by sudden onset of severe headaches described as “thunderclap” with reversible, segmental, bilateral, diffuse, and multifocal constriction of cerebral arteries (1–3). There is a clear female predilection, with a mean age of onset around 42 years (4). The headaches are recurrent in more than 95% of patients and occur over the course of 1 to 3 weeks (4, 5). The headaches are described as bilateral, with posterior onset and subsequent generalized pain. They can last for minutes to days with an average of four attacks (4). A single attack is uncommon (3). Moderate headaches are seen between the more severe bouts, accompanied by nausea, vomiting, photophobia, and phonophobia (6). In 8% to 40% of patients, RCVS can also present with transient or persistent neurologic deficits, including encephalopathy, dysarthria, ataxia, focal numbness, weakness, seizures, and visual changes such as scotomas, blurry vision, hemianopsia, and cortical blindness (3, 4). Visual symptoms are the most commonly encountered. Seizures occur in up to 17% of RCVS cases (3).

Digital subtraction cerebral angiography reveals no abnormalities within the first week of symptom onset in 30% of cases (4). Subsequently, a “string and beads” or “sausage on a string” appearance develops that corresponds to generalized bilateral and diffuse segmental constriction and dilation of cerebral arteries (3, 5). One-third of patients can develop ischemic or hemorrhagic strokes (1). RCVS typically resolves spontaneously within 3 months.

Diagnostic criteria for RCVS have been proposed by Calabrese et al (7) and include 1) multifocal segmental cerebral artery vasoconstriction on direct or indirect cerebral angiography; 2) no evidence of aneurysmal subarachnoid hemorrhage; and 3) normal or near-normal CSF analysis (normal glucose, protein

**Figure 2.** (a) Focused three-dimensional rendering of the source data of the intracranial CT angiogram (frontal view) shows severe right supraclinoid internal carotid artery stenosis (medial arrow) and mild right M1 segment middle cerebral artery stenosis (lateral arrow). (b) Corresponding image from a digital subtraction angiogram obtained 4 days after the CT angiogram shows resolution of the referenced sites of intracranial vascular stenoses.

**Figure 3.** Electroencephalogram recording shows left brain onset partial seizure (15 sec/page, 10 mm/sec, 7 uV/mm).
<100 mg/dL, <15,000 white blood cells/μL); 4) severe, acute headaches, with or without additional neurologic signs or symptoms; and 5) reversibility of angiographic abnormalities within 12 weeks of onset.

RCVS may be primary (idiopathic) or secondary (60% to 80%) with multiple precipitants (5). The most common are vasoactive substance use and a postpartum state. The exact pathogenesis of RCVS is unknown, with “disturbance of cerebral vascular tone” being the most widely accepted hypothesis.

Primary angiitis of the central nervous system (PACNS) was recognized to be distinct from RCVS only in 1990 (3). Headaches tend to be more insidious in PACNS, which follows a more progressive-chronic course with a stepwise deterioration (3, 5). CSF is significant for a marked inflammatory profile and can also reveal oligoclonal bands. Brain magnetic resonance imaging may reveal deep infarcts and contrast enhancements of the vessel wall (3, 4). It is of some importance to accurately distinguish these two entities, since treatment for PACNS with corticosteroids can be harmful in RCVS. Conversely, RCVS stabilizes and improves more quickly (3). There is no specific proven therapy for RCVS.

A respiratory epithelial adenomatoid hamartoma (REAH) is a hamartoma arising from the nasal cavity, paranasal sinuses, or nasopharynx (1). REAH was first described in 1995 by Wenig and Heffner (2). Since then, at least 394 cases of REAH have been reported, with a 3:2 male-to-female ratio (3). REAH displays distinct histopathological features characterized by polyps with pseudoglandular proliferation lined by ciliated respiratory epithelium (4). The etiology of REAH is unknown and appears to be multifactorial (4). Most reports indicate that REAH occurs in the presence of sinonasal inflammation (1–3, 5, 6). Presenting signs and symptoms include nasal obstruction, nasal congestion, deviated septum, epistaxis, rhinorrhea, chronic sinusitis, facial pain, headache, and olfactory dysfunction (7, 8). Complete surgical resection is the preferred treatment (8). We present a case of bilateral REAH originating from the anterior olfactory clefts.

CASE DESCRIPTION

A 75-year-old man was referred to the otolaryngology department due to anosmia. He reported 10/10 loss of sense of smell that began in the early 1990s. He denied additional nasal symptoms. His medical history was significant for progressive dementia, coronary artery disease, and a cerebrovascular accident 3 years prior.

Diagnostic endoscopy revealed bilateral masses in both the right and left anterior olfactory clefts, with a larger right mass than left. Magnetic resonance imaging (MRI) of the skull base demonstrated heterogeneity of the mass with enhancement, findings not suggestive of simple nasal polyposis (Figure 1). The patient was taken to the operating room and underwent endoscopic resection of the lesion. Both lesions had lateralized the middle turbinate, allowing direct access and complete removal endoscopically without complications. The lesions appeared to be fibrous polyps on gross examination and were easily resected with Blakley forceps. Approximately 20 cc of blood loss occurred during the resection. Histologically, both right and left nasal contents revealed inflamed polypoid fragments of respiratory mucosa with features consistent with REAH (Figure 2). At 2- and 14-month follow-up, there was no recurrence of REAH bilaterally, as verified by diagnostic endoscopy, and our patient
patients with NP and a comorbidity of asthma have an increased risk of developing REAH (14). With our patient’s 20+ years of anosmia, it is unclear when REAH formed and if an inflammatory process was associated with its formation.

One of the most common presenting symptoms of REAH is hyposmia or anosmia (8). This is likely caused by local impingement or loss of olfactory nerves within the affected olfactory clefts. In one study, the prevalence of anosmia among participants diagnosed with REAH dropped from 72% to 44% with surgical resection (12). Our patient had no changes to his anosmia after surgery. His history of dementia and length of symptoms may have played an independent role in his anosmia and the lack of improvement in his olfaction despite adequate resection of the hamartomas. To date, there are no reported studies investigating the relationship between the duration of anosmia and postoperative olfactory outcomes in patients with REAH.

It is important to differentiate REAH from more aggressive tumors to avoid excessive surgical intervention. In one retrospective study of REAH surgical subjects, no difference was noted in outcomes between standard endoscopic sinus surgery and aggressive resection with subperiosteal dissection and drilling into the adjacent bone (8). Along with a computed tomography scan and MRI with contrast medium to evaluate the site and the extent and features of the lesion(s), some have recommended a preoperative biopsy in cases of a unilateral lesion or widening of the olfactory cleft (1–3, 8, 15). Appropriate caution should be taken when considering the differential of olfactory cleft masses to minimize surgical risks to patients. While there is insufficient evidence tracking the recurrence of REAH, available data have shown no benefit in preventing recurrence with more aggressive removal, including subperiosteal dissection (8). Standard endoscopic resection without subperiosteal involvement was performed to remove REAH from our patient, and there has been no evidence of recurrence on endoscopy in a 14-month postoperative period or by MRI in a 27-month period.

DISCUSSION

The histopathological features of REAH are dominated by a polypoid pseudoglandular proliferation (4). These characteristics include widely spaced, small- to medium-sized pseudoglands that invaginate directly into the submucosa and are separated by stroma tissue. The glands are round to oval and are composed of multilayered ciliated respiratory epithelium (3). These features were identified in the lesions resected from the bilateral olfactory clefts of our patient (Figure 2).

When REAH was first described in 1995, it was considered extremely rare and isolated (2). We now know that REAH is not as uncommon as originally thought and is often present with other inflammatory processes (3). In a case series, 73% of 45 patients with REAH had an additional associated pathological process, most commonly nasal polyps (NP) (9). Recent studies have shown that REAH was found in 35% to 47% of patients with NP who were treated surgically (10–12). Supporting the hypothesis of an inflammatory pathogenic mechanism, Gu et al identified significantly higher levels of T-helper cells (Th9) that secrete a proinflammatory cytokine IL-9 in REAH patients versus controls. They suggested that Th9 cells may play a significant role in the development of REAH (13). One prospective study suggested that those with a ≥10-year history of NP, patients requiring more than one NP-related surgery, and patients with NP and a comorbidity of asthma have an increased risk of developing REAH (14). With our patient’s 20+ years of anosmia, it is unclear when REAH formed and if an inflammatory process was associated with its formation.

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**Avocations**

A young lion in Tanzania. Photo copyright © Jed Rosenthal, MD. Dr. Rosenthal is a cardiologist in Dallas, Texas (e-mail: jedr2@sbcglobal.net).
Ambulatory extracorporeal membrane oxygenation with subclavian venoarterial cannulation to increase mobility and recovery in a patient awaiting cardiac transplantation

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Venoarterial extracorporeal membrane oxygenation (ECMO) can provide temporary cardiopulmonary support for patients in hemodynamic extremis or refractory heart failure until more durable therapies—such as cardiac transplantation or a left ventricular assist device—can be safely implemented. Conventional ECMO cannulation strategies commonly employ the femoral artery and vein, constraining the patients to the supine position for the duration of ECMO support. We have recently adopted a modified cannulation approach to promote patient mobility, rehabilitation, and faster recovery and to mitigate complications associated with femoral arterial cannulation, such as limb ischemia and compartment syndrome. This technique involves cannulation of the subclavian artery and vein. The current case report details our recent experience with this approach in a critically ill patient awaiting cardiac transplantation.

Extracorporeal membrane oxygenation (ECMO) is increasingly utilized in patients with refractory cardiopulmonary disease (1). For patients with refractory heart failure, venoarterial ECMO can provide temporary hemodynamic stabilization as a bridge to more durable therapies. In most instances, venoarterial ECMO is achieved via femoral cannulation, rendering patients supine for the entire duration of support and susceptible to limb ischemia associated with femoral arterial cannulation. We previously reported good outcomes with subclavian arterial cannulation to avoid these complications (2). We recently modified this strategy to concomitant arterial and venous subclavian cannulation to enable ambulation and to promote potentially faster recovery. Here we report a recent patient supported with ambulatory subclavian venoarterial ECMO who was successfully bridged to left ventricular assist device (LVAD) implantation and is currently awaiting cardiac transplantation.

**CASE REPORT**

A 59-year-old man with hypertension and sleep apnea was diagnosed with heart failure secondary to nonischemic cardiomyopathy. A recent echocardiogram revealed a left ventricular ejection fraction of 7% and moderate aortic valvular insufficiency. His heart failure symptoms progressed, and he presented to our institution with repeated episodes of ventricular fibrillation, requiring cardiopulmonary resuscitation and defibrillation shocks. Amiodarone infusion and inotropic support with milrinone and dobutamine were started. An intraaortic balloon pump was placed, and he was tentatively listed status 1A for cardiac transplantation. However, despite the level of support and continued escalation of inotropic agents, he failed to achieve adequate hemodynamics or normalizing indices of end-organ perfusion.

Consequently, we proceeded with urgent venoarterial ECMO support in an effort to stabilize him before deciding on advanced therapy. To provide the patient with more flexibility and mobility, we opted for subclavian venoarterial cannulation. The left side was chosen because of his right-handedness. The subclavian artery was exposed through a left infraclavicular incision along the level of the deltopectoral groove and was mobilized circumferentially. The brachial plexus was preserved. After heparin was administered, a side-biting Satinsky vascular clamp was applied to the subclavian artery, a 1-cm arteriotomy was created, and an 8-mm Gelsoft Plus graft (Sulzer Vascutek, Austin, TX) was sewn onto the artery in end-to-side fashion. The graft was tunneled subcutaneously down to the nipple level. A 21F arterial cannula was placed through the externalized graft and directed to within 1 cm of the anastomosis. The graft was secured to the cannula by tying umbilical tapes and to the skin by multiple silk sutures. The venous cannulation was achieved percutaneously under fluoroscopic guidance using the Seldinger technique. A 22F QuickDraw venous cannula (Edwards Lifesciences, Irvine, CA) was secured to the skin with multiple sutures after being tunneled subcutaneously, as with the arterial cannula (Figure).

The patient was extubated on day 1 after surgery, sat on a chair on day 2, and rode a stationary bicycle on day 4. His listing status remained the same, but no suitable donor was found for 9 days, during which he remained on ECMO. The 3.5 to
5.0 L/min flow was considered adequate with reversal of end-organ dysfunction and no evidence of metabolic acidosis. A more durable LVAD (HeartWare HVAD, Framingham, MA) was implanted with aortic valve replacement and concomitant ECMO decannulation. There was no evidence of wound complications, infections related to the exposed graft, or limb complications, and recovery was unremarkable. On day 14, the patient received an automatic implantable cardioverter defibrillator and was discharged home the next day without complications. He is still awaiting a donor heart.

**DISCUSSION**

ECMO has become an essential tool in the care of patients with severe cardiac and pulmonary dysfunction who are refractory to conventional management. The technique has become more reliable due to improvements in equipment and increased experience (3). The indications have been extended to more prolonged use in the intensive care unit, such as for bridge to transplant for both cardiac and lung transplantation and for support in cardiopulmonary replacement therapy in unstable patients (4, 5). ECMO support can be deployed with multiple techniques, including peripheral or central cannulation. Both methods of cannulation carry risks of bleeding, while peripheral cannulation carries an added risk of limb ischemia (2).

The most common route for peripheral cannulation in venoarterial ECMO involves the common femoral artery and vein (3). However, in addition to the risk of injury to the artery, blood flow to the heart and brain is mostly retrograde with direct cannulation of the femoral artery. Although we have adopted the former technique in our center, we shifted our practice toward subclavian venoarterial cannulation in order to reduce complications and to increase flow to the upper body. Potential risks of this new subclavian technique include cannula dislodgement during ambulation or physical therapy, subclavian vein thrombosis, arterial “overcirculation”/edema to the upper extremity, requirement of imaging techniques for cannula placement, and arterial or venous injury from cannulation.

Patients on venoarterial ECMO support have traditionally been considered too unstable for active physical therapy, are frequently heavily sedated, and occasionally are on neuromuscular blocking agents. However, the ability to ambulate while on venoarterial ECMO has been facilitated by advances in extracorporeal technology and cannulation techniques (6). Neuromuscular weakness and impairment in physical functioning are common sequelae of immobilization during critical illness. Active participation in physical and occupational therapy is not only considered safe and feasible, but is also the preferred approach to minimize debilitation in critically ill patients. Early rehabilitation is associated with improved rates of return to independent functioning, decreased rates of delirium, shorter durations of mechanical ventilation, and shorter length of stay in the intensive care unit and the hospital (7). Thus, subclavian venoarterial cannulation for ECMO may increase patient mobility and lead to quick recovery. Moreover, this methodology may enable longer durations of venoarterial ECMO support, potentially allowing patients to achieve multisystem recovery and a lower risk profile for undergoing cardiac transplantation or LVAD implantation.


Use of a MitraClip for severe mitral regurgitation in a cardiac transplant patient

Fayez S. Raza, MD, Paul A. Grayburn, MD, and James W. Choi, MD

Severe mitral regurgitation (MR) in patients after cardiac transplant has not been well studied. Traditionally, patients have undergone corrective surgery. We report a 64-year-old man who presented with new heart failure symptoms 6 months after cardiac transplantation. He was found to have severe MR and underwent successful implantation of a MitraClip® with reduction of his MR to mild as well as improvement in his symptoms. Six months later he was still doing well, and a repeat echocardiogram showed good results. We found two previously reported cases using the MitraClip to treat severe MR in adult cardiac transplant patients. The MitraClip is a viable treatment option for MR in cardiac transplant patients despite their distorted anatomy.

In nontransplant patients at prohibitive surgical risk, the MitraClip® (Abbott Vascular, Santa Clara, CA) provides a therapeutic treatment option for mitral regurgitation (MR). The MitraClip is a Food and Drug Administration–approved percutaneous mitral valve repair system for severe degenerative MR. Current trials are evaluating its role in functional regurgitation. The system utilizes a cobalt-chromium clip covered with a polypropylene fabric to grasp the mitral leaflets, thus reducing regurgitation by increasing leaflet coaptation. Insertion of the MitraClip is a challenging procedure and must be performed by a well-trained team under fluoroscopic and echocardiographic guidance.

Traditionally, severe mitral valve disease after transplantation has been addressed by a surgical approach (1–3). Unfortunately, many patients may be at high surgical risk for complications due to comorbidities, functional status, and need for repeat sternotomy. It has not been well studied how best to treat these high-risk patients and whether the MitraClip is a feasible and safe option in this population.

CASE PRESENTATION

A 64-year-old man with idiopathic dilated cardiomyopathy underwent cardiac transplantation for end-stage heart failure.

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failure. He had a prolonged postoperative course complicated by primary graft dysfunction, respiratory failure requiring tracheostomy, renal failure, and malnutrition. After an extended hospital and rehabilitation stay, he did make significant functional recovery on goal-directed medical therapy. Six months after transplantation, he developed symptoms concerning of heart failure. Acute cellular rejection was ruled out. A repeat echocardiogram showed mild to moderately depressed systolic function (stable posttransplant) and severe functional MR (vena contracta, 0.7 cm; proximal isovelocity surface area, 0.8 cm; effective regurgitant orifice area, 0.3 cm²; systemic blunting of pulmonary venous flow) due to a retracted posterior leaflet and failure to coapt adequately (Figure 1).

Given his medical comorbidities, poor functional status, and need for another sternotomy, he was deemed to be a high-risk surgical candidate. The decision was made for him to undergo treatment with a MitraClip. The procedure was performed using both fluoroscopy and 3-dimensional transesophageal guidance. The standard right femoral venous approach was used to gain access for the MitraClip apparatus. A transseptal puncture was performed to gain access into the left atrium from the right atrium. A single MitraClip was successfully placed across the A2-P2 leaflets of the mitral valve. Confirmation of correct placement was obtained via concurrent transesophageal echocardiography, with reduction of the MR from severe to mild (Figure 2). The patient was seen in the clinic 6 months after the procedure and was doing well, with improvement in his symptoms and functional status. A repeat echocardiogram showed sustained reduction of the MR with the MitraClip.

**DISCUSSION**

Our case highlights the potential role for the MitraClip device in treating severe MR in adult cardiac transplant patients who are at high risk for mitral valve surgery. As the MitraClip is a relatively novel device, there is limited data for its use in cardiac transplant recipients. Our review revealed two other reported cases in which the MitraClip device was used to treat MR in a cardiac transplant patient. Ferraro et al (4) reported a patient who presented almost 20 years posttransplantation with severe degenerative MR. He underwent successful placement of two MitraClips with reduction from severe to mild MR. Iorio et al (5) reported a patient who presented approximately 1 year posttransplantation with severe MR secondary to a prolapsed leaflet and failure of adequate coaptation. Their patient also had successful reduction of his MR after MitraClip placement. The MitraClip may be a feasible option for post–cardiac transplant patients with severe MR who are at high surgical risk.

Two causes in one patient for extremely low voltage on the electrocardiogram

William C. Roberts, MD, Melody Joy Sherwood, MD, and Paul A. Grayburn, MD

An 80-year-old woman is described with two different causes (pericardial effusion and cardiac amyloidosis) for low QRS voltage on the electrocardiogram. Total 12-lead QRS voltage (from the peak of the R wave to the nadir of either the Q or the S wave, whichever is deeper) was only 34 mm (10 mm standard in all leads), the lowest we have encountered among 331 previously reported patients with 10 different cardiac conditions.

Among the causes of extremely low voltage on the electrocardiogram are large pericardial effusions and cardiac amyloidosis. The occurrence of both conditions in the same patient can lead to extremely low voltage on the electrocardiogram. The occurrence of such a situation prompted this report.

CASE DESCRIPTION

An 80-year-old woman with dementia was hospitalized because of worsening confusion and lower leg edema. She was known to have systemic hypertension and diabetes mellitus. She was in no acute distress. Her blood pressure was 85/60 mm Hg. Her body mass index was 18 kg/m². No abdominal organs or subcutaneous lymph nodes were palpated. The electrocardiogram showed total 12-lead QRS voltage of 17 mm (standard = 20 mm; double standard) (Figure 1). An echocardiogram disclosed pericardial effusion, thickened right and left ventricular walls, and low (=20%) ejection fraction (Figure 2). Both ventricular cavities were of normal size.

DISCUSSION

Total 12-lead QRS voltage was introduced in 1982 as a means to predict the presence of left ventricular hypertrophy (1) (Figure 3). Subsequently, total 12-lead QRS voltage has been described in 10 different disease states involving 331 patients and compared in all to heart weight (2). It has been found to be a better predictor of left ventricular hypertrophy than any previous criteria.

The concept of low QRS voltage was described initially when only three electrocardiographic leads were available. The 12-lead

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Figure 1. Electrocardiogram in the patient described. The standard is 20 mm, rather than the usual 10 mm.
total QRS voltage has rarely been employed as an indicator of low QRS voltage. Among the 10 conditions in which total QRS voltage was measured and reported, those with the lowest voltage included cardiac amyloidosis, 58–199 mm (mean 104); cardiac adiposity, 73–210 mm (mean 120); and the carcinoid syndrome, 48–227 mm (mean 117). Thus, to have an electrocardiographic total 12-lead QRS voltage of only 34 mm, as in the present patient, is indeed unusual.

A limitation of the present report is the lack of anatomic confirmation of cardiac amyloidosis. The echocardiogram, however, is virtually diagnostic of extensive cardiac amyloidosis.


2. Roberts WC, Filardo G, Ko JM, Siegel RJ, Dollar AL, Ross EM, Shirani J. Comparison of total 12-lead QRS voltage in a variety of cardiac conditions and its usefulness in predicting increased cardiac mass. Am J Cardiol 2013;112(6):904–909.

Figure 2. Transthoracic echocardiographic views—(a) parasternal short-axis view, (b) short-axis parasagittal view, and (c) apical four-chamber view—showing a brightly echogenic myocardium, thickened right ventricular and left ventricular walls, thickened valve leaflets, dilated right atrium, dilated left atrium, and a pericardial effusion. (d) A “bulls-eye” map of peak systolic longitudinal strain showing the characteristic “cherry-on-top” pattern of myocardial amyloidosis with preserved strain at the apex (dark red center) and abnormal strain elsewhere (pink or blue).

Figure 3. Various QRS complexes showing how each was measured. Reproduced from Siegel and Roberts (1) with permission of the authors and the publisher.
Successful treatment of a cardiac resynchronization therapy nonresponder by identifying lead malpositioning

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This case describes some of the commonly overlooked device-related issues in patients who have reportedly failed to respond to cardiac resynchronization therapy (CRT). The case demonstrates voltage-dependent right ventricular capture instead of right atrial capture by a subtly malpositioned right atrial lead. CRT therapy failed to improve symptoms of heart failure and the diagnosis of “CRT nonresponder” was made. With a detailed fact-finding approach, the mechanism behind this nonresponse was identified, and the outcome of CRT was significantly improved with rectification of the problems.

Case Description

An 80-year-old woman with paroxysmal atrial fibrillation, left bundle branch block (QRS of 154 ms), and severe nonischemic cardiomyopathy (ejection fraction of 30%) underwent implantation of a CRT with a defibrillator for management of severe HF cardiomyopathy (ejection fraction of 30%) underwent implantation of a CRT with a defibrillator for management of severe HF symptoms despite optimal medical therapy. Three months later, she continued to have HF class III–IV symptoms. Device interrogation showed 74% biventricular pacing and 74% right atrial (RA) pacing with stable lead impedances since implant. Pacing thresholds of the right ventricular (RV) and left ventricular (LV) lead were 0.9 V at 0.5 ms and 0.75 V at 0.5 ms, respectively. During a detailed and step-by-step RA lead capture threshold testing with continuous 12-lead electrocardiogram monitoring, RV capture instead of RA capture starting at 5 V at 0.8 ms down to 1.75 V at 0.8 ms was discovered. Interestingly, at or lower than 1.5 V at 0.8 ms, RV capture by pacing through RA lead was switched to RA capture only, with an RA capture threshold of 0.75 V at 0.8 ms (Figures 1 and 2). Malposition of the RA lead was suspected.

After chest radiography was found to be inconclusive, a computed tomography scan demonstrated that the RA lead tip was near the atrioventricular groove abutting the base of the RV outflow tract (Figure 3). As such, the RA lead pacing at pulse amplitude ≥1.75 V was indeed capturing the RV, and true biventricular pacing using the RV and LV lead was not happening, as the RV had already been inappropriately captured by RA lead pacing. In other words, DDD pacing (atrial-paced biventricular paced rhythm) with RA pacing amplitude at or above 1.75 V was resulting in right ventricular VVI pacing only, as there was no RA capture (loss of atrial kick), RV and LV were in the refractory period, and pacing through the RV and LV leads was not capturing (effectively 0% biventricular pacing). Pacing outputs were therefore reprogrammed (RA 1 V at 0.8 ms, RV 2 V at 0.5 ms, and LV 1 V at 0.5 ms). At follow-up, the patient reported a significant improvement of HF symptoms (from HF class III–IV to class II), and device interrogation revealed 99% appropriate atrial-paced and biventricular-paced rhythm via RV and LV leads.

Discussion

We described this case to highlight the importance of performing detailed troubleshooting of various components of a CRT system when managing HF patients. Demonstration of effective and optimal biventricular pacing is critical in patients undergoing CRT. Current consensus recommends that atrial fibrillation and/or ventricular arrhythmias should be controlled pharmacologically or with invasive procedures to allow for over 90% of biventricular pacing in order to improve HF symptoms. In this case, placement of the RA lead tip on the atrioventricular groove was the cause of the loss of RA capture and in fact inappropriate RV capture with higher pulse amplitude. This could have potentially been avoided at the time of implant by more careful fluoroscopic imaging in different views and more careful attention to the morphology of evoked response to the pacing in a given chamber. A detailed device interrogation incorporated with simultaneous detailed electrocardiogram analysis was the only way to troubleshoot and eventually rectify the problem. A computed tomography scan further confirmed the diagnosis. The discovery that the higher output pacing via the RA lead was capturing the RV rather than the RA resulting in no
RA capture and loss of atrial kick along with 0% biventricular pacing explained why this patient was a CRT nonresponder.

Previous reports have discussed two similar concepts: “cross-stimulation,” described as capture of the RV by high-output RA pacing due to malposition of the RA lead in the anterior tricuspid annulus (1), and “intermittent capture” of the RV outflow tract from a malpositioned RA lead in the anteromedial RA (2). The RA appendage lies adjacent to the RV outflow tract, making it challenging at times to evaluate the location of the tip of the pacing lead on fluoroscopy or chest radiography. A noncontrast computed tomography scan might be beneficial in these scenarios, highlighting the importance of lead position verification prior to a diagnosis of CRT nonresponder.

Care of HF patients undergoing device therapy should be an integrated approach involving HF and electrophysiology specialists during routine follow-up. Periodic device interrogations, electrocardiogram, and multimodality imaging should be used in these patients prior to premature diagnosis of CRT nonresponse. A more careful review of fluoroscopic images in different views and careful attention to the evoked response to pacing in a given chamber are the key elements in reducing the rate of CRT nonresponse.

A 56-year-old woman had a history of acute rheumatic fever with polyarthritis at age 6 years. She had been seen intermittently as an outpatient at our hospital over the past 6 years with systemic arterial hypertension, obesity, adult-onset diabetes mellitus, and peptic ulcer disease. All of her electrocardiograms over that period showed left atrial enlargement, and many had large QRS voltage consistent with left ventricular enlargement. She was never told of rheumatic heart disease.

On the day of admission, she came to the emergency department with the new onset of palpitations, diaphoresis, and dyspnea. An electrocardiogram showed atrial flutter/fibrillation with an irregular ventricular response at 156 beats/minute, Ashman's phenomenon, and nonspecific ST-T changes (Figure). The couplet of wide QRSs with right bundle branch block configurations just past the middle of the tracing could have been a couplet of left ventricular premature complexes, but was not followed by a pause and was more likely an example of Ashman's phenomenon. The first wide QRS followed a short R-R interval that followed a longer R-R interval. The longer interval caused the refractory period after the last narrow QRS to lengthen, and when the next impulse from the atria entered the atrioventricular conduction system early, it was blocked

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in the right bundle branch, the part of the atrioventricular conduction system with the longest refractory period. The distal part of the right bundle branch was depolarized late, probably by transseptal conduction, and thus was refractory when the next impulse arrived. Even longer runs of aberrant ventricular conduction due to persistent functional refractoriness of the right bundle branch have been misdiagnosed as ventricular tachycardia, an error recognized by Ashman and his colleagues (1).

An hour after she arrived in the emergency department, the patient spontaneously reverted to sinus rhythm. With her lying on her left side, a soft opening snap and a low-pitched diastolic murmur of mitral stenosis were heard, as well as a soft murmur of mitral regurgitation. On chest radiograph, the pulmonary arteries and the left atrial appendage were large and produced a straight left heart border.

A transthoracic echo-Doppler study demonstrated a dilated left atrium with an anteroposterior diameter of 5.6 cm (reference, 1.9–4.0). The other chamber sizes were normal. The thicknesses of the ventricular septum and left ventricular posterior wall (1.2 cm) were just above the upper limit of normal. The mitral valvular leaflets were thick, calcified, and noncompliant. The peak diastolic pressure gradient across the mitral valve was 20 mm Hg with a mean gradient of 9 mm Hg. The mitral valvular orifice area was 0.8 cm² both by measurement of the two-dimensional image and by the pressure halftime. Left and right ventricular systolic function were normal. Mild mitral and tricuspid regurgitation were noted, and pulmonary arterial systolic pressure was 60 mm Hg (reference, 15–30). Cardiac catheterization confirmed the echocardiographic findings, and coronary arteriography was normal. Mitral valve replacement with a 33 mm St. Jude mechanical prosthesis and the postoperative course were uneventful.

Cardiac rehabilitation for a skydiver after aortic valve replacement for pure aortic regurgitation and resection of the ascending aorta complicated by active infective endocarditis and heart block requiring a pacemaker

Tonja R. Solomon, BSN, RN-BC, Sandra DeJong, BSN, RN-BC, Tim Bilbrey, MBA, Pasquale Carbone, MS, Mark Campbell, BSc, MSc, Robert D. Parker, PhD, Alessandra Lira, Diogo Amarante, MD, Jeffrey M. Schussler, MD, and Jenny Adams, PhD

A professional skydiver underwent aortic valve and ascending aorta replacement complicated by infective endocarditis with root abscess and pacemaker implantation. He then enrolled in the Baylor Heart and Vascular Hospital cardiac rehabilitation (CR) program as part of its specificity of testing and exercise training facility. He performed specific skydiving cardiovascular and muscular strength tests at the beginning and the end of the CR program. His pacemaker was interrogated to ascertain any arrhythmias or lead displacement over the course of the CR program. Daily exercise training was customized to match the physical demands of skydiving, including two sessions at iFLY Dallas. Upon completion of the daily exercise sessions, the patient performed a simulated free-fall drop test. He then performed a true jump at Dallas Skydive Center and subsequently traveled to Arizona for a skydiving competition, where he performed 35 true jumps with no adverse events or symptoms. This case illustrates how CR, tailored to a patient’s specific needs, can aid in the return to rigorous activity.

CASE REPORT

A professional skydiver underwent aortic valve surgery, complicated by infective endocarditis with root abscess. He chose the Baylor Hamilton Heart and Vascular Hospital cardiac rehabilitation (CR) program because of its specificity of testing and exercise training facility. His particular goal was to participate in an Arizona skydiving competition in 1.5 months. This case report details the specific testing, exercise training, and pacemaker device interrogation that he underwent during CR.

The patient, a 39-year-old professional skydiver who had logged 2500 jumps, presented with severe aortic regurgitation and left ventricular dilation as a result of a bicuspid aortic valve. He underwent valve replacement and implantation of an aortic tube graft. The surgery was complicated by subsequent infective endocarditis and ascending aortic abscess, and he underwent further surgery on an emergency basis. A dual-chamber permanent pacemaker was implanted because of frequent manifestations of symptomatic bradycardia with periods of advanced atioventricular block. The pacemaker was placed in the left mid chest wall so the patient would not suffer pressure generated by the chute-pack harness. The patient spent 74 days in the hospital.

During the recovery period and treatment of the endocarditis, the patient had venous thrombosis of the upper limbs and left jugular vein, requiring continuous use of anticoagulant therapy. He moved to a CR program in Rio de Janeiro, Brazil, during which he was limited in recovery by periods of atrioventricular block and bradycardia during exercise. The amiodarone and bisoprolol were suspended to promote improvement in cardiac performance and exercise tolerance. An echocardiogram showed good ventricular systolic function, and the aortic valve prosthesis was in good working condition. Due to his prolonged hospitalization, the patient was very weak and debilitated. The patient searched on the Internet for a facility that would provide specificity of testing and exercise training and subsequently enrolled in the Baylor Hamilton Heart and Vascular CR program in Dallas, Texas.

Upon entry to CR, the patient’s body mass index was 26.5 kg/m², and his waist circumference was 36.5 inches; medications included both the rivaroxaban and losartan. Specific skydiving cardiovascular and muscular strength tests were performed at the beginning and the end of the CR program. The cardiovascular tests were performed on a treadmill while the patient wore a 20-pound chute-pack harness, helmet, and a calibrated desktop metabolic system (Fitmate MED, Cosmed USA Inc., Chicago, IL) (Figure 1a) that captured his oxygen consumption data. Protocols included 2-minute stages at speeds of 3.3 to 4.2 mph with changes in grade from 0% to 25%. The indications for terminating the test were those designated by the American College of Sports Medicine (1). The muscular strength tests (line gripping, line pulling, and abdominal core) were performed using a static force gauge that was attached to a multidimensional strength assessment system (IsoTrack Pro, JTECH Medical, Midvale, UT) (Figure 1b).

The patient attended 25 CR exercise sessions, 3 times per week for 8 weeks. Exercise sessions were 75 minutes long and

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customized to simulate the sport of skydiving (Figure 1c). The patient's blood pressure was measured before and after exercise. In keeping with the standard protocol of our CR program, we used telemetry (TeleRehab VersaCare, ScottCare Corp., Cleveland, OH) to monitor the patient's electrocardiogram. The patient's pacemaker was evaluated 6 times over the course of CR by an electrophysiology nurse specialist. These device interrogations were done using the manufacturer's programmer (Biotronik PSW 1307.U, Biotronik, Inc., Lake Oswego, OR) to retrieve data and analyze the device settings. Each device interrogation consisted of a lead impedance test, an electrogram amplitude or sensing test, a capture threshold test, and retrieval of any recorded arrhythmias. The parameter criteria, according to the American College of Cardiology and the American Heart Association, were as follows: 1) the sensitivity threshold was 2.4 mV in the atrium (P waves) and 4.8 mV in the ventricle (R waves); 2) for pacing threshold, the loss of capture was 0.06 V at 0.4 ms in the atrium and 5.3 V at 1.0 ms in the ventricle; and 3) atrial lead impedance values were approximately 290 Ω and ventricular lead impedance was 312 Ω. The electrophysiology nurse specialist reviewed each transmission for proper functioning of the device and for the presence of arrhythmias.

CR staff (registered nurses and exercise physiologists) provided telemetry monitoring, testing, and exercise training. The testing and exercise training were symptom regulated, and as such were monitored for the peak rate-pressure product threshold (>36,000) (2), angina pectoris, dizziness, pain, dyspnea, lead displacement, and arrhythmias. Peak heart rate and blood pressure measurements were successfully recorded (18 out of 25 sessions). During the sessions, the patient’s heart rate, blood pressure, and rating of perceived exertion remained within acceptable ranges (means, 153 beats/min, 160/73 mm Hg, and 7, respectively). His mean peak rate-pressure product value (24,624) was consistent with the 36,000 threshold. The patient achieved 9.65 metabolic equivalents (METS, defined as the energy cost of exercise, where 1 MET = 3.5 mL O2 per kg of body weight per minute) on the post-CR program metabolic stress test. He also demonstrated gains in muscular strength (mean change = 22.5%) on the post-CR program static force gauge tests. Physiological data obtained during these tests are shown in the Table. Over the course of the exercise sessions, various arrhythmias were noted: occasional preventricular contractions, couplets and triplets, and one 4-beat run of preventricular contractions; all were deemed clinically insignificant by the CR staff. The patient had no adverse events or symptoms that required the discontinuation of any exercise session.

The patient attended iFLY Dallas during exercise sessions 10 and 14, where he performed skydiving maneuvers including the belly-fly (Figure 2a), sit-fly, and head-up. There were no adverse events or symptoms during the performance of these maneuvers.

To simulate the force of the chute-pack harness on his torso and, thus, the pacemaker leads, the patient reported to CR on exercise session 23 to perform a simulated free-fall drop test (Figure 2b). Before the test began, an electrophysiology nurse specialist performed a device interrogation in which appropriate lead placement was confirmed. The patient and CR staff then

<table>
<thead>
<tr>
<th>Category</th>
<th>Test</th>
<th>Pre</th>
<th>Post</th>
<th>Change</th>
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<tbody>
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<td>62.9</td>
<td>86.4</td>
<td>4%</td>
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<td></td>
<td>Right maximum grip</td>
<td>93.2</td>
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<td>Left sustained grip</td>
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<td>82.1</td>
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<tr>
<td></td>
<td>Right sustained grip</td>
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<td>54</td>
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<tr>
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<td>139</td>
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<td></td>
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<td>41</td>
<td>21%</td>
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<td>Rotate left</td>
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<td>36</td>
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</tr>
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<td>Skydiving cardiovascular</td>
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<td>33.8</td>
<td>2%</td>
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<tr>
<td></td>
<td>Metabolic equivalents</td>
<td>9.42</td>
<td>9.65</td>
<td>2%</td>
</tr>
</tbody>
</table>
walked to the nearby fitness center where he put on his chute-pack harness. Two sets of 5 carabiners were linked together and attached to handles on an 8-foot squat rack platform. The bottom carabiners on each side were attached to each side of the top of the patient’s chute-pack harness. The patient was asked to hold the handles on the squat rack while two CR staff members pushed his legs and body horizontally until he was parallel to the floor. The patient was asked to release the handles while the CR staff simultaneously let go of his legs. Before being stopped by the carabiners, this maneuver resulted in a 0.35 second free-fall drop at a speed of 11.3 feet per second and was repeated five consecutive times. Immediately following the test, the patient returned to CR, where the electrophysiology nurse specialist performed a device interrogation and confirmed that no change in lead status had occurred during the simulated free-fall drop test.

The patient was released to perform one true jump at the Dallas Skydive Center (Figure 2c). He subsequently traveled to Arizona 10 days later for a skydiving competition, during which he successfully jumped 35 times. He then returned to the Baylor CR facility where a final device interrogation was performed. One arrhythmia was noted: a single 6-beat run of nonsustained supraventricular tachycardia that was deemed clinically insignificant by the supervising electrophysiology nurse specialist. No change in lead status had occurred during the jumps.

DISCUSSION

The sport of skydiving requires specific cardiovascular endurance and muscular strength. A skydiver “free falls” after he leaves the aircraft, reaching speeds of 100 miles per hour in about 15 seconds. After the lines are pulled and the parachute opens, the force on the skydiver is approximately 4 times the force of gravity (4 “g’s”) (3). Patients who have endured pacemaker implementation may be precluded from skydiving due to the risk of arrhythmias and the potential for pacemaker lead displacement. On the simulated free-fall drop test, the patient endured five consecutive free-fall stop forces, calculated to be 175% of the “g” force one endures during an actual parachute jump. From device interrogation reports obtained over the course of the CR program, no recurrent sustained arrhythmias or lead displacement had occurred. Approximately 17 months after completion of CR, the patient had performed 800 true skydiving jumps without any adverse events, symptoms, or lead displacement.

Acknowledgments

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Baylor Scott & White Health news

■ Baylor Scott & White Health opening Austin-area primary care clinics, offering app-based care delivery downtown

In January 2017, Baylor Scott & White Health announced new clinics in downtown Austin and in Austin off of North Burnet Road; in November 2016, a clinic was also opened in Southwest Austin.

Baylor Scott & White Clinic—Austin Downtown will introduce a series of tech-driven initiatives never before offered at Baylor Scott & White. Enhancements include an innovative patient check-in via tablet, interactive room displays to track health progress, Bluetooth wireless technology to transfer vitals as they are taken, text appointment reminders, and more. Remote services include allowing patients the ability to begin the check-in process prior to arrival, to consult remotely with nurse staff, and to utilize Pager—an interactive, on-demand health care app for use on Apple or Android phones and tablets.

“Each patient has the power to control their own health path; we’re simply a guide along the way,” said Nick Reddy, chief digital officer, Baylor Scott & White. “Typically in a doctor visit, you don’t have direct visibility to your health records at your appointment. Now, with the exam room display we are piloting at the downtown clinic, patients will be able to see trends and track progress over time. At this clinic, patients will have a unique opportunity to see first-hand what we might eventually roll out to more clinics across the state. It will serve as our testing ground for new, tech-driven processes that will aim to improve both the patient and caregiver experience.”

■ New family medicine and internal medicine residency programs to begin at Baylor Scott & White–Round Rock

A dozen new internal medicine and family medicine residents will join the team at Baylor Scott & White Medical Center–Round Rock and three of its local clinics in July 2017. These residents will work under the supervision of Baylor Scott & White physicians, with the internal medicine program directed by Suneel Vallabhaneni, MD, and the family practice program directed by Patricia Lopez-Gutierrez, MD. These medical school graduates will help meet the primary care needs of the community and ultimately may help alleviate the shortage of primary care physicians in Central Texas should they choose to stay after their training.

A recent Travis County community health needs assessment identified a lack of community-based and preventive care services, as well as a shortage of providers and safety net clinics. A continuous increase in local Baylor Scott & White patient volume and the success of graduate medical education programs in Temple further supported the creation of these two residency programs. Dr. Vallabhaneni anticipates that 30% to 35% of the residents will practice locally.

Graduate medical education at Baylor Scott & White’s Central Texas division is affiliated with Texas A&M Health Science Center College of Medicine and has a longstanding history of success, with 21 residency programs and 24 fellowship programs. It is one of the largest GME programs in the country.

■ Baylor Scott & White Health, United Way of Metropolitan Dallas, and City of Dallas join efforts to combat diabetes

A community-based pilot program offered at three Dallas recreation centers promotes healthy behaviors among those who may be at risk for diabetes and other chronic illnesses. Baylor Scott & White Health, United Way of Metropolitan Dallas, and the City of Dallas Park and Recreation Department are collaborating on the Healthy Cities initiative. The 10-week program led by community health workers includes ongoing follow up with participants.

Healthy Cities, provided at no charge, is offered at the Anita N. Martinez Recreation Center, Cummings Recreation Center, and Samurai-Grand Recreation Center. The program builds on the accomplishments of the Baylor Scott & White Health and Wellness Center at Juanita J. Craft Recreation Center, which opened in 2010 and has seen success with diabetes and healthy behaviors education for southern Dallas residents.

The program’s first 6 weeks teach participants about making healthy lifestyle choices. The remaining 4 weeks focus on the cooking and nutrition aspects of healthy living. Additional highlights of the program include on-site farm stands with fresh produce (open to the public); collaboration with the City of Dallas Park and Recreation Department to offer recreation and physical activity programs; and text reminders to participants with healthy lifestyle tips, tools, and resources.

Following the completion of the current programs, new 10-week programs will launch quarterly at each of the three locations. The program will be delivered in English or Spanish based on the needs of the community and audience.

■ Baylor Scott & White Health increasing health and wellness options with new medical center in Pflugerville

Baylor Scott & White Health leaders joined Pflugerville city officials on February 8, 2017, to celebrate the start of construction on a new medical center set to open in 2018. In addition

UPCOMING CME PROGRAMS

The A. Webb Roberts Center for Continuing Education of Baylor Scott & White Health is offering the following programs:

- **Complex Care: Treatment Trends and Improved Outcomes**, April 8, 2017, at Baylor Sammons Cancer Center, Dallas, Texas
- **Management of IBD—State of the Art**, April 22, 2017, at Baylor University Medical Center, Dallas, Texas
- **Family Medicine Review**, April 12–15, 2017, at Doubletree Hotel, Austin, Texas
- **Everett R. Veirs Lecture and Ophthalmology Conference**, May 19, 2017, at Schoepf’s Bar-B-Que in Belton, Texas

For more information, visit http://cmebaylor.org/conferences.
to offering the quality medical care available at centers throughout the health system, the medical center in Pflugerville will have a greater focus on activities and programs designed to highlight healthy living habits.

"After more than a decade serving this community, we are renewing our commitment and expanding our services in Pflugerville," said Jay Fox, president, Baylor Scott & White Austin/Round Rock Region. "We are always looking for ways to advance our mission of creating a healthier population in Texas by serving more people and communities. We take a team approach to caring for every patient so they get the highest quality care possible."

The new medical center is designed to grow as the population of Pflugerville continues to increase. It will include a hospital and an integrated multispecialty medical clinic, a unique model of care delivery that allows for greater coordination among hospital and clinic medical team members where health care providers can work on the same patients in tandem. Coupled with an electronic medical record used across the care continuum, this model helps improve the patient experience and prevent unnecessary medical tests, while aiming to reduce the amount of time a patient spends in the hospital.

Dallas colorectal surgeon’s research named in 2016 top clinical cancer advances

One of 2016’s major achievements in clinical cancer research and care was a study led by James Fleshman, MD, chief of surgery at Baylor University Medical Center, according to the American Society of Clinical Oncology. Dr. Fleshman’s research was selected for inclusion in Clinical Cancer Advances 2017, the society’s annual review of progress against cancer and emerging trends in the field. The study, originally published in JAMA, found that laparoscopic surgery for stage II and stage III rectal cancer patients may not be a superior option to open surgery.

“I’m honored that our work was considered among the major advances in cancer research last year,” Dr. Fleshman said. “We’re pleased to contribute to ongoing trials that will help give cancer patients the best possible outcome and chance for survival.”

**RECENT GRANTS**

- **Baylor core clinical center for the Cardiothoracic Surgical Network**
  Principal investigator: Michael Mack, MD
  Sponsor: National Institutes of Health
  Funding: $200,000
  Award period: 9/30/2016–9/29/2017

- **North Texas Hepatitis B Consortium: hepatitis B clinical research network**
  Principal investigator: Robert Perillo, MD
  Sponsor: University of Texas Southwestern Medical Center/National Institutes of Health
  Funding: $119,345
  Award period: 6/1/2016–5/31/2017

- **Decision making and clinical work of test result follow-up in health IT setting**
  Principal investigator: Samuel Forjuoh, MD
  Sponsor: Baylor College of Medicine/National Institutes of Health
  Funding: $87,655
  Award period: 8/1/2016–7/31/2017

- **NanoString nCounter research project**
  Principal investigator: Faryin Meng, MD
  Sponsor: Temple Health and Bioscience Economic Development District
  Funding: $25,000
  Award period: 9/29/2016–8/31/2017

- **Surveillance of the RADARS system by poison control centers**
  Principal investigator: David Baker, PharmD
  Sponsor: Denver Health & Hospital Authority
  Funding: $773,670
  Award period: 9/30/2016–9/29/2017

- **An evaluation of the efficacy of peer support training and supervision for Texas firefighters**
  Principal investigator: Suzy Gulliver, PhD
  Sponsor: Texas A&M University Health Science Center/Hogg Foundation for Mental Health
  Funding: $7,778
  Award period: 7/1/2016–6/30/2017

- **AUGS quality improvement and outcomes research network participation agreement: Quality in anti-incontinence surgery and quality in prolapse surgery**
  Principal investigator: Wilma Larsen, MD
  Sponsor: American Urogynecologic Society
  Funding: $4,350
  Award period: 9/21/2016–9/20/2019

- **Molecular recognition of environmentally relevant anions with synthetic clefts**
  Principal investigator: Mohammad Uddin, PhD
  Sponsor: Jackson State University/National Institutes of Health
  Funding: $3,000
  Award period: 4/1/2016–3/31/2017

- **Comparison of sleep apnea assessment strategies to maximize TBI rehabilitation participation and outcome**
  Principal investigator: Marie Dahdah, PhD
  Sponsor: Tampa VA Research & Education Foundation/PCORI
  Funding: $294,842
  Award period: 11/1/2016–10/31/2019

- **Glycemia reduction approaches in diabetes: a comparative effectiveness study**
  Principal investigator: Priscilla Hollander, MD
  Sponsor: George Washington University/National Institutes of Health
  Funding: $253,710
  Award period: 8/1/2016–7/31/2017

- **Coordinating center for research and training to promote the health of people with developmental and other disabilities**
  Principal investigator: Katherine Froehlich-Grobe, PhD
  Sponsor: University of South Carolina/National Institutes of Health
  Funding: $200,000
  Award period: 9/30/2016–9/29/2017

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PHILANTHROPY NOTES

■ Lee Jarmon Alzheimer’s Pro Am Golf Tournament benefits Baylor AT&T Memory Center
This fall, Rowland K. Robinson, president of Baylor Health Care System Foundation, gratefully received a check for $145,000 in support of the Baylor AT&T Memory Center. The check represented proceeds from the Lee Jarmon Alzheimer’s Pro Am Golf Tournament at Gleneagles Country Club, chaired by Steve Folsom and Matt Bryan.

Baylor Scott & White Health serves a population of more than 9.3 million Texans in North and Central Texas. As this population ages, health care providers are challenged to provide medical support for patients afflicted with dementia and Alzheimer’s disease.

In 2013, philanthropic support launched the Baylor AT&T Memory Center, an innovative model of care that provides important, enhanced capabilities and resources to diagnose, treat, and provide social, emotional, and spiritual support for patients afflicted with Alzheimer’s and dementia and their families.

■ Gifts from Meadows Foundation and Colonnetta family have tails wagging
On the anniversary of its first year in operation, the Canine Companions for Independence® Baylor Scott & White Health–Kinkeade Campus received two generous gifts that will help pair trained assistance dogs with people with disabilities. Joe and Kimberly Colonnetta recently gave $100,000, and the Meadows Foundation, which has a special interest in both companion animals and programs serving the disabled, gave $150,000 in support of Canine Companions. After attending a Baylor Health Care System Foundation board meeting where they learned about the program, Kimberly Colonnetta and her husband were inspired to provide support. The Colonnettas also decided to train a puppy for the program, a yellow Labrador named Atlas.

Baylor Scott & White Health affiliated with Canine Companions in 2014. The 9-acre campus opened in November 2015 and includes dormitory rooms, kennels, indoor and outdoor training areas, and multipurpose spaces. It also has areas for grooming, food preparation, and a veterinary clinic and lab. The average cost to train and provide follow-up services for one assistance dog is more than $50,000. The dogs are provided free of charge to people with physical or developmental disabilities, so this philanthropic support is important.

Each participant completes a 2-week course at the campus—designed to match the person and the dog and to prepare them to work together while becoming responsible for the care, feeding, housing, and medical needs of the dog. We continue to raise funds to develop and support the Kinkeade Campus.

For information on how you can support these or other initiatives at Baylor Scott & White Health—North Texas, please contact Baylor Health Care System Foundation at 214.820.3136.

Reader Comments

Tribute to Dr. John Hyland

The article on Dr. Hyland (1) is a well-deserved tribute to a highly respected teacher and a very successful administrator from one of his most accomplished and grateful disciples (the latter kind is in short supply!). If I had been offered the opportunity to add my secondary contribution to Rolando Solís’s piece, I would have given him credit for resurrecting the Heart Transplantation Program after the disastrous losses in 1991. Under his guidance and firm stewardship, we performed then 30 consecutive heart transplants without a single loss, at the same time embarking on lung transplantation (51 transplants), which led to the latter program’s accreditation. I cannot even now thank him enough, so I am limiting myself to wishing him longevity and very good health.

—Peter A. Alivizatos, MD
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For more than four decades, I have been jotting items in a little black notebook. I decided to leaf through the notebook and share some thoughts, in the following categories, in hopes that they might be of help for young physicians.

PREVENTIVE CARDIOLOGY

For over 1400 years, medical students were taught that the liver was the center of the blood circulation and that blood was formed in this organ from ingested food. It wasn’t until the 1600s, Shakespeare’s era, that a British physician, William Harvey, disproved the teachings of Greco-Roman physician Galen. Harvey stated, after careful anatomical studies:

The heart... is the beginning of life, the sun of the microcosm... the heart of the world; for it is the heart by whose virtue and pulse the blood is moved perfected, made apt to nourish, and is preserved from corruption and coagulation. . . .

[It] nourishes, cherishes, quickens the whole body, and is indeed the foundation of life, the source of all action (1).

No wonder this organ has captivated the imagination of writers and poets and has been my focus of medical interest for the past 45 years.

Antoine de Saint Exupéry, in The Little Prince, wrote that “it is only with the heart that one can see rightly. What is essential is invisible to the eye.” And Zelda Fitzgerald added, “Nobody has ever measured, even poets, how much the heart can hold.” Blaise Pascal stated, “The heart has its reasons which reason knows nothing of.”

Flash forward from England in the 1600s to 1912. A Chicago cardiologist, James B. Herrick, who was 1 year behind my grandfather at Rush Medical School, presented a paper before the American Medical Association (2). He stated, based on pathology studies, that heart attacks were caused by a blood clot that occluded an atherosclerotic coronary artery. His findings fell on deaf ears. It wasn’t until 70-plus years later that cardiologists began to recognize and understand this, and that clot-dissolving medications and balloon angioplasty with stents became commonplace therapies.

The problem with coronary disease, though, is that the very first symptom is a fatal heart attack in up to 25% of such cases. Because of this, the focus of my interest has been the prevention and early recognition of this disease. Thomas Edison, a bright inventor, once predicted that “the doctor of the future will give no medicine, but will interest his patients in the care of the human frame, in diet, and in the care and prevention of disease.” And way back—325 bc—Herophilus, physician to Alexander the Great, stated: “When health is absent, wisdom cannot reveal itself, art cannot become manifest, strength cannot fight, wealth becomes useless, and intelligence cannot be applied.”

What stimulated me to become a preventive cardiologist was a lecture and book by Northwestern professor Jeremiah Stamler, entitled Your Heart Has 9 Lives (3). In it, Dr. Stamler identified the major coronary risk factors that can predispose one to early cardiac disease and premature death. Looking back at his book 52 years later, the coronary risk factors still apply, especially cigarette smoking, sedentary living, hypertension, obesity, high blood fats and sugar, and family history.

VOCATION

Vocation was described by Peter Gomes as “the place where your great joy meets the world’s great need.” In choosing your future life work, I hope you have tried to blend in your avocation with your vocation. I like what musician Les Paul wrote at age 92:

Work is a privilege, the more so the older you get. It’s a privilege to be able to do what you love to do and be good at it. My hobby is my work, and my work is my hobby. That’s the secret. There is no distinction.

Eric Greitens is a former Rhodes scholar and Navy Seal, now the governor of Missouri. His thoughts on one’s vocation mirror Les Paul’s:

A master in the art of living draws no sharp distinction between his work and his play; his labor and his leisure; his mind and his body; his education and his recreation. He hardly knows which is which. He simply pursues his vision of excellence through whatever he is doing, and leaves others to determine...
whether he is working or playing. To himself, he always appears to be doing both (4).

That has been my own experience, reflecting upon it at my present age of 76. I loved what Leila Denmark, MD, age 100, replied when I visited her office and asked how much longer she was going to work. “This isn’t work. Work is something you have to do. I don’t have to do this” (5).

I enjoyed sports as a youth and didn’t seem to have much of an interest in or aptitude for science. Perhaps a future in coaching would have seemed logical, and indeed I have great respect for the impact coaches can have on young lives. I was intrigued, however, by the impact my physician-father (Figure 1) had in our community. He was a man so highly respected that one would seek his thoughts and advice on various problems. I decided to take a leap of faith, enduring the likes of long organic chemistry labs on beautiful afternoons at Duke University to follow in his footsteps.

Along the way, I’ve tried to merge what Paul and Greitens espoused to my profession. For 41 years, I was a team physician for the Atlanta Braves. For 36 years, I have been the team cardiologist for Georgia Tech athletes, screening each freshman for any potential heart problems. The only downside of the latter job is that each year the athletes are always age 18, while I am always another year older. We have been fortunate in such screening in conditions, the coming to grips with the intimate conditions of their lives, when they were being born, when they were dying, watching them die, watching them get well when they were ill, has always absorbed me (6).

Figure 1. My medical school graduation present from my dad, a used 1965 red Mustang convertible which I wish I still had.

Figure out what you are good at, what you really enjoy doing, and pursue it. I hope that when you reach my age you can look back with the same satisfaction I feel.

BOOKS AND LIFELONG READING AND LEARNING

Erasmus once wrote: “When I get a little money I buy books; and if any is left I buy food and clothes.” That could almost be said about me.

I didn’t read much as a kid, for I was too wrapped up in sports. I did begin to read for enjoyment in summers out of college. That pattern has gradually increased to where I probably read at least two books a week, usually nonfiction. It helps that we don’t have a television set.

As S. I. Hayakawa has written:

In a very real sense, people who have read good literature have lived more than people who cannot or will not read. It is not true that we can have only one life to live. If we can read, we can live as many lives and as many kinds of lives as we wish.

Perhaps I should take a speed-reading course, like Woody Allen did. He said he was able to read War and Peace in 20 minutes, adding, “It’s about Russia.”

In her autobiographical work, One Writer’s Beginnings, Eudora Welty tells about how important books were to old Chinese scholars. During World War II, fearing that their great library would be destroyed, these scholars “took the books up in their hands, and put them onto their backs and carried all of them, on foot, over long mountain paths, away to safety.” Welty also tells of her mother, who once went back into a burning building, on crutches no less, to “rescue her set of Dickens which she flung, all 24 volumes, from the window before she jumped out after them, all for Daddy to catch.”

As for her own passion, Eudora Welty writes:

I cannot remember a time when I was not in love with them—with the books themselves, cover and bindings and the paper they were printed on, with their smell and their weight and with their possession in my arms, captured and carried off to myself. Still illiterate, I was ready for them, committed to all the reading I could give them.
John Keats felt likewise and summed up my feelings when he wrote, “Give me books, fruit, French wine and fine weather.” Notice that he listed books first.

**TRAVEL**

The world has certainly shrunk in my lifetime. In high school I recall riding a bus to nearby Green Bay on spring break. My 16-year-old granddaughter went to Patagonia this past spring.

I began to travel when our children were young. There were places I wanted to see before I became too elderly or debilitated. I was motivated to begin early, during my medicine residency, when a colleague developed leukemia and died 3 months later, his dreams and goals unfulfilled. I also encountered patients who desired to travel after retirement, only to develop a stroke or cancer that made such plans unattainable. I would try to seize the moment, avoid procrastination, and learn all that I could in journeys to the seven continents.

I found that travel was a wonderful way to shrink the world. When I read of events in Berlin, I think of Wolfgang Barth, a physician-colleague in the former East Berlin. When troubles flare in Bosnia, I reflect on a beautiful day in Mostar, viewing young daredevils diving off the Stari Most Bridge, built in 1566 by Suleyman the Magnificent. The splendid stone structure had lasted for 424 years. It would exist for only 3 more years before it was destroyed by a mindless Croatian bomber, a symbol of the destruction that was permeating every facet of that country’s society. When apartheid ended, I was happy for Dr. Tim Noakes, a friend in Cape Town, and for the residents I met in Soweto, outside Johannesburg, who now had the potential to be truly free. When Nepal suffered the terrible earthquake in May 2015, I could empathize, for we had trekked through some of the Himalayan villages that had been devastated (Figure 2).

As Tennyson wrote:

’Tis not too late to seek a newer world . . . for my purpose holds
To sail beyond the sunset, and the baths
Of all the western stars, until I die.

I am occasionally asked what propels me to travel to remote regions of the world, dealing with the inconveniences of third world countries, enduring seasickness, foods teeming with Coliform bacteria, and high-altitude illness. Why do people climb mountains, other than that “they are there”? Maybe Rene Daumal said it best:

You cannot stay on the summit forever,
You have to come down again . . .
So why bother in the first place?
Just this: what is above knows what is below,
But what is below does not know what
Is above.
One climbs, one sees. One descends.
One sees no longer: but one has seen.

My family and I have fortunately seen some incredible things: the ink-black sky and radiant stars, with snow-capped Himalayan peaks soaring 25,000 feet or more on either side of the glacier; the first view of the Matterhorn through our hotel window in Zermatt; Masai warriors, trekking up to our game park in Kenya to view the placenta of a newborn elephant, an act said to bring good luck; the little wave of an Israeli shepherd boy, as our van followed a twisting road beneath his pastureland; the breathtaking view of the illuminated Parthenon, as I sipped red Bouliari wine from a rooftop restaurant; the harbor of Portofino, the walled city of Dubrovnik, the fiords of Milford Sound, Chateau Pontet Canet in Bordeaux.

I have seen. And I plan to keep seeing, whenever the opportunity arises. I share the spirit T.S. Eliot wrote about in “Little Gidding”:

We shall not cease from exploration,
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.

**HEROES**

It’s good to have heroes. As mentioned earlier, my father was the main reason I went into medicine. In sports, my first football hero was Doak Walker, Southern Methodist University Heisman Award winner in 1949. I read Doak’s autobiography when I was 10 and decided afterward to become a triple-threat left halfback too (7). I even wore Doak’s number (37) one season. Even today I honor him by using his name or number in my electronic medical password.

When I was 14, the Boston Braves moved to my home state of Wisconsin. I admired their young second baseman-outfielder, Hank Aaron. Little could I have imagined that years later I would become his personal physician (Figure 3).

One has to realize that heroes are, indeed, human. It cannot be easy to be one. Emily Dickinson wrote:

I’m nobody! Who are you?
Are you nobody, too?
How dreary to be somebody
How public, like a Frog
To tell your name the lifelong day
To an admiring bog! (8)
One especially memorable hero I got to meet was Sir Roger Bannister, the first to break the 4-minute barrier in the mile run. I wanted to talk with Dr. Bannister (a noted neurologist) about his memorable run. Instead, he wanted to focus on me—what I did, my family and special interests. Unlike some heroes, he had the ability to focus on others, rather than only on himself.

I was fortunate to have done my cardiology fellowship under Gene Braunwald and J. Willis Hurst, both larger-than-life heroic figures, masterful teachers, both editors of major cardiology textbooks. Dr. Hurst continued to teach until his death at 90. Dr. Braunwald, in his mid-80s, remains vitally involved in research projects, lectures, and writing. Ken Cooper (Figure 4) a long-time friend, continues to be an inspiration, also in his mid-80s. He has done more to motivate children and adults to be physically fit than any single person I know.

The very definition of heroes needs careful attention. Some sports superstars I have known are much less heroic to me than are some seemingly ordinary patients I have encountered through the years. Victor Hugo once observed, “Life, misfortunes, isolation, abandonment, poverty, are battlefields which have their heroes; obscure heroes, sometimes greater than the illustrious heroes.” As Clif Cleveland writes in his book, Healers and Heroes, we need “to look anew at the ‘ordinary’ people who surround us on a daily basis.” In them, he points out, you are “likely to find your own heroes who define the very essence of humanity and good” (9).

MARRIAGE

Greg Maddux once said about pitching that “it ain’t always as easy as it might appear.” The same can be said about a marriage. Fifty-two years after my wedding day, I don’t have all the answers (as I’m still learning), but as Robert Frost said, “I do know the questions.”

Our children gave us a family trip to celebrate our golden anniversary. We were told only that the destination was within 10 hours of Atlanta. A week before our departure, our six grandchildren organized a scavenger hunt for my wife and me. The final clue was a brochure to lovely little St. Simon’s Island, where we celebrated amid the beauty of nature, devoid of social media and television.

I am sometimes asked what makes a successful marriage. I would list the following answers.

1. Realize that our concept of love evolves over time. Some people, especially around middle age, get divorced because their love doesn’t seem like it once was. Tolstoy wrote, however, that “each time of life has its own kind of love.” I have an elderly woman patient, severely crippled with arthritis. Her husband always comes with her and attends to her needs. I’m sure their relationship is different than it once was. I’m also sure that their love is deeper than it has ever been.

2. Have a mutual trust in God. Things might occur in a marriage that are difficult to resolve, given human imperfections. By trusting in a higher power and following biblical guidelines, one can successfully negotiate the minefields of life.

3. Affair-proof your marriage. An elderly minister once advised the young Billy Graham to avoid three big pitfalls: problems with money, sex, and pride. Regarding sex, he advised Graham to avoid “any one-on-one encounters with a person of the opposite sex, to both remove temptation and the threat of a perceived impropriety.” A certain president might have benefited from such an approach. Remember to be true to yourself and that guilt can do a number on you. In the movie City Slickers, Billy Crystal’s friend is giving him various scenarios for an affair, only to be rejected. Finally, he proposes that a spaceship appears and a beautiful woman beckons him, after which the spaceship...
will leave and nobody will know. Crystal still refuses, saying, “I will know.”

4. Have the ability to forgive and move on, if mistakes are made and the offender is truly contrite. I recently attended the remarriage of friends, 11 years after he ran off with a younger woman. The new wife, in turn, eventually left him for a younger man. “What comes around goes around,” according to the old saying. Fortunately for my friend, his first wife was forgiving, and he, in turn, has learned to dearly appreciate her virtues.

Some of the happiest people I know are elderly couples, who, at family reunions, are surrounded by their children and grandchildren and who have given the latter a living example of the joys of maintaining vows and bonds.

SUMMARY

I periodically delve into my little black book for inspiration. I would encourage young professionals to collect meaningful things read and heard, if not in old-fashioned notebooks, maybe in newfangled social media devices. I have focused on preventive cardiology, choice of a vocation, the importance of lifelong reading and learning, the value of travel, the importance of having heroes, and the challenges and joys of a good marriage. I’d like to conclude with the words of Epictetus:

We are like actors in a play. The divine will has assigned us our roles in life without consulting us. Some of us will act in a short drama, others in a long one. We might be assigned the part of a poor person, a cripple, a distinguished celebrity or public leader, or an ordinary private citizen.

Although we can’t control which roles are assigned to us, it must be our business to act our given role as best as we possibly can and to refrain from complaining about it. Wherever you find yourself and in whatever circumstances, give an impeccable performance (10).

TBA for OT HHC vs OPC f/u

Herbert L. Fred, MD

If the title of this editorial confuses you, it should. And if it also intrigues you and compels you to seek its meaning, read on.

As shown in the Figure, the title is an exact replica of a rehabilitation recommendation recently posted in the electronic health record of a patient in a local teaching hospital. Although I have seen some real doozies in my medical career, this one takes the cake.

Which brings me to my first important point.

We tend to forget that the only person who invariably knows what an abbreviation stands for is the person who uses it. In that regard, the doctor of the patient mentioned above took the best option he had—to track down the perpetrator of the recommendation and have her decode it for him. She readily complied, adding, “I assumed you knew what I meant. Everyone in my group is familiar with those abbreviations. In fact, we use them all the time.”

Which brings me to my second important point.

Abbreviations that are obvious to members of one specialty can be, and often are, foreign to members of another specialty. Even within the same specialty, an abbreviation can have a specific meaning in one hospital and no meaning in another. Years ago, I attended medical grand rounds at a hospital in San Francisco. In her oral presentation of a case, the chief resident kept repeating what sounded like “alkep.” Mystified, I interrupted her for an explanation. “Oh, that’s alcoholic hepatitis,” she said. “I thought everyone knew that.”

Point #3: Interpreting an abbreviation correctly depends to a large extent on one’s frame of reference. Consider CHF. To most general internists, CHF stands for congestive heart failure. To infectious disease specialists, it might suggest Crimean hemorrhagic fever. To gastroenterologists, it could signal congenital hepatic fibrosis. And to researchers, it can trigger chick heart fibroblast.

Point #4: Because of their ambiguity, abbreviations can be dangerous, especially in medical settings. If they are not routinely questioned, particularly in doctors’ orders or in doctors’ prescriptions, the patient might undergo the wrong test or receive the wrong medication, with devastating results. I know of two patients—one in Houston and one in Iowa—who were killed when a nurse erroneously thought that the order for “IVP” meant intravenous potassium instead of intravenous pyelogram and proceeded accordingly.

Why are abbreviations so prevalent in the health care community? For physicians, this custom begins in medical school, where students are bombarded with abbreviations in their lectures, in their patients’ medical records, and on their teaching rounds. Consequently, they assume that abbreviations are acceptable, quickly adopt the habit of using them, and perpetuate the habit thereafter. And, of course, abbreviations “save time”—except for the host of individuals who struggle to decipher them.

Final point: All of us are guilty of using abbreviations in the care of our patients. Regrettably, however, many abbreviations are simply covert expressions of self-importance. Most of us, I believe, would prefer clarity and precision over these self-serving shortcuts. And we would concede, I hope, that abbreviations do nothing for our patients other than place them at increased risk—financial, emotional, and physical.

So, like the consultant who prompted this editorial, I offer my own recommendation—DNA. (Warning: that abbreviation does not stand for deoxyribonucleic acid, did not attend, did not answer, or does not apply) (1).

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So, like the consultant who prompted this editorial, I offer my own recommendation—DNA. (Warning: that abbreviation does not stand for deoxyribonucleic acid, did not attend, did not answer, or does not apply) (1).

PS. If you have read this entire piece searching for a translation of its title, your search is over: “To be assessed for occupational therapy home health care versus outpatient clinic follow-up.”


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SLEEP DEPRIVATION
Arianna Huffington has produced a terrific book entitled *The Sleep Revolution: Transforming Your Life, One Night at a Time* (1). Her approach includes discussions of important recent scientific discoveries on sleep and many human stories and experiences. Sleep is one of Ms. Huffington’s passions. She dedicated this book to “the millions of people around the world who are sick and tired of being sick and tired and longing for a good night’s sleep.” The rest of this piece comes from her book.

The medical consequences of sleep deprivation have only recently been recognized. In the 1970s there were only three centers in the USA devoted to sleep disorders; by the 1990s that number had increased to >300, and today, there are >2500 accredited sleep centers. The delusion persists that we can do our jobs just as well on 4 or 5 or 6 hours of sleep as we can on 7 or 8. It is a delusion that affects not only our personal health but our productivity and decision-making. She writes, “The surrendering to sleep every night is the ultimate letting-go.” More than 40% of American adults get less than the recommended minimum 7 hours of sleep per night. Huffington continues, “We are only now beginning to come out of a phase that started with the Industrial Revolution in which sleep became just another obstacle to work. The veneration of sleep as a unique portal to the sacred was sacrificed to the idea of progress and productivity.”

Sleep deprivation has become an epidemic. Both our daytime hours and our nighttime hours are under assault as never before. As the number of things we need to cram into our day has increased, the value of our awake time has skyrocketed. Scientists are resoundingly confirming what our ancestors knew instinctively: that our sleep is not empty time; sleep is a time of intense neurologic activity—a rich time of renewal, memory consolidation, brain and neurochemical cleansing, and cognitive maintenance.

Our sleep time is as valuable a commodity as the time we are awake. In fact, getting the right amount of sleep enhances every minute we spend with our eyes open. And it is a collective delusion that sleep is simply time lost. Sleep deprivation is glamorized and celebrated: “You snooze, you lose.” The distractions and temptations of a 24/7 wired world have imperiled our sleep as never before. Most of us are paying a high price for cheating sleep. Sleep is just as important as good nutrition, physical activity, and wearing a seatbelt. Sleep deprivation is our most underrated health habit.

The crisis is global. The unquestioning belief that work should always have the top claim on our time has been a costly one, and it has gotten worse as technology has allowed a growing number of us to carry our work with us in our pockets and purses in the form of our phones. Being perpetually wired is now considered a prerequisite for success. In the last 50 years, our sleep on work nights has dropped from 8.5 to just under 7.0 hours per night. Thirty percent of employed Americans now report getting 6 hours of sleep or less per night, and nearly 70% describe their sleep as insufficient. Getting less than 7 hours of sleep per 24 hours is one of the biggest factors in job burnout.

The lower the socioeconomic position, the poorer the subjective sleep quality, the greater the sleepiness and sleep complaints. Where we live also affects our sleep. There appears to be a direct association between neighborhood quality and sleep. The annual cost of sleep deprivation to the US economy was estimated recently to be $63 billion in the form of absenteeism and presenteeism (when employees are present at work physically but not really mentally focused). A tired worker accomplishes less than a nontired worker. Our loss of sleep, despite the extra hours we put in at work, adds up to more than 11 days of lost productivity per year per worker, or nearly $2300. Besides lost productivity, sleep deprivation leads to driving and workplace accidents.

Women need more sleep than men. Poor sleep is strongly associated with high levels of psychological distress and greater feelings of hostility, depression, and anger. Women who work outside the home work more at home than most male mates.

Good sleep lengthens lifespan. Death rates from all causes go up 15% when we sleep 5 hours or less per night, and sleep

From the Editor

Facts and ideas from anywhere
deprivation makes us dangerously less healthy. About 60% of men who suffer a heart attack also have a sleep disorder. Adults who have trouble falling asleep are involved in a third more fatal car accidents than those who do not have trouble. And those with symptoms of insomnia are nearly three times more likely to die from a fatal injury. Sleep deprivation also makes us more susceptible to garden-variety illnesses, like the common cold.

Sleep deprivation has a major impact on our ability to regulate our weight. In a Mayo Clinic study, sleep-restricted subjects gained more weight than their well-rested counterparts over the course of the week, consuming an average of 560 extra calories a day. People who get 6 hours of sleep a night are nearly 25% more likely to be overweight than those who get more than that. Getting <4 hours of sleep per night increases the likelihood of being overweight by nearly 75%. In other words, cutting back on sleep is a fantastic way to gain weight.

And sleep deprivation plays havoc with our skin. In a Swedish study, untrained participants were asked to look at sleep-deprived and well-rested people. Participants judged those in the sleep-deprived group as “less healthy, more tired, and less attractive.” The skin was analyzed and photographed after they slept for 8 hours and then again after sleeping 6 hours for 5 nights in a row. Fine lines and wrinkles increased by 45%, blemishes went up by nearly 15%, and redness increased by nearly 10%. In other words, we wear our lack of sleep on our faces.

Good sleep is also a key to mental health. Sleep affects our mental health every bit as profoundly as it does our physical health. Sleep deprivation has a strong connection with practically every mental health disorder, especially depression and anxiety. One study showed that sleep-deprived people were 7 times more likely to experience feelings of helplessness and 5 times more likely to feel lonely than controls. Sleep deprivation takes a toll on our mental abilities. Our cognitive performance is reduced greatly, memory capacity is reduced, and social competence is reduced. In just 2 weeks of getting 6 hours of sleep per night, the performance drop-off is the same as going 24 hours without sleep. For those getting just 4 hours, the impairment is equivalent to going 48 hours without sleep. The side effects of not getting enough sleep include having difficulty concentrating, losing interest in hobbies and leisure activities, falling asleep at inappropriate times throughout the day, losing our temper or behaving inappropriately with children or partners, and behaving inappropriately at work.

In terms of driving while drowsy, one study found that after being awake from 17 to 19 hours, we can experience levels of cognitive impairment equal to having a blood alcohol level of 0.5% (just under the legal limit in many US states). And, if we are awake just a few hours more, we are up to the equivalent of 0.1%—legally drunk. There is of course a roadside test for drunk driving; there is no equivalent test for sleep-deprived driving. Awareness of the impact of sleep deprivation on driving is important. Nearly 60% of train operators, 50% of pilots, 44% of truck drivers, and 29% of bus and taxi drivers admit that they never or rarely get a good night’s sleep on work nights.

So why do we tolerate, much less venerate and applaud, sleep deprivation? In much of our culture, especially in the workplace, going without sleep is considered a badge of honor. Yet since the effects of sleepiness are largely the same as those of being drunk, when we get behind the wheel of a car without enough sleep, we are engaging in behavior that is dangerous to both ourselves and others. Sleepiness-related motor vehicle crashes have a fatality rate and injury severity level similar to those of alcohol-related crashes. Drowsy drivers are involved in 330,000 accidents each year, 6400 of which result in death.

Sleep experts have a name for the phenomenon of nodding off: “microsleep.” Microsleep occurs when we unknowingly fall asleep from a few seconds to a minute or so. It is a terrifying phenomenon when one is behind the wheel of a car. Imagine commuting home from work driving down the highway at 60 miles per hour. At that speed, the car is traveling 88 feet per second. If your eyes close for only 4 seconds, your car has traveled roughly the length of a football field before you jerk awake, and the consequences, of course, can be deadly. And nowhere is this truer than in the trucking industry. There are now an estimated 2 million truckers on our highways, and accidents involving trucks and buses are responsible for 4000 deaths and >100,000 injuries in the US each year. More than 60% of the drowsy drivers involved in fatal crashes were driving trucks, and nearly half of all truckers have said in a survey that they had fallen asleep behind the wheel in the previous year. Several states are considering measures that would make driving while sleep deprived a criminal offense.

Airlines have stricter standards, with rules mandating specific rest periods for commercial pilots between flights and dictating how many hours they are allowed to fly in a given period of time. One pilot of a Boeing 747 said in the PBS documentary Sleep Alert, “It is not unusual for me to fall asleep in the cockpit, wake up 20 minutes later and find the other two crew members totally asleep.” Luggage screeners deteriorate rapidly when they are sleep deprived. Air traffic controllers averaged only 5.8 hours sleep per night, which dropped to 3.25 hours per night when they worked overnight shifts. Of the controllers who made safety errors on the job, 56% attributed the mistake to fatigue. Train accidents from sleep deprivation also occur.

Of course, physicians and nurses commonly are sleep deprived. Sleep-deprived health care workers show less empathy, among other consequences. Sleep-deprived adolescents (those getting <7 hours of sleep per night) were at a higher rate of failing and had higher dropout rates than those sleeping >7 hours nightly. Politicians, soldiers, and law enforcement officers are burdened considerably with sleep deprivation.

I found the book to be superb. Every page is loaded. And she advises how to sleep better. She has never taken a sleeping pill.

BELLEVUE

David Oshinsky, who previously authored Polio: An American Story, has produced a terrific book entitled Bellevue: Three Centuries of Medicine and Mayhem at America’s Most Storied Hospital (2). The information that follows comes entirely from his 2016 book.

Bellevue started as a small infirmary built in the 1660s for soldiers overcome with “bad smells and filth,” and it was replaced
in 1736 by a two-story almshouse that served 19 paupers, included a prison, and had a room for the sick and insane. By 1795, the almshouse had become home to 800 people. Bellevue Hospital opened on its present site—30th Street and the East River—in 1816 and contained an almshouse, orphanage, lunatic asylum, prison, and infirmary.

The hospital then and still today serves what a 1900 city official said were the “dregs of society”—a dumping ground for poor patients who could not pay and for those who were dying. Through every major epidemic, Bellevue has provided free care to the medically indigent. From the yellow fever outbreak at the end of the 19th century to the AIDS epidemic of the 1980s, when Bellevue treated more AIDS patients than any other hospital in America, the hospital “has borne witness to every imaginable public health scare, every economic swing and population surge, every medical breakthrough and controversy.” During the great influenza epidemic of 1918–1919, no one was turned away, “forcing the patient overflow to sleep on doors ripped from hinges and piles of damp, fetid straw.”

“What set Bellevue apart, even in the worst of times,” Oshinsky writes, “was its powerful connection to New York City's top medical schools.” By the mid-19th century, Columbia College of Physicians and Surgeons and the Medical College of New York (later New York University [NYU]) sent their students to Bellevue. The city’s “elite physicians for whom the lure of interesting patients outweighed the fear of deadly miasmas and physician blight” were applying for visiting positions. Soon after it opened in 1898, Cornell Medical School joined Columbia and NYU in sending its medical students to Bellevue. The training the young physicians received in the early 1960s may have been the best any physician could receive, largely for two reasons: the dedication of many faculty members and the fact that the hospital was “a virtual war zone.” Because the patient population came largely from New York City’s foreign-born residents and its underclass—immigrants, derelicts, alcoholics, addicts, the homeless, the mad, and the discarded and dying sent from other hospitals—students became familiar with a wide range of illnesses few other medical students would ever see elsewhere.

The students and young house officers worked under abysmal conditions. More than 100 tuberculosis patients were often stacked in corridors awaiting beds. Operations were routinely canceled during heat waves because there was no air conditioning. Stray cats roamed the doctors’ basement dining rooms to ease the invasion from the hospital’s maze of rat-infested underground tunnels.

By the time of the Civil War (1861–1865), Bellevue “had become both our nation’s largest hospital and its most important medical training ground.” Medical training could be summed up in a single word: immigration. Early waves of immigrants were mostly Irish and Germans; after them came Italians and Jews; and then Hispanics, Haitians, Africans, South Asians, and Chinese. Most of Bellevue’s patients—the poor, the mad, and the despised—have been those who had nowhere else to go. In its >280 years of existence, Bellevue has never turned away a patient! Just as Irish immigrants were considered dangerous foreigners inflicting a typhus epidemic on New York in the mid-19th century, so Jewish immigrants were later thought to have a “tailor’s disease” that was causing an epidemic of tuberculosis. In recent times, gays, blacks, Hispanics, drug addicts, and homeless people have been vilified as carriers of AIDS. No matter which ethnic group is alleged to spread disease in New York, Bellevue has not only persisted in providing medical care for generations of the city’s residents, but has served as a model of how a public hospital can survive and give excellent care. Bellevue handles nearly 670,000 non-emergency clinic visits and nearly 116,000 emergency visits each year. Approximately 80% of those it serves are either uninsured or poor enough to be covered by Medicaid.

More than 3 million of New York City’s 8.5 million residents are foreign-born, many of whom are undocumented. As many as 800 languages are spoken in New York, making it the most linguistically diverse city in the world, and at Bellevue >100 languages are translated. Among them are Mandarin, Cantonese, Polish, Bengali, French, Spanish, and Haitian Creole. As Oshinsky writes, “Doctors and patients communicate on dual telephones through an interpreter trained in the nuances of regional dialects. The directional signs that guide visitors through the hospital are multilingual—the destinations now include a Muslim prayer room and a clinic for the survivors of political torture.”

During its 300-year history, Bellevue Hospital has always been short of funds. Somehow Bellevue has always survived, probably because of the quality of its medical care, the fact that it provides unique services to the city (e.g., the medical examiner’s office and forensic labs), and its ongoing relation to NYU Medical School, an affiliation that has served both well for over 100 years. It is unlikely that Bellevue will go away. NYU’s physicians, medical students, residents, and attendees train and work at Bellevue. And Bellevue pays NYU an annual sum for these services. Bellevue’s increasing lack of funds remains a major concern for the city presently.

There was never a time when Bellevue appeared to be even remotely trouble free. Yet, while caring for millions of patients other hospitals turned away and often on the verge of being closed down by the city, it was also among the nation’s leaders in medical research and innovation. Bellevue, for example, was the first American hospital to establish a maternity ward (1799), a nursing school (1873), a children’s clinic (1874), an emergency department (1876), a psychiatric ward (1879), an ambulance corps (1869), a pathology laboratory (1884), and a medical photography department. It produced lasting innovations in amputations, anesthesia, antisepsis, and the treatment of tuberculosis, heart disease, and AIDS. Throughout its history, its physicians constantly demanded that the city provide decent conditions for their patients and humane conditions for the city’s poor and underserved citizens.

Bellevue’s faculty and graduates read like a “Who’s Who” of modern American medicine: Hermann Biggs, a pioneer in the prevention of tuberculosis; Walter Reed and William Gorgas, who tamed the ravages of yellow fever; William Hallock Park, who brought the lifesaving diphtheria antitoxin to the US;
Joseph Goldberger, who discovered the cause of pellagra; Thomas Francis, whose influenza research revolutionized the study of virus strains; André Cournand and Dickinson Richards, who introduced cardiac catheterization as a clinical tool; and Albert Sabin and Jonas Salk, who developed the two successful polio vaccines still in use today. Two of the most influential figures—William Welch, the father of modern pathology in the USA, and William Halsted, the era’s most innovative surgeon—bonded as interns at Bellevue in the bitter struggle to bring antiseptic methods to the profession.

By the early 1900s, Bellevue seemed less a city hospital than a hospital city, with 2000 beds, a nursing school, the city morgue, a massive psychiatric pavilion, a special prison ward, top-flight laboratories, a maintenance force of 4000, and a medical staff provided by the three best medical colleges in New York. A major facelift came in 1973 with the addition of a 25-story patient tower. The impact on New York City was dramatic.

Bellevue today remains a buttress against unforeseen crises that periodically arise. Its resilience was displayed in the heroic patient evacuation during Superstorm Sandy, the largest storm ever recorded in the Atlantic Ocean, with a diameter approaching 1000 miles. It hit New York City full on October 29, 2012, when the hospital became flooded and its elevators went out of service. The staff began carrying patients down the stairwells led by medical students and residents holding flashlights. Houseofficers were dispatched with oxygen tanks to the beds of every ventilated patient. Intravenous infusions were converted to subcutaneous injections, and prescriptions filled by flashlight were taken by medical student runners to various floors. The National Guard arrived, and together with physicians, nurses, medical students, technicians, and secretaries they passed 5-gallon jugs of gasoline hand-to-hand until the jugs reached the backup generators on the 13th floor. If the jugs stopped moving and the generators died, so would patients. No patients died. The bucket brigade staved off disaster, and all 700 patients were saved, including surgical patients, alcoholics, drug addicts, hundreds of psychiatric patients, and 61 criminal patients locked up on the 19th floor. Superstorm Sandy closed the hospital for the only time in its history. Bellevue reopened a few months later. The patients it currently serves are every bit as poor and needy as the patients who preceded them in centuries past. Those with viable options almost always wind up going somewhere else. That is what makes Bellevue so comforting and so disquieting. It stands for all its troubles as a vital safety net—a place of last resort.

GUNS IN THE USA

Individuals in the USA own far more guns than populations of any other country in the world (3, 4). In the USA there are 114 guns per 100 citizens. The US gun-ownership level in 1968, 48 years ago, was 56 per 100 people, or half of what it is today. The estimated number of civilian-owned guns per 100 people in other countries is as follows: Serbia, 76; Yemen, 55; Switzerland, 46; Cyprus, 36; Saudi Arabia, 35; Iraq, 34; Uruguay, 32; Sweden, 32; Norway, 31; France, 31; Canada, 31; and Australia, 22. There are >33,000 gun deaths annually in the US, according to averages from 2014 to 2016. Terrorism and mass shootings grab the headlines but make up a small percentage of US gun deaths, numbering 45 in 2016. Other deaths, by comparison, include armed toddlers, 21; lightning strikes, 31; and lawnmowers, 69. Since the mass shooting at Sandy Hook Elementary, an American child under age 12 has died by intentional or accidental gunfire every other day. More than half of all homicide victims are young men and two-thirds are black. Among blacks, 82% of fatalities are homicide and 18% are suicide, and among whites, 23% are homicide and 77% are suicide. Gun manufacturing is big business in the USA. The 2015 revenue from manufacturing guns and ammunition was $15 billion; that’s more than the 2015 combined government funds for medical research.

Gun deaths in Australia have dropped dramatically since 1996 when its buyback program began (5). Since the massacre that year in Australia, where 35 people were killed and 23 wounded by a semiautomatic rifle used by a 28-year-old man on the island of Tasmania, off the southern coast of Australia, the country’s criminal justice system quickly held Martin Bryant responsible, and he is serving a life sentence. Just-elected Prime Minister John Howard, a conservative, led the charge for a bipartisan deal with state and local governments to enact far-reaching gun laws. A conservative-led government action contradicts those who maintain that the gun problem is unconquerable, that smart laws cannot make a difference. Australia put its national firearms agreement into action within 2 months of Bryant’s rampage. The law prohibits automatic and semiautomatic assault rifles and pump action weapons; it also requires residents who already owned high-powered long guns to sell them back to the government. More than 650,000 firearms were handed in, at a cost of $350 million funded by a temporary federal tax. The law also made buying other guns more difficult. People no must pass a safety test, show good moral character, and wait at least 28 days to make their purchase. And they must qualify under carefully defined “genuine needs” to own a gun. Private sales are prohibited, and all weapons must be individually registered to their owners.

In the two decades prior to the reform, Australia saw 13 fatal mass shootings, defined as those with five or more victims. In the two subsequent decades, not another mass killing has occurred! The law also appeared to accelerate a reduction in firearm-related homicides and suicides without prompting a rise of alternative means of death. Thus, an intervention designed to stop mass shootings also has limited other gun-related deaths. The daunting size of America’s gun violence does not have to paralyze us. Large-scale change is possible.

GUN-RELATED VERSUS MOTOR VEHICLE DEATHS IN THE USA

For the first time in decades, the annual number of gun-related deaths in the US is expected to surpass the annual number of automobile fatalities (6). In 2013, the most recent year for which data is available, motor vehicles killed 33,804 people and firearms killed 33,636, according to the US Centers for Disease Control and Prevention. Firearm deaths and injuries pose a major public health problem.
TEXAS PRISON POPULATION

In 1985, it was 37,488 and in 2016 it was 146,843 (7). The annual budget of the Texas Department of Criminal Justice is $3.4 billion, and for the entire US it is roughly $80 billion. The USA, with 5% of the global population, leads the world in people locked in prisons. Presently, the US imprisons approximately one-fourth of all the world’s prisoners. Black and Latino men make up >60% of the prison population, including two-thirds of those locked up in Texas’ 109 facilities. One problem is the 1994 Omnibus Crime Bill that gave birth to the federal three-strike rule that mandated life sentences for criminals convicted of a felony after two prior convictions, including drug crimes. Although these numbers are high, Texas is beginning to see a drop in the number of prisoners, thanks both to a budget pinch and to a shift in philosophy.

TEXAS EXECUTIONS DECLINING

Texas executions and death sentences are occurring at the lowest rate in decades (8). Only three people in the state were sentenced to death in 2016, and seven others were executed. The numbers are still higher than in most other states, but represent a sharp decrease for Texas. There are now 242 inmates on death row in Texas—the fewest since 1987. Death sentences in 2016 are at their lowest level in 30 years and executions at their lowest level in 20 years.

ALCOHOL DRINKING IN WOMEN

According to a recent analysis by two writers of The Washington Post, women in the USA are now drinking far more alcohol and far more frequently than their mothers and grandmothers, and alcohol consumption is killing them in record numbers (9). White women are particularly likely to drink dangerously, with more than a quarter drinking multiple times a week, and the share of their binge drinking is up 40% since 1999. In 2013, more than 1 million women of all races wound up in emergency rooms as a result of heavy alcohol consumption, with women in middle age most likely to suffer severe intoxication. This behavior has contributed to a startling increase in early mortality. The rate of alcohol-related deaths for white women aged 35 to 54 in 2015 was 8% of deaths in this age group, twice that in 1999.

Some of this increase has been attributed to advertisements in social media—Facebook, Twitter, and Instagram—focusing on the most eager consumers. Jokes about becoming inebriated are common. One Twitter ad featured a bottle the size of a refrigerator tilted toward a woman’s lips. Its contents: Fireball Cinnamon Whiskey. Women also are frequently shown drinking alcohol to cope with daily stress. In one image that appeared on a company website, two white women wearing prim, narrow-brimmed hats, button earrings, and wash-and-set hair confer side-by-side. “How much do you spend on a bottle of wine?” one asks. The other answers, “I would guess about half an hour . . . .” At the bottom is the name of the wine: “Mommy’s Time Out.”

Drinking alcohol can be especially hazardous for women. Women, of course, tend to have smaller bodies than men and differences in physiology that make blood-alcohol levels climb faster and stay elevated longer than in men. Some studies have found that women have lower levels of the stomach enzymes needed to process the toxins in alcoholic beverages. As a result, according to the Centers for Disease Control and Prevention, women are more prone to suffer brain atrophy, heart disease, and liver damage. Even if a woman stops drinking, liver disease may continue to progress in ways it does not do in men. There is no gender equity when it comes to the effects of alcohol on men vs. women. Women are more susceptible to the unwanted biologic effects of alcohol when they consume the same amount of alcohol and at the same frequency, even when there is an adjustment for weight.

DRY EYES AND CELLPHONES

According to an article by Ann Lukits (10), pediatric dry-eye disease can negatively affect vision and school performance and is believed by many specialists to be underdiagnosed. Staring at smartphones, computers, and other screens has been linked to reduced blinking, which can lead to faster evaporation of the tear film and increase the risk of dry-eye disease. Smartphones also have a short watching distance due to their small screens that can tire the eyes. Researchers in South Korea conducted eye exams on 916 children aged 7 to 12 years: 60 (7%) of the total met the criteria for dry-eye disease based on various assessments including tear-breakup time, a test that measures the stability of tear film. Of those 60 children, 58 (97%) reported on questionnaires that they used smartphones an average of 3.2 hours a day. In contrast, of the 856 children without dry-eye symptoms, the control group, 55% used smartphones 37 minutes a day. The latter group also spent more time outside—an average of 2.3 hours a day compared with 1.5 hours by the dry-eye group. The prevalence of dry-eye disease was higher among students in urban than in rural schools.

US ABORTION RATES

The rate of abortions in the US has fallen to its lowest level since the 1973 Roe vs. Wade Supreme Court decision (11). In 2014, there were 14.6 abortions per every 1000 women aged 15 through 44 in the US, down 50% from a peak of 29.3 abortions per 1000 in the early 1980s. The number of abortions fell to 926,200 a year for the first time since 1975. The number of abortions in the US reached a peak of 1.6 million in 1990. The decline in numbers of abortions is likely the result of reduced unintended pregnancies due to the increased availability of affordable, long-lasting contraceptives, such as IUDs.

MANDATORY IUDS IN CHINA

Thirty years ago, China began demanding that women be fitted with an intrauterine device after they had one child and sterilized after they had two (12). From 1980 to 2014, 324 million Chinese women were fitted with IUDs. Now these IUDs can be sterilized after they had two (12). From 1980 to 2014, 324 million Chinese women were fitted with IUDs. Now these IUDs can be removed free of charge at government expense. While IUDs in other countries often can be removed with a tug on their strings in a physician’s office, surgery is usually needed in China because most devices were designed or altered to be more difficult to

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HOTTEST YEAR

The average temperature in 2016 was the hottest recorded since 1880, when records started being kept (13). In 2015, the temperature was the hottest up to that point, and in 2014, the hottest up to that point. According to the National Oceanic and Atmospheric Administration, the average surface temperature in 2016 was 0.07°F warmer than 2015 and featured eight successive months (January through August) that were individually the warmest since the agency’s recording began.

That the earth is heating up is a point long beyond serious scientific dispute, and one becoming more evident each year. Temperatures are rising toward levels that many experts believe will pose profound threats to both the natural world and to human civilization. In 2015 and 2016, the planetary warming was intensified by the weather pattern known as El Niño, in which the Pacific Ocean released a huge burst of energy and water vapor into the atmosphere. The biggest factor in setting the records, however, is the increasing levels of carbon dioxide and other greenhouse gases. The heat extremes were especially pervasive in the Arctic where temperatures in the fall ran 20° to 30°F above normal. Sea ice in that region has been in precipitous decline for years. Arctic communities are already wrestling with enormous problems, such as rapid coastal erosion, caused by the changing climate.

Since 1880, the planet has now warmed about 1.1°C or 2°F. That is very significant because the global community has been striving to limit overall warming to considerably below a 2°C rise, and even, if possible, to hold it to a 1.5°C increase. That is now only about 0.4° away.

The warming in 2016, of course, was not limited to the Arctic. Off the coast of Northeastern Australia, the Great Barrier Reef experienced its worst coral bleaching on record. Extremely high temperatures were seen in India—where the city of Phalodi recorded temperatures of 124°F in May—and Iran, where temperatures of 127°F were recorded in Delhoran on July 22.

El Niño has now ended, and climate scientists almost universally expect 2017 to be cooler than the year before. But the scale of the heat burst has been startling to many experts, and some of them fear that an accelerated era of global warming could be at hand over the next few years. Even at current temperatures, billions of tons of land ice are melting or sliding into the ocean. The sea is also absorbing most of the heat trapped by human emissions. These factors are causing the ocean to rise at what appears to be an accelerating pace, and coastal communities in the US are now spending billions of dollars to fight increased tidal flooding.

SLOWING US POPULATION GROWTH

The US population in 2016 grew at its lowest rate since the Great Depression, and the population of the State of New York shrank for the first time in a decade (14). An uptick in deaths, a slowdown in births, and a slight drop in immigration all damped US population growth for the year ending July 2016. The 0.7% increase, to 323 million, was the smallest on record since 1936–1937. Americans continue to leave the North for Western states, with Utah, Nevada, Idaho, and several others in the region topping the country in percentage growth. Besides New York, Pennsylvania and Illinois also shrank, with Illinois losing more people than any other state. About 593,000 people left the Northeast and Midwest to move to the South and West in 2016, slightly more than during the prior 1-year period.

SELF-DRIVING CARS

The race to get humans to give up the wheel is picking up speed (15). Self-driving cars have rapidly moved from science fiction to actual fact and will start hitting the road within 5 years. After 7 years and >2 million miles of road testing, Google’s self-driving car project, “Waymo,” which uses sensors and processors to drive a car without human input, will be sold commercially for a variety of uses by the end of 2017. Plenty of carmakers are getting ready to build their own driverless cars: Tesla Motors, BMW, Ford Motor Company, and Volvo Cars have all promised to have fully autonomous cars on the road within 5 years. The technology is expected to transform transportation as mobility becomes a service one orders from an app, rather than an expensive machine bought and mostly stored in a parking space. The use of self-driving cars could drastically reduce urban congestion and dramatically reduce or even eliminate the 1.25 million road deaths a year globally. Human error is the cause of 94% of roadway fatalities, and robot drivers never get drunk, sleepy, or distracted. These autonomous vehicles are presently being tested on the streets in Pittsburgh, Boston, and Singapore.

IF TEXAS WERE A COUNTRY

Only nine countries and one US state (California) have a larger gross domestic product than Texas (16). The 2015 gross domestic product in trillions is as follows: USA, 17.9; China, 11.0; Japan, 4.1; Germany, 3.4; United Kingdom, 2.8; California, 2.5; France, 2.4; India, 2.1; Italy, 1.8; Brazil, 1.8; and Texas, 1.6. Public education is underfunded in Texas. Among the US states in 2015, it ranked 43rd. It is also behind in health care availability. No state had more to gain from Obamacare, and Texas lawmakers fought it at every turn. They rejected Medicaid expansion, even though the feds covered over 90% of the costs. Access to health care for over 1 million low-income residents of Texas apparently is lacking.

MONEY AND AGING

Spending tends to decline as we age (17). Spending tends to peak in our early 50s and then it declines until it levels out in our mid 80s. With the exception of medical spending, our costs decline across the board: shelter, food, cars, clothing, and entertainment—all of it. The decline is not due to running out of money to spend. It is due to changes in what is important to
us and to changes in our physical capacities. André Gild may have said it best: “Our judgments about things vary according to the time left us to live—that we think is left us to live.”

William Clifford Roberts, MD
February 3, 2017

17. Editorial. The older we get, the less money we spend. Dallas Morning News, January 5, 2017.
Original Research

138 Personalized treatment of heart failure with biomarker guidance using a novel disease severity score by A. Vasudevan et al

143 Emergency department discharge prescription errors in an academic medical center by K. A. Murray et al

147 Pre and post hoc analysis of electronic health record implementation on emergency department metrics by K. J. Piza et al

151 Perineal body length and perineal lacerations during delivery in primigravid patients by T. L. Lane et al

154 Anatomic relation between single-incision slings and the obturator vessels by A. L. D’Baye et al

Reviews

157 Practical and ethical considerations in the management of pacemaker and implantable cardiac defibrillator devices in terminally ill patients by M. M. Benjamin and C. A. Sorkness

161 Relation of left ventricular free wall rupture and/or aneurysm with acute myocardial infarction in patients with aortic stenosis by J. M. Sheldon and W. C. Roberts

163 Heterogeneity of systematic reviews in oncology by J. Holmes et al

Case Studies

167 Hemodialysis failure secondary to hydroxocobalamin exposure by K. Lim et al

169 Acquired S-proline acidemia successfully treated with N-acetylcysteine by G. L. Hundemer and A. Z. Fenves

171 Nitrous oxide–induced vitamin B12 deficiency by L. Stockton et al

173 Systemic infection and spinal abscesses by A. R. Belknap and J. Guileyard

175 Tularemia presenting as pulmonary nodules in an immunocompromised patient by T. Akas et al

177 Benign pancreatic hyperenzymemia (Gullo syndrome), histamine intolerance, and carbohydrate malabsorption by W. J. Schnedl et al

179 Pott puffy tumor by F. Sharma et al

182 Acquired thrombotic thrombocytopenic purpura and atypical hemolytic uricemic syndrome successfully treated with eculizumab by A. Sasapu et al

184 A rare hemoglobin variant, Hb Belliard by S. Murphy and R. Berenades

186 Asian-variant intravascular large B-cell lymphoma by D. W. Su et al

190 Bile duct lymphoma disguised as cholangiocarcinoma by C. Durham et al

192 Plasma cell myeloma with lymphoplasmacytic morphology and cyclin D1 expression, an uncommon variant by D. L. Glancy

195 Myeloid sarcoma causing airway obstruction by A. R. Belknap and J. R. Krause

197 Diagnosis of sarcoidosis from a biopsy of a dilated mammary duct by C. Masson et al

200 Primary small-cell carcinoma of the breast by B. Raber et al

203 Plasmaphilastic plasmacytoma of the breast by D. K. Le et al

205 Primitive neuroectodermal tumors of the kidney by M. Hardy et al

209 Giant cystic umbilical cord associated with patent urachus and intrauterine fetal demise by K. Brooks et al

211 Evaluation and management of an unusual congenital nevus by K. Brodman and M. A. Menter

213 Leukocytoclastic vasculitis drug reaction to certolizumab pegol by M. N. Cato and L. Cato

215 Dental arteriovenous fistula as a treatable dementia by J. Enne et al

218 Right hemispheric reversible cerebral vasoconstriction syndrome in a patient with left hemispheric partial seizures by G. S. Perez et al

221 Bilateral respiratory epithelial adenomatoid hamartomas originating from the anterior otolaryngologic cartilage by J. J. Falco et al

224 Ambulatory extracorporeal membrane oxygenation with subcostal venoarterial cannulation to increase mobility and recovery in a patient awaiting cardiac transplantation by S. Jacobs et al

226 Use of a MitraClip for severe mitral regurgitation in a cardiac transplant patient by F. S. Piza et al

228 Two causes in one patient for extremely low voltage on the electrocardiogram by W. C. Roberts et al

230 Successful treatment of a cardiac resynchronization therapy nonresponder by identifying lead malpositioning by K. V. Prasad et al

232 Atrial fibrillation 50 years after acute rheumatic fever as the first manifestation of rheumatic mitral stenosis by D. L. Glancy

234 Cardiac rehabilitation for a skydiver after aortic valve replacement for pure aortic regurgitation and resection of the ascending aorta complicated by active infective endocarditis and heart block requiring a pacemaker by T. R. Solomon et al

Editorials

240 From my little black notebook: lessons for young physicians and medical students by J. D. Cantwell

245 TBA for UT vs OPC by H. L. Fred

From the Editor

246 Facts and ideas from anywhere by W. C. Roberts

Miscellany

138 Clinical research studies enrolling patients

165 Assignments: Photograph by T. C. Lairmore

194 Assignments: Photograph by W. L. Rayburn

199 Assignments: Photograph by M. A. Menter

223 Assignments: Photograph by J. Rosenthal

237 Baylor Scott & White Health news

239 Reader comments: Tribute to Dr. John Hyland by P. A. Alivizatos